THEME [HEALTH.2010.2.4.1-3]
[Structuring clinical research in paediatric and adolescent oncology in Europe. FP7-HEALTH-2010-single-stage]

Grant agreement for: Network of Excellence*

Annex I - "Description of Work"

Project acronym: ENCCA

Project full title: " EUROPEAN NETWORK for CANCER research in CHILDREN and ADOLESCENTS "

Grant agreement no: 261474

Version date: 2014-06-16

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Part A

Workplan Tables

A1:
Project summary

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per project

General information			
Project title [3]	EUROPEAN NETWORK for CANCER research in CHILDREN and ADOLESCENTS		
Starting date [4]	01/01/2011		
Duration in months [5]	60		
Call (part) identifier [6]	FP7-HEALTH-2010-single-stage		
Activity code(s) most relevant to your topic [7]	HEALTH.2010.2.4.1-3: Structuring clinical research in paediatric and adolescent oncology in Europe. FP7-HEALTH-2010-single-stage		

Abstract [9]

ENCCA aims to establish a durable, European Virtual Institute clinical and translational research in childhood and adolescent cancers that will define and implement an integrated research strategy and will facilitate the necessary investigator-driven clinical trials to introduce the new generation of biologically targeted drugs into standard of care for children and adolescents with cancer. This will lead to more efficacious and less toxic therapies that will maximise the quality of life of the increasing number of survivors of cancer at a young age in Europe and allow them to assume their proper place in society. This biologically-driven research agenda will improve training of the clinical investigators and translational scientists of the future to spread excellence, increase capacity to participate in research and monitor outcomes across Europe. Patients and their families will be full partners and will be better informed about the need for and processes of clinical research. They will be in a better situation to care from their long term health risks for children. Drug development will be accelerated in partnership with industry through improved access to young patients with cancer, to academic expertise in care, clinical and biological research. All of this will be achieved with respect for the highest ethical and patient safety standards. ENCCA will bring all stakeholders to the table in a timely and efficacious manner. It will address the needs of all the current multinational clinical trial groups for the benefit of children with cancer. It will provide them with common tools and approaches to solve the bottlenecks in testing new therapeutic strategies for those rare diseases in a vulnerable age group and in running a competitive clinical research agenda. Ongoing efforts to coordinate EU and US clinical research will be reinforced. ENCCA will be led by the most active EU institutes in the field (31), recognised as being at the forefront of excellence.

A2:
List of Beneficiaries

Project Number [1]	261474	Project Acronym [2]	ENCCA

List of Beneficiaries

No	Name	Short name	Country	Project entry month[10]	Project exit month
1	ST. ANNA KINDERKREBSFORSCHUNG	CCRI	Austria	1	60
2	SIOP Europe	SIOPE	Belgium	1	60
4	UNIVERSITY COLLEGE LONDON	UCL	United Kingdom	1	60
5	CHRISTIAN-ALBRECHTS-UNIVERSITAET ZU KIEL	CAU	Germany	1	60
6	INSTITUT GUSTAVE ROUSSY	IGR	France	1	60
7	UNIVERSITA CATTOLICA DEL SACRO CUORE	UCSC	Italy	1	60
8	UNIVERSITAETSKLINIKUM ESSEN	UKE	Germany	1	30
9	UNIVERSITA' DEGLI STUDI DI MILANO-BICOCCA	UNIMIB	Italy	1	60
10	ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM	EMC	Netherlands	1	60
11	FUNDACION PARA LA INVESTIGACION DEL HOSPITAL UNIVERSITARIO LA FE DE LA COMUNIDAD VALENCIANA	LaFe	Spain	1	60
12	GDANSKI UNIWERSYTET MEDYCZNY	MUG	Poland	1	60
13	THE UNIVERSITY OF BIRMINGHAM	UOB	United Kingdom	1	60
14	THE LEEDS TEACHING HOSPITALS NATIONAL HEALTH SERVICE TRUST	LTHTNHS	United Kingdom	1	60
15	ISTITUTO GIANNINA GASLINI	IGG	Italy	1	60
16	INSTITUT CURIE	CURIE	France	1	60
17	FOUNDATION FOR RESEARCH AND TECHNOLOGY HELLAS	FORTH	Greece	1	60
18	AIT Austrian Institute of Technology GmbH	AIT	Austria	1	60
19	CONSORZIO INTERUNIVERSITARIO CINECA	CINECA	Italy	1	60
20	ESQH VIENNA OFFICE - EUROPAISCHE GESELLSCHAFT FUR QUALITAT IM GESUNDHEITSWESEN - WIENER BURO VEREIN	ESQH	Austria	1	60
21	Academisch Medisch Centrum bij de Universiteit van Amsterdam	AMC	Netherlands	1	60
23	CENTRE ANTICANCEREUX LEON BERARD	CLB	France	1	60

A2:
List of Beneficiaries

No	Name	Short name	Country	Project entry month[10]	Project exit month
24	CENTRE INTERNATIONAL DE RECHERCHE SUR LE CANCER	IARC	France	1	60
26	ACADEMISCH ZIEKENHUIS LEIDEN - LEIDS UNIVERSITAIR MEDISCH CENTRUM	LUMC	Netherlands	1	60
27	KAROLINSKA INSTITUTET	KI	Sweden	1	60
28	UNIVERSITEIT GENT	UGent	Belgium	1	60
30	CHARITE - UNIVERSITAETSMEDIZIN BERLIN	CHARITÉ	Germany	1	60
31	ASSISTANCE PUBLIQUE - HOPITAUX DE PARIS	AP-HP	France	1	60
32	LANDESHAUPTSTADT STUTTGART	OLGA	Germany	1	60
34	European CanCer Organisation	ECCO	Belgium	1	60
35	Osterreichische Kinder-Krebs-Hilfe verband der Osterreichischen kinder krebs hilfe organisationen	ÖK	Austria	1	60
36	UNIVERSITA DEGLI STUDI DI PADOVA	UNIPD	Italy	1	60
37	WESTFAELISCHE WILHELMS-UNIVERSITAET MUENSTER	WWU	Germany	1	60
38	UNIVERSITY OF SOUTHAMPTON	SOUTHAMPTON	United Kingdom	1	60
39	UNIVERSITY OF LEEDS	UoL	United Kingdom	1	60

A3:
Budget Breakdown

Project Number [1]	261474	Project Acronym [2]	ENCCA

One Form per Project

Participant number in this project [11]	Participant short name	Fund. % [12]	Ind. costs [13]	Estimated eligible costs (whole duration of the project)				Requested EU contribution
				RTD (A)	Management (B)	Other (C)	Total A+B+C	
1	CCRI	75.0	T	910,141.00	611,940.37	572,492.39	2,094,573.76	1,643,402.80
2	SIOPE	50.0	F	30,403.38	14,895.08	519,984.63	565,283.09	550,080.40
4	UCL	75.0	T	724,027.33	4,000.00	192,298.48	920,325.81	739,313.60
5	CAU	75.0	T	664,992.61	1,006.24	195,913.81	861,912.66	695,664.50
6	IGR	75.0	T	576,536.00	20,000.00	377,600.00	974,136.00	830,002.00
7	UCSC	75.0	T	16,938.72	2,000.00	434,755.97	453,694.69	449,460.00
8 (TERMINATED)	UKE	75.0	T	165,581.75	0.00	22,784.05	188,365.80	146,970.36
9	UNIMIB	75.0	T	179,625.20	0.00	197,089.20	376,714.40	331,808.10
10	EMC	75.0	T	184,152.00	0.00	128,880.00	313,032.00	266,994.00
11	LaFe	75.0	T	302,133.33	0.00	36,528.00	338,661.33	263,128.00
12	MUG	75.0	T	198,555.20	0.00	0.00	198,555.20	148,915.60
13	UOB	75.0	T	321,019.01	0.00	86,555.34	407,574.35	327,319.60
14	LTHTNHS	75.0	T	396,469.06	0.00	47,098.93	443,567.99	344,450.71
15	IGG	75.0	T	350,493.87	2,000.00	173,144.00	525,637.87	438,014.40
16	CURIE	75.0	T	287,868.64	2,000.00	420,471.73	710,340.37	638,373.21
17	FORTH	75.0	A	188,263.74	0.00	198,423.20	386,686.94	339,621.00
18	AIT	75.0	A	162,855.95	2,000.00	380,774.17	545,630.12	504,788.95
19	CINECA	75.0	A	154,153.77	0.00	202,313.29	356,467.06	273,791.25
20	ESQH	75.0	T	0.00	0.00	111,960.00	111,960.00	111,960.00
21	AMC	75.0	T	22,476.00	2,450.00	500,000.00	524,926.00	519,307.00
23	CLB	75.0	T	135,136.00	0.00	38,601.38	173,737.38	130,152.00

A3:
Budget Breakdown

Participant number in this project [11]	Participant short name	Fund. %[12]	Ind. costs[13]	Estimated eligible costs (whole duration of the project)				Requested EU contribution
				RTD (A)	Management (B)	Other (C)	Total A+B+C	
24	IARC	75.0	T	270,663.06	0.00	54,766.40	325,429.46	257,763.29
26	LUMC	75.0	T	11,200.00	0.00	145,983.01	157,183.01	154,383.00
27	KI	75.0	T	2,301.12	0.00	26,139.76	28,440.88	27,860.80
28	UGent	75.0	T	2,491.79	0.00	52,611.57	55,103.36	54,480.40
30	CHARITÉ	75.0	T	489,199.62	3,000.00	550.00	492,749.62	370,372.14
31	AP-HP	75.0	T	50,870.40	0.00	31,152.00	82,022.40	69,304.80
32	OLGA	75.0	F	132,294.62	0.00	111,760.58	244,055.20	210,981.50
34	ECCO	50.0	F	683.40	0.00	320,381.52	321,064.92	320,723.20
35	ÖK	50.0	S	125,140.00	0.00	220,680.00	345,820.00	283,214.99
36	UNIPD	75.0	T	197,772.40	0.00	44,982.00	242,754.40	193,311.30
37	WWU	75.0	T	3,200.00	0.00	67,600.00	70,800.00	70,000.00
38	SOUTHAMPTON	75.0	S	300,520.00	0.00	0.00	300,520.00	225,389.50
39	UoL	75.0	T	68,772.06	0.00	15,077.54	83,849.60	66,656.50
Total				7,626,931.03	665,291.69	5,929,352.95	14,221,575.67	11,997,958.90

Note that the budget mentioned in this table is the total budget requested by the Beneficiary and associated Third Parties.

*** The following funding schemes are distinguished**

Collaborative Project (if a distinction is made in the call please state which type of Collaborative project is referred to: (i) Small of medium-scale focused research project, (ii) Large-scale integrating project, (iii) Project targeted to special groups such as SMEs and other smaller actors), Network of Excellence, Coordination Action, Support Action.

1. Project number

The project number has been assigned by the Commission as the unique identifier for your project, and it cannot be changed. The project number **should appear on each page of the grant agreement preparation documents** to prevent errors during its handling.

2. Project acronym

Use the project acronym as indicated in the submitted proposal. It cannot be changed, unless agreed during the negotiations. The same acronym **should appear on each page of the grant agreement preparation documents** to prevent errors during its handling.

3. Project title

Use the title (preferably no longer than 200 characters) as indicated in the submitted proposal. Minor corrections are possible if agreed during the preparation of the grant agreement.

4. Starting date

Unless a specific (fixed) starting date is duly justified and agreed upon during the preparation of the Grant Agreement, the project will start on the first day of the month following the entry info force of the Grant Agreement (NB : entry into force = signature by the Commission). Please note that if a fixed starting date is used, you will be required to provide a detailed justification on a separate note.

5. Duration

Insert the duration of the project in full months.

6. Call (part) identifier

The Call (part) identifier is the reference number given in the call or part of the call you were addressing, as indicated in the publication of the call in the Official Journal of the European Union. You have to use the identifier given by the Commission in the letter inviting to prepare the grant agreement.

7. Activity code

Select the activity code from the drop-down menu.

8. Free keywords

Use the free keywords from your original proposal; changes and additions are possible.

9. Abstract

10. The month at which the participant joined the consortium, month 1 marking the start date of the project, and all other start dates being relative to this start date.

11. The number allocated by the Consortium to the participant for this project.

12. Include the funding % for RTD/Innovation – either 50% or 75%

13. Indirect cost model

A: Actual Costs
S: Actual Costs Simplified Method
T: Transitional Flat rate
F :Flat Rate

Workplan Tables

Project number

261474

Project title

ENCCA—EUROPEAN NETWORK for CANCER research in CHILDREN and ADOLESCENTS

Call (part) identifier

FP7-HEALTH-2010-single-stage

Funding scheme

Network of Excellence

WT1
List of work packages

Project Number [1]	261474	Project Acronym [2]	ENCCA

LIST OF WORK PACKAGES (WP)

WP Number [53]	WP Title	Type of activity [54]	Lead beneficiary number [55]	Person-months [56]	Start month [57]	End month [58]
WP 1	Management Activities	MGT	1	73.05	1	60
WP 2	European sustainable strategy for clinical trial paediatric oncology	OTHER	1	44.85	1	60
WP 3	Establishment of the Virtual Institute information portal	OTHER	18	95.10	1	60
WP 4	Clinical Trial Facilitation	OTHER	1	73.85	1	60
WP 5	Biology to guide innovative targeted therapy development	OTHER	30	235.20	1	60
WP 6	Standardised and innovative methodology for clinical trial design and analysis	OTHER	9	80.60	1	60
WP 7	Integrating clinical trials and tumor biology research in bone sarcoma	OTHER	32	53.24	1	60
WP 8	Early evaluation and prioritisation of new anticancer drugs	RTD	6	133.10	1	60
WP 9	Improved therapeutic strategies using predictive biomarkers in leukaemias	RTD	5	142.50	1	60
WP 10	Risk adaptation of therapeutic strategies using prognostic biomarkers in malignant solid tumors	RTD	11	103.20	1	60
WP 11	Clinical epidemiology and prospective registries for patients on standardised protocols	RTD	4	122.24	1	60
WP 12	Clinical research in very rare tumours	RTD	12	48.90	1	60
WP 13	Quality of survivorship	RTD	15	95.70	1	60
WP 14	Dissemination activities	OTHER	2	113.97	1	60
WP 15	Education and training	OTHER	7	103.40	1	60
WP 16	Facilitation of Industry Collaboration with Pharmaceutical Companies and SME for dissemination, expl	OTHER	6	28.95	1	60
WP 17	Improving Outcomes for Teenagers and Young Adults with Cancer	OTHER	14	52.57	1	60
WP 18	Ethical aspects of clinical trials	OTHER	16	48.35	1	60
			Total	1,648.77		

WT2:
List of Deliverables

Project Number [1]	261474	Project Acronym [2]	ENCCA

List of Deliverables - to be submitted for review to EC

Delive-rable Number [61]	Deliverable Title	WP number [53]	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D1.1	Quality assurance plan including guidelines, best practices, project handbook	1	1	6.00	R	CO	12
D1.2	Project Identity Set (logo, brochure, public website)	1	1	6.00	O	PU	12
D2.1	Establishment of the Paediatric Oncology Clinical Trial Council and advisory committees	2	2	0.25	R	PU	12
D2.2	Reports on the current situation and access to clinical trials in Europe	2	5	7.50	R	PU	12
D2.3	Strategy for paediatric oncology platform integration.	2	5	10.15	R	PU	12
D2.4	Guidelines for efficient access in common facilities.	2	2	16.50	R	PU	36
D2.5	Creation of e-Mobility Centre.	2	4	3.15	R	PU	36
D2.7	Guides for new common financial resources.	2	1	2.50	R	PU	60
D2.8	Decision for the establishment of a legal entity.	2	2	0.25	R	PU	60
D3.1	Multi-stage release of communication	3	2	8.00	P	RE	12

WT2:
List of Deliverables

Delive-rable Number [61]	Deliverable Title	WP number [53]	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
	platform including specified modules.						
D3.2	Productive knowledge management platform.	3	2	8.00	P	PU	30
D3.3	Overview on applications, applied standards, workflows, and selected integration scenarios.	3	17	19.50	R	PU	24
D3.4	Recommendation on selected standards, workflows and profiles.	3	19	10.50	R	PU	60
D3.5	Design specifications of the virtual institute ICT infrastructure.	3	18	10.50	R	RE	36
D3.6	Validated operational prototype of the virtual institute ICT infrastructure.	3	18	10.90	P	RE	60
D4.1	Templates for clinical trials (including informed consent) and frame contracts ailable.	4	2	5.70	O	PU	12
D4.3	Definition of risk categories in IDCT undertaken on paediatric oncology platforms.	4	1	1.00	R	PU	12
D4.5	Consensus conference on an improved CTA process	4	1	1.50	O	RE	48

WT2:
List of Deliverables

Delive-rable Number [61]	Deliverable Title	WP number [53]	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
	for IDCT in paediatric oncology.						
D4.6	Consensus workshop on sensible pharmaco-vigilance reporting & quality assurance measures in paediatr	4	20	10.66	O	RE	60
D4.7	Syllabus to educate stakeholders involved in IDCT.	4	20	10.66	O	PU	60
D4.8	Conference for European parent and patient cancer groups	4	20	10.68	R	PU	60
D5.1	Development of data storage and analysis tools to integrate molecular profiling and drug testing dat	5	30	78.00	R	RE	24
D5.2	Generate and update databases for existing material/data, genomic characterisation and clinical resp	5	15	77.00	R	RE	24
D5.3	Contribute SOPs, algorithms and uniform approaches to wet-lab and in silico preclinical drug develop	5	30	77.00	R	RE	12
D6.1	Guidelines for novel trial designs in paediatric oncology and	6	6	41.10	R	RE	48

WT2:
List of Deliverables

Delive-rable Number [61]	Deliverable Title	WP number [53]	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
	validating risk-based patient stratifi						
D6.2	Guidelines for the analysis of safety data, competing events and long-term outcome.	6	1	15.00	R	RE	60
D6.3	Prototype of core data sets and report on their analyses for specific tumours.	6	9	22.00	R	RE	60
D7.1	Develop key agreed research objectives for the bone sarcoma framework with proposed time-table	7	32	7.55	R	PU	12
D7.2	Restructure existing Eurobonet virtual tumor bank to open access for ENCCA partners and other	7	26	7.55	O	PU	24
D7.3	Implementing SOP for entering cases into the virtual databank	7	26	6.25	O	PU	36
D7.4	Integrated clinical trial and translational research proposal for osteosarcoma and Ewing sarcoma	7	4	4.85	R	PU	12
D7.5	Consensus on phase II/III protocol definitions	7	4	7.55	O	PU	60
D7.6	Implementation of early clinical trials in relapsed	7	14	4.19	O	PU	24

WT2:
List of Deliverables

Delive-rable Number [61]	Deliverable Title	WP number [53]	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
	and high risk patients						
D7.7	Regular international tumour board sessions	7	37	7.55	R	PU	24
D7.8	Meta-analyses of specific primary tumour sites and development of evidence-based standards	7	37	7.75	R	PU	60
D8.1	Strategy for new drug development in the main paediatric leukaemias and malignant solid tumours	8	6	19.90	O	RE	60
D8.2	Guidelines with EMEA for the development of clinical and preclinical Paediatric Investigation Plans	8	6	19.90	R	RE	60
D8.3	A consortium of academic institutions to sponsor phase I and II trials.	8	1	19.90	O	PU	30
D8.4	At least three EMEA-ENCCA Task force face-to-face meetings is set-up.	8	10	19.90	O	RE	60
D8.5	The recruitment in at least one trial in haematological malignancies and malignant solid tumours.	8	13	20.00	O	PU	60
D9.1	Common guidelines	9	10	30.20	R	PU	24

Delive-rable Number [61]	Deliverable Title	WP number [53]	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
	for diagnostic approaches to leukaemias.						
D9.2	Infrastructure of an European virtual laboratory for molecular diagnostics of leukaemias.	9	5	30.20	O	RE	36
D9.3	Algorithm application for identification and priorisation of molecular targets for leukaemias	9	9	25.00	D	RE	36
D9.4	A European infrastructure for the early introduction of molecularly targeted treatment in leukaemias	9	30	30.20	O	PU	60
D10.1	Launch LINES in Europe by getting EudraCT number, contract signatures and SOPs for running the study	10	11	47.20	R	PU	12
D11.1	Use of population-based cancer registries for enhanced clinical follow up.	11	24	31.50	R	PU	60
D11.2	Methods for use of record linkage for enhanced clinical follow up	11	15	31.50	R	PU	60
D11.3	Prospective data collection and evaluation of biological and clinical risk factors in Standard Risk	11	4	43.24	R	RE	60

WT2:
List of Deliverables

Delive-rable Number [61]	Deliverable Title	WP number [53]	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D11.4	Collection of detailed data on infants with neuroblastoma through population-based cancer registries, analysis and report by IARC	11	24	3.50	R	RE	60
D12.1	Creation of Liver Tumours Warehouse database and development of the new global diagnostic	12	12	13.47	R	PU	24
D12.2	Design and implementation of new Remote Data Entry and E-learning Platform.	12	19	13.47	R	PU	24
D12.3	New hepatoblastoma study protocol based on the newly introduced patient stratification	12	6	13.46	R	PU	60
D13.1	On-line tool for assessing childhood cancer outcome	13	38	17.80	O	PU	24
D13.2	PNET5 and PNET6 trials.	13	38	17.80	O	RE	60
D13.3	Salivary DNA database for same survivors.	13	38	17.80	O	RE	60
D13.4	Database for complete survivor medical history	13	16	17.80	O	RE	12
D13.5	Survivorship passport template with guidance for	13	16	17.70	O	RE	60

WT2:
List of Deliverables

Delive-rable Number [61]	Deliverable Title	WP number [53]	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
	long-term follow-up						
D14.1	Action Plan in order to establish efficient communication tools	14	2	16.70	O	PU	12
D14.2	The creation of a website for the ENCCA project	14	2	16.70	O	PU	12
D14.3	The creation and maintenance of a contact list/database of relevant bodies	14	2	16.70	O	PU	12
D15.1	List of centres that fullfil the EUMS standards for training in paediatric haematology and oncology	15	7	21.90	O	PU	12
D15.2	A biannual meeting on SIOPE- ENCCA activity and dedicated space on SIOPE website.	15	35	21.90	O	PU	24
D15.3	Production of guidelines indicating how to improve relationships among parents/patients	15	35	20.05	R	PU	60
D15.4	Implementation of a population-based approach in teaching material on cancer in children and adolesc	15	24	21.90	R	PU	24
D16.1	Publication of the BDA meetings	16	6	11.50	O	PU	42

WT2:
List of Deliverables

Delive-rable Number [61]	Deliverable Title	WP number [53]	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
	summary and action plan.						
D16.2	Publication of guidelines for partnership with Pharmaceutical companies when running IDCTs	16	6	11.45	O	PU	60
D17.1	1st report of European Steering Group Development of TYA oncology Framework.	17	14	6.00	R	PU	12
D17.2	1st TYA oncology Framework Educational meeting Programme.	17	39	6.00	R	PU	12
D17.3	Register of open trials in Europe for major TYA tumour groups.	17	14	6.00	O	PU	12
D17.4	Develop key agreed research objectives for the TYA oncology Framework with proposed time-table.	17	14	6.00	O	PU	12
D17.5	Document scoping fertility preservation practices in different institutions and countries.	17	23	6.00	R	PU	12
D17.6	Young people's views and advocacy organisations representing a range of countries integrated into al	17	1	6.17	O	PU	24
D18.1	Identification of ethical issues during paediatric	18	16	8.00	R	PU	24

WT2:
List of Deliverables

Delive-rable Number [61]	Deliverable Title	WP number [53]	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
	hemato-oncoloy clinical trials						
D18.2	Guidelines on clinical trials in paediatric oncology.	18	35	8.00	R	PU	36
D18.3	Workshop with tumour group representatives.	18	35	8.00	O	PU	24
D18.4	Description of discrepancies in Europe.	18	16	8.00	O	PU	60
D18.5	Guidelines on confidentiality issues regarding human tissues, cells, DNA, sera and collected protein	18	16	8.00	R	PU	24
D18.6	Training for clinical trial staff for ethical guidelines implementation.	18	16	8.35	O	PU	60
			Total	1,268.00			

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP1	Type of activity [54]	MGT
Work package title	Management Activities		
Start month	1		
End month	60		
Lead beneficiary number [55]	1		

Objectives

To ensure efficient project coordination adapted to the specificities of the project and to achieve the project objectives and goals, the management is divided into the following sections:
Day-to-day management
Financial follow-up
Technical reporting
Consortium animation
Other management-related issues
The management organization is described in detail in Part 2.1. The management strategies, internal rules and quality procedures will be detailed further in the Quality Assurance Plan to be delivered at the beginning of the project.

Description of work and role of partners

Task 1.1 Day to day management CCRI, SIOPE, IGR, UCL, CAU (M1 – M48)
Objective:
The Project Manger (PM) in the CCRI is responsible for the technical, financial and administrative management on a day-to-day basis. In order to ensure an efficient and active management of these tasks the PM will be supported by the Project Management Team. Haeded by the NoEM (at the CCRI), the DM (at SIOPE) and the three activity coordinators (IAC/JRAC/SEAC). Involved will be all concerned partners in the respective work packages committees. A Quality Assurance Plan will be applied to define the internal management rules and methodologies.
Task description:
The PM as a support to the NoEM ,both at the CCRI, will be mainly in charge of:
- Managing the delivery and the follow-up of administrative and financial documents;
- Being a permanent contact point for all the partners regarding their participation in the project, responding to any relevant requests;
- Based on the project management team advice and decisions needed adaptation of tasks and budget re-allocations according to the fulfilment and success of the respective tasks within WPs as needed.
- Based on ExeCom advice and General Assembly (GA) decisions, managing major changes in the grant and consortium agreement supervised by the NoEM.
- Creating common working and reporting tools;
- Following and updating the project indicators (Gantt chart, manpower matrix, deliverables list).
The aim is to ensure that the technical objectives are followed but also to ensure that the project is completed within the approved budget.
For the control of costs, the consortium will follow the FP7 requirements, including:
- Monitoring cost performance to detect deviations from plan (regular follow-up by PM at the CCRI),
- Ensuring that all appropriate changes are recorded accurately in the cost baseline;
- Preventing incorrect, inappropriate, or unauthorized changes (toward contract);
- Informing the relevant contact in the European Commission of ENCCA developments.
In accordance with the accounting system, and using the audit certificates system, PM and NoEM at the CCRI will follow-up the project expenses and track deviations. In particular, the PM at the CCRI will be in charge of obtaining certificates on financial statements when relevant.

As a support to the NoEM and PM the DM at SIOPE will be mainly in charge of:
- Easing the NoEM of administrative tasks in particular with regard to meeting organisations, notifying the ENCCA consortium of due dates and/or dissemination of project results
- Preparing and supporting the official meetings;
- Following up of actions and decisions

Task 1.2 Financial follow-up CCRI, IGR, UCL, CAU, all partners (M1 – M48)
Objective:
The PM at the CCRI will take the necessary measures to ensure the appropriate use of the FP7 grant between the participants by providing a time schedule for the transferring of funds allocated within the consortium. The work will be done in collaboration via agreed procedures in the Consortium Agreement. The NoEM will supervise the PMs actions.
“Easy-to-use” templates for time and cost reporting adapted to the ENCCA project will be implemented.
Task description:
The PM at the CCRI will consolidate and analyze financial data on a 6-monthly basis to:
- Ensure proper use of resources (compare planned versus actual);
- Ease processing of certificates on financial statements whenever relevant;
- Anticipate any deviations (over or under consumption).
The PM at the CCRI will notify the due dates to the partners for financial reporting, provide support for the completion of the annual financial reports (and certificates on financial statements if relevant) and will collect the documents for submission to the relevant EU Commission body.
CCRI will be a day-to-day contact for the whole consortium to provide answers to queries such as costs eligibility, financial reporting and the official process for fund transfer. It will ensure that EC rules are respected for cost reporting on the basis of the information provided by the partners.

Task 1.3 Technical reporting CCRI, SIOPE, all WP leaders (M1 – M48)
Objective:
Timely technical reports.
Task description:
CCRI (PM and NoEM) will ensure efficient reporting of ENCCA by:
- Proposing common templates adapted to the ENCCA project and partners for official progress reporting for the EU Commission body (PM).
- Notifying due dates and deadline reminders (PM).
- Assisting partners to respect indications and guidelines assigned by FP7 (PM).
- Collecting the WP leaders contributions (WP leaders will consolidate data at each WP level and CCRI will consolidate all WP leaders inputs) (PM)
- Representing the central contact point for checking that the data provided are in line with the FP7 NoE rules and requirements (PM).
- NoEM and PM will prepare the consolidated annual (including the final) project progress reports.
The PM and NoEM at the CCRI, will consolidate with the support of the Work Package leaders the progress, deliverables and milestone reports to be submitted to the Project Management Team for final approval before submission to the relevant FP7 body. In addition, as a yearly reporting is not sufficient for a good internal follow-up, WP leaders will be requested to update the NoEM every six months with a short written report. It is their responsibility to track any deviation and delay and propose appropriate solutions. It will ensure the NoEM is kept well-informed about the progress of the project by all partners.

Task 1.4 Consortium animation CCRI, SIOPE, AIT, activity coordinators (at IGR,UCL,CAU) (M1– M48)
Objective:
NoEM and PM at the CCRI, ACs and DM at SIOPE will support the partners in their decision-making process as needed as well as in challenging situations. They will create a group dynamic within the project through coordinated actions.
NoEM and PM at the CCRI, ACs and DM at SIOPE will promote exchanges between partners and prevent lack of involvement of some partners through regular contact. To stimulate communication, the consortium will use a dedicated interactive website that enables them to share and stock documents, follow the execution plan, organise meetings and discuss special issues online .
Task description:
A Project Identity Set will be created by CCRI and SIOPE in order to promote the Project and facilitate dissemination. This set will include the creation of a logo, a brochure, a website and a slide template.

Task 1.5 Other management-related issues CCRI, all partners (M1-M48)
Objective:
The NoEM, in collaboration with the Project Management Team will coordinate other related topics that will be addressed in the course of the project e.g. gender equity, relations with other projects.
Ethical as well as development, standardisation and dissemination aspects will be organised within the respective work packages and be brought to harmonisation through the ExeCom members (PMT, NoEM, representatives of the ECRC, one representative each of the PAC, EAC, SAC) and IPRC and ICI , as needed.
Task description:
Confidentiality, IPR, dissemination and exploitation issues are addressed by the Consortium Agreement that will be signed before the signature of the FP7 NoE contract.
During the project, amendments can be proposed in order to refine the conditions based on tangible results.
The NoEM and PM at the CCRI are responsible to interact whenever needed with all issues related to the Consortium Agreement and partners concerned.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	CCRI	62.00
5	CAU	2.75
6	IGR	6.50
18	AIT	1.80
	Total	73.05

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D1.1	Quality assurance plan including guidelines, best practices, project handbook	1	6.00	R	CO	12
D1.2	Project Identity Set (logo, brochure, public website)	1	6.00	O	PU	12
		Total	12.00			

Description of deliverables

D1.1) Quality assurance plan including guidelines, best practices, project handbook: [month 12]

D1.2) Project Identity Set (logo, brochure, public website): [month 12]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS1	Consortium Agreement signed by all partners (CCRI)	1	1	Signed document distributed to partners

WT3:
Work package description

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS2	Quality Assurance Plan inc. guidelines, best practices, project handbook approved by the ExecutiveCo	1	12	Finalised version distributed to partners
MS3	Yearly reporting consolidated and approved by the ExecutiveCommittee and the EC (CCRI)	1	12	Acceptance letter received from the EC
MS4	Creation of templates for the reporting (including deliverable and milestone templates, Costs follow	1	12	
MS5	Implementation of the collaborative tool	1	12	
MS6	Minutes of the official meetings	1	12	
MS7	Amendements to the Consortium Agreement	1	12	

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP2	Type of activity [54]	OTHER
Work package title	European sustainable strategy for clinical trial paediatric oncology		
Start month	1		
End month	60		
Lead beneficiary number [55]	1		

Objectives

The objective of this WP is to establish the basis of an efficient coordination and strategy of the therapy platforms integrated in the Network in order to provide accelerated answers and efficient results for children and adolescents cancer.
The project includes the platform organisation, strategy definition but also the actions for a financial and structural sustainability of the Network. Relationships with all the clinical actors will be also one or the priorities of the Network design and all the groups will be represented for a better coordination and a high integration of the aspects allowing the reduction of research fragmentation.
The cost effectiveness of paediatric oncology clinical trials will be studied in the long-term, especially if clinical trials show the equivalent (or better) efficacy of new treatments together with a decreased morbidity, these new treatments offer a chance to decrease the cost of care for long-term side effects
The strategic aspects of material and equipment integration as well as the management of a reinforced mobility and European careers are part of this WP. The WP also the organisation and function of the different advisory committees.

Description of work and role of partners

Task 2.1 Design and implementation of a European clinical research council SIOPE, CCRI, CAU, IGR, ÖK, ECCO (M12)

Objective:
The objective is to organise and implement a European Clinical Research Council , constituted by the Chairs or nominated representatives for paediatric oncology clinical research from each National Group, the Chair or nominated representatives, form each of the SIOPE diseases specific co-operative groups, the ITCC (Innovative Therapies for Children with Cancer) and the I-BFM Study group, a nominated representative for adolescent oncology clinical research form each National Group (where available), a nominated representative from ICCCPO (International Confederation of Childhood Cancer Parent Organisation) , the Chair from other International co-operative groups working in the fields of paediatric and /or adolescent oncology, legal advisory members representing expertise in the regulations associated with clinical research and international contracts and agreements. Paediatric and Adolescent Tumour and Leukaemia Group Council
The ECRC aims to become a single voice representing the paediatric and adolescent oncology clinical research community across Europe. It will promote a European-wide infrastructure to deliver academic sponsored clinical trials with the established paediatric and adolescent oncology network.
It will be able to integrate all the paediatric oncology clinical trial platforms presented in the Network as well as to create the necessary synergies with all the clinical actors' clinicians, biologists, patient organisations, regulators, industrials, ethical committees participating in clinical trials.
Task description:
Initially it is important to establish the structure and management of the ECRC, that will become a Council of SIOPE, as well the modalities of exchanges and communication. The Council will be managed by a Steering Committee that will be elected by the Members of the Council and will comprise a Chair, a vice Chari plus 5 additional members.

Task 2.2 Design of a strategy for Paediatric Oncology clinical trials IGR, CCRI, CAU, ÖK, AIT (M12)
Objective:

The Council will redesign a sustainable strategy of clinical trials in paediatric oncology including research portfolios and priorities and advise for eventual reallocation of resources or need for new resources and will lead to a higher integration and better distribution for a higher efficiency.
Task description:
The task consists of:
- Description of the current situation;
- Easibility of definition of the standard treatment;
Cost-effectiveness calculation: clinical trials are expensive in a shot-term view but in a long-term viewpoint, if we cure more children with less late effects, there will be more young adults able to work and less adults who depend on others: this is possible to evaluate the “cost of clinical trials” choosing specific examples;
Special task about the access to new drugs in Europe:
- Description of the current situation, identify the risks situation (use of new drugs outside a clinical trial) and challenges for accessibility of new drug development within Europe;
- Definition of a cost-effective strategy for participation and realisation of clinical trials in paediatric oncology.

Task 2.3 Define a strategy of integration of European actors stakeholders (Industry, Patients/Parents advocacy, Scientific advisory group) SIOPE, IGR, ÖK, CAU, ECCO (M12)
Objective:
The clinical development process is a complex task that needs a strong collaboration between all actors participating in the chain (clinicians, regulators, investigators, industrials and SMEs, patent agencies, patients/parents) for a successful long-term improvement of the quality and efficacy of clinical trials in paediatric oncology. The aim of this task is to create powerful links with all the actors related to clinical trials. The project will create the Patients/Parents Advocacy Group; the Scientific Advisory Group and the Club of Industrial Interest Committees (Patients/parents advocacy; Scientific advisory and Industry) that will represent the groups in the ENCCA Activities.
Task description:
The task comprises of the establishment of the three groups and their mode of organisation and function as well as their interactions with the Network. Two annual meetings will be organised in conjunction with the NoE. The needs of the different actors will be translated in network activities and will be integrated in the work programme and outstanding clinical and research project.

Task 2.4 Common plan for mobility and work position improvement UCL, UCSC (M12- M36)
Objective:
The ENCCA NoE multidisciplinary approach offers individual researchers and clinicians unique opportunities to develop their own careers. However mobility is required to exploit these benefits and this is not enough principally due to the lack of information, the attraction of foreign research culture, social and employment conditions and issues of mobility.
ENCCA aims to implement a common action plan in order to:
Enhance transnational mobility of clinicians in paediatric oncology and strengthening the European dimension of research careers;
Make ENCCA and its research more attractive to researchers and retaining researchers in Europe and attracting third-country researchers in the EU;
Stimulate enhanced mobility between academia and industry.

Task Description:
Improve information about mobility and provision for practical assistance to researchers: An e-Mobility Centre will be created to assist researchers in clinical research dealing with legal and administrative matters and provide training facilities; the centre will provide practical information on day-care education for children and advise on job opportunities for the accompanying partner.
Reinforce the mobility framework: The network will encourage where appropriate the organisation of inter-directorate meetings on current obstacles of direct concern to develop integrated strategies for clinician mobility. ENCCA expects to conduct best practice exchanges with other NoEs.

Task 2.5 Strategic efforts towards long term sustainability of the Network (creation and financial durability) IGR, CCRI, SIOPE (M12– M48)
Objective:
The objective of this task is to prepare the financial autonomy of the Network through the creation of a Financing Option Assessment Office.
Task description:

The concept is to create a strategy to achieve the financial autonomy and sustainability of the Network. A team will be dedicated to define this strategy and create mechanisms to be able to integrate financial incomes from different resources (such as current resources, academic/industrial cooperation, Marie Curie Networks, others) and distribute equitably in research labs and consequently ensure that paediatric oncology clinical trials are more efficient.

Task 2.6 Towards a new legal entity SIOPE, CCRI, KI, ECCO (M36– M48)
Objective:
To ensure ENCCA's sustainable integration, it needs to be linked with a strong and durable structure able to efficiently manage the network activities and quickly transfer the results produced.
This task aims at evaluating the possibility of creating a new legal entity, A European Economic Interest Group could be an option . Task description:
The work comprises:
- Consortium discussion and evaluation of the potential of possible legal structures.
- Identifying the needs of the consortium and the issues relevant to each participant.
- Defining the rules in order to establish the legal statutes of the entity considering all the previous elements.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	CCRI	2.50
2	SIOPE	8.00
4	UCL	3.00
5	CAU	9.75
6	IGR	6.00
7	UCSC	2.00
18	AIT	0.80
27	KI	4.00
34	ECCO	7.00
35	ÖK	1.80
	Total	44.85

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D2.1	Establishment of the Paediatric Oncology Clinical Trial Council and advisory committees	2	0.25	R	PU	12
D2.2	Reports on the current situation and access to clinical trials in Europe	5	7.50	R	PU	12
D2.3	Strategy for paediatric oncology platform integration.	5	10.15	R	PU	12
D2.4	Guidelines for efficient access in common facilities.	2	16.50	R	PU	36

WT3:
Work package description

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D2.5	Creation of e-Mobility Centre.	4	3.15	R	PU	36
D2.7	Guides for new common financial resources.	1	2.50	R	PU	60
D2.8	Decision for the establishment of a legal entity.	2	0.25	R	PU	60
		Total	40.30			

Description of deliverables

D2.1) Establishment of the Paediatric Oncology Clinical Trial Council and advisory committees: Establishment of the Paediatric Oncology Clinical Trial Council and Advisory Committees D2.1 [month 12]

D2.2) Reports on the current situation and access to clinical trials in Europe: Reports on the current situation and access to clinical trials in Europe and feasibility of defining standard treatment (M12); Report on the cost-effectiveness calculation of phase III clinical trials aiming to reduce toxicity (M24);Report on the cost effectiveness calculation of early clinical trials instead of use of new drugs outside a clinical trial (M24). D1.1.2.1 [month 12]

D2.3) Strategy for paediatric oncology platform integration.: Strategy for paediatric oncology platform integration. D2.3 [month 12]

D2.4) Guidelines for efficient access in common facilities.: Guidelines for efficient access in common facilities. D2.4 [month 36]

D2.5) Creation of e-Mobility Centre.: Creation of e-Mobility Centre. D2.5 [month 36]

D2.7) Guides for new common financial resources.: Guides for new common financial resources. D2.7 [month 60]

D2.8) Decision for the establishment of a legal entity.: Decision for the establishment of a legal entity. D2.8 [month 60]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS8	Implementation of a new strategy	2	12	Common acceptance by the GA
MS10	Establishment of efficient financial structure	2	60	Operational guides for financial resources
MS11	Evaluation of possibility for a durable administrative identity	2	60	Establishment of a legal entity

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP3	Type of activity [54]	OTHER
Work package title	Establishment of the Virtual Institute information portal		
Start month	1		
End month	60		
Lead beneficiary number [55]	18		

Objectives

Due to its wide geographical distribution and the limitations in finding suitable dates for plenary meetings, the Paediatric Oncology Network of Excellence will require the development of solid and secure communication tools. The tools will be designed to allow partners to communicate easily and efficiently with one another, and to create opportunities for lasting integration in clinical trials.
Converting a new organised Network into a virtual European cancer research institute also implies managing the generated knowledge in a common way in order to make European research more efficient, in particular:
- Managing new knowledge and its controlled diffusion at European and international level and
- Overcoming geographical remoteness of the research teams by common policy of data and scientific information sharing,
- Facilitating data exchange of DICOM images for review in clinical trials.
The aim of this Work Package is to ensure that each participating organisation will have real time and full-scale access to the knowledge that accumulates within the network and also to the knowledge that will be generated by the Joint Programme of Activities. To achieve this, it is necessary to implement a common collaboration and research infrastructure that integrates appropriate and available data and makes them accessible to all members.

Description of work and role of partners

Task 3.1 Electronic communication platform SIOPE, AIT, CCRI, ECCO (M1 – M24)
Objective:
This task will consist of implementing an extranet-based secure collaborative portal for effective and secure communication that will be accessible to the ENCCA coordinator and partners under secured access control. Additionally, it will enable the FP7 relevant body to remain in close contact with the NoE.
Task description:
The collaboration portal includes the following modules:
- Public information portal for publishing content and progress of the project directed at the general public.
- Newsletter module that will provide general information on the project and technical objectives. A newsletter will be published at regular intervals to inform partners about task progression, scientific news related to ENCCA (references, linked websites, practical information and details about the agenda and organisation of upcoming meetings as well as possibilities for other collaborative and/or partner opportunities to ensure a truly integrated Network of Excellence.
- Secure a document exchange module (publication of meeting minutes, technical reports, consolidated annual reports, progress within individual wps). The coordinator can restrict access to several documents. The work also comprises the harmonisation of electronic documents in order to make communication more effective.
- Secure a message exchange module between all partners where all messages related to the project will be collected in a common base allowing better control and follow-up of information.
- Establish and maintain virtual permanent discussion groups through an Internet portal amongst research groups regarding technical aspects that will facilitate coordination of activities relevant to the NoE.
- Voice- and video-conferencing to foster real-time collaboration.

Task 3.2 Content and Knowledge-Management Platform SIOPE, AIT,CCRI, ECCO (M12 – M24)
Objective:

This task involves the design and implementation of an intranet platform enabling a secure and structured information-exchange between all participants of the project in order to encourage pro-active dialogues and to ensure an optimised dissemination of knowledge generated by the joint research activities.
Depending on the classification of information (i.e. confidential, restricted, public), the content of the public information portal should be updated automatically.
Task description:
- Identification of relevant information in various fields such as clinical trial design, education and training, therapy management and techniques.
- Evaluation of common standards on information collection, storage, and content design.
- Evaluation of existing knowledge management platforms supporting collaborative authorship, document and permission management, content syndication and editorial workflow.
- Establishment and maintenance of a knowledge management platform on the intranet amongst the research groups regarding technical aspects that will facilitate the coordination of activities relevant to the network.
-Maintenance of the cloud-based portal including helpdesk and management of user requests (AIT)

Task 3.3 Analysis of existing systems and solutions FORTH, AIT, CINECA, LUMC (M1 – M24)
Objective:
Following the basic concept of the Work Package (to integrate existing and well-established ICT solutions for patient administration and clinical trial data management supporting cancer research instead of replacing them), in-depth analysis of already available systems and solutions is compulsory. Aside from a survey of utilized technical solutions (hardware and software), like picture archiving and communication system (PACS), electronic data capture (EDC) system, bioinformatics and systems biology analysis tools, established workflows and tasks also need to be identified to serve as a foundation for subsequent integration. This analysis is also directed to identify possible interfaces on a technical and semantic level. During the planned on-site visits of potential partners in the network, local security policies as well as national legal regulations and obligations will also be examined to achieve a Europe-wide overview on technical frameworks and the research environment. This task will particularly focus on the needs for ICT-support of WP 5, 6, 7, 11, 12, 13, and 17.
Task description:
- Analysis of applications and applied standards
A challenge for the work package is to ensure a sustained use of well-established ICT components (such as image archives, EDC, analysis tools) with a simultaneous consideration of a seamless integration into a collaborative research network based on standardised interfaces. Currently applied systems and available standards and technologies need therefore to be analysed to identify possible points of application.
- Identification of existing workflows.
Besides technical components, participating institutions or trial groups are characterised by individual workflows and standard operating procedures for research activities or exchanges of information. Providing a support system for collaborative research implies a comprehensive understanding of this field.
- Identification of integration scenarios with participating partner institutions
Based on the results of a preceding technical and workflow analysis, potential integration scenarios for collaboration will be identified. This process will primarily focus on the needs of the various clinical trial groups and their need to exchange information between them.

Task 3.4 Definition and management of standards and workflows CINECA, AIT, FORTH, SIOPE (M12 – M36)
Objective:
Based on the results of task 3.3 (analysis of existing systems and solutions) this task deals with the establishment of a set of technical standards and interfaces as well as applied workflows, mainly to achieve comprehensive interoperability across all participating institutions and connected systems within the NoE to a large extend. All identified interfaces should ideally be based on already widely accepted or upcoming future standards to guarantee sustainability beyond the project period. The set of standards and workflows will cover all aspects, ranging from low-level communication standards (e.g. TCP/IP, HTTPS), data representation (e.g. ICD10, LOINC), application and domain specific concepts (e.g. HL7, DICOM, CDISC, MIAME, MIAPE) to extensive guidelines mainly based on Integrating the Healthcare Enterprise (IHE) profiles for sharing information across institution boundaries. Since integration is a stepwise approach, selected standard and workflows will be continuously evaluated and adapted to keep track of ongoing national and international standardisation activities as well as changing requirements of the consortium. Therefore this task covers the majority of the project period and requires the involvement of all ICT partners.
All selected standards and workflows will be defined based upon an agreement of all stakeholders in order to achieve a high level of acceptance for all activities regarding the integration of existing solutions and

applications. Jointly made decisions, however, shall then be compulsory for systems that will be linked to the virtual research infrastructure.
Task description:
Elaboration of recommendations, in agreement with all stakeholders, as well as the publishing of those recommendations on the communication platform after approval by the Executive Board, on:
- Communication standards
- Data representation standards
Application specific standards and workflows
- Integration of standards and workflows based on IHE-profiles

Task 3.5 Design and specification of the data exchange and inter-operability infrastructure AIT, CINECA, FORTH (M12 – M36)
Objective:
In order to establish a common virtual collaboration and research network, the architecture of the virtual institute is a pivotal task. Based on the results of the previous tasks 3.3 (analysis of existing systems and solutions) and 3.4 (definition and management of standards and workflows), the architecture has to support a distributed solution, linking existing or planned applications of participating research and trial groups based on previously defined profiles to organize the NoE in a grid-like manner. Similar to the recommendations of the European Commission on cross-border interoperability of electronic health record systems, this infrastructure shall consider both technical and semantic interoperability. The solution to be designed should facilitate a cross-border information transfer by adapting or extending existing ICT solutions (used in patient care and clinical research) with standardized interfaces. Simultaneously, all required data protection regulations (primarily through pseudonymisation) to enhance the effectiveness and efficiency in cancer research and treatment across Europe shall be considered.
Task description:
- Definition of networking concept
Since a distributed ICT architecture strongly relies on a stable and secure networking concept, the networking infrastructure needs to be designed together with participating partners and needs to consider all local restriction and obligation for external access. This will include minimal requirement in terms of bandwidth and network latency as well as concepts for virtual private networks (VPN) and access control.
- Specification of required features and central indexing infrastructure
According to many national and international activities and efforts to establish central registries for indexing and searching documents as part of regional or national electronic health record systems (primarily based on IHE-profiles like cross-institutional patient identification – PIX Profile, cross enterprise document sharing – XDS), a major task will be the identification of the required function range as well as the design and establishment of a virtual collaboration and research network acting as a central instance linking all involved partners and technical systems. Similar to the cloud computing approach a central paradigm is to separate requested services form the underlying infrastructure. Provided interfaces shall offer defined functionality that will be transparently relayed to processing subsystems.
- Safety and Security in a distributed environment
Since a trustworthy safety and security concept is crucial for any computer use in the medical domain, especially in a distributed environment, this task will deal with the legal regulations coupled with the requirements and the conceptual design to guarantee compliance with all data protection and privacy obligations. The security concept will focus on the CIA triad:
- Confidentiality … prevent disclosure to unauthorized individuals or systems
- Integrity … no data modification without authorization
- Availability … data must be available at the time it is needed and will be primarily based on the “Audit Trial and Node Authentication (ATNA)” IHE-profile for secure nodes. This implies concepts and workflows for user identification, authentication, access control, transport layer security (TLS), audit repositories and so on. Wherever possible, extended kerberized communication protocols (for authentication and encryption) that are currently under development should be applied.

Task 3.6 Development and setup of an infrastructure prototype AIT, CINECA, FORTH (M24– M48)
Objective:
This task covers the development and setup of the data exchange and interoperability infrastructure based on the resulting design specification and defined standards from the previous tasks. Since the main aspect is interoperability, primarily based on already existing standards, commercially or freely available products and services will be utilised where appropriate to accelerate the development process.
Task description:

- Selection of standard compliant products and services
This subtask comprises a market research and selection of already available standards compliant products, in order to optimize the development and setup phase of the data exchange and interoperability infrastructure. This probably includes existing solutions for IHE-compliant image archives, identification cross reference systems, registries and repositories, etc.
- Software development
This subtask comprises the development of individual software modules to link the selected products to finally fulfil the defined specification and includes both detailed functional specification of these modules as well as coding.
- Setup and maintenance of data exchange and interoperability infrastructure
After the setup of the infrastructure the system will be constantly monitored and maintained during the whole project period.
- Interface definition and implementation assistance.

As existing ICT systems will not be replaced, in selected cases support for adaptation of existing or the implementation of new interfaces is expected and part of this task.

For the proposed comprehensive demonstration use case portfolio, the following existing or evolving sub-networks will be supported regarding the export and registration of core data sets to the ABCD-4-E:
- Neuroblastoma research network SIOPEN-R-NET (AIT)
- ALL research network (CINECA)
- WILMS tumor research network (FORTH)
- Biobanks
Interfaces to query and download datasets from the ABCD-4-E are intended to be established for the following consumer systems:
- European Patients in clinical trials statistics (AIT)
- Survivorship Passport Generator (CINECA)
- Biomarker Analysis Suite (FORTH)
- Support the development and maintenance of standardised core datasets for selected biobanks and selected clinical trials

Task 3.7 Pilot operation and system validation AIT, CINECA, FORTH (M36 – M48)
Objective:
The developed data exchange and interoperability infrastructure needs to be validated in a well-defined scenario in conjunction with selected systems (e.g. trials including image management) in order to demonstrate interoperability according to the specifications. The pilot operation also serves as test bed for performance monitoring and to identify issues that have to be considered for a subsequent European-wide roll-out.
Task description:
- Definition of validation scenario

The processes as defined in the selected use case portfolio will be used needs to be identified to validate the features of the infrastructure and shall include a set of major stakeholders, systems and workflows. Additionally, metrics for the assessment of the system performance will be defined.

- Configuration of the collaboration platform
As the data exchange and interoperability infrastructure is the central component of the whole validation environment, all involved systems and network partners have to be registered and configured for proper operation.
- Demonstration of interoperability workflows
Finally, the correct interaction of all involved parties according to the validation scenario will be demonstrated.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
2	SIOPE	8.00
17	FORTH	28.00

WT3:
Work package description

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
18	AIT	29.00
19	CINECA	22.00
26	LUMC	0.10
34	ECCO	8.00
	Total	95.10

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D3.1	Multi-stage release of communication platform including specified modules.	2	8.00	P	RE	12
D3.2	Productive knowledge management platform.	2	8.00	P	PU	30
D3.3	Overview on applications, applied standards, workflows, and selected integration scenarios.	17	19.50	R	PU	24
D3.4	Recommendation on selected standards, workflows and profiles.	19	10.50	R	PU	60
D3.5	Design specifications of the virtual institute ICT infrastructure.	18	10.50	R	RE	36
D3.6	Validated operational prototype of the virtual institute ICT infrastructure.	18	10.90	P	RE	60
		Total	67.40			

Description of deliverables

D3.1) Multi-stage release of communication platform including specified modules.: Multi-stage release of communication platform including specified modules. D3.1 [month 12]

D3.2) Productive knowledge management platform.: Productive knowledge management platform. D3.2 [month 30]

D3.3) Overview on applications, applied standards, workflows, and selected integration scenarios.: Overview on applications, applied standards, workflows, and selected integration scenarios. D3.3 [month 24]

D3.4) Recommendation on selected standards, workflows and profiles.: Recommendation on selected standards, workflows and profiles. D3.4 [month 60]

D3.5) Design specifications of the virtual institute ICT infrastructure.: Design specifications of the virtual institute ICT infrastructure. D3.5 [month 36]

D3.6) Validated operational prototype of the virtual institute ICT infrastructure.: Validated operational prototype of the virtual institute ICT infrastructure. D3.6 [month 60]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead beneficiary number	Delivery date from Annex I [60]	Comments
MS13	Operational knowledge management platform	18	30	Content available in knowledge management platform
MS14	Completed analysis of existing systems and list of proposed standards	18	36	Confirmation of agreement between partners
MS15	Design Specification of Virtual European Research Institute	18	36	Design document
MS16	System validation completed	18	60	Metrics for system performance available

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP4	Type of activity [54]	OTHER
Work package title	Clinical Trial Facilitation		
Start month	1		
End month	60		
Lead beneficiary number [55]	1		

Objectives

This Work Package will review the needs and elaborate solutions for the full scope of studies needed in paediatric and adolescent oncology, thus enabling clinical and translational research in this orphan disease sector. This encompasses the needs of early drug development studies (Phase I/ II) supported by industry or driven by academia, investigator-driven, academic phase III / IV settings and prospective clinical studies that may not fall within the remit of the EUCTD, all with respect to ICH guidelines, EC Directives and Member State laws.
Specific objectives are:
- To increase the efficiency of implementation of pan-European multinational clinical research, in particular investigator driven trials (ICDT) in paediatric and adolescent oncology, by agreeing and adopting standardised procedures to ease the bureaucratic burden under the EUCTD.
- To facilitate and increase the capacity for investigator-driven trials (ICDT) by agreeing and adopting standardised risk-based approaches, clinical trial templates and standardised datasets;
- To reduce fragmentation and duplication of effort by facilitating multinational clinical studies with appropriate numbers of patients to produce statistically reliable results;
- To agree on a definition of what is an investigational medical product (IMP) within IDCTs when paediatric use is ‘off-label’ and to agree the associated safety reporting requirements;
- To streamline the procedures to obtain authorisation for IDCTs in children and adolescents by integrating the experience of clinical researchers, parents and patients to better inform the harmonisation of European national authorities’ rules and EC regulations as well as European ethical committee opinions;
- To facilitate the clinical trial authorisation process (CTA) through interaction with authorities and EC to contribute to the harmonization and common approach between national and EC -- To develop a contract framework to support the model whereby academic institutions can assume the role of pan-European coordinating sponsors with delegation of tasks to a national legal entity (national sponsor), thus sharing sponsor duties and obligations;
- To harmonise insurance requirements aiming to identify/achieve a not-for-profit insurance organisation for clinical trials in paediatric and adolescent oncology. To explore the possibility to insure studies through the national public health system in these orphan indications;
- To assure informed consent procedures appropriate to the patient’s age and capacity and the scope of the clinical research;
- To define cost effective infrastructures needed for clinical data centres;
- To harmonize data management systems by creating a European standard;
- To overcome fragmentation by introducing better definitions for data ownership to allow data-sharing while assuring the rights and protection of individuals on trials;
- To lower the bureaucratic burden through intelligent IT solutions for clinical trial centres;
- To facilitate pharmacovigilance reporting.

Description of work and role of partners

Task 4.1 Providing templates to facilitate design and implementation of IDCT. SIOPE, CCRI, ESQH, UNIMIB, OLGA, UOB, LaFe, CURIE, IGR, IGG, ÖK, CAU, ECCO (M1-M24)
Objective:
Definition of the specific needs of IDCT in paediatric and adolescent oncology in compliance with European and national authorities and offering solutions to facilitate trial implementation.

Task description:
- To develop GCP-compliant European master trial protocol formats that address the additional, specific requirement for clinical research (phase I-III) in children, encompassing all necessary requirements according to ICH guidelines (CCRI, SIOPE, ESQH, IGR, UOB, UNIMIB, OLGA)
- To develop age-specific informed consent templates for the scope of studies and associated research tasks to facilitate translational research activities across Europe (CCRI, SIOPE, UOB, IGR, CURIE, ÖK)
- To develop frame contracts needed to allow for a pan-European sponsorship , i.e. A single coordinating European academic sponsor to delegate tasks to national level thus sharing sponsor duties and obligations with a national legal entity (national sponsor) according to ICH guidelines for clinical trials (CCRI, SIOPE, ESQH, UOB, IGR,IGG, LaFe) –
- To achieve European agreement on a definition of what is an investigational medical product (IMP) within IDCTs and associated requirements in paediatric oncology (CCRI, SIOPE, ESQH, RECRC, IGR, UCL).

Task 4.2 Facilitate the start-up process of clinical trials CCRI, SIOPE, ECCO, ESQH, ÖK, CURIE, OLGA, UOB, IGR, UCL (M1-M48)
Objective:
Highlight the specific needs of IDCT in paediatric and adolescent oncology and to offer solutions for the facilitation of the conduct of clinical trials in compliance with European and national authorities with the focus on requirements for the clinical trial approval processes, risk definition of clinical trials and insurance requirements.
Task description:
- Establishment of a clinical trial working group defining the risk categories within paediatric oncology trials (CCRI, SIOPE, ESQH, OLGA, UCL, IGR, RECRC).
- Identification of not-for-profit insurance organisations for clinical trials in paediatric oncology to lower the financial burden for IDCT regarding insurance requirements (CCRI, SIOPE, ESQH, ÖK, RECRC)
- Exploration of the possibility to insure studies through the national public health systems in this orphan indication (CCRI, SIOPE, ESQH, RECRC, UCL, IGR, IGG, La Fe)
- Share European efforts (EFGCP) to explore the possibility for a single CTA application in paediatric oncology (Advisory committee for multinational trials) to increase the competiveness of clinical trials by shortening the length of the application period [CCRI, SIOPE, ESQH, OLGA, IGR, UCL]).
- Encourage the creation of a European advisory network of ethical committee representatives devoted to sharing and developing paediatric expertise across Europe to speed the process of trial approval and make recommendations for a more standardised approach to evaluating paediatric and adolescent oncology trials. To include the development of a European ethical forum for reviewing and harmonising informed consent requirements together with stakeholders (parent and patient advocacy groups) [CCRI, SIOPE, CURIE, ÖK, OLGA, IGR, UCL, IGG, La Fe] .

Task 4.3 Improving the framework for IDCT. ESQH, CCRI, SIOPE, OLGA, UNIMIB, FORTH, CINECA, CURIE, AIT, ÖK, UCL, CAU, LaFe(M1-M48)
Objective:
Maximize the benefit of efforts through the enhancement of synergies and the reduction of redundant procedures with particular weight on quality assurance and pharmacovigilance reporting: Harmonised operating procedures for administration, reporting, documentation, the creation of study documents, documentation/archiving and quality assurance.
Task description:
Consensus on the needs of quality assurance procedures within IDCTs including (ESQH, CCRI, UOB, IGR, IGG, UCL, OLGA, LaFe, AIT, FORTH, CINECA, UNIMIB):
-To agree on general rules for the degree of monitoring needed in non-commercial research (Best Practice according to GCP and economic specifications);
- To agree on general rules for the amount of audits needed in non-commercial research (Best Practice according to GCP and economic specifications);
- To agree on guidelines for a monitoring management system saving resources through the implementation of integrated feasibility checks and warning functions for falling below/exceeding critical values;
- To agree on guidelines for a standardised multilingual reporting system for monitors with an action plan and tracing of the subsequent activities;
- To agree on a work flow for continuous transfer of anonymised, approved, closed data sections to statistics experts taking account of toxicity profiles in IDCT aiming to firstly provide relevant toxicity data within the respective trial context to data monitoring committees and secondly to provide the background needed to better understand certain events with the necessity of expedited reporting rules under the definitions of SAE/SUSARS.

Achieve common definitions and tools for improved and stringent pharmacovigilance reporting to regulatory bodies to lower the unnecessary bureaucratic burden (ESQH, CCRI, SIOPE,UOB, IGR, IGG, UCL, OLGA, LaFe, AIT, FORTH, CINECA):
- Create intelligent IT solutions with IT partners for clinical trial centres supporting standardised reporting systems for study documents and all types of adverse events allowing to record, select and approve events with the need of expedited reporting;
- Development of software/database tools for the automatic documentation of SAES /SUSARS with appropriate anonymisation;
- Development of IT tools allowing forwarding of blinded data sets to members of the international safety boards and regulatory bodies as needed;
- Workshops to create a common understanding of stakeholders preparing a consensus conference.
Adequate harmonised education for monitoring, investigating and training staff (including updates, assignments and examinations) (ESQH, CCRI, SIOPE, UOB, IGR, IGG, OLGA, LaFe, AIT, FORTH, CINECA)
Implementation of patient info-centres and information material (especially for children on reflection of their age group (ESQH, CCRI, SIOPE, ÖK, CURIE, UOB, IGR, IGG, UCL, OLGA, LaFe, AIT, FORTH, CINECA)

Task 4.4 Creating a clinical trial advisory board SIOPE, CCRI, UOB, CAU, UNIMIB, IGR, UCL (M 1-12)
Objective:
A clinical trial advisory board shall be created to assure that IDCTs that run within the network are scientifically sound, foster translational research, do not duplicate any previous clinical trials unnecessarily and fulfil all the requirements of quality standards,
Task description:
- Election of members for the clinical trial advisory board;
- Definition of work flow of the advisory process.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	CCRI	2.50
2	SIOPE	8.00
4	UCL	1.00
5	CAU	3.00
6	IGR	6.00
9	UNIMIB	1.50
11	LaFe	2.00
13	UOB	5.00
15	IGG	4.40
16	CURIE	2.00
17	FORTH	1.00
18	AIT	4.10
20	ESQH	22.50
32	OLGA	2.00
34	ECCO	3.45
35	ÖK	5.40
	Total	73.85

WT3:
Work package description

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D4.1	Templates for clinical trials (including informed consent) and frame contracts ailable.	2	5.70	O	PU	12
D4.3	Definition of risk categories in IDCT undertaken on paediatric oncology platforms.	1	1.00	R	PU	12
D4.5	Consensus conference on an improved CTA process for IDCT in paediatric oncology.	1	1.50	O	RE	48
D4.6	Consensus workshop on sensible pharmaco-vigilance reporting & quality assurance measures in paediatr	20	10.66	O	RE	60
D4.7	Syllabus to educate stakeholders involved in IDCT.	20	10.66	O	PU	60
D4.8	Conference for European parent and patient cancer groups	20	10.68	R	PU	60
		Total	40.20			

Description of deliverables

D4.1) Templates for clinical trials (including informed consent) and frame contracts ailable.: Templates for clinical trials (including informed consent) and frame contracts ailable. D4.1 [month 12]

D4.3) Definition of risk categories in IDCT undertaken on paediatric oncology platforms.: Definition of risk categories in IDCT undertaken on paediatric oncology platforms. D1.3.2.1 [month 12]

D4.5) Consensus conference on an improved CTA process for IDCT in paediatric oncology.: Consensus conference on an improved CTA process for IDCT in paediatric oncology. D4.5 [month 48]

D4.6) Consensus workshop on sensible pharmaco-vigilance reporting & quality assurance measures in paediatr: Consensus workshop followed by publication on sensible pharmaco-vigilance reporting & quality assurance measures in paediatric IDCT. D4.6 [month 60]

D4.7) Syllabus to educate stakeholders involved in IDCT.: Syllabus to educate stakeholders involved in IDCT. D4.7 [month 60]

D4.8) Conference for European parent and patient cancer groups: Conference for European parent and patient cancer groups to disseminate information on standards of care, value of IDCTs and new information portal. D4.8 [month 60]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS17	Templates available for stakeholders on the WEB side	1	12	Visibility on the official ENCCA Website

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP5	Type of activity [54]	OTHER
Work package title	Biology to guide innovative targeted therapy development		
Start month	1		
End month	60		
Lead beneficiary number [55]	30		

Objectives

The aim of this workpackage is to integrate and harmonise existing biological datasets and experimental data allowing therapy choices guided by biology and innovations to improve treatment outcome for children and adolescents with cancer. To achieve this central aim, we perceive the realisation of seven goals:
1) to set up and manage a network of pre-clinical research groups for high-risk childhood and adolescent cancers
2) to ensure integration and accessibility of high-quality, existing data on drug target, drug target validation and (targeted) drug testing for high-risk childhood and adolescent cancers by building a common bio-informational data storage and analysis tool (including compiling a database with full profiling data from tumour series in ongoing clinical trials)
3) to develop new analytical tools for molecular drug targets, biomarkers and drug efficacy testing, and to perform cross-platform and cross-tumour bioinformatics analyses
4) to set up and harmonise integrated biobanking for characterisation, storage and distribution of clinical specimens, and for the generation and utilisation of molecular data characterising paediatric cancer
5) to integrate and share profiling and experimental data accumulated as data packages providing the biological rationale for the clinical development of new treatment strategies based on algorithms for identification and prioritisation of molecular targets
6) to structure data-sharing and integration for the development of biological signatures to select patients for new treatment strategies ('predictive biomarkers')
7) to structure data-sharing and integration for the development of biological signatures for risk stratification ('prognostic biomarkers')
Coordination Structure

The University Hospital Essen (UKE) and CHARITE will coordinate this Work Package and will integrate feedback from the AMC and CAU as well as subnetwork leaders via close collaborative communication in this project. This WP will draw on the experience of A. Eggert (UKE/CHARITE), who has coordinated research consortia at both the national and European levels, and is the director of the West German Cancer Center.
The primary focus of the AMC and CAU will be the coordination of bioinformatics approaches and database development, and the coordination of biology approaches in leukaemias, respectively.

To realise the seven Work Package goals, the following coordination structure is foreseen:

The coordination and integration of the current European tumour biology research networks (goal 1) will be executed by the UKE/CHARITE
Data analyses and integration, as well as shared bioinformatic approaches will be coordinated by AMC.

Biobanking concepts will be coordinated by the IGG and CHARITE
Working parties of leading European tumour biology research groups will be implemented to realise goals 2-4.

Tumour-specific subnetworks will be implemented including labs selected based on expertise and past performance to achieve goals 5-7.

Description of work and role of partners

Task 5.1 Coordination and integration of research networks. CHARITE, UKE, AMC, CAU (M1-M48)

Objective:
The aim of this working party is to set up and manage a network of pre-clinical research groups for high-risk childhood and adolescent cancers. The central coordinator will be stationed in Essen (UKE) until June 2013, then in CHARITE, and will maintain a constant dialogue with the affiliated partner institutions to support harmonious decision-making. This working party will rely heavily on the bioinformatic workforce of the working party, “data-sharing and bioinformatical tools”, coordinated by the AMC (Task 5.2).
Task description:
- Set up and manage biology network and tumour subnetworks.
- Organise annual meetings of the tumour biology research groups involved.
- Set up structures for sharing technical expertise.
- Oversee and keep timelines for the production of systematic literature reviews on drug targets and drug efficacy in the tumour subnetworks.
- Provide algorithms for the stepwise development and validation of molecular profiles/signatures for patient selection (‘biomarkers of sensitivity’, i.e. Predictive biomarkers) and for pharmacodynamics (‘biomarkers of biological effect’, i.e. Efficacy biomarkers).
- Establish uniform approaches and reporting for in silico drug target identification and drugged pathway analyses in large datasets from high-throughout profiling techniques including mrna arrays, DNA copy number arrays, mirna arrays, etc.
- Harmonise minimal requirements and reporting of drug target and drug testing data packages.
- Coordinate the development of algorithms for identification and prioritisation of molecular targets based on biological data by tumour-specific subnetworks
- Ensure efficient two-way communication and links with the clinical trial groups, including direct links with the tumour-specific biology subnetworks.
- Link to all other wps in the noe, especially (1) WP8 ‘Early evaluation and prioritisation of new anticancer drugs’ by providing Task 8.1 with pre-existing knowledge and data as input to assist the evaluation of new anticancer drugs, (2) WP9 ‘Risk adaptation of therapeutic strategies using predictive biomarkers in leukaemias’ by providing algorithms for testing and development of improved risk stratification in treatment of leukaemias and (3) WP10 ‘Risk adaptation of therapeutic strategies using prognostic biomarkers in malignant solid tumours’ by integrating feedback and data from Task 10.3, which is an example of how molecular translational research can be applied within a clinical trial and is the aim of WP1.4 to advance towards with other molecular data and knowledge from paediatric cancer research.
- Coordinate training and courses.
- Contribute actively to the dissemination of results obtained by ENCCA members to professionals, patients, pharmaceutical industry, policymakers and the general public.

Task 5.2 Data-sharing and bioinformatics tools. AMC, UKE, CHARITE, CAU, CURIE (M1 – M48)
Objective:
The aim of this working party is to better integrate cancer-oriented data and bioinformatics resources to improve the accessibility and impact from pre-clinical research. The coordinator will maintain communication with cooperating organisations in other WPs involving tools for molecular data storage and usage (i.e. ACGT solution package applied in Task 11.3 and in WP9) in order to provide optimal dissemination of information and resources to the NoE.
Task description:
Support data integration and sharing by developing a data storage and analysis tool for molecular profiling data and experimental drug target/testing data, encompassing all tumour-specific subnetworks. This activity will build on the successful KCK experience with the R2 database and bioinformatical tools and will draw on the bioinformatics experience from the research groups in the tumour-specific subnetworks. All tumour-specific subnetworks will be actively engaged in decision making on bioinformatics priorities.
Connect with ACGT (FP6 integrated project) to ensure maximum connection and incorporation of their knowledge and tools;
Ensure maximum inclusion of profiling data, clinical data and experimental drug target and drug testing data from laboratories in ENCCA as well as publicly available data.
Integrate systematic drug target and efficacy reviews from all tumour subnetworks in the bioinformatical storage and analysis tool;
Contribute to uniform approaches and reporting for in silico drug target identification and drugged pathway analyses in large datasets of high throughout profiling techniques including mrna arrays, DNA copy number arrays, mirna arrays, etc.

Contribute to developing algorithms by tumour-specific subnetworks for identification and prioritisation of molecular targets based on biological data.

Support in the harmonisation of minimal requirements and reporting of drug target and drug testing data packages
Conduct cross-platform and cross-tumour drug target analyses to identify and validate shared drug targets between tumour types
Ensure access to additional large datasets (integrated molecular profiling + clinical data) from paediatric and adolescent cancers by establishing formal collaborations with research groups or consortia outside ENCCA, e.g. PPTP, the TARGET initiative and COG in the USA
The bioinformatic workforce (1.5fte) will be primarily stationed in the AMC and UKE. Prioritisation of bioiformatic activities will be based on discussions carried out together with the heads of the tumour-specific subnetworks. Temporary stationing of bioinformatic workforce, as needed, in the lead labs of the tumour-specific subnetworks is envisaged.

Task 5.3 Biobanking CHARITE, IGG, CCRI, LUMC (M1– M48)
Objective:
The aim of this working party is to develop a strategy to have a unique access point with standardised dataset to existing biobanks and databases, to facilitate data analysis and eventually new studies in paediatric oncology, to provide ENCCA partners with a reliable source of material for further analysis and complete datasets describing the molecular profiles of each sample.
A solid and integrated biobanking structure is an absolute requirement for high quality research on paediatric cancers. Presently, several local biobanks in different centres exist that exhibit various degrees of sophistication in the spectrum of operation and integration. A strong coordinated effort will allow rapid resource sharing, and more importantly, full usage of the existing molecular data generated at several translational research labs throughout Europe. Harmonisation of procedures utilised by local biobanks and uniform definition of clinical parameters stored with the samples will additionally strengthen the quality of service provided to the network.

Several ENCCA partners had already invested considerable time, effort and money to develop local, regional or even national solutions for biobanking.

Two of these, PÄDONKO for ALL and ObTima for nephroblastoma, are developing links to clinical data that allow searches that satisfy data protection restrictions for all parties viewing the results.

The molecular database and research tool, R2, has likewise invested strongly in various other tumor entities and in the development of this resource.
Clinical trial databases are also developed for ENCCA partners involved in clinical trials.

Under these circumstances, it is essential to allow the continued use of existing resources. Whenever there is a need of exchanging information regarding existing biosamples networking and information exchange ideally involving eHealth tools (in compliance with respective EU data protection laws) is mandatory.

Development of a federation of ENCCA biobanking resources is intimately intertwined with the introduction of a unique patient identifier for every paediatric cancer patient treated in Europe as well as the development of a unified concept for patient consent forms that is in accordance with national data protection laws in European countries.
Further this ENCCA will support new developments in molecular analysis of tumor samples, particularly next-generation sequencing, and patient/parent wishes and ethical considerations.

To best avoid duplication of effort and to produce an additive effect, we will coordinate the efforts of all relevant stakeholders and ENCCA in WPs 3, 5, 7, 9 and 18 all involved .

CHARITE (A.Eggert) will coordinate the groups of stakeholders (managers and developers of existing IT resources, legal experts for data protection in European countries and patient/parent advocacy groups and ethics experts) for a federation of ENCCA biobanking resources, meeting organisation for this part of the biobanking task (development of the federation of ENCCA biobanking and molecular database resources) for the remaining project period (July 2013 - December 2014).

ENCCA will capitalize on pre-existing /established knowledge of networks EU funded.

The SIOPEN Biology Group (CCRI, SIOPEN-r-Net) was the first in Europe to provide the necessary standardised guidelines and quality control regulations for the integration of genetic information into treatment regimens for neuroblastoma patients. The SIOPEN tumour bank is a virtual tumour bank designed to provide research groups with well-
defined tumour tissue for in-depth molecular studies. Tumour cell content of the sample(s) is provided together with the tumour. The national biology reference centre extracts DNA/RNA/protein and performs necessary analyses (I-FISH, aCGH, SNP array, MLPA).
Genetic results, analysis date and sample amount are entered into the SIOPEN-R-NET database. This database also contains all clinical, radiological, surgical, pathological, bone marrow and biological information for NB patients registered in a SIOPEN study.
EuroBoNeT aims at increasing and disseminating knowledge of primary bone tumours at the molecular level for the development of new tools for patient care and cure and technology by staff exchange and website-based discussion forums. This virtual BioBank provides statistically significant datasets by integration of exchange of material, SOPs and the use of technology platforms. With this integration, molecular portraits of tumours are obtained by genome-wide expression and genomic aberration studies. This virtual tumour bank is designed to provide research groups with well-defined bone tumour tissues for in-depth molecular studies through a complete infrastructure for the exchange of frozen tumour samples between European labortories. Well functioning concepts of these existing European biobanks will be integrated to form a new concept for a European paediatric oncology biobank.

Task description:

- Harmonise SOPs for handling, storing and distributing biological specimens.
- Design quality control to verify tumour biomaterial storage and processing.
- Identify and network existing biobanks capable of and willing to adhere to SOPs outlined by ENCCA.
- Harmonise ENCCA biobanking activities and goals with the existing European translational research networks SIOPEN-R-NET and EuroBoNeT.
- Coordinate consolidation of the storage of specimens at the participating local biobanks.

Task 5.4 Tumour-specific Subnetworks CHARITE, UKE, AMC, CAU, UGent, CCRI, UCL, UNIPD, LUMC, EMC, IGG, FORTH, CINECA, IGR (M1– M48)
Objective:
Tumour-specific subnetworks for the 11 tumour types accounting for the highest mortality rates in childhood and adolescent cancers will be set up (Figure 10). The lead for establishing a tumour-specific subnetwork will be taken by labs participating in the active EU-funded networks and the IBFM research network for leukemia. The ambition of the tumour-specific subnetworks will be to involve the entire landscape of high-quality experimental research groups on these paediatric tumours across Europe.
Figure 10: The numbers of cases from 2002 to 2005 are depicted for children and adolescents in the pie charts. The actual numbers of cases, the population-weighted 5-year survival and the absolute numbers of deaths are related under each cancer type. Adapted from EUROCARE4, Eur. J. Cancer 2009.
The recruitment of labs into the tumour subnetworks will be based on scientific quality and commitment to contribute and share data within the tumour subnetwork. For leukemia, we will build on the already established and fully functioning IBFM pre-clinical research network. The research integration activities of each of the tumour-specific subnetworks will be assisted by task and subnetwork coordinator support and by travel costs for meetings. The integration of subnetworks in a pan-European effort should better support integration of biological data and ideas interesting across different cancer entities to support better translation of basic and preclinical research to clinical application. The integration structure and subnetwork participants are presented in Figure 3 and Appendix I.
Figure 11: Organisational structure of WP5 ‘Biology to guide innovative targeted therapy development’
Task description:
- Share profiling and experimental data to integrate research activities.
- Develop algorithms for identification and prioritisation of molecular targets based on biological data.
- Perform systematic literature reviews on drug targets (presence and validation) and on drug efficacy (preclinical and clinical) for the tumour types represented in each of the subnetworks and deliver those systematic reviews to the bioinformatical storage and analysis tool built for ENCCA.
- Deliver data packages for biologically rational choices/prioritisation for clinical development.
- Communicate with and link to clinical trial groups
- Provide infrastructure for profiling (all) samples in prospective (future) clinical trial(s).
- Contribute to cross-tumour analyses.

- Contribute SOP's for key experiments in preclinical drug development, e.g. target validation by RNAi and/or mutation, in vitro drug efficacy testing, drug testing in vivo models/
- Contribute to uniform approaches and reporting for in silico drug target identification and drugged pathway analyses in large datasets from high-throughout profiling techniques including mRNA arrays, DNA copy-number arrays, miRNA arrays, etc.
- Contribute to the harmonisation of minimal requirements and reporting of drug targets and drug testing data packages
- Contribute to algorithms for the stepwise development and validation of molecular profiles/signatures for patient selection ('biomarkers of sensitivity', i.e. predictive biomarkers) and for pharmacodynamics ('biomarkers of biological effect', i.e. efficacy biomarkers).

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	CCRI	8.50
4	UCL	8.50
5	CAU	17.00
6	IGR	6.00
8	UKE	36.00
10	EMC	5.50
15	IGG	28.00
16	CURIE	4.70
17	FORTH	2.00
19	CINECA	0.50
21	AMC	96.00
26	LUMC	3.00
30	CHARITÉ	12.00
36	UNIPD	7.50
	Total	235.20

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D5.1	Development of data storage and analysis tools to integrate molecular profiling and drug testing dat	30	78.00	R	RE	24
D5.2	Generate and update databases for existing material/data, genomic characterisation and clinical resp	15	77.00	R	RE	24
D5.3	Contribute SOPs, algorithms and uniform approaches to wet-lab and in silico preclinical drug develop	30	77.00	R	RE	12

WT3:
Work package description

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
		Total	232.00			

Description of deliverables

D5.1) Development of data storage and analysis tools to integrate molecular profiling and drug testing dat: Development of data storage and analysis tools to integrate molecular profiling and drug testing data from all tumour-specific subnetworks that is connected with FORTH. D5.1 [month 24]

D5.2) Generate and update databases for existing material/data, genomic characterisation and clinical resp: Generate and update databases for existing material/data, genomic characterisation and clinical responses. D5.2 at M24 and 48. [month 24]

D5.3) Contribute SOPs, algorithms and uniform approaches to wet-lab and in silico preclinical drug develop: Contribute SOPs, algorithms and uniform approaches to wet-lab and in silico preclinical drug development, target identification and validation, and harmonise minimal requirements across subnetwork participants. D5.3, at M12, 24, 36 and 48. [month 12]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS20	Yearly distribution of the guidlines from D1.4.4 to participating labs and networks	30	12	Guidelines will be distributed as written reports
MS21	Design of final bioinformatics tool based on prototype and user-feedback	30	60	Written reports containing feedback on 'bioinfo tool' by 3 working parties and 11 tumour subnetworks
MS22	Database of tumour specimens from virtual and local biobanks existing at project begin	30	60	Availability of dataset
MS23	Annual meetings and disseminate meeting discussion points and results to all WPs participants	30	24	Organise annual meetings and disseminate meeting discussion points and results to all Work Package participants to maintain good two-way information flow between subnetworks and remaining partners of

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP6	Type of activity [54]	OTHER
Work package title	Standardised and innovative methodology for clinical trial design and analysis		
Start month	1		
End month	60		
Lead beneficiary number [55]	9		

Objectives

- Developing methods of trial design for clinical research in rare diseases
- Improving statistical approaches for the definition and validation of risk-based patient stratifications
- Developing statistical approaches for the analysis of recurrent events (SAE) and competing events (composite endpoints) and long-term outcome;
- Defining core datasets for pooled analyses

The scope is to enhance in the network the expertise in methodology for design and analysis of clinical studies in paediatric oncology. This will be done by linking in a “virtual office” the biostatisticians who are already involved in the various areas of paediatric oncology or who have interest in related topics. Methodological support, with appropriate study design and statistical analysis, will be given to collaborative trials on new treatment options/strategies and to studies directed at investigating new prognostic/predictive factors and more sophisticated patient stratification, jointly with other work packages in the project (especially 5, 8, 9, 10, 11, 12). In this “virtual office”, information on projects, methods and software will be shared by the participants.
In paediatric oncology we face an increasing complexity of biological and bio-molecular studies where new (targeted) therapies need to be studied in often rare subgroups of patients. Thus study design for early phase or for phase III needs to be made more efficient by adopting novel methodologies that come from the Bayesian framework or that are more flexible than standard designs (task 6.1). The evaluation of new prognostic factors that derive from the growing knowledge of the cancer genetics and biology has to be done jointly with traditional prognostic factors and requires application of recent developments in the field of complex statistical modelling and an adaptation to the needs of research in paediatric oncology (task 6.2). Moreover, there is growing attention to the evaluation of safety, jointly with efficacy and in long-term evaluation of survival and side effects after successful therapies (task 6.3).
All these aspects underline the increasing need to harmonise data collection and comparability among leading groups in Europe and between studies. This requires that we define within Europe the minimum set of core data that we need to collect for evaluation of treatment results as well as of prognostic impact of advances in biology and genetics (task 6.4). This WP on standardising and updating research methodology will allow Europe to speak with a common voice in collaborating and comparing with research centres outside Europe, especially the Children’s Oncology Group of North America.

Description of work and role of partners

Task 6.1 Statistical approaches to trial design for clinical research in rare diseases IGR, UOB, UNIMIB, CAU, CCRI (M1-M48)
Objective:
The work will aim at reviewing, exploring and developing innovative approaches with the following sub-tasks.
Task description:
- Phase I-II-III study designs for drug development (Bayesian, adaptive…)
- Phase III studies testing treatment strategies/improved risk stratifications for guiding clinical practice in rare subpopulations;
- Studies to assess biomarkers in clinical practice.
The issue of endpoint in dose-finding trials is crucial since the conventional approach with Dose-Limiting Toxicity as the only endpoint is no longer relevant for targeted therapies. Other endpoints should be considered, such as all grades of toxicity (even mild or moderate), summarised in the score of toxicity as proposed by Beleke

and Thall in 2004 efficacy endpoints with joint efficacy-toxicity modelling; biomarkers; PK. Methodological developments are requested to use such endpoints in dose-finding trials.
One issue frequently discussed by the paediatricians is how to speed up drug development in children and, when starting a phase I trial in children, data available in adults could probably be taken into account to increase efficiency.
We plan also to work on the Time-to-Event methods developed by Cheung for the Continual Reassessment Method (TITE-CRM, Cheung 2000). These methods take into account all available data, including incomplete observations when a new patient may be recruited. It may therefore avoid waiting lists and shorten duration of accrual. The second interest of the theses TITE-methods is that they can be used to take into account late-onset toxicities, which is important when assessing a new treatment planned to be given continuously for a prolonged period.
Trials in rare diseases are problematic because it is not feasible to collect sufficient data to make definitive conclusions regarding the effectiveness of a treatment. Bayesian analysis enables treatment effects to be estimated from a combination of prior evidence and data accumulated in a clinical trial. As the certainty in the prior evidence increases so the amount of trial data that is needed for a decision-making reduces. This makes a Bayesian approach an attractive option for trials in rare diseases where prior evidence is available. This approach is particularly relevant in the paediatric setting because prior evidence is often available from adult studies. The construction of a 'prior' is not straightforward and can involve subjective judgements as well as hard evidence. One approach is to combine the information available outside of the trial into a prior using a scoring system with weights applied according to pertinence, validity and precision (Tan et al BMJ 2003). Alternatively the prior could be constructed by eliciting expert opinion (Hiance, 2009The Bayesian approach has rarely been implemented in paediatric trials and requires a close collaboration between statisticians and physicians. Further investigation of the methodology in this setting would be valuable.
Areas of application of these methodologies will be in the design of a new EsPhALL study on TKI inhibitors in the rare subgroup of Ph+ ALL and the AYA study on intensive multi modality therapy including double 131I-MIBG therapy for adolescents and young adults with neuroblastoma, both in collaboration with COG, and the randomised Phase II study assessing the efficacy of nilotinib in combination with vinblastine in relapsed and recurrent low grade Glioma.

Task 6.2 Statistical methods for the definition and validation of risk-based patient stratifications. UNIMIB, IGR, CCRI, CAU (M1-M48)
Objective:
The work will aim at reviewing, exploring and developing innovative approaches to the analysis of data on the identification and evaluation of new prognostic/predictive biomarkers and to the definition of new risk-based stratification with the following sub-tasks.
Task description:
- Models for analysis of complex longitudinal biomarkers with survival outcome;
- Statistical methods for assessing the predictive ability of complex patient stratifications;
- Design and analysis of case-cohort studies on new genetic or molecular markers.
We will consider the risk group stratifications in a limited number of clinically relevant categories at different risk of developing disease or progression. This is crucial to guide clinical decision in disease screening, inclusion in clinical trials and for treatment tailoring.
The project will review recent advances in methods for defining prognostic factors or prognostic stratifications (such as regression trees, joint modelling of longitudinal biomarkers and survival, bagging…) and for assessing the predictive ability of stratifications (summary indicators of discrimination, calibration, accuracy such as Brier's score and reclassification index). Some of these methods still need extensions to properly account for the presence of censoring (Antolini et al, Statistics in Medicine, 24, 2005).
The recently proposed proposed 'non-summary' measures represented by the predictivness curve, contrasting and clarifying their meanings and clinical interpretations, will be evaluated and adapted to the context of paediatric cancers (Pepe MS et al, American Journal of Epidemiology 167(3), 2008).
The methods previously outlined are based on data collected on all the patients involved in previous clinical trials. Sometimes the potential stratification factors are genetic markers and their values are not available on the entire study population due to cost considerations. In this context, case-cohort design can be useful in order to make laboratory analyses only on a fraction of the cohort that is selected, often on the base of auxiliary variables in order to reach statistical efficiency (Kulathinal et al, Epidemiologic Prospectives & Innovation, 4 (15), 2007).
Recent literature has developed methods of analysis with particular attention to time-to-event methods that are more efficient because they recover information from the main cohort through inverse probability sampling weights (Breslow et al, American Journal of Epidemiology ,169, 2009; Onland-Moret et al, Journal of Clinical

Epidemiology, 60, 2007). The design of case-cohort studies has gained relatively little attention in the literature. Further investigation on the methodology in this setting would be relevant.
Areas of application of these methodologies will be the definition of the predictive role of early response as measured by minimal residual disease at different time points and with different methodologies (flow cytometry or PCR) in ALL (Task 9.2) and of genomic and expression data generated at diagnosis of Neuroblastoma (WP 5 and 10).

Task 6.3 Statistical approaches for the analysis of recurrent events (SAE) and competing events (composite endpoints) and long term outcome CCRI, CAU, IGG, UOB, UCL, UNIMIB (M1-M48)
Objective:
The work will aim at reviewing, exploring and developing innovative approaches basically in the field of survival analysis. The work will be articulated in the following sub-tasks.
Task description:
- Methods for analysis of recurrent events with specific attention to the analysis of recurrent episodes of toxicity and complications (SAE);
- Methods for the analysis of outcome data in the presence of competing risks (of relapse/progression; death not for progression);
- Cure models for long term evaluation of outcome.
Commonly, safety data are included in standard reporting of trials as tabulation of row numbers and percentages because there is a lack of guidance on statistical methodology to define proper methods for the analysis of safety data and for the joint analysis of safety and efficacy data (Nishikawa et al, Statistics in medicine, 25 (23), 2006).
The project will study the application to safety analysis of methods used in event history data analysis for the description of the probability of occurrence/recurrence of events over time (Cook and Lawless, Springer-Verlag 2007). The use of competing risks methodology for the analysis of an efficacy end-point (i.e. event free survival), adjusting for adverse events that may eventually occur will also be evaluated.
The project will review recent models for competing risks, with a focus on specific issues in paediatric oncology. The aim is to give some guidance about which model to use depending on the aim of the analysis (Ambrogi F et al, Statistics in Medicine, 27(30), 2008; Lau et al. American Journal of Epidemiology , 2009, 170).
In paediatric oncology long-term outcome is often the main interest. Cure models explicitly allow for the proportion of long-term survivors to be directly modelled. This, without emphasising failure times like standard survival models. We plan to review the use, values and limitation of different types of Cure models and contrast them to standard survival models. The aim is to give some guidance about which model to use especially in the analysis of cohorts of patients with a good prognosis (in collaboration with WP 11). With regard to the investigation of long-term outcome important questions (e.g. power calculations, interim-analysis, the inclusion of time-dependent covariates, competing risks etc.) are not fully clear. We plan to investigate, if and how these problems can be addressed within the framework of Cure models.
The above methodology will be applied to the evaluation of risk of acute toxicity (such as liver venoocclusive disease in Wilms tumour or fungal infections in ALL) and long term (cardiac) serious toxicity in subgroups with high chance of cure, such as for a high fraction of Wilms tumour or ALL patients.

Task 6.4 Definition of disease specific core data sets for pooled analysis. UNIMIB, CCRI , UCL, CAU, IGR, IGG, UOB (M1-M48)
Objective:
Many of the projects in the network involve various countries and laboratories who have already in place their individual database structure or are linked to a common project-directed structure (for example the WEB-based Interfant 06 database with electronic data capture on trial data and biomolecular data). The objective of this task is to facilitate cooperative studies by agreeing on a common data set (where data can be extracted from different sources) that includes the data regarded as essential for pooled statistical evaluation across groups/trials of results in specific diseases.
Task description:
- Facilitate data exchange by defining what type of data is essential for research;
- Improve information and increase knowledge through the statistical evaluation of pooled data from different groups/trials/laboratories on prognostic and predictive factors in specific diseases.
The definition of essential data for a disease that should be collected with common standards regardless of the system used by different groups/trials/laboratories will permit:
i) to perform pooled analyses on the same type or subtype of cancer across groups in the network and between the network and other networks (COG, for example, in USA),), strengthening conclusions on individual comparable but not identical trials, e.g. different trials testing the use of TKI inhibitors in Ph+ ALL;

ii) to have a standard set of core clinical data that can be linked to core data from various tumor tissue banks allowing the analysis of the impact of genome-wide and biological findings on the clinical course of the disease, as a basis for future stratifications and molecular-based treatment interventions. The comparability and reliability of biological measurements (e.g. different platforms for microarray analysis) will be addressed;
iii) to integrate data with the aim to identify new prognostic factors and to improve information on the clinical behaviour of rare tumour types and subgroups, with the proposal of risk stratifications for future studies.
A similar approach has already proved successful in informing outcomes according to initial treatment approach in a small subset of good risk Rhabdomyosarcoma (Oberlin et al, JCO 19 (1), 2001), in the description of heterogeneity of the rare subset of Ph+ ALL patients (Aricò et al, NEJM 342 (14), 2000), in the description of the adverse prognostic impact of hypodiploidy (Nachman et al, Blood 110 (4), 2007), and in the analysis of MLL-rearrangements in AML (Balgobind et al, Blood 114 (12), 2009). This strategy should be improved and extended to other tumour types to increase knowledge on risk stratification and clinical decision making regarding therapy for small subgroups. This approach will challenge the development of a database structure including metadata that defines an agreed level of standardization and integration of existing (and future) databases. The metadata will include also the mapping of existing databases to the common structure. Tools and methods which will be developed in WP 3 will be used for this purpose. Interaction with WP 11 will also be relevant in developing the core data sets.

In order to achieve these results the work will require the organisation of small international working groups (one for each of 4 target tumour groups) in which expert clinicians, biologists and statisticians will define the set of core data, identify those subgroups that would benefit from a statistical evaluation of either treatment strategies or new prognostic or predictive factors. Each group will meet at least once, in the form of workshops: the workshop will be to define the existing datasets and clinical problems and agree the analysis pathway. Presentation of the findings, implementation and dissemination of results will be done in collaboration with clinical experts of the specific diseases in their meetings. Innovative statistical approaches developed in WP 6.2 will be used for the definition and validation of risk-based patient stratifications.
The identified areas of application, which will serve as a model system for areas worthy of future investigation are: ALL (in collaboration with WP 9), Neuroblastoma, and Wilms tumour (WP 11). In these three diseases, the challenge is to define international risk stratifications which include novel biomarkers and imaging staging or response criteria.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	CCRI	15.00
4	UCL	1.00
5	CAU	11.00
6	IGR	5.50
9	UNIMIB	38.00
13	UOB	8.00
15	IGG	2.10
	Total	80.60

WT3:
Work package description

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D6.1	Guidelines for novel trial designs in paediatric oncology and validating risk-based patient stratifi	6	41.10	R	RE	48
D6.2	Guidelines for the analysis of safety data, competing events and long-term outcome.	1	15.00	R	RE	60
D6.3	Prototype of core data sets and report on their analyses for specific tumours.	9	22.00	R	RE	60
		Total	78.10			

Description of deliverables

D6.1) Guidelines for novel trial designs in paediatric oncology and validating risk-based patient stratifi: Guidelines for novel (early phase) trial designs in paediatric oncology and validating risk-based patient stratifications. (IGR and UNIMIB) [month 48]

D6.2) Guidelines for the analysis of safety data, competing events and long-term outcome.: Guidelines for the analysis of safety data, competing events and long-term outcome. [month 60]

D6.3) Prototype of core data sets and report on their analyses for specific tumours.: Prototype of core data sets and report on their analyses for specific tumours. [month 60]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS24	Innovative and recent statistical methodology: review and recommendations	6	48	Workshop,guidelines and publication(s)
MS25	Methodology and review on current practice of adverse event and toxicity reporting, competing risks	1	60	Workshops
MS26	Core data set and relevant analyses identified for the 4 identified tumors	9	24	Workshops
MS27	Data pooling and analyses performed	9	60	Report and publication after second workshop

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP7	Type of activity [54]	OTHER
Work package title	Integrating clinical trials and tumor biology research in bone sarcoma		
Start month	1		
End month	60		
Lead beneficiary number [55]	32		

Objectives

The primary objective of this WP is to establish a platform for multinational, intergroup bone sarcoma trials (phase 2-4) with integrated tumour biology research questions by linking major bone sarcoma groups and networks such as EURAMOS, EURO-E.W.I.N.G. and EuroBoNeT. For this purpose, active collaboration with leading institutions and research groups from the aforementioned networks which are not formal members of the ENCCA platform will also be sought. Examples from EuroBoNeT would be the Universities of Oxford, Salamanca, and Bologna .
Secondary objectives are to use this platform to develop and implement specific clinical trials for osteosarcoma and Ewing sarcoma, to improve the infrastructure for the collection of bone sarcoma specimens for translational biology studies within these trials, and to improve the access to expert care for patients outside of established trial infrastructures.

Description of work and role of partners

Task 7.1 Develop models for the integration of tumour biology research questions into clinical bone sarcoma trials. OLGA, LUMC, LTHTNHS, WWU, IGR, CURIE, UCL, CCRI (M1 – M48)
Objective:
Use the collaborative experience gained through successful multi-national and multi-professional collaboration such as that in the EURAMOS, EURO-E.W.I.N.G., and EuroBoNeT (EU-FP6 NoE) - groups to implement a Pan-European bone sarcoma infrastructure which guarantees the incorporation of robust biological studies into clinical trials.
Task description:
- identify European study groups and international partners with a shared commitment to integrate biological studies into clinical trials on bone sarcoma
- integrate bone sarcoma trial groups from inside and outside paediatric oncology into a collaborative infrastructure, expanding the strong basis established by the EURAMOS and EURO-E.W.I.N.G. trials
- use the knowledge and experience of these groups to lobby for a more harmonised and trial-friendly regulatory environment in Europe and member countries
- improve the access of teenagers and young adults into clinical trials in these rare cancers (link with WP 17).

Task 7.2 Optimizing the availability of bone sarcoma tissue for biobanks. LUMC, EMC, OLGA, LTHTNHS, WWU, IGR, CURIE, UCL, CCRI (M1 – M48)
Objective:
Guarantee the availability of sufficient material for biology research in bone sarcoma.
Task description:
- perpetuation and expansion of the virtual bone tumor biobank established within the EuroBoNeT FP6 NoE;
- identify existing European physical biobanks storing bone sarcoma tissue;
- supply expertise to foster the development of additional local, regional, and national physical bone sarcoma biobanks (link with task 5.3);
- linking of physical biobanks with the EuroBoNeT virtual bone tumor biobank;
- establish a procedure for biobank access and prioritization for use of samples;
- link with tasks 7.3. and 7.4. in order to formulate biology driven research questions.

Task 7.3 Developing a European platform for clinical trials in osteosarcoma. UCL, OLGA, LUMC, IGR, CURIE (M1 – M48)
Objective
Build a European infrastructure for intergroup phase II-III osteosarcoma trials which incorporate translational studies.
Task description:
- agree on core definitions for eligibility criteria, endpoints, sample collection, response critieria, consent;
- engage European patient advocacy groups in future trial planning, design and conduct;
- explore trial design options for complex therapeutic evaluation including interaction with WP 6;
- achieve methodological concensus for future large randomised studies and early phase studies;
- disseminate knowledge and experience gained through successfully running of EURAMOS1 as a Pan-European trial under EU Directive 2001/20, in order to provide improved access of potential new partners to osteosarcoma trials and to multinational clinical trials in general;
- Improved trial recruitment especially of TYA in future international trials of osteosarcoma;
- Initiate an international trial in newly diagnosed osteosarcoma.
Four Workshops:
Workshop 1: Phase II/III osteosarcoma Trial protocols - standardising core elements
Workshop 2: Public and Patient Involvement in osteosarcoma trials
Workshop 3: New study designs for evaluation of targetted agents in osteosarcoma
Workshop 4: Overcoming barriers to recruitment to bone sarcoma trials

Task 7.4 Developing a European platform for clinical trials in Ewing sarcoma. LTHTNHS, WWU, IGR, CURIE, CCRI, LUMC, UCL (M1 – M48)
Objective
Create the environment that integrates Ewing's biology into the existing and proposed clinical trial programme.
Task description:
- facilitate the development of an upfront randomized controlled trial in newly diagnosed Ewing sarcoma;
- develop an international approach to studies in relapsed Ewing sarcoma;
- develop a common staging system for stratification of Ewing’s sarcoma according to risk factors in common with the COG US group;
- deliver clear biological outcomes from such trials.

Task 7.5 Developing a European Tumour Board for Centralised Local Therapy Planning. WWU, LTHTNHS, IGR, CURIE, OLGA, UCL (M1 – M48)
Objective:
- to develop international standards and guidelines for surgery, radiotherapy and the combination of both, surgery and radiotherapy, for patients with Ewing sarcoma, depending on age, tumour site and response to initial chemotherapy.
Task description:
- establish a virtual interdisciplinay Ewing tumour board between national reference paediatric and medical oncologists, orthopaedic surgeons and radiotherapists;
- develop valid standards and guidelines based on meta-analyses of existing data banks;
- facilitate international, interdisciplinary workshops to assure an appropriate level of training;
- increase the number of patients within and outside clinical trials with access to the tumour board infrastructure.

Task 7.6 Roll-out of referral schemes for patients outside of trials. WWU, LTHTNHS, UCL, LUMC, OLGA (M1 – M48)
Objective:
To ensure that patients outside of clinical trials have access to appropriate care and expertise and that the proportion of European bone sarcoma patients treated on trials is increased.
Task description:
- roll-out of referral schemes established by selected bone sarcoma groups to provide patients without access to such infrastructure with access to expert centres and networks of care;
- support the development of bone sarcoma groups in European countries currently without such groups, particularly in Eastern Europe;
- education of oncologists caring for teenagers, young and older adults about possibilities to enrol their patients into “pediatric” trials;
- increase the number of patients with access to an infrastructure which will allow future participation in biology driven clinical trials.

WT3:
Work package description

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
6	IGR	7.50
10	EMC	1.00
14	LTHTNHS	0.24
16	CURIE	5.00
26	LUMC	12.00
32	OLGA	21.50
37	WWU	6.00
	Total	53.24

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D7.1	Develop key agreed research objectives for the bone sarcoma framework with proposed time-table	32	7.55	R	PU	12
D7.2	Restructure existing Eurobonet virtual tumor bank to open access for ENCCA partners and other	26	7.55	O	PU	24
D7.3	Implementing SOP for entering cases into the virtual databank	26	6.25	O	PU	36
D7.4	Integrated clinical trial and translational research proposal for osteosarcoma and Ewing sarcoma	4	4.85	R	PU	12
D7.5	Consensus on phase II/III protocol definitions	4	7.55	O	PU	60
D7.6	Implementation of early clinical trials in relapsed and high risk patients	14	4.19	O	PU	24
D7.7	Regular international tumour board sessions	37	7.55	R	PU	24
D7.8	Meta-analyses of specific primary tumour sites and development of evidence-based standards	37	7.75	R	PU	60
		Total	53.24			

Description of deliverables

D7.1) Develop key agreed research objectives for the bone sarcoma framework with proposed time-table: D 1.1: Develop key agreed research objectives for the bone sarcoma framework with proposed time-table (M12) and organize an intergroup bone sarcoma biology meeting and minutes (M12) [month 12]

D7.2) Restructure existing Eurobonet virtual tumor bank to open access for ENCCA partners and other: D. 1.2 Restructure existing Eurobonet virtual tumor bank to open access for ENCCA partners and other non-EuroBoNet, non-ENCCA centers [month 24]

D7.3) Implementing SOP for entering cases into the virtual databank: D 1.3 Implementing SOP for entering cases into the virtual databank and implement user manual for exchange of tissue specimens for research purposes [month 36]

D7.4) Integrated clinical trial and translational research proposal for osteosarcoma and Ewing sarcoma: D 1.4. Integrated clinical trial and translational research concept proposal for osteosarcoma and for Ewing Sarcoma(M24) and reports from 4 workshops (M12; 24; 36) [month 12]

D7.5) Consensus on phase II/III protocol definitions: D 1.5 Consensus on phase II/III protocol definitions (M48) [month 60]

D7.6) Implementation of early clinical trials in relapsed and high risk patients: D 1.6. Implementation of early clinical trials in relapsed and high risk patients for rapid testing of new agents (M 24, 48) [month 24]

D7.7) Regular international tumour board sessions: D 1.7 Regular international tumour board sessions, discussing local therapy in critical cases and providing reports and minutes (M24) [month 24]

D7.8) Meta-analyses of specific primary tumour sites and development of evidence-based standards: D 1.8 Meta-analyses of specific primary tumour sites and development of evidence-based standards and guidelines for local therapy of Ewing tumours (report and publication) (M48) [month 60]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead beneficiary number	Delivery date from Annex I [60]	Comments
MS28	Optimised trial accrual	32	60	>75% eligible patients accrued in bone sarcoma trials
MS29	Steering Group establishment, meetings and annual reports.	32	12	Steering Group establishment, meetings and annual reports
MS30	Meetings of the European Bone Sarcoma Trials	37	12	Meetings of the European Bone Sarcoma Trials with invitation of representatives of other groups and countries
MS31	Workshops and Observerships for oncologists in training	37	12	Workshops and Observerships for oncologists in training from groups and countries outside existing trials

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP8	Type of activity [54]	RTD
Work package title	Early evaluation and prioritisation of new anticancer drugs		
Start month	1		
End month	60		
Lead beneficiary number [55]	6		

Objectives

The goal is to facilitate and increase the capacity to run early evaluation of new anticancer compounds (phase I, phase II trials) in children with leukaemias and malignant solid tumours in Europe through an integration of this activity in between the ITCC consortium (early drug development in all tumour types) and the European disease groups such as I-BFM (leukaemias), SIOPEN (neuroblastoma), EpSSG (Soft tissue sarcomas), SIOPE Brain (brain tumours) and Euro-Ewing. Prioritisation of compounds to be studied in children will be based on tumour biology and target validation as accessible through WP5. A strategy for new drug development in the different paediatric malignancies will be established and discussed with EMEA and the Paediatric Committee (PDCO). Guidelines will be proposed. Based on these disease-dased strategies that will be reassessed on a yearly basis, discussion with pharmaceutical companies (facilitated by WP16 and the Club of Industry Interests) will be held to have access to the relevant compounds and to run phase I and II trials, in anticipation of introduction of those targeted compounds in phase III trials and then in standard care.
Innovative designs developed in WP6 will be implemented and evaluated in early drug clinical trials to speed-up their development and to increase the capacity to study relevant compounds in a timely fashion. Both industry-sponsored and investigator-led trials will be performed and the goal is to facilitate the increase in the number of innovative drugs accessible for patients in Europe. Four drugs will be studied as single agent and in combination with haematological malignancies and in solid tumours through investigator-driven clinical trials in order to demonstrate the proof of principle of the WP that will facilitate integration in between the existing groups and increase the collaboration with both regulatory agencies and pharmaceutical companies.

Description of work and role of partners

Task 8.1 Establishment and evaluation of a new drug development strategy for each of the main paediatric tumour types IGR CCRI, UNIMIB, EMC, CAU, UCL, UOB, CURIE, AMC, APHP, OLGA, UGent (M1 – M48)
Objective:
Biology drives the current development of anticancer drugs in adults. A strategy for new drug development will be defined first for the main paediatric malignancies that are responsible for the larger number of deaths yearly (such as AML, Neuroblastoma, High Grade Gliomas, Medulloblastoma, Ewing tumours, Osteosarcoma, Rhabdomyosarcoma,) and then for rare paediatric cancers (such as hepatoblastoma, non rhabdomyosarcoma soft tissue sarcomas,) and malignancies with a good prognosis with current treatments (such as Hodgkin and non-Hodgkin lymphoma, Wilm's tumour).
Task description:
A strategy will be defined on the basis of:
- Current knowledge (published and non-published data) on tumour biology identifying the main biological pathways that are functionally involved in tumour initiation and progression, as well as those involved in the interaction in between the tumour and its environment,
- Results of preclinical evaluation of anticancer compounds on relevant tumour models to confirm drugable targets and identify drugs of interest,
- State of the art of the multidisciplinary care of patients and ongoing and planned clinical research (phase III trials).
The Strategy will be established through stakeholder workshops (one for each main tumour type) involving a small number of key opinion leaders and experts in the fields of biology, drug development, and clinical research for the given disease along with methodologists. This will be performed in connection with the disease-sub-netwoks in WP5 and the relevant disease-groups from the Council. Those strategies will implement

innovative designs and methodology from WP6. They will be shared and discussed with EMEA and the PDCO to streamline the evaluation of paediatric investigation plans.
Contact with pharmaceutical companies will be done individually and through the Club of Industrial Interest and will be based on the defined strategies. The Implementation of those strategies will be steered on an annual basis and amended when needed. A report detailing the implementation will be provided every 18 months.

Task 8.2 Set-up collaboration with EMEA and the Paediatric Committee IGR, EMC, CAU, UOB, APHP (M1-M24)
Objective:
To contribute and streamline both the development and the evaluation of Pedatric Investigation Plans (PIPs), by pharmaceutical companies and by EMEA, respectively, in the field of oncology in order:
- To better integrate these drug-development plans into the clinical research research strategy run by the European disease groups and thus to increase their capacity to fulfill the currently unmet paediatric needs;
- To increase access to innovative therapies for children with cancer in Europe;
- To anticipate introduction of targeted compounds in strandard care;
In late 2008, EMEA initiated a taskforce in oncology improbe collaboration between EMEA and the paediatric oncology community. This taskforce has just started to operate and needs to be renewed and strengthened to achieve the goals set out for it. ENCCA will be committed to reinforce the collaboration with EMEA within this taskforce.
Task description:
- Renew the EMEA Taskforce in oncology with a restricted number of key opinion leaders who represent the major fields in paediatric oncology;
- Propose and establish guidelines for the development of pips based on a biology driven drug development strategy for the main pediatric malignancies;
- Establish through a strong collaboration with WP6 new methodology standards for the development of anticancer drugs in children and to establish them as guidelines for Industry;
- Propose guidelines for the preclinical evaluation of targeted compounds, in collaboration with expert from WP5;
- Facilitate access to expertise in the field of pediatric oncology.

Task 8.3 Establishment of a consortium of institutions to speed up the administrative process for the implementation of investigator- driven phase I and II trials. IGR, CCRI, EMC, CAU, UOB, UCSC, UGent (M1 – M24)
Objective: To create a consortium of academic institutions to sponsor and run phase I and II investigator- driven clinical trials in order to speed up the development of those short trials (12 -18 months).
Task description:
Part of the early evaluation of anticancer drugs (optimal dose finding studies, biologically driven phase II trials, combination studies) will be run as academia-sponsored trials co-funded by industry (through investigator initiative study processes) and public funding. Contrary to phase III trials run by the European tumour committees, those studies are short (ideally 12 to 18 months) and should be numerous to comprehensively address the goals. It is crucial to facilitate and speed-up all the administrative processes.
A consortium of a small number of academic institutions will be set-up to sponsor and run (according to the EUCTD) these early drug trials in each of the participating Member States.

Task 8.4 Conduct the early evaluation of 2 targeted compounds in haematological diseases EMC, CCRI, UNIMIB, CAU, UOB, IGG, AMC, APHP (M12-M48)
Objective:
To evaluate two drugs (a demethylating agent and an aminopeptidase inhibitor) in haematological diseases through investigator-driven clinical trials as proof of the increased integration between the ITCC and IBFM through the ENCCA project and the added-value of the network.
Task description:
Development of a demethylating agent for the treatment of paediatric myelodysplastic syndrome and juvenile myelomonocytic leukemia (investigator-initiated study)
Phase III data in adults with myelodysplastic syndrome showed benefit leading to registration of this drug for adult MDS
Preclinical data suggest that hypermethylation is present in these tumours and hence an appropriate target for treatment
No drugs are registered for paediatric MDS and JMML; currently stem cell transplantation is the only treatment available
Phase I and II data in children will be developed
Development of an aminopeptidase inhibitor for paediatric leukaemia (investigator-initiated study)

This drug is an example of a new class of anti-cancer drugs, which has shown considerable activity in adult acute myeloid leukemia in phase I/II studies
This drug is synergistic with well-known anti-cancer drugs such as cytarabine and/or bortezomib
No data is currently available on child patients, and hence phase I/II studies are needed.
This drug may also exert activity in paediatric ALL and not just in paediatric AML

Task 8.5 Conduct the early evaluation of 2 targeted compounds in paediatric solid malignancy UOB, CCRI, IGR, EMC, UCL, IGG, UCSC, CURIE, AMC, CLB, OLGA (M1-M48)
Objective:
To evaluate two drugs (an IGF1R monoclonal antibody and an antiangiogenic) as single agents and in combination with malignant solid tumours through investigator-driven clinical trials as a proof of increased integration between ITCC and the European tumour groups through the ENCCA project and the added-value of the network.
Task description:
- Development of an IGF1R monoclonal antibody in paediatric solid tumours;
- A target involved in several paediatric malignancies (Ewing, Neuroblastoma, Rhabdomyosarcoma, Wilms tumour, Atypical Teratoid brain tumour);
Preliminary phase I and phase II single agent data in adolescents and adults showed a good safety profile and some evidence of antitumour activity in patients with advanced sarcomas;
- A strong rational to combine with other targeted compounds such as mtor inhibitors;
- Negotiations are ongoing with several pharmaceutical companies to have access to an IGF1R moab;
- Development of an antiangiogenic compound;
- Angiogenesis is a target in several paediatric malignancies;
- Many compounds are under development (monoclonal antibodies and small molecules);
- Data is available in phase I for bevacizumab, an anti-VEGF MOAB, in children showing positive short-term safety;
- There is an ongoing bevacizumab trial in metastatic rhabdomyosarcoma through collaboration between ITCC and EPSSG;
- Bevacizumab showed activity as single agent in glioblastoma and adults. Its roles will be evaluated in combination with chemotherapy in relapsed pediatric brain tumours and in neuroblastoma.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	CCRI	38.50
4	UCL	5.00
5	CAU	7.00
6	IGR	7.50
7	UCSC	2.00
9	UNIMIB	4.00
10	EMC	7.70
13	UOB	32.50
15	IGG	3.50
16	CURIE	2.80
21	AMC	2.00
23	CLB	0.90
28	UGent	5.00
31	AP-HP	12.00

WT3:
Work package description

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
32	OLGA	2.70
	Total	133.10

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D8.1	Strategy for new drug development in the main paediatric leukaemias and malignant solid tumours	6	19.90	O	RE	60
D8.2	Guidelines with EMEA for the development of clinical and preclinical Paediatric Investigation Plans	6	19.90	R	RE	60
D8.3	A consortium of academic institutions to sponsor phase I and II trials.	1	19.90	O	PU	30
D8.4	At least three EMEA-ENCCA Task force face-to-face meetings is set-up.	10	19.90	O	RE	60
D8.5	The recruitment in at least one trial in haematological malignancies and malignant solid tumours.	13	20.00	O	PU	60
		Total	99.60			

Description of deliverables

D8.1) Strategy for new drug development in the main paediatric leukaemias and malignant solid tumours: A Strategy for new drug development in each of the main paediatric leukaemias and malignant solid tumours have been established and reevaluated once. [month 60]

D8.2) Guidelines with EMEA for the development of clinical and preclinical Paediatric Investigation Plans: Guidelines with EMEA for the development of clinical and preclinical Paediatric Investigation Plans in oncology. [month 60]

D8.3) A consortium of academic institutions to sponsor phase I and II trials.: A consortium of academic institutions to sponsor phase I and II trials. D2.3 [month 30]

D8.4) At least three EMEA-ENCCA Task force face-to-face meetings is set-up.: At least three EMEA-ENCCA Task force face-to-face meetings is set-up. [month 60]

D8.5) The recruitment in at least one trial in haematological malignancies and malignant solid tumours.: The recruitment in at least one trial in haematological malignancies and malignant solid tumours has been completed. [month 60]

WT3:
Work package description

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS33	The consortium of Insitutions is up and running	6	24	Minutes of the working group
MS34	Agreement with at least one pharmaceutical company for access to an innovative compound for leukaemi	6	24	Agreement possibility

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP9	Type of activity [54]	RTD
Work package title	Improved therapeutic strategies using predictive biomarkers in leukaemias		
Start month	1		
End month	60		
Lead beneficiary number [55]	5		

Objectives

This WP aims to establish a harmonised and integrated approach to the rational introduction of molecularly targeted treatment in clinical trials on leukaemias. In order to achieve this ultimate goal, we will develop standardised comprehensive diagnostic approaches as well as biobanking, and establish a common pipeline for molecular diagnostics in a European virtual laboratory on leukaemias. Through the application of algorithms developed in WP1.4 for the identification and prioritisation of molecular targets based on biological data, we will be able to focus on the most promising molecular targeted treatments in preclinical model systems. The international multicentre clinical trials AIEOP-BFM ALL 2009 and INTERFANT-06 will serve as infrastructural platforms and treatment backbones to implement and prospectively validate these objectives in a daily-life clinical setting. The close association with the European Relapsed trial in ALL (INTREALL) will finally allow integration of the respective Phase III elements for identified subgroups in experimental protocols

Description of work and role of partners

Task 9.1 Standardized comprehensive diagnostic approaches in leukemias EMC, CAU, UNIMIB, UNIPD, CHARITE, CCRI, APHP (M1– M24)
Objective
A common approach to characterise and classify patients using standard diagnostic techniques is a prerequisite for all activities towards identification of new molecularly based patient populations. For this purpose, the I-BFM Committee on Biology & Diagnosis will initiate a survey on diagnostic approaches of all national study groups within the I-BFM-SG for acute lymphoblastic as well as myeloid leukaemias and develop consensus guidelines regarding existing standard morphological, immunological, and cyto- as well as molecular genetic analyses in close cooperation with WP 5.
Task description:
This activity will provide a common ground for a systematic implementation of molecularly-based diagnostic strategies to be developed in this WP and shared with he working party "biobanking" in WP 5. The nucleus of our initial activities will be the I-BFM core study AIEOP-BFM ALL 2009, a 7-country-based international frontline treatment trial on acute lymphoblastic leukaemia (ALL) in children and adolescents. Participating countries are currently Austria, the Czech Republic, Germany, Israel, Italy, Switzerland, and Australia. This large trial will serve as the first practical application of the developed consensus guidelines on diagnostics and biobanking. Activities will be extended to other entities and study groups (e.g. INTERFANT and INTREALL) and experiences shared with WP 5 and WPs 2 on solid tumour entities.

Task 9.2 Establishment of a harmonised pipeline for molecular diagnostics in a European virtual laboratory setting using very high-risk ALL (VHRL) as a model system. CAU, UNIMIB, UNIPD, CHARITE, EMC, CCRI, FORTH (M1 – M36)
Objective:
By applying extended minimal residual disease (MRD) analyses during the last 10 years in our recently completed frontline ALL trial AIEOP-BFM ALL 2000, we were able to identify a subgroup of MRD high-risk ALL patients we termed very high-risk ALL (VHRL). This subgroup comprises roughly 3% of the entire ALL patient population and is characterised by molecular persistence of leukaemia cells at a defined threshold of > 10-3 after 22 weeks of treatment application. These refractory VHRL patients have an extremely poor prognosis, do not seem to be curable by current application of chemotherapy or hematopoietic stem cell transplantation (HSCT) (Figure 1), and are in urgent need of alternative treatment approaches. This particular patient population

will serve as our initial model system for the establishment of a harmonised pipeline for molecular diagnostics within I-BFM in order to allow early identification of VHRL patients. Standardised extended MRD analyses and biobanking have already been implemented in trial AIEOP-BFM ALL 2009 and provide the basis for the identification and further comprehensive molecular characterisation of the target population at an international core level. In a systematic approach, molecular information on VHRL patients already gathered by the different national groups participating in the I-BFM ALL core trial will be collected and assembled in a central database. In addition, molecular information gaps on VHRL patients in the central database will be filled by a coordinated distribution of specimens to defined expert laboratories within the core group.
Task description:
This activity will lead to a virtual virtual European laboratory setting bringing together valuable leukemia sample resources and molecular expertise in a variety of technical approaches. The latter will include genome-wide techniques such as profiling of gene expression, copy number, methylation, and microRNA, supplemented with a broad characterisation – including sequencing approaches – of relevant candidate genes.
These combined resources will guarantee the necessary infrastructure to develop and prospectively validate a molecular diagnostic tool for the early identificaton of VHRL patient already at diagnosis using a dismal MRD response as a phenotype, serve as a basic module for additional I-BFM-associated study groups as well as other groups to join this system, and will be open to other leukemic or solid tumour entities to serve as a model system for providing the necessary infrastructure for a realistic future implementation of molecular-based treatment interventions. All activities will be shared in close communication with WP1.4 and WPs 2 on solid tumour entities. For the development of the necessary IT infrastructure, activities in this area will rely on the support of partners from WP1.2 – mainly on the experience of the ACGT initiative.

Task 9.3 Integration of a molecular diagnostic pipeline with preclinical model systems for molecular targeted treatment and application of algorithms for identification and priorisation of molecular targets UNIMIB, CAU, CHARITE, CCRI, EMC, FORTH, UNIPD (M1 – M48)
Objective:
Genome-wide expression profiling as well as other comprehensive molecular approaches hold the potential to translate diseases, gene function, and drug action into the same language. The initiation of the comprehensive virtual European laboratory setting for molecular diagnostics of leukemias described in Task 9.2 will not only allow early detection of suitable target populations for molecularly guided therapeutic interventions, but also promote the discovery of possible biological relationships between identified genes or other molecular markers and treatment. In a recent proof-of-principle approach, screening of a database of drug-associated gene expression profiles for molecules whose profile overlapped with a gene expression signature of glucocorticoid resistance in ALL cells identified the mTOR inhibitor rapamycin as an inducer of glucocorticoid sensitivity in these cells (Wei et al. 2006). Similarly, preliminary analysis of our already existing gene expression profiles of VHRL patients revealed overexpression of druggable pro-survival genes (e.g., BCL2) as a common feature in this patient group (O'Neill et al. 2004; Cario et al. 2008).
Task description:
This Work Package will do the following:I 1) continue conventional analytical approaches to search for and validate druggable candidates; 2) use our complex data sources for Connectivity Map query-based target identification (Lamb. 2007); and 3) employ preclinical models including cell lines (existing and newly established ones) as well as ALL xenograft models using NOD/SCID mice (Shultz et al. 2005) for the amplification of VHRL patient samples and validation of identified targets. Algorithms for identification and priorisation of molecular targets will be applied and further developed in close cooperation with the working party "bioinformatics" in WP5, and based on a synthesis of information derived through the above mentioned three approaches applied in this task. An I-BFM xenotransplant bank for VHRL diagnostic specimens has already been established for use in this activity. Making use of this infrastructure, it was recently demonstrated in a cooperative I-BFM project that low dose arsenic trioxide sensitises glucocorticoid-resistant ALL cells to dexamethasone via an Akt-dependent pathway (Bornhäuser et al. 2007). Several thousand representative ALL samples at different stages of the disease (e.g., initial diagnosis and at relapse) are available for support of decision making processes. Activities in this Work Package will be in close communication with all other WP, especially WP 8.

Task 9.4 Harmonization and integration of clinical platforms for the introduction of molecularly targeted treatment in leukaemias CHARITE, CAU, UNIPD, UNIMIB, CCRI, EMC, FORTH (M1 – M48)
Objective:
With a long-standing experience in designing, conducting, analysing, and interpreting results of clinical trials in pediatric ALL (e.g. the ESPHALL trial incorporating imatinib into first-line treatment of Ph+ childhood ALL) the partners aim to this experience to finally initiate clinical trials for first-line treatment of VHRL patients that incorporate the timely introduction of targeted therapy based on individual molecular characteristics of leukemic

cells. Such approaches will be evaluated in close context with “classical” risk-adapted treatment strategies and early efficacy evaluation by molecular monitoring of treatment response. However, as molecularly defined target populations for future clinical trials will be likely to derive from different “classically-defined” leukaemic entities, it will be necessary to harmonise clinical trial activities across conventional leukaemic subgroups and phenotypes. Such a harmonisation across myeloid and lymphoid leukaemias as well as first- and second-line treatment populations will facilitate the acquisition of knowledge on relevance of specific targeted approaches for different phenotypes and stages of disease.
Task description:
In order to improve the currrent partly fragmented infrastructure, we will implement a platform, where evaluations are synchronised between the relevant clinical trials. Such an initial synchronization of information will speed up the identification of common patterns across entities and provide the necessary infrastructure for future clinical trials based on molecular characteristics crossing the current classical diagnostic boundaries. An essential role of this task will be taken over by the newly developed INTREALL clinical trial platform which will initially be directed towards the introduction of new phase III elements for the treatment of recurrent ALL, but in the future may serve as a broader infrastructure for the implementation of molecularly guided treatment of a variety of specific leukemias. Besides others, activities in this WP will be tightly coordinated with WPs in the area 1 and 2. Of particular importance will be the close communication with partners in WP 6 and 8.
References
Bornhäuser, B.C., Bonapace, L., Lindholm, D., et al. (2007). Blood, 110, 2084-91.
Cario, G. , Schrauder, A., Möricke, A., et al. (2008). Blood (Abstract), 112, 754.
Lamb, J. (2007). Nat Rev Cancer, 7, 54-60.
O’Neill, J., Manion, M., Schwartz, P., et al. (2004). Biochim Biophys Acta, 1705, 43-51.
Shultz, L.D., Lyons, B.L., Burzenski, L.M., et al. (2005). J Immunol, 174, 6477-89.
Wei, G., Twomey, D., Lamb, J., et al. (2006). Cancer Cell, 10, 331-42.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	CCRI	20.50
5	CAU	37.00
9	UNIMIB	25.00
10	EMC	5.50
17	FORTH	5.00
30	CHARITÉ	26.50
31	AP-HP	12.00
36	UNIPD	11.00
	Total	142.50

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D9.1	Common guidelines for diagnostic approaches to leukaemias.	10	30.20	R	PU	24
D9.2	Infrastructure of an European virtual laboratory for molecular diagnostics of leukaemias.	5	30.20	O	RE	36

WT3:
Work package description

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D9.3	Algorithm application for identification and priorisation of molecular targets for leukaemias	9	25.00	D	RE	36
D9.4	A European infrastructure for the early introduction of molecularly targeted treatment in leukaemias	30	30.20	O	PU	60
		Total	115.60			

Description of deliverables

D9.1) Common guidelines for diagnostic approaches to leukaemias.: Common guidelines for diagnostic approaches to leukaemias. D9.1 [month 24]

D9.2) Infrastructure of an European virtual laboratory for molecular diagnostics of leukaemias.: Infrastructure of an European virtual laboratory for molecular diagnostics of leukaemias. D9.2 [month 36]

D9.3) Algorithm application for identification and priorisation of molecular targets for leukaemias: Algorithm application for identification and priorisation of molecular targets for the treatment of leukaemias. D9.3 [month 36]

D9.4) A European infrastructure for the early introduction of molecularly targeted treatment in leukaemias: A European infrastructure for the early introduction of molecularly targeted treatment in leukaemias to clinical trials. D9.4 [month 60]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS35	Common guidelines for diagnostic approaches to leukaemias	5	24	Publication
MS36	European virtual laboratory for molecular diagnostics of leukaemias	5	36	Method (Validated diagnostic I-BFM tool for identification of VHRL patients)
MS37	Trial platform for early implementation of molecularly targeted treatment of leukemias	5	60	Clinical protocol

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP10	Type of activity [54]	RTD
Work package title	Risk adaptation of therapeutic strategies using prognostic biomarkers in malignant solid tumors		
Start month	1		
End month	60		
Lead beneficiary number [55]	11		

Objectives

Objectives
The aim of this workpackage is to provide the methodical and logistic prerequisites for the implementation of quality controlled biological and imaging defined risk factors to adapt therapies for neuroblastoma and medulloblastoma patients with the final goal to reach cure with minimal sequelae. The Low and Intermediate Risk Neuroblastoma SIOPEN study (LINES), which will be launched in 2010, is intending to stratify patient's treatment according to biological and clinical biomarkers in order to: i) minimise burden of treatment in those low-risk patients who in previous studies have shown an excellent long-term outcome, ii) intensify treatment in those patients with biologically unfavourable but not MYCN amplified neuroblastoma for progression-free survival improvement. This goal will be reached by implementing new image–defined risk factors and, for the first time, by applying the presence or absence of segmental chromosome aberrations in the decision making process.
To de-escalate therapy in a subgroup of medulloblastoma patients, new criteria for low risk, i.e. a biological profile corresponding to the WNT pathway, will be implemented. Furthermore, amplification of MYC and MYCN will be used to identify high risk patients.
Our main goal is to reach maximal safety of the provided biomarkers and in order to do so, the following actions will be carried on:
To strengthen and expand the current European infrastructure in clinical and translational neuroblastoma and medulloblastoma research activities
Neuroblastoma:
Implementation of risk adapted therapies according to international standards and regulations
The set up and management of clinical networks and subnetworks to implement and quality control the application of the International Neuroblastoma Risk Group Surgical System (INRGSS)
Management of the pathology network to quality control the histological diagnoses according to the International Neuroblastoma Pathology Classification (INPC)
Establishment of a classification of low and intermediate risk neuroblastomas based on the genomic profile
Stimulation and performing of scientific projects based on well defined tumour samples and quality controlled genomic data (see WP 5)
Implementation of continuous quality assessment and control of genetic markers by:
Performing all validation steps to allow implementation of genomic techniques newly developed for neuroblastoma for clinical routine
Uploading genomic data into a central data bank (SIOPEN-R-NET) allowing online reviewing before clinical use
Conducting quality control of the pan-/multigenomic techniques
Medulloblastoma:
To validate inclusion criteria with tumor samples circulation in a network of National referring centres using shared and already established SOPS for biological criteria identification
To exchange DICOM images for staging confirmation and for radiotherapy treatment planning

Description of work and role of partners

Task 10.1 Implementation of risk-adapted therapies in low and intermediate risk neuroblastoma. LaFe, CCRI, AIT, CURIE (M1-M48)
Objective:

To implement risk-adapted therapies in low and intermediate risk neuroblastoma (LINES) according to international standards and regulations
Task description:
LINES study comprises nine different therapeutic groups, including a randomized one. It will be followed by different clinical institutions in the framework of SIOPEN. Stratification will be done according to stage, age, tumor genotyping, clinical symptoms and histological information in a complex decision-making process.
The task leader will have to supervise the dynamics and correct flow of it, according to common European Legislation. That means:
Approval and launch of LINES in Europe by implementing standard procedures in clinical trials to assure compliance with Good Clinical Practice, Helsinki's Declaration, Confidentiality and Respect to Children's rights.
Development of the data base, tools and SOPs for continuous information and data flow with individual institutions recruiting patients on day-to-day basis.

Task 10.2 Quality control. LaFe, CCRI, AIT, CURIE (M1-M48)
Objective:
Establishment and monitoring of quality control criteria and tools applicable to all disciplines
Risk-adapted therapies are based on a correct assignment of "risk" by individual/local institutions by applying "objective criteria". For the first time in Europe, LINES incorporates three important 'tools' in a prospective pan-European study: 1) a new Staging System developed by a worldwide Neuroblastoma consortium (according to International Neuroblastoma Risk Group Surgical System, INRGSS), 2) the INPC (International Neuroblastoma Pathology Classification) for therapeutic stratification and 3) pan- or multi-genomic data in the decision making process in the LINES study.
Task description:
- Set up and manage clinical network and subnetworks to implement and quality control the application of the International Neuroblastoma Staging System;
- Manage pathology network to quality control the histological diagnoses according to the International Neuroblastoma Pathology Classification (INPC);
- Set up and manage quality control of pan- or multigenomic data (see 10.3).

Task 10.3 Use and quality control of tumor genotyping as a prognostic biomarker in low and intermediate risk neuroblastoma patients. CURIE, CCRI, AIT (M1 – M48)
Objective:
Classification of low and intermediate risk neuroblastic tumors according to the genomic profile and quality control of pan-/multigenomic data
Task description:
Genomic classification: Genomic profiling will be performed on all low and intermediate risk neuroblastomas. Following the confirmation of a sufficient tumor cell content in the tumor sample obtained at diagnosis (> 60% tumor cells), DNA will be extracted according to standard procedures in a National Reference Laboratory of the SIOPEN Biology group, and the genomic profile will be determined using either MLPA (multiplex ligation-dependent probe amplification), array-CGH or SNP arrays. MLPA is a recent PCR-based technique which allows detection of segmental aberrations and gene amplifications in a robust manner by simultaneous investigation of all currently known recurrent aberrant regions in neuroblastoma in a single assay. The reliable nature of the results, validated by the SIOPEN Biology group in interlaboratory testing and quality control essays, and the relatively low cost of the MLPA kits make this technique attractive for routine NB analysis. Following uploading of the genomic profiling results in the SIOPEN-R-NET database, results will undergo central review, and doubtful results will be confirmed using a second technique. Tumors will be classified according to the genomic type: 1. numerical alterations only; 2. any segmental alteration observed recurrently in neuroblastoma; 3. no informative result; and results will be returned to the clinicians within 4 weeks following diagnosis. The genomic classification will be used to identify patients with a favourable genomic profile who can possibly benefit from treatment reduction, or patients with an unfavourable genomic profile requiring more intensive treatment up front. This is the first time in Europe that this approach will be used to prospectively stratify a subset of patients. Funding of € 100 per case (n=585) will be an incentive to enter all relevant data into the SIOPEN-R-NET database in real-time and to perform online reviewing of genomic data before releasing the data to the clinician.
Quality control of genomic markers: Following levels of quality control shall be applied: implementation of continuous quality assessment and control of genetic markers by:
Performing all validation steps to allow implementation of genomic techniques newly developed for neuroblastoma for clinical routine
Uploading genomic data into a central data bank (siopen-r-net) allowing online reviewing before clinical use
Quality control of the pan-/multigenomic techniques

The SIOPEN Biology Group has a long-standing tradition in cooperating. This group started in 1994 by facilitating the implementation of FISH data on MYCN copy number as decision-making marker in neuroblastoma molecular diagnosis. Along this line, the group undertook major efforts to harmonize and standardize different techniques, to build up a uniform nomenclature, set up guidelines and, importantly, to work out a quality control system to minimize the error rate in molecular diagnosis. This EC funded quality control studies were first done by physical meetings and later on the web based SIOPEN-R-NET database. The work, directed by the CCRI, was published in 2003 and builds the basis of the worldwide-accepted INRG guidelines, which were published in 2009. The past efforts of the SIOPEN Biology Group created the basis for the reliable use of genetic parameters for therapy stratification used in the LNESG I (Localized Neuroblastoma European Study Group) Study and LNESG II. Furthermore, MYCN status has provided the therapeutic decision for the INES (Infant Neuroblastoma European Study) and in a subgroup of patients enrolled in the HR (High Risk) Study.

Task 10.4 Assess molecular diagnostics as prognostic biomarkers in low risk medulloblastoma patients. CURIE, CLB (M1– M48)
Objective:
Application of molecular diagnostics as prognostic biomarkers in low risk medulloblastoma patients throughout Europe
Task description:
- It is the first time that molecular diagnostics (beta-cathenin mutations and MYC-gene status) is going to be applied prospectively in an international or even multicentric study, in order to propose an adaptation of treatment intensity according to biological risk profiling in clinically standard risk group medulloblastoma.
- Asess feasibility and quality control of these studies would be of great importance.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	CCRI	62.00
11	LaFe	26.00
16	CURIE	2.80
18	AIT	11.00
23	CLB	1.40
	Total	103.20

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D10.1	Launch LINES in Europe by getting EudraCT number, contract signatures and SOPs for running the study	11	47.20	R	PU	12
		Total	47.20			

Description of deliverables

D10.1) Launch LINES in Europe by getting EudraCT number, contract signatures and SOPs for running the study: Launch LINES in Europe by getting EudraCT number, contract signatures and SOPs for running the study. D10.1, at M12 and 24 [month 12]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead beneficiary number	Delivery date from Annex I [60]	Comments
MS38	EudraCT number	11	12	Check EudraCT web site
MS39	Initiation of LINES in different European Countries (along first year)	11	12	Date of Ethics Approval and Contract Signature with European sponsor
MS40	Compliance with Low-risk neuroblastoma study defined aims	11	24	Annual Report at SIOPEN General Assembly and final paper
MS41	Compliance with Intermediate-risk neuroblastoma study defined aims	11	24	Annual Report at SIOPEN General Assembly and final paper
MS42	Compliance with PNET-V aims	11	60	Annual Report at the SIOP Brain Tumor Committee and final paper.
MS43	Publication of SOPs for genomic profile studies of tumour in multicenter multinational studies	11	12	Peer-reviewed journal.
MS44	Elaborate and apply guidelines to control image-defined-risk- factors, to review histological materi	11	12	Elaborate and apply guidelines to control image-defined-risk-factors, to review histological material according to the INPC.
MS45	Make interim analyses and reporting of the entered data.	11	60	Make interim analyses and reporting of the entered data.
MS46	Establish SOPs for genomic profiling in LINES	16	12	Establish SOPs for genomic profiling in LINES, to set up and maintain an online review process for genomic data including interlaboratory testing and training.
MS47	Implementation of guidelines for collection, storage of biological material and molecular diagnostic	16	12	Implementation of guidelines for collection, storage of biological material and molecular diagnostics in medulloblastoma. Perform quality control of images for inclusion criteria and treatment plannin

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP11	Type of activity [54]	RTD
Work package title	Clinical epidemiology and prospective registries for patients on standardised protocols		
Start month	1		
End month	60		
Lead beneficiary number [55]	4		

Objectives

1. To develop and evaluate mechanisms for collection of a standardised 'enhanced' dataset through population-based cancer registries or record linkage approaches for all tumour types to facilitate prospective multinational clinical studies (Tasks 11.1 and 11.2).
2. To evaluate the ACGT platform for integrated analysis of clinical data with imaging and biological data to improve risk stratification by incorporating data from the ongoing multi-national clinical trial in renal tumours of childhood (Task 11.3).
3. To lead the international workshops organised in Task 6.4 for renal tumours. These will use "meta-data" analyses between international clinical trial groups for comparison of risk groups, overall burden of therapy and outcomes, including late sequelae, to improve treatment stratification and long term outcomes.
4. Cancer registry-wide study in infants with neuroblastoma (Task 11.4)

Tasks 11.1 and 11.2 will be undertaken in close collaboration with ongoing initiatives within the EUROCOURSE EU FP7 project, founded by the European network of Cancer Registries (ENCR) for which the task leader of 11.1 is scientific coordinator. These tasks will also link closely with the electronic 'Health Passport' proposed in WP 13.2, to ensure integration of efforts towards enhanced long term follow up of all childhood cancer survivors. This integration will be assured as the same people are involved in both WPs and the task leader of 11.2 is a member of the Board of PanCare, the Pan-European group for Childhood and adolescent cancer survivor studies. Ethical aspects of enhanced life-long data collection by registries and data sharing/integration from multiple sources will be considered in WP 18. The data analysis within the ACGT platform on the Wilms tumour trial patients will contribute to the evaluation of IT systems in WP 3 and the identification of new biomarkers for future therapeutic applications through links to WP 5.

The impact will be to establish, ideally at a population level, methods for continuously evaluating the success of first line therapies in terms of event free survival and burden of therapy, either through population-based cancer registration processes or prospective clinical registries. This will improve the quality of care for children with cancer by increasing the expertise of their treatment centres through involvement in clinical research and structured outcome monitoring by centre, region or country. This should maintain the excellent survival rates and ensure they can be achieved across Europe. Data collection systems will be established for very long term follow-up to monitor survival and health status of all childhood cancer survivors and to establish an important resource for clinical epidemiological studies, particularly of young adults, who represent the population in which the burden of late sequelae is present now.

Task 11.4 is complementary task to WP10 and WP11 and will have a major impact on the management of neuroblastoma low risk patients showing in a proof of principle if low risk cancer is well treated according to guidelines when the ultimate outcome can only be controlled through population based registries.The need for more stringent structures than guidelines only (i.e. low risk clinical trials) could be evident if the outcome indeed worsened in the period without an open clinical trial in this rare disease population

Description of work and role of partners

Task 11.1 Evaluation of use of cancer registries for prospective collection of enhanced clinical data IARC, UCL, CLB, IGG (M1 - M48)

Objective: To evaluate the feasibility of and resources required by cancer registries to undertake enhanced prospective data collection to include information to agreed standards on the diagnosis and initial risk group (histology/imaging/biology), tumour response (histology/imaging/biology) and events (treatment, toxicity,

relapse, cause of death). Integration of the expertise from the clinical and population-based research will enhance simultaneously the potential of data collected in both types of resources and if successful, will create a cost-effective solution to the management of selected groups of childhood cancer patients.
Task description:
1. Survey the practices in the European population-based cancer registries
2. Set-up groups of registries for provision of data on different levels of detail
3. Investigate the possibilities of extension of data collection
4. Develop standards for collection and coding for international comparisons
5. Implement collection of the new data items
6. Evaluate the output
The information gathered will allow for comparison between patients groups with defined treatments and also between groups of patients with the same tumour type with non-standard therapy or with no therapy data available, to distinguish outcomes related to specific treatment (which may vary across countries) from those related to other factors (such as non-protocol treatment, late diagnosis or referral, etc.). This will allow generalisation of the results to unselected patient groups.

Task 11.2 Evaluation of record linkage to administrative and clinical data for follow up in the absence of national population cancer registries IGG, CINECA, CLB, UCL, IARC (M1-M48)
Objectives:
To evaluate the feasibility of prospective and retrospective record linkage procedures in order to obtain clinical relevant information in selected countries without nationwide cancer registries. In particular linkage will be performed between clinical trial group data, institutional clinical databases or regional cancer registries where they exist, and other sources of publicly available administrative, clinical and outcome data.
To compare the exhaustiveness and efficacy of different record linkage.
To develop follow-up procedures for data retrieval of information or end-points of interest (burden of treatment received, relapse, vital status, causes of death, cancer status, other medical conditions, and access to healthcare) and test their accessibility in field studies and in existing cohorts. Pilot the study in three countries with different legislations and administrative organisations.
Task description:
Definition of an ideal minimum follow-up database and of outcomes of interest.
Identification in each country of the publicly available databases from which data of interest could be retrieved.
Evaluate coding methods and data base structure of each data provider. Agree with those responsible for each source of data on the collaborative protocol.
Analyze any differences in personal data protection and informed consent regulations
Define data transfer procedures for different sources of data, allowing routines for periodic access to data bases
Test data collection procedures.
Compare different record linkage procedures for accuracy, exhaustiveness and feasibility
Justification and review of applicability across countries and types of data providers

Task 11.3 Implementation of a prospective WT clinical study in the ACGT system UCL, FORTH, CLB (M1 – M48)
Objective: To implement prospective clinical, imaging and biological data collection on patients treated according to the standard arms of the SIOP Wilms tumour 2001 clinical study using the ACGT platform. This will permit integration of complex data from the current clinical database with existing and prospectively acquired molecular biology data and imaging studies (DICOM data) to underpin identification and evaluation of biomarkers (linked to WP6.2). The ultimate aim is to implement a Web-based integrated data collection tool for studies on Wilms tumour patients as a proof of principle for other prospective data collections and clinical trials in patient groups with a very favourable prognosis.
Task description:
Pilot ObTiMA (Ontology based Trial Management Application) as an ACGT tool for data management on patients registered in the current SIOP WT 2001 trial and study.
Establish a DICOM-server and a system for international central imaging review.
Define a database for the logistics of bio-banking of Wilms tumour material throughout Europe to test the decentralised storage of Wilms tumour biomaterial.
Evaluate and enhance the ACGT Master Ontology for Paediatric Oncology
Use the ACGT workflow enactor to develop workflows for the analysis of molecular biological data derived from these Wilms tumours by the seamless integration of clinical, imaging data and web based data in a standardised way to define new risk factors for the stratification of Wilms tumour patients.

Task 11.4 Cancer registry-wide study in infants with neuroblastoma IARC, UCL, LaFe, IGG (month 42-60)
This pilot project will develop the mechanisms and methods of collaborative work between the population-based cancer registries and the clinical databases. The aim will be to link the series of cases arising in a well-defined general population and registered in cancer registries with detailed information on diagnosis, treatments, short term follow-up and any adverse effects, including cause of death, held in the clinical databases.
This work will be conducted in tandem between the cancer registry and clinical personnel in several steps:
1. Discussion between the delegated representatives of the cancer registries and the clinical databases in each participating country to define and agree on principles of access to the data and methods of work.
2. Development of the protocol of data collection in each centre, in collaboration with IARC to ensure that the data collected are defined the same way and that any deviations from the definitions are well documented.
3. Data collection, recording, coding and submission to IARC for analyses.
4. Data validation by IARC in collaboration with the individual centres.
5. Data analyses by IARC.
6. Data interpretation and reporting in collaboration with all involved.
The objective of this pilot study is highly topical. It was observed in the UK that survival of infants (children under 1 year of age) with neuroblastoma worsened over the recent period despite the favourable prognosis of these cases [www.ncin.org.uk/view?rid=2133 Fig 3.115]. In Spain the overall survival was not jeopardize but EFS (event free survival) was worse in children not enrolled in trials (data unpublished from Spanish Cooperative Neuroblastoma Group SEHOP)
We hypothesise that this is due lack of clinical trials for these patients and possibly due to reduced adherence to the treatment guidelines.
Therefore we will collect information on diagnosis, tumour characteristics, treatment administered and short-term outcomes, including detailed information on cause of death from the treating centre. We estimate that information would be collected on about 1600 neuroblastomas in infants in the targeted centres over the 10-year period 2000-2009. As the group of patients is relatively homogeneous, combination of the population-based approach with detailed clinical information will result in important conclusions and possibly a policy. The data may also create new knowledge about the intriguing features of neuroblastoma.
IARC will have the following target centers as subcontractors linked by a Collaborative Research Agreement:
France, national paediatric cancer registry
Germany, national paediatric cancer registry
UK, cancer registry of England

It has to be stressed that a prospective collection of clinical, imaging and postgenomic data needs a legal framework. This is especially true as these data are used by many different and sometimes multi-role end-users. Within this task the legal framework of ACGT will be tested based on contracts with hospitals, informed consents with patients, and IT tools for data security. This aspect will be integrated with the relevant tasks in WPs 3 and 18.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
4	UCL	27.84
15	IGG	30.00
17	FORTH	28.00
19	CINECA	0.50
23	CLB	0.90
24	IARC	35.00
	Total	122.24

WT3:
Work package description

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D11.1	Use of population-based cancer registries for enhanced clinical follow up.	24	31.50	R	PU	60
D11.2	Methods for use of record linkage for enhanced clinical follow up	15	31.50	R	PU	60
D11.3	Prospective data collection and evaluation of biological and clinical risk factors in Standard Risk	4	43.24	R	RE	60
D11.4	Collection of detailed data on infants with neuroblastoma through population-based cancer registries, analysis and report by IARC	24	3.50	R	RE	60
		Total	109.74			

Description of deliverables

D11.1) Use of population-based cancer registries for enhanced clinical follow up.: Use of population-based cancer registries for enhanced clinical follow up. D 2.4.1 [month 60]

D11.2) Methods for use of record linkage for enhanced clinical follow up: Methods for use of record linkage for enhanced clinical follow up. Report & Guidelines for application to other countries. D 2.4.2 [month 60]

D11.3) Prospective data collection and evaluation of biological and clinical risk factors in Standard Risk: Prospective data collection and evaluation of biological and clinical risk factors in Standard Risk Wilms Tumour within as a test of principle for Integrated IT platforms. D 2.4.3 [month 60]

D11.4) Collection of detailed data on infants with neuroblastoma through population-based cancer registries, analysis and report by IARC: Data will be collected in collaboration between population-based cancer registries and clinical databases on infants diagnosed with neuroblastoma between 1999 and 2011 in France, Germany and England and in the specified regional population of Italy and Spain (a total of about 3000 cases) according to a predefined agreed dataset. The collected data will be analysed and interpreted with focus on differences in the outcome (vital status, relapse, cause of death) in relation to the explanatory variables (diagnosis, treatment) collected. [month 60]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS48	Minimal standard datasets by tumour type The continued development of data sources over the NoE life	24	24	Publication of standard datasets
MS49	Collaboration agreements with data providers taking into account confidentiality and ethics aspects	24	24	Copy of agreements

WT3:
Work package description

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS50	Enhancement of the ACGT Master Ontology for Paediatric Oncology and seamless integration and analysi	4	24	Interim data report and demonstration of the ontology

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP12	Type of activity [54]	RTD
Work package title	Clinical research in very rare tumours		
Start month	1		
End month	60		
Lead beneficiary number [55]	12		

Objectives

The objective of this WP is to improve quality of care for children with rare tumours, namely hepatoblastoma as a template for international clinical research for rare childhood cancers. Structuring of research in rare tumours remains a major challenge in Europe and worldwide. To achieve progress in very rare malignancies, novel approaches to clinical trial design are required, alongside the collaborative organisation of international trials with global participation of study groups across Europe, as well as non-European partners.
The organisation of the treatment of hepatoblastoma within Europe, as well as many other non-European countries is under the framework of the SIOPEL (International Childhood Liver Tumours Strategy Group) and exemplify the pivotal role appropriate infrastructure can play in improving outcomes. The principal aim of 'SIOPEL' is the harmonisation of international research in hepatoblastoma through cooperation across Europe and with the American Children's Oncology Group (COG) and Japanese Paediatric Liver Tumour group (JPLT). Truly global clinical research leads to several difficulties, is challenging and is resource intensive. Success is dependent on appropriate administrative/secretarial support, development of common databases, including web-based remote patient data-entry systems, development of common tumour classification and stratification systems and real-time centralised imaging and centralised pathology slide review, as well as rapid clinical consultation service.

The first objectives will focus on expanding the SIOPEL model to a more global and formalised infrastructure with the aim of establishing:
1) A validated standardised international risk stratification of childhood liver tumours
2) A unified international web platform for data entry and central pathology and imaging review, as well as consultation service including clinical assistance from centers of excellence/internationally recognized experts, when necessary.
3) A new international hepatoblastoma randomised, controlled trial answering the questions that aim towards personalised therapy based on risk stratification, improving survival and decreasing therapy-related side-effects in survivors

The subsequent objectives are the further development of the SIOPEL model as a template for clinical research in other rare tumours of childhood. Results of this WP (particularly new prognostic criteria and patients' stratification) will be presented during international pediatric oncology congresses (SIOP- Auckland, New Zealand 2011 and London 2012, ECCO) and annual SIOPEL group meetings.
The project will generate new knowledge in the field of rare malignant liver tumours, predominantly involving very young children. Ultimately it will lead to harmonisation of international clinical research efforts in the field of very rare tumours tumours by proposing of solutions which may be of use for other study groups and other clinical trials.

Description of work and role of partners

Task 12.1 Standardising international risk stratification of childhood liver tumours MUG, UOB, CINECA, IGR,UNIPD, AMC (M1-M18)
Objective: In rare cancers, current trend to develop more personalised medical approach becomes very difficult due to the need of an excessive fragmentation of patient populations studied, resulting in very small patient numbers in spite of participation of several countries. The only answer to this challenge is to organise global networks of researchers sharing common data and cooperating in pursuing new therapeutic concepts. This

requires a uniform scientific language to be developed which will lead to the standardisation of risk criteria and development of the new patient stratification.
Task description: An overall strategy will be defined on the basis of currently existing knowledge (published and unpublished data collected within environment of international studies), as well as analysis of the newly arranged global patient database.
This will be achieved through the following steps:- Foundation and maintaining of the SIOPEL group secretarial office (dealing with administrative business and coordination of research plans).- Definition of the minimal patient data set required.- Creation of a retrospective global patient database (with incorporation of German GPOH, COG and JPLTclinical data) – 'Liver Tumours Warehouse'.- Statistical analyses of the retrospective hepatoblastoma cohort data (around 1000 cases) with regard to dentification of prognostic factors (meta-data analysis).- Development of the new international pathological classification of hepatoblastoma.- Development of of the pathology images databank in hepatoblastoma based upon scanned and digitalized images from the patients included in the CHIC database (International Pediatric Liver Tumors Warehouse - IPLTW).- Development and validation of the new diagnostic patient stratification based on the retrospective database analyses, including correlation with pathology and biological findings.- Dissemination of results through publications in international medical journals and presentations during pediatric oncology congresses (SIOP – Auckland 2011 and London 2012, Hong Kong 2013 and Toronto 2014, European and world meetings of pediatric surgeons in Leipzig and Berlin 2013, Dublin 2014, ECCO congresses), as well SIOPEL group annual symposiums.
This will be established through founding of the worldwide retrospective patient database, including data from all major study groups. This will be followed by organisation of workshops between European, American and Japanese researchers (in the following fields: radiology, pathology and focusing on new patient stratification) with a participation of the key opinion leaders and experts in the fields of pathology, biology, radiology and clinical research, which will be invited as external consultants. This task requires also travel costs coverage by the WP leading institution.
Task 12.4 International pathology cases web-based digitalized repository and virtual biobank as additional IPLTW (CHIC database) features
This new task, added to the project, requires scanning and digitalization of pathology images of patients included in the CHIC database coming from the SIOPEL, GPOH, JPLT and COG. This in turn requires an extra manpower effort, not originally planned in the initial project, although American and Japanese groups will take care of their cases digitalization free of charge. Apart from this a centralized pathology review module with virtual microscope for viewing and zooming in high resolution pathology slides needs to be developed in association with the SIOPEL website (as a new addition to the Task 12.2). Some preliminary models of this pathology tool have been already developed. The tool prototype is already available on the test site with a module that allows web visualization of svs format files for high resolution slides. However it requires to undergo extensive usability tests with the pathology community in order to confirm and improve its usefulness.
This approach would allow to re-categorize the CHIC patients according to the new International Pathology Liver Tumors Consensus Classification by the specially appointed central review pathology committee. This in turn will make possible to identify correlation between pathologic tumor subtype and prognosis., as well as to incorporated the pathology aspect into the CHIC Risk Grouping. It will require a new run of unifactorial and multifactorial CHIC statistical analyses with a subsequent two workshops in order to create a new Clinico-Pathological CHIC Risk Grouping.
The future sustainable bonus feature of this development would be an on-line pathology consultation tool.

As a new development to the Task 12.2 the patients' file in the IPLTW will be subsequently annotated to selected, most representative pathology images. Additionally, patients' file in the IPLTW would be also linked with a virtual biobank information allowing to identify for every patient whether, where and what kind of tumor and patients tissue is stored (tumor sample, blood sample, normal liver sample). This requires a significant upgrade of the current CHIC database by CINECA. Such approach would largely facilitate linking the clinical data with pathology and allow for easy identification of patients cohorts for the future biology studies allowing for more efficient translational research in the field of very rare tumor setting.
Results will be summarised in the final report and used for the subsequent task: development of E-RDE platform.
Task 12.2 Improving E-RDE platforms and cross-talk / data sharing in order to make feasible global data sets for clinical research in very rare tumours. CINECA, MUG, IGR, UOB, UNIPD, AMC (M1-M24) Objective: Research in the field of paediatric liver malignancies, due to their relative rarity (1-1,5% of all neoplasms in children), requires multi-center cooperation at the international or even multi-continental level. Further improvement of patient outcome in paediatric liver cancer depends on the implementation of innovative patient-tailored strategies assessed within the framework of consecutive clinical trials. The only answer to this challenge is to organise

global networks of researchers sharing common data, and cooperating in pursuing new therapeutic concepts. However such a global network requires a special E-RDE platform in order to communicate and work efficiently. The web-based platform developed will incorporate e-learning modules and a patient/parent education module. It might serve as an example of the future European Virtual University dispersing the knowledge on rare tumours and providing rapid consultation services for less experienced centres. This will also include development of international referral schemes for patients which should contribute to better quality of care. An additional advantage will be integration of WEB based trial management efforts to foster translational research in very rare tumours on an international bases.
Task description: A strategy of E-RDE platform organisation will be developed on the basis of:- Centralised radiology review module.- Centralised pathology review module.- E-learning module for physicians.- Parents/patients information module.- Rapid clinical consultation service with patients' referral scheme.
As a new development the patients' file in the IPLTW will be subsequently annotated to selected, most representative pathology images. Additionally, patients' file in the IPLTW would be also linked with a virtual biobank information allowing to identify for every patient whether, where and what kind of tumor and patients tissue is stored (tumor sample, blood sample, normal liver sample). Such approach will largely facilitate linking the clinical data with pathology and allow for easy identification of patients cohorts for the future biology studies allowing for more efficient translational research in the field of very rare tumor setting. Proper trilateral legal contracts between the biology researcher and local/national tissue bank, as well as the trusted facilitator, ensuring data protection and patient's privacy will be developed in cooperation with the p-medicine project.

- Dissemination of the platform presentations during pediatric oncology congresses (SIOP 2011 London, Hong Kong 2013 and Toronto 2014, European and world meetings of pediatric surgeons in Leipzig and Berlin 2013, ECCO congresses), as well SIOPEL group annual symposiums. The E-RDE platform will be established through utilisation of knowledge obtained during phase I of the project(task 12.1). This task will be interrelated to the WP 3 (Establishment of the virtual institute information portal) and WP 15 (Education and training).
Task 12.3 Design and implementation of the new trial UOB, MUG, IGR, UNIPD, AMC (M24 – M48)
Objective:
Expected aims of the new approach tested within the frames of a new hepatoblastoma trial are to decrease therapy side-effects (mainly late cardiac toxicity, nephrotoxicity and hearing loss) in survivors by more appropriate treatment choice (personalised therapy), as well as to improve outcome of high-risk patients via their identification at diagnosis and proper, timely intensification of therapy. More importantly, this venture will serve as a model of global, academia-driven, cooperation in the field of rare tumours, which is of paramount significance to paediatric cancer. This new approach should contribute to overcoming problems resulting from the European Clinical Trials Directive, which is important for other paediatric study groups. Proposed solutions will be of use for other rare tumour study groups and clinical trials.
Task description:New therapeutic protocols will focus on optimisation of the health care for patients with very rare liver tumours. Avoidance of trial sng fragmentation and duplication through multinational clinical studies should ensure appropriate number of patients to produce statistically reliable results so that trials are correctly powered. Healthcare optimisation will be achieved not only through development of clear and more individualised treatment guidelines based on introduction of innovative trials designs and on the new patient stratification (task 12.1), but also on the implementation of a patient referral scheme, especially for difficult and ultra-rare cases, which require additional expertise. This will be achieved through:- Development of new trial designs and treatment protocols for the newly established stratification groups in hepatoblastoma: low, standard, high and very high-risk hepatoblastoma).- Preparation of trial committee composition, incl. principal investigators at international and national level.- Development of referral and expertise centres network on the national and pan-European level.- Preparing funding model for international funding applications to support the trial.- Trial preparatory work (ethics and EUDRACT registration).- Establishment of the framework to conduct the proposed international trials within the EU Directive regulatory requirements, including trial monitoring and pharmacovigilance.- Trial promotion through international congresses (SIOP – 2014, Toronto - 2014) and SIOPEL annual meetings. Our approach should lead to the development of harmonised and coordinated therapeutic protocols in Europe and overseas, allowing for rapid testing of new approaches (i.e. via up-front therapeutic window), which in turn, will lead to achievement of the ultimate goal of more personalised medicine in the field of very rare tumours. This task will be interrelated to the WP 4 (Clinical Trial Facilitation), WP 6 (Common and innovative methodology for clinical trial design), WP 8 (Early evaluation and prioritisation of new anticancer drugs) and its task 8.1, as well as to the WP 11 (Clinical epidemiology and prospective registries for patients on standardised protocols).

WT3:
Work package description

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
6	IGR	6.00
12	MUG	11.70
13	UOB	17.00
19	CINECA	10.00
21	AMC	1.20
36	UNIPD	3.00
	Total	48.90

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D12.1	Creation of Liver Tumours Warehouse database and development of the new global diagnostic	12	13.47	R	PU	24
D12.2	Design and implementation of new Remote Data Entry and E-learning Platform.	19	13.47	R	PU	24
D12.3	New hepatoblastoma study protocol based on the newly introduced patient stratification	6	13.46	R	PU	60
		Total	40.40			

Description of deliverables

D12.1) Creation of Liver Tumours Warehouse database and development of the new global diagnostic: Creation of Liver Tumours Warehouse database and development of the new global diagnostic patient stratification for hepatoblastoma. D 2.5.1 [month 24]

D12.2) Design and implementation of new Remote Data Entry and E-learning Platform.: Design and implementation of new Remote Data Entry and E-learning Platform. D 2.5.2 [month 24]

D12.3) New hepatoblastoma study protocol based on the newly introduced patient stratification: New hepatoblastoma study protocol based on the newly introduced patient stratification followed by agreement on European trial sponsorship and trial management framework. D 2.5.3 [month 60]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS51	Identification and selection of prognostic factors in hepatoblastoma	12	12	Statistical analysis followed by publication.

WT3:
Work package description

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS53	Development of the new patient stratification in hepatoblastoma.	12	24	Report

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP13	Type of activity [54]	RTD
Work package title	Quality of survivorship		
Start month	1		
End month	60		
Lead beneficiary number [55]	15		

Objectives

Evaluate quality of survivorship (QoS) in a selected group of subjects treated for particular high-risk childhood cancers and / or at critical ages during psychological development. In particular, this WP will focus on long-term survivors of medulloblastoma treated with standardised protocols Identify treatment-related risk factors for poor outcome. Develop on-line cost-effective tools for assessment of QoS, suitable for use in all forms of childhood cancer.. The on-line method of QoS assessment will be applied, and a databank of salivary DNA will be obtained.
Develop a 'survivorship passport', in which cancer history and therapy information can be provided for the individual patient at the moment of the elective end of therapies. Advice and guidance on long-term follow-up of possible late effects will be tailored to each patient's medical exposures. Pilot the passport on paper and on electronic files in selected ENCCA institutions and in the cohort of medulloblastoma survivors.

Description of work and role of partners

Task 13.1 Quality of survivorship in medulloblastoma patients. SOUTHAMPTON, CURIE, IGG (M1 – M48)
Objective:
Evaluate quality of survivorship in medulloblastoma survivors
Task description:
Develop on-line 'Health-tracker' module for assessing QoS in survivors of childhood brain tumours treated in multicentre international studies that also will be adaptable for use in survivors of other childhood cancers. "Health tracker" already contains on-line assessments developed for use in children with neurological impairments of other causes. This module will add specific, standardised questionnaires that have already shown to be appropriate for use in paper form.
Complete the task of translation of this module of those sections not already translated. (N.B. Both the standardised questionnaires and also other modules of Health-tracker have already been translated into all relevant European languages.)
Identify eligible survivors of childhood medulloblastoma enrolled in European treatment trials through already available PNET4, PNET5 and PNET6 trial registries.
Use the on-line module to measure health status, including neuro-cognitive and executive function, growth and endocrine function, behavioral difficulties, and quality of life, including reports by parents and by survivors.
Use additional information already collected as part of the trials, regarding pre- and post-operative developmental and neurological status, treatments received, and educational and social information to help interpret the outcome data
Collect saliva samples in PNET 4, 5 and 6 participants, as a source of DNA to be analysed after the end of this project for future molecular genetic analysis of host factors relevant to neurological recovery from medulloblastoma and its treatment

Task 13.2 Survivorship passport IGG, ÖK, CLB, CINECA (M1– M48)
Objective:
Pilot in selected institutions a template for paper and electronic storage of a summary of medical history and treatment exposure of each subject who electively ends cancer treatment. Promote a "survivorship passport" for long-term follow-up.
Task description

- Survey available systems which at therapy completion provide summaries of previous medical history (treatment abstracts).
- Survey (questionnaire) parents and survivors for advice about methods and procedures for long-term follow-up. Analyse possible intercultural differences
- Propose a treatment summary template for electronic database storage and for provision as a paper document to each individual who electively ends cancer treatment.
- Translate into different European languages.
- Pilot the development of a “survivorship passport” with information on previous medical history and guidance for follow-up according to guidelines.
- Evaluate and test possible electronic versions of the passport. These may become either an additional module to the Health-tracker QoS developed in task 13.1 or an independent system.
- Translate into different European languages.
- Pilot a follow-up system through WP 3, and in selected ENCCA institutions.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
15	IGG	31.00
16	CURIE	2.80
19	CINECA	8.00
23	CLB	5.90
35	ÖK	12.00
38	SOUTHAMPTON	36.00
	Total	95.70

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D13.1	On-line tool for assessing childhood cancer outcome	38	17.80	O	PU	24
D13.2	PNET5 and PNET6 trials.	38	17.80	O	RE	60
D13.3	Salivary DNA database for same survivors.	38	17.80	O	RE	60
D13.4	Database for complete survivor medical history	16	17.80	O	RE	12
D13.5	Survivorship passport template with guidance for long-term follow-up	16	17.70	O	RE	60
		Total	88.90			

Description of deliverables

D13.1) On-line tool for assessing childhood cancer outcome: On-line tool for assessing childhood cancer outcome (M18) and its application to provide outcome data, in survivors of PNET4. [month 24]

D13.2) PNET5 and PNET6 trials.: PNET5 and PNET6 trials. [month 60]

D13.3) Salivary DNA database for same survivors.: Salivary DNA database for same survivors. [month 60]

D13.4) Database for complete survivor medical history: Database for complete survivor medical history, which allows automatic download of treatment history summary that will be tested in selected ENCCA institutions for medulloblastoma patients in at M12 and 24 [month 12]

D13.5) Survivorship passport template with guidance for long-term follow-up: Survivorship passport template with guidance for long-term follow-up based on treatment history and available guidelines (multilingual). [month 60]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead beneficiary number	Delivery date from Annex I [60]	Comments
MS54	Completion of Health Tracker outcome module and translation into all relevant languages	38	12	View on line
MS55	Completion of PNET4 salivary DNA collection	38	24	View database of DNA samples
MS56	Submission of PNET4 outcome study for publication	16	36	View manuscript
MS57	electronic data base for treatment summary reports	16	24	View data base
MS58	Development of a prototype of passport for survivorship	16	60	View prototype and report

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP14	Type of activity [54]	OTHER
Work package title	Dissemination activities		
Start month	1		
End month	60		
Lead beneficiary number [55]	2		

Objectives

Objectives
The main objectives of this work package are to continuously monitor and provide the necessary support for the ENCCA partners in order to facilitate knowledge-exchange and activity-integration within the consortium.

Moreover, to ensure that information is exchanged across the paediatric oncology spectrum, the activities, outcomes and conclusions will be disseminated to the community at large. This will provide the right platform for a combined dissemination venture that brings together the results and outcomes for all the key players.
These objectives will be achieved through the following tasks:
Dissemination of relevant information to the scientific and clinical communities involved in (Paediatric) Oncology to raise awareness about the need to create a virtual European research institute in paediatric and adolescent oncology;
Investigate the most efficient and innovative communication tools that can best promote the ENCCA messages to all relevant bodies;
Inform and collaborate with parent/patient groups via numerous innovative communication channels to raise awareness about the positive outcome of creating an EU paediatric oncology network on clinical trials. Particular attention will be paid to reaching out to patient and family support groups in central and eastern European countries;
Create awareness at the political level for the need and maintenance of a virtual European research institute in paediatric and adolescent oncology;
Communicate relevant new breakthroughs by the ENCCA network to a wide audience including international organisations (e.g. SIOP (International Society of Paediatric Oncology), ICCCPO);
Facilitate dialogue between all clinical groups associated with paediatric oncology, who are collaborating both within ENCCA and clinical and research groups outside this Network of Excellence;
Investigate and contact potential industrial partners interested in being integrated as a member of the“Club of Industrial Interest” of ENCCA.

Description of work and role of partners

Task 14.1 Dissemination to Academic and Scientific Community SIOPE, ECCO, All Partners (M1– M48)
Objective
Disseminate all relevant information from the ENCCA partners via a variety of communication tools to the European and International Scientific Communities. This will assist in improving information-exchange, avoid overlap and increase overall cooperation and build linkages between all relevant bodies.
Task description
Dissemination via scientific workshops, seminars, forums and publications, namely:
SIOP Congress, 2010 (Boston, USA)
ECCO 16 – ESMO 36 Multidisciplinary Congress, 2011 (Stockholm, Sweden)
SIOP Congress, 2011 (Auckland, New Zealand)
ECCO 17 – ESMO 38 Multidisciplinary Congress, 2013 (Amsterdam, The Netherlands)
SIOP Congress, 2012 (London, UK)
A dissemination project is planned specifically for the educational courses and training seminars that are outlined in WP 15.

Content will consist of experiences, methodologies and results (Science-specific and Non-Science specific) gathered and developed within ENCCA, and will be presented to the relevant stakeholders in order to increase knowledge as well as encourage debate and discuss strategies to enhance future clinical trial studies.

Task 14.2 Dissemination to Industry SIOPE, CCRI, CAU, LaFe, UCL, UoL, KI, APHP, ECCO (M1– M48)
Objective
The objective is to disseminate relevant information from the ENCCA partners to the pharmaceutical industry via numerous different communication channels.
Task description
The dissemination of information to the pharmaceutical industry will occur via workshops, forums and publications in order to exchange knowledge, expertise, challenges and obstacles experienced by the different ENCCA partners. Moreover, this will provide the optimum opportunity for industry to engage and build relations with the structured paediatric oncology community created within ENCCA. Two such communication outlets are:
ECCO 16 – ESMO 36 Multidisciplinary Congress, 2011 (Stockholm, Sweden)
ECCO 17 – ESMO 38 Multidisciplinary Congress, 2013 (Amsterdam, The Netherlands)

Task 14.3 Public Awareness SIOPE, ÖK, CURIE, CAU, LaFe, UCL, UoL, KI, APHP, ECCO (M1– M48)
Objective
This task will aim to increase public awareness of the challenges encountered by young cancer patients and their families. It will also communicate the objectives and the progress made by ENCCA to address these challenges.
Task description
Collect and disseminate data on the challenges confronted by paediatric and adolescent patients and potentially translate this information into multiple languages, adapted to the needs of different countries;
Promote networking opportunities for ENCCA to engage with the wider health community and public at large;
Establish stronger relations with policy-makers and demonstrate ENCCA's expertise, particularly future web-based resources;
Enhance communication with interested associations such as national and pan-European cancer societies, particularly building links with societies from Central and Eastern Europe. Related to this, the task leader and partners will engage with all relevant stakeholders of the SIOPE project, the European Standards of Care for Children with Cancer, a project created to address the disparity between European countries on the care and treatment standards of our young cancer patients.
Ensure that ENCCA's online communication tools explain in detail the mission and work of ENCCA and provide easy, accessible information to the public.
Tools include:
Web Newsletter, interactive website and other communication tools will be explored and developed.

Task 14.4 Dissemination to parent/patient groups SIOPE, ÖK, CURIE, ECCO (M1– M48)
Objective
Inform and connect patients and parents to ENCCA, and bridge the gap between family groups and professionals by identifying and quantifying the patients' and parents' concerns and expectations in terms of the availability of new therapies. Assist in providing information on the potential impact of the European virtual platform for paediatric oncology clinical trials.
Task description
Create long-standing relationships with patient/parent organisations in Europe and globally, in order to collect information about their concerns and expectations in terms of new therapies;
Disseminate information and report on developments taking place within ENCCA that are particularly relevant to patient/parent groups via different communication channels;
Promote multidisciplinary interaction between ENCCA partners, patients and their families through the dissemination tools produced;
Set up and organise dissemination actions in collaboration with the "Club of Industrial Interest", non-governmental organisations (NGOs) and patient/parent organisations in order to answer concerns and expectations from the stake holding public.
Outlets for dissemination include:
ICCCPO Latin American Regional Parent Meeting, 2010 (Guadalajara, Mexico)
'February Campaign' to coincide with International Childhood Cancer Day (15th February) and European Rare Disease Day (28th or 29th February, depending on the year). Links will be made with the relevant paediatric cancer and rare disease patient groups.

WT3:
Work package description

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	CCRI	13.00
2	SIOPE	36.00
4	UCL	6.50
5	CAU	7.00
11	LaFe	2.00
16	CURIE	1.75
27	KI	2.00
34	ECCO	32.00
35	ÖK	13.60
39	UoL	0.12
	Total	113.97

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D14.1	Action Plan in order to establish efficient communication tools	2	16.70	O	PU	12
D14.2	The creation of a website for the ENCCA project	2	16.70	O	PU	12
D14.3	The creation and maintenance of a contact list/database of relevant bodies	2	16.70	O	PU	12
		Total	50.10			

Description of deliverables

D14.1) Action Plan in order to establish efficient communication tools: Action Plan in order to establish efficient communication tools for the different project partners and the other communities involved in the Network of Excellence. M12,24,36 and 48. [month 12]

D14.2) The creation of a website for the ENCCA project: The creation of a website for the ENCCA project (+ translations of key results in different languages for parents and nurses). [month 12]

D14.3) The creation and maintenance of a contact list/database of relevant bodies: The creation and maintenance of a contact list/database of relevant bodies for dissemination and interaction. [month 12]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead beneficiary number	Delivery date from Annex I [60]	Comments
MS59	Creation and rolling out of the ‘February Campaign’	2	12	Visibility raised through PR reports and features
MS60	Organisation of the workshops/meetings within the congresses	2	12	Will be verified by the number of attendees and expected PR features and reports..
MS61	Development of the website for dissemination activities	2	12	Innovative online communication tool and monitoring of website hits/downloads
MS62	The organisation of workshops/meetings within various congresses.	2	12	The organisation of workshops/meetings within various congresses.
MS63	Organising the "February Campain" presenting the challenges faced by childhood cancer patients	2	12	Organising the "February Campain" presenting the challenges faced by childhood cancer patients

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP15	Type of activity [54]	OTHER
Work package title	Education and training		
Start month	1		
End month	60		
Lead beneficiary number [55]	7		

Objectives

Paediatric oncology is a well-defined paediatric sub-specialty in Europe, identified and characterised almost one decade ago by SIOPE and Esphi (European Society for Paediatric Haematology and Immunology) educational and training committee (ETC). ETC defined a syllabus as well as duration and modules of the training process that qualifies paediatric oncologists. The European Board of Paediatrics (EBP) approved the training programme in 2000, by CESP (Confederation of European Specialists in Paediatrics) in May 2001 and by the European Union of Medial Specialists on October 2001. However, except for a few countries, the recognition of paediatric oncology and haematology as well as the implementation of related educational and training activity remains limited throughout Europe. The lower survival rate (from 10 to 20%) of children with cancer observed in some Europeans countries may be at least in part related to lack of adequate training and educational programs. The rapidly changing needs related to advancement of basic and clinical knowledge also requires improvement and dissemination of education and training in paediatric oncology to adapt to the demanding new scenarios.
One of our main goal will be to identify in the different European Nations the current status of the training programme to be followed by Pediatric Oncologists , the recognition of Pediatric Oncology as a sub specialty of pediatric training , possible lack of training and possible way to evaute the programs quality and to propose to implement and harmonize training activity in European nations
Definition of European Nation can be based on political , geographical , and even historical reasons Our goal will be to evaluate and to support Pediatric Oncology in all nations involved in multinational treatment protocol
A standardised, comprehensive and accessible educational and training programme is essential for optimal clinical results of paediatric oncology in Europe.
The trainig programme should be enforced and updated by training course devoted to offer to children with cancer the best available tretment .
Existing courses supporting education and training in paediatric oncology and haematology, although excellent in the areas they cover, show the following deficiencies that must be overcome:
1. Lack of co-ordination of the course leaders to ensure comprehensive provision of relevant training which is important to ensure a properly trained work-force for the future in order to deliver investigator-driven clinical trials.
2. Lack of specific provision to train the specialists together that are needed to treat adolescents in order to promote multi-disciplinary (different medical disciplines) and multi-professional (ie including nurses, psychologists and other professions) care, especially in this age group and the tumour types they commonly suffer from.
3. Lack of trained research nurses for implementing clinical trials in children and adolescents.
4. Barriers to attendance, because of difficulties in mobility, language or lack of time.
5. Insufficient involvement of patient/parent groups in the clinical research process.

Solutions for these problems could be:
- To bring together current leaders of clinical trials courses and assess the gaps in coverage. This would lead to a plan for comprehensive courses on implementation and management of clinical trials across Europe.
- To standardise courses on specific treatment protocols to facilitate the use of new agents that improve the skills of clinicians, research nurses, psychologists and all professions involved in translational clinical trials.
- To organise multi-disciplinary and versatile courses covering aetiology, epidemiology, pathology and treatment of solid tumours and leukemias.
- Implement e-learning activities including on-site training course

- Plan workshops and specific sessions on the role of patients and parents in the clinical research process, how to propose phase I-II trials to them through discussion and informed consent/ assent.
- Exchange faculties for courses and develop joint modules (solid tumours/ leukaemia for translational research; youngsters and adolescents needs for optimal follow up).

Based on the above consideration, the education and training delivered within the proposed Network of Excellence will focus on the following fields:
- Implementation of standards for training in Paediatric Oncology in Europe;
- Training courses for clinicians and research nurses on new protocols and standards for clinical trials;
- Collection, interpretation and use of population-based data on cancer in children and adolescent;
- Improving information for parents/patients.

There will be close liaison with Professor Evelyne Jacqz-Aigrain, WP leader for education and training in the planned EU-US Transatlantic Paediatric network of excellence (GRIPP) to develop shared paediatric pharmacology modules and courses for doctors and research nurses in the field of oncology drugs.
In addition there will contacts with all existing training activity in pediatric oncology community aiming at avoiding duplicates and to sinergize with all EC funded activity.

Description of work and role of partners

Task 15.1 Implementation of standards for subspecialist training in paediatric oncology across Europe UCSC, CAU, UCL, UOB (M1-M48)
Objective:
Implementation of a Paediatric Oncology Training Programme based on the syllabus of pediatric Hem /Onc training, approved by EUMS in 2004, is to be adopted with the final goal of reaching national recognition of paediatric oncology /haematology as a subspecialty in all EU nations.
Task description:
Within European member states and candidate coutries we will:
- Identify Universities and regulatory Bodies, then prepare and submit a synthetic questionnaire concerning the existence of paediatric oncology/ haematology as an established paediatric subspecialty to these identified entities. The questionnaire will help to identify type and length of training and regulatory authorities surveying the training programme.
- Evaluate training quality in paediatric oncology in the different EU nations through a self-addressed questionnaire with a follow-up site visit. The final goal is creating a list of centres qualified for up-to-date treatment of paediatric cancer. The questionnaire should differentiate among treatment for leukemias, solid tumours and brain tumours.
- Define training programme (length, topics, Institutions) in participating nations.
- Organise in selected cases local meetings in order to label the training centres as SIOPE centres for solid tumours and brain tumours or as IBFM centers qualified for the treatment of leukemias. Visiting committee will include up of 3 experts chosen among the project partners.
- Implement extensive use of e web based test to evaluate knowledge and clinical capability of medical staff training.
- Exchange of personnel in different stages at leading institutions.
- “E-mobility centres” for easier mobility of researchers and clinicians in Europe.
- Yearly updated booklet for young haemato/oncologists.

Task 15.2 Improvement of existing training Courses for clinicians and research nurses on new protocols and standards for clinical trials UCSC, CAU, UCL, UOB, APHP, ECCO (M12 – M48)
Objective:
- Improve knowledge and skills of medical personnel involved in clinical trials including early translational trials.
- Overview and integration of current courses content and provision to ensure adequate capacity and comprehensive portfolio including emphasis on multi-disciplinary training.
- Mandatory written report to be completed by faculty members with evaluation and possible future goals.

Task description:
- Favour and enhance development of new Programme /omponents of existing couses to address any gaps identified in the above overview.
- Enhancement of course contents to cover all the elements defined in the European Science Foundation syllabus for training for investigator-driven clinical trials.

- Training of paediatric research nurses to implement the IDCT - this could be achieved through a link with the SIOP nurses group or EONS to adapt these courses to paediatric cancer.
- Exchange faculties for courses and develop joint modules (solid tumours/ leukaemia for translational research; youngsters and adolescents needs for optimal follow up).
- Courses to address the specific needs of adolescent oncology (joint medical and paediatric oncology training and multi-professional training courses)
The existing training activity such as SIOPE/ESO Masterclass , ITCC Training Days , Flims annual workshop and ECCO paediatric track yearly advanced courses for leukemia from I-BFM group “Acute leukemias in childhood: update on biology, treatment and management of complications” as well as E-Learning activities will be improved with exchange of faculty experts members of ENCCA Institutions and will be oriented toward the aims of ENCCA NoE.

Task 15.3 Improving information for parents/patients ÖK, UCL, UCSC, UOB (M1 - M48)
Objective:
Parents should have easy access to updated and reliable information on their child's disease and its optimal treatment. This will include the reference centres from different nations and knowledge of on-going treatment protocols both at diagnosis and at relapse. The aim is to improve patient/parent awareness of on-going new agent trials and allow the possibility of enquiry about new treatment options advice from qualified experts.
Task description:
- A specific space devoted to parent enquiries will be set up on the SIOPE website.
- Links to disease-specific websites or associations will be also provided together with detailed information on parents groups existing in the countries of origin. This web session will be multilingual.
- Biannual meetings of parent associations of the different European nations will be organised. Presentation of all information needed by parents/patients from a qualified faculty with simultaneous translation will be provided.

Task 15.4 Collection, interpretation and use of population-based data on cancer in children and adolescents IARC (M 1-48)
Objective:
To develop and administer training module addressing the specific topics of paediatric oncology to (1) improve understanding of epidemiologists in the specific issues of childhood cancer, and (2) set clinical oncology into the context of the European population. Training and education will comprise three complementary phases: (1) training course, (2) individual mentoring and (3) on-site consultation.
Task description:
A specific module on childhood cancer will be developed and implemented, including the following topics as examples:
Incidence of cancer in children and adolescents – overview Impact of registry data on clinical practice
Survival of children and adolescents with cancer – overview Impact of registry data on public health
Pathology overview Treatment protocols
Risk factors Clinical trials in paediatric oncology
International classification Clinical data collection
Population-based cancer registry – examples Long-term follow-up
Presentation of population-based data Registration of long-term survivors

The course programme will be developed in cooperation with ENCR and IARC using relevant input from the EUROCOURSE project (FP7 funds), which will become available in the near future. The childhood cancer module will complement other modules covering the principles of cancer registration, classification and coding, data analysis, and others. These general issues have evolved over the years through IARC teaching programmes.
A limited number of mentorships are also planned. They will allow interested individuals and institutions to benefit from individual advice in establishing or improving a population-based registry of cancers in children and adolescents according to the aims of the registry. This, in turn, will allow data collection unavailable thus far. Mentees will be selected by a committee composed of the task partners. Mentees may also benefit from on-site consultation to evaluate the quality of procedures and data collected methodologies relevant to paediatric oncology to allow improvement within sites in participating European countries. The target audience for courses and mentorships will be the staff of cancer registries with specific interest in childhood cancer and paediatric oncologists with an interest in epidemiology.
Individual supervision and training per country:
Mentor-Mentee-System: one mentor (e.g. data manager, from a population-based registry) will individually train one mentee, who wants to develop structures of registration-routines in his/her country

Physical supervision within country (two-three days): One person from a country with population-based registry will come to the country without population-based registry and provide individual training and education; e.g. support in means of epidemiology and data management training
Fortnightly tele-conferences after on-site training

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
2	SIOPE	8.00
4	UCL	3.50
5	CAU	3.00
7	UCSC	60.00
13	UOB	2.20
24	IARC	2.30
31	AP-HP	11.80
34	ECCO	8.00
35	ÖK	4.60
	Total	103.40

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D15.1	List of centres that fullfil the EUMS standards for training in paediatric haematology and oncology	7	21.90	O	PU	12
D15.2	A biannual meeting on SIOPE-ENCCA activity and dedicated space on SIOPE website.	35	21.90	O	PU	24
D15.3	Production of guidelines indicating how to improve relationships among parents/patients	35	20.05	R	PU	60
D15.4	Implementation of a population-based approach in teaching material on cancer in children and adolesc	24	21.90	R	PU	24
		Total	85.75			

Description of deliverables

D15.1) List of centres that fullfil the EUMS standards for training in paediatric haematology and oncology: List of centres that fullfil the EUMS standards for training in paediatric haematology and oncology. Once the list is defined, a self-assessment questionnaire will be sent to monitor the paediatric oncology training program. [month 12]

D15.2) A biannual meeting on SIOPE- ENCCA activity and dedicated space on SIOPE website.: A biannual meeting on SIOPE- ENCCA activity and dedicated space on SIOPE website. M24 and 48. [month 24]

D15.3) Production of guidelines indicating how to improve relationships among parents/patients: Production of guidelines indicating how to improve relationships among parents/patients, medical institution, parents associations and government bodies. [month 60]

D15.4) Implementation of a population-based approach in teaching material on cancer in children and adolesc: Implementation of a population-based approach in teaching material on cancer in children and adolescents in Europe. Two course and mentorship reports. M24,36 and 48 [month 24]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS64	Yearly report on courses and update on clinical treatment standards	7	12	Analyses of results and Report
MS65	General parent/patient information convention	7	24	Assessment of Report
MS66	List of centres to be evaluated	7	12	Level of training in countries
MS67	Initial structural organisation, information and dissemination of training courses.	7	12	Initial structural organisation, information and dissemination of training courses.

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP16	Type of activity [54]	OTHER
Work package title	Facilitation of Industry Collaboration with Pharmaceutical Companies and SME for dissemination, expl		
Start month	1		
End month	60		
Lead beneficiary number [55]	6		

Objectives

The 1st objective of this WP is to increase and facilitate contacts and collaborations between ENCCA and pharmaceutical companies within the European Paediatric Medicines Regulation, in order to introduce well studied, safe and effective targeted therapies into clinical research, and subsequently, standard care.
The 2nd objective is to implement a sustainable survey of Intellectual Property Rights within the clinical trial environment and technologies and to increase awareness for the benefit of researchers, European industry and patients.
WP 16 aims to create the necessary mechanisms and links of communication with the European Industry (pharmaceutical companies, diagnostic companies, SMEs) in order to find sustainable solutions for new drug development for children and adolescents.

Description of work and role of partners

Task 16.1 Creation of a platform for communication and interaction with Industry.IGR, EMC, CCRI, CAU, KI (M1– M18)
Objective:
To create a platform for communication and interaction with Industry.
Task description:
This platform will be created in collaboration with the Biotherapy Development Association (BDA) to address improvement in pediatric new oncology drug development, facilitating interactions between academia, the industry and regulatory authorities.
BDA is a not-for-profit association whose mission is to provide a unique platform to facilitate interactions between academia, the industry and regulatory authorities in order to improve the efficiency of cancer drug development. ENCCA will propose to BDA to address the topic of pediatric oncology drug development and will created with BDA a unique platform for interaction, communication and collaboration between the Industry and the Pediatric Oncology Community, as well as Parents Organisations and Regulators. ENCCA representatives will participate in meetings and workshops focused on specific oncology themes to address hurdles and explore potential solutions together with experts from academia, pharmaceutical industry, regulatory authorities, patient advocates and policymakers.

Task 16.2 Improving IPR knowledge and awareness IGR, EMC, EMC, CCRI, CAU, KI (M1– M48)
Objective:
The aim is to increase awareness of researchers and clinicians for a better monitoring of knowledge protection and exploitation of clinical research and technologies, and serve as a resource to help partners and European disease groups to protect their intellectual property rights.
Task description:
Most institutions hosting a biology research programme on paediatric malignancies have their own policy and staff to protect intellectual property. On the other hand, there is no culture of intellectual property rights among clinicians and teams running clinical trials in paediatric oncology. The number of investigator-driven clinical trials through investigator-initiated studies partly funded by pharmaceutical companies will increase, as well as translational and biological research within those phases I, II and III trials. It is crucial to adequately protect knowledge and know-how that will be generated.

This task includes the creation of a working group (the so-called IPR committee) composed by one pediatric oncologist/hematogist and one IPR experts from 6 ENCCA partners institutions, namely Gustave Roussy, CCRI, UOB, CAU, UNIMIB and Erasmus, chosen on the basis of their involvement in running and sponsoring pan-European IDCTs. Meetings will be held to define and write guidelines to be approved by the general assembly and publish.

Task 16.3 Mechanisms to favour links and technology transfer to industry IGR, EMC (M1-M48)
Objective:
The task aims to establish mechanisms for more efficient collaboration and communication with pharmaceutical industry and SMEs.
Task description:
This will be possible through:
- Organisation of workshops with industry partners :
- Facilitating access to expertise for advice of pharmaceutical companies in PIP establishment;
- Dissemination of information through newsletters and clinical trial presentations;

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
1	CCRI	14.00
5	CAU	1.00
6	IGR	4.50
10	EMC	5.45
27	KI	4.00
	Total	28.95

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D16.1	Publication of the BDA meetings summary and action plan.	6	11.50	O	PU	42
D16.2	Publication of guidelines for partnership with Pharmaceutical companies when running IDCTs	6	11.45	O	PU	60
		Total	22.95			

Description of deliverables

D16.1) Publication of the BDA meetings summary and action plan.: Publication of the BDA meetings summary and action plan. [month 42]

D16.2) Publication of guidelines for partnership with Pharmaceutical companies when running IDCTs: Publication of guidelines for partnership with Pharmaceutical companies when running IDCTs [month 60]

WT3:
Work package description

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS68	Creation of a platform for communication and interaction with Pharmaceutical industry	6	24	Minutes of the first meeting (report)
MS69	Creation of an IPR committee	6	30	Annual activity reports of the Club of Industrial Interest.
MS70	Approval by the ENCCA general assembly of a strategy for collaboration with Industry	6	60	Annual activity reports of the IPR committee.

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP17	Type of activity [54]	OTHER
Work package title	Improving Outcomes for Teenagers and Young Adults with Cancer		
Start month	1		
End month	60		
Lead beneficiary number [55]	14		

Objectives

Create a framework of professionals and centres who lead in TYA oncology to share practice, promoting and developing research initiatives to improve outcomes leading to service development, interdisciplinary support and the development of specific practice guidance of relevance to TYA cancer.

Description of work and role of partners

Task 17.1 Creating a European Multidisciplinary Framework for TYA cancer. LTHTNHS, UoL, CLB, (M1 – M48)
Objective: Create a framework of leading professionals and centres in TYA oncology to share practice and promote service development, interdisciplinary support and develop specific practice guidance relevant to TYA cancer.
Task description:
Phase 1: Identify key TYA leadership and stakeholders from different disciplines, centres and countries, and establish a European Steering Group, including clinicians from both paediatric and adult oncology
Phase 2: Use Steering Group to define the scope and plan the Europe-wide agenda, then develop an implementation plan for TYA service developments and practice guidance. Round-table discussions and open invitation meetings are planned.
Phase 3: Implementation of plan and service guidance.

Task 17.2 Developing TYA multi-professional education UoL (M1 – M48)
Objective: Promote and develop TYA-appropriate educational opportunities for professionals within Europe including the identification of relevant competencies
This task will work in close collaboration with the Education and Training WP.
Task description:
- To develop an educational programme of events open to a range of professionals addressing TYA cancer in Europe.
- To develop an agreed set of professional competencies for inclusion in core training and continuing educational programmes.
- To identify workforce requirements – including new roles – for managing TYA cancer.

Task 17.3 Task Title: Improving access to clinical trials for teenagers and young adults IGR, UoL (M1 – M48)
Objective: Promote and identify opportunities for TYA to receive treatment within high quality research trials and increase their accrual in patient trials. Standard of care for young people with cancer is to be treated within a recognised national or international clinical trial.
Task description:
Phase 1: Identify existing trials and opportunities for young people, aged 15 – 25, to be enrolled in clinical trials for common TYA cancers (lymphomas, leukaemias, germ cell tumours, CNS tumours and sarcomas).
Phase 2: Develop a dialogue – co-hosted meetings – with relevant European and National Trial Groups to address existing eligibility criteria for randomised trial entry to ensure equity of access.
Phase 3: Promote changes in eligibility to encourage trial entry.

Task 17.4 Developing a European TYA Research Initiative LTHTNHS, UoL, IGR, CLB (M1– M48)
Objective: Initiate development of research initiatives relevant for TYA, to address issues including, TYA epidemiology, delayed diagnosis, health service research related to best models of care and TYA-specific tumour biology in collaboration with WP 5.

Task description:
- Develop specific aims of the research element of TYA oncology Framework – likely proposed aims that would require bids for additional external funding.
- Linking treatments and outcomes to age and biology requires increased sample collection, storage and developing a biological network. This research activity will take place within tumour groups and bio-banking.
- Promote links between registries to establish Europe-wide information network regarding incidence, treatment-related knowledge and outcome, in conjunction with WP 11.
- Explore differences in time to diagnosis for TYA (diagnostic delay), and develop research proposals to address this.
- Explore models of TYA service provision and develop methodologies for assessing benefits.
- Explore benefits of international multidisciplinary decision making for local therapy in specific cancers, to be piloted for Ewing's sarcoma. In conjunction with WP 7.

Task 17.5 Promote healthy lifestyles in TYA population and cancer survivors CLB, UoL (M1 - M48)
Objective: Promoting healthy behaviours in the young person with cancer or to prevent cancer
Task description:
- Identify and disseminate good practice in existing 'survivorship' programmes.
- Scope fertility preservation practice across Europe and identify and disseminate good practice.
- Identify existing interventions aimed at modifying the exposure of TYAs to potentially modifiable cancer risk factors (e.g. human papillomavirus, ultraviolet light, poor diet, lack of physical activity, obesity, tobacco use, genetic predisposition in 2 groups a) – the TYA cancer population; b) the non-cancer TYA population.

Task 17.6 Establish links to patient and support organisations LTHTNHS, CLB, IGR, (M12-M48)
Objective: Link to relevant patient and charitable organisations to ensure that young people's voices are heard
Task description:
- Identify a list of relevant patient, family and advocacy organisations through international contacts, which have declared interest in TYA cancer within the scope of their activities.
- Convene a joint professional / advocacy organisation meeting to share progress and develop ideas.
- Integrate advocacy organisations and young people with cancer into all task groups.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
6	IGR	10.50
14	LTHTNHS	36.70
23	CLB	2.25
39	UoL	3.12
	Total	52.57

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D17.1	1st report of European Steering Group Development of TYA oncology Framework.	14	6.00	R	PU	12
D17.2	1st TYA oncology Framework Educational meeting Programme.	39	6.00	R	PU	12
D17.3	Register of open trials in Europe for major TYA tumour groups.	14	6.00	O	PU	12

WT3:
Work package description

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D17.4	Develop key agreed research objectives for the TYA oncology Framework with proposed time-table.	14	6.00	O	PU	12
D17.5	Document scoping fertility preservation practices in different institutions and countries.	23	6.00	R	PU	12
D17.6	Young people's views and advocacy organisations representing a range of countries integrated into al	1	6.17	O	PU	24
		Total	36.17			

Description of deliverables

D17.1) 1st report of European Steering Group Development of TYA oncology Framework.: 1st report of European Steering Group Development of TYA oncology Framework. [month 12]

D17.2) 1st TYA oncology Framework Educational meeting Programme.: 1st TYA oncology Framework Educational meeting Programme. [month 12]

D17.3) Register of open trials in Europe for major TYA tumour groups.: Register of open trials in Europe for major TYA tumour groups. [month 12]

D17.4) Develop key agreed research objectives for the TYA oncology Framework with proposed time-table.: Develop key agreed research objectives for the TYA oncology Framework with proposed time-table. [month 12]

D17.5) Document scoping fertility preservation practices in different institutions and countries.: Document scoping fertility preservation practices in different institutions and countries. [month 12]

D17.6) Young people's views and advocacy organisations representing a range of countries integrated into al: Young people's views and advocacy organisations representing a range of countries integrated into all groups. [month 24]

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead benefi-ciary number	Delivery date from Annex I [60]	Comments
MS71	Establish 1st full meeting European Steering Group for ENTYAC	14	12	Report / minutes
MS72	Trial availability and entry of TYA in Europe	14	36	First publication
MS73	Steering Group minutes and annual report.	14	12	Steering Group minutes and annual report.
MS74	Ongoing programme and reports.	39	12	Ongoing programme and reports.

WT3:
Work package description

Project Number [1]	261474	Project Acronym [2]	ENCCA

One form per Work Package

Work package number [53]	WP18	Type of activity [54]	OTHER
Work package title	Ethical aspects of clinical trials		
Start month	1		
End month	60		
Lead beneficiary number [55]	16		

Objectives

The objective is to formulate a general ethics guidance for clinical trials that will be reviewed by an Ethics Advisory Group (EAG), composed of external experts and parents/patients representatives, not only in charge of ensuring respect of fundamental ethical principles but also to evoke continuous attention to aspects of ethical handling.
This objective will be achieved by:
Pointing out the ethically sensitive issues and informing the clinicians about them. These issues are of course very different according to the phase (I, II or III) of the clinical trials and are also probably variable according to cultural background in northern and southern parts of Europe. A study will be performed in order to analyse these differences;
Discussing and establishing internal ethical questions and recommendations for the application of clinical trials in children and adolescents;
Evaluating application and disseminating knowledge about all relevant existing regulations to the partners;
Disseminating the rationale of internal guidance within the paediatric cancer community in Europe
Interacting with an Ethical Advisory Group of external experts that will serve the project with an ethical review and screen for compliance with the network guidelines.

Description of work and role of partners

Task 18.1 Review of ethical issues regarding the involvement of children in the investigations and Specific ethical issues in paediatric oncology. CURIE, ÖK (M1 – M12)
Objective:
The ENCCA network aims to review the ethical issues that are encountered in paediatric oncology clinical trials of all phases. This task will be performed under the guidance (or with input from) the Ethics Advisory Group and in collaboration with parents/patients participating in the such trials, including those run across the Network. Indeed parents/patients have crucial insights to bring to the dialogue on issues such as the benefit/risk ratio, as well as considerations of the therapeutic alternatives. They will therefore be encouraged to actively participate in the debate on ethical issues both at the national and European level.
Task description:
An extensive review of the relevant European guidelines and directives regarding paediatric clinical trials will be performed in order to follow the principles of beneficence, justice and respect to persons;
Meetings of parents/patients in the different countries will be organised in order address the different issues met by current and former patients and families.
Building of parents/patients awareness regarding the consent/assent procedure will be established. The goal is to clearly review the nature, significance, implications and risks related to a clinical trial procedure.
European meetings will be organised with national ethics representatives, and a summary of the current national laws recommendations, including the specifics of trials in children, will be communicated to ENCCA partners;
Sociological analyses of differences and discrepancies according to countries (north versus south) will be performed to define a common mission for national ethics committees, harmonise national procedures and increase ethical standards for paediatric clinical trials;
Establishment of a network of national review boards with experience in reviewing paediatric oncology trials to promote a common understanding of key ethical issues and develop relevant expertise within and between national ethical review systems;
Parallel reflection about who actually represent the parents/patients taking part in parents/patients association.

Task 18.2 Establishment of ENCCA guidelines for clinical trials in children and adolescents with cancer ÖK, CURIE (M1 – M48)
Objective:
This task aims at defining the ethical justification and identifying the ethical pitfalls of performing:
- drug development clinical trials (phase I and II)
- phase III randomised clinical trials
Task description:
These two parallel objectives will entail reviews of literature dedicated to the aforementioned issues.
In addition to this study, audits of specific organisations will be performed as follows:
Audit of the national groups and ITCC for early drug development trials
Audit of SIOP tumour groups for phase III and non interventional studies
As a conclusion of these actions, a summary of consensus recommendations and of the countries particularities will be established by ENCCA partners with collaboration of the EAG independent experts.

Task 18.3 Review on-going protocols from an ethical point of view CURIE, ÖK (M1 – M24)
Objective:
Parents and external experts, (i.e. specialised investigators in leukaemia reviewing solid tumours protocols) will be reviewing the ethical aspects of the different ongoing European protocols.
Task description:
Following the Directive 2001/20/ EC, relating to good clinical practice in the conduct of clinical trials on medicinal products for human use, the clinical trial protocols established by the clinical tumour and leukaemia groups will be analysed in order to define current good practices.
Development of new harmonised evaluation procedures;
An extensive study of information and consent forms will be performed in the different European countries to establish a coherent communication to parents/patients as well as help national ethics committees to harmonise ethical review procedures for paediatric clinical trials;
Confidentiality issues will be reviewed following the European and national directives and guidelines on protection of clinical trial subjects.
This analysis will contribute to a detailed description of the current status of clinical research in Europe for young people with cancer. It will greatly help to identify ways of improving the approach to future clinical research in this field, including production of guidelines for use by national ethical review boards.

Task 18.4 Quality and safety of human tissues, cells, DNA, sera, protein collection CURIE, ÖK, (M1– M48)
Objective:
Parents, clinicians and scientists will together define how to fully protect confidentiality of sensitive data, such those connected with biological materials, including tissue samples, cells, DNA, sera and collected proteins, in the era of high-throughput technologies.
Task description:
Establishment of rules of confidentiality in the context of high-throughput and genome-wide technologies for genomic and constitutional genetics analyses;
Organisation of meetings with researchers, clinicians and parents/patients to discuss the necessity of research on children and the consequences of not performing those studies.
Evaluation of practices regarding respect of implementation of recommendation regarding the rules of confidentiality

Task 18.5 Training in implementation of Ethical guidelines ÖK, CURIE (M24-M36)
Ethical issues are everyday issues, and should always be a part of the clinical practice including during clinical trials. A training module will be prepared with the aim to prepare clinicians and supporting clinical staff in new guidelines prepared by ENCCA. The training course will be organised in different EU countries to increase impact and support rapid implementation of common standards.

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
16	CURIE	34.75
35	ÖK	13.60

WT3:
Work package description

Person-Months per Participant

Participant number [10]	Participant short name [11]	Person-months per participant
	Total	48.35

List of deliverables

Delive-rable Number [61]	Deliverable Title	Lead benefi-ciary number	Estimated indicative person-months	Nature [62]	Dissemi-nation level [63]	Delivery date [64]
D18.1	Identification of ethical issues during paediatric hemato-oncoloy clinical trials	16	8.00	R	PU	24
D18.2	Guidelines on clinical trials in paediatric oncology.	35	8.00	R	PU	36
D18.3	Workshop with tumour group representatives.	35	8.00	O	PU	24
D18.4	Description of discrepancies in Europe.	16	8.00	O	PU	60
D18.5	Guidelines on confidentiality issues regarding human tissues, cells, DNA, sera and collected protein	16	8.00	R	PU	24
D18.6	Training for clinical trial staff for ethical guidelines implementation.	16	8.35	O	PU	60
		Total	48.35			

Description of deliverables

D18.1) Identification of ethical issues during paediatric hemato-oncoloy clinical trials: Document including the identification of ethical issues during paediatric hemato-oncoloy clinical trials. [month 24]

D18.2) Guidelines on clinical trials in paediatric oncology.: Guidelines on clinical trials in paediatric oncology. [month 36]

D18.3) Workshop with tumour group representatives.: Workshop with tumour group representatives. [month 24]

D18.4) Description of discrepancies in Europe.: Description of discrepancies in Europe. [month 60]

D18.5) Guidelines on confidentiality issues regarding human tissues, cells, DNA, sera and collected protein: Guidelines on confidentiality issues regarding human tissues, cells, DNA, sera and collected proteins from paediatric cancer patients. [month 24]

D18.6) Training for clinical trial staff for ethical guidelines implementation.: Training for clinical trial staff for ethical guidelines implementation. [month 60]

WT3:
Work package description

Schedule of relevant Milestones

Milestone number [59]	Milestone name	Lead beneficiary number	Delivery date from Annex I [60]	Comments
MS75	Review on current practice of ethical issues during paediatric hemato-oncology clinical trials	16	16	Analytic results of literature survey on ethical issues during paediatric hemato-oncology clinical trials
MS76	Methodology and review on current practice of clinical trials in paediatric oncology	35	24	Analytic results of literature survey on clinical trials in paediatric oncology
MS77	Minutes of the workshop with tumour group representatives	35	24	Minutes of workshop with tumour group representatives
MS78	Minutes of roundtables on ENCCA guidelines (in a view of identifying local discrepancies and obstacl	16	36	Minutes of roundtables on ENCCA guidelines
MS79	Methodology and review on current practice of confidentiality issues regarding human tissues, cells	16	16	Analytic results of literature survey on confidentiality issues

WT4:
List of Milestones

Project Number [1]	261474	Project Acronym [2]	ENCCA

List and Schedule of Milestones

Milestone number [59]	Milestone name	WP number [53]	Lead beneficiary number	Delivery date from Annex I [60]	Comments
MS1	Consortium Agreement signed by all partners (CCRI)	WP1	1	1	Signed document distributed to partners
MS2	Quality Assurance Plan inc. guidelines, best practices, project handbook approved by the ExecutiveCo	WP1	1	12	Finalised version distributed to partners
MS3	Yearly reporting consolidated and approved by the ExecutiveCommittee and the EC (CCRI)	WP1	1	12	Acceptance letter received from the EC
MS4	Creation of templates for the reporting (including deliverable and milestone templates, Costs follow	WP1	1	12	
MS5	Implementation of the collaborative tool	WP1	1	12	
MS6	Minutes of the official meetings	WP1	1	12	
MS7	Amendements to the Consortium Agreement	WP1	1	12	
MS8	Implementation of a new strategy	WP2	2	12	Common acceptance by the GA
MS10	Establishment of efficient financial structure	WP2	2	60	Operational guides for financial resources
MS11	Evaluation of possibility for a durable administrative identity	WP2	2	60	Establishment of a legal entity
MS12	Recommendations of the Groups		2	12	
MS13	Operational knowledge management platform	WP3	18	30	Content available in knowledge management platform

WT4:
List of Milestones

Milestone number [59]	Milestone name	WP number [53]	Lead beneficiary number	Delivery date from Annex I [60]	Comments
MS14	Completed analysis of existing systems and list of proposed standards	WP3	18	36	Confirmation of agreement between partners
MS15	Design Specification of Virtual European Research Institute	WP3	18	36	Design document
MS16	System validation completed	WP3	18	60	Metrics for system performance available
MS17	Templates available for stakeholders on the WEB side	WP4	1	12	Visibility on the official ENCCA Website
MS18	Consensus Conference on IDCT facilitation measures		1	48	Report and consensus paper on achievements for IDCT in paediatric oncology
MS19	Foundation of the Clinical Trials		2	12	Foundation of the Clinical Trials Approval Board followed by annual activity reports
MS20	Yearly distribution of the guidlines from D1.4.4 to participating labs and networks	WP5	30	12	Guidelines will be distributed as written reports
MS21	Design of final bioinformatics tool based on prototype and user-feedback	WP5	30	60	Written reports containing feedback on ‘bioinfo tool’ by 3 working parties and 11 tumour subnetworks
MS22	Database of tumour specimens from virtual and local biobanks existing at project begin	WP5	30	60	Availability of dataset
MS23	Annual meetings and disseminate meeting discussion points and results to all WPs participants	WP5	30	24	Organise annual meetings and disseminate meeting discussion points and results to all Work Package participants to maintain good two-way information flow between subnetworks and remaining partners of
MS24	Innovative and recent statistical methodology: review and recommendations	WP6	6	48	Workshop,guidelines and publication(s)

WT4:
List of Milestones

Milestone number [59]	Milestone name	WP number [53]	Lead beneficiary number	Delivery date from Annex I [60]	Comments
MS25	Methodology and review on current practice of adverse event and toxicity reporting, competing risks	WP6	1	60	Workshops
MS26	Core data set and relevant analyses identified for the 4 identified tumors	WP6	9	24	Workshops
MS27	Data pooling and analyses performed	WP6	9	60	Report and publication after second workshop
MS28	Optimised trial accrual	WP7	32	60	>75% eligible patients accrued in bone sarcoma trials
MS29	Steering Group establishment, meetings and annual reports.	WP7	32	12	Steering Group establishment, meetings and annual reports
MS30	Meetings of the European Bone Sarcoma Trials	WP7	37	12	Meetings of the European Bone Sarcoma Trials with invitation of representatives of other groups and countries
MS31	Workshops and Observerships for oncologists in training	WP7	37	12	Workshops and Observerships for oncologists in training from groups and countries outside existing trials
MS33	The consortium of Insitutions is up and running	WP8	6	24	Minutes of the working group
MS34	Agreement with at least one pharmaceutical company for access to an innovative compound for leukaemi	WP8	6	24	Agreement possibility
MS35	Common guidelines for diagnostic approaches to leukaemias	WP9	5	24	Publication
MS36	European virtual laboratory for molecular diagnostics of leukaemias	WP9	5	36	Method (Validated diagnostic I-BFM tool for identification of VHRL patients)

WT4:
List of Milestones

Milestone number [59]	Milestone name	WP number [53]	Lead beneficiary number	Delivery date from Annex I [60]	Comments
MS37	Trial platform for early implementation of molecularly targeted treatment of leukemias	WP9	5	60	Clinical protocol
MS38	EudraCT number	WP10	11	12	Check EudraCT web site
MS39	Initiation of LINES in different European Countries (along first year)	WP10	11	12	Date of Ethics Approval and Contract Signature with European sponsor
MS40	Compliance with Low-risk neuroblastoma study defined aims	WP10	11	24	Annual Report at SIOPEN General Assembly and final paper
MS41	Compliance with Intermediate-risk neuroblastoma study defined aims	WP10	11	24	Annual Report at SIOPEN General Assembly and final paper
MS42	Compliance with PNET-V aims	WP10	11	60	Annual Report at the SIOP Brain Tumor Committee and final paper.
MS43	Publication of SOPs for genomic profile studies of tumour in multicenter multinational studies	WP10	11	12	Peer-reviewed journal.
MS44	Elaborate and apply guidelines to control image-defined-risk-factors, to review histological materi	WP10	11	12	Elaborate and apply guidelines to control image-defined-risk-factors, to review histological material according to the INPC.
MS45	Make interim analyses and reporting of the entered data.	WP10	11	60	Make interim analyses and reporting of the entered data.
MS46	Establish SOPs for genomic profiling in LINES	WP10	16	12	Establish SOPs for genomic profiling in LINES, to set up and maintain an online review process for genomic data including interlaboratory testing and training.
MS47	Implementation of guidelines for collection, storage of biological material and molecular diagnostic	WP10	16	12	Implementation of guidelines for collection, storage of biological material and molecular diagnostics in medulloblastoma. Perform

Milestone number [59]	Milestone name	WP number [53]	Lead beneficiary number	Delivery date from Annex I [60]	Comments
					quality control of images for inclusion criteria and treatment plannin
MS48	Minimal standard datasets by tumour type The continued development of data sources over the NoE life	WP11	24	24	Publication of standard datasets
MS49	Collaboration agreements with data providers taking into account confidentiality and ethics aspects	WP11	24	24	Copy of agreements
MS50	Enhancement of the ACGT Master Ontology for Paediatric Oncology and seamless integration and analysi	WP11	4	24	Interim data report and demonstration of the ontology
MS51	Identification and selection of prognostic factors in hepatoblastoma	WP12	12	12	Statistical analysis followed by publication.
MS53	Development of the new patient stratification in hepatoblastoma.	WP12	12	24	Report
MS54	Completion of Health Tracker outcome module and translation into all relevant languages	WP13	38	12	View on line
MS55	Completion of PNET4 salivary DNA collection	WP13	38	24	View database of DNA samples
MS56	Submission of PNET4 outcome study for publication	WP13	16	36	View manuscript
MS57	electronic data base for treatment summary reports	WP13	16	24	View data base
MS58	Development of a prototype of passport for survivorship	WP13	16	60	View prototype and report

WT4:
List of Milestones

Milestone number [59]	Milestone name	WP number [53]	Lead beneficiary number	Delivery date from Annex I [60]	Comments
MS59	Creation and rolling out of the 'February Campaign'	WP14	2	12	Visibility raised through PR reports and features
MS60	Organisation of the workshops/meetings within the congresses	WP14	2	12	Will be verified by the number of attendees and expected PR features and reports..
MS61	Development of the website for dissemination activities	WP14	2	12	Innovative online communication tool and monitoring of website hits/downloads
MS62	The organisation of workshops/meetings within various congresses.	WP14	2	12	The organisation of workshops/meetings within various congresses.
MS63	Organising the "February Campain" presenting the challenges faced by childhood cancer patients	WP14	2	12	Organising the "February Campain" presenting the challenges faced by childhood cancer patients
MS64	Yearly report on courses and update on clinical treatment standards	WP15	7	12	Analyses of results and Report
MS65	General parent/patient information convention	WP15	7	24	Assessment of Report
MS66	List of centres to be evaluated	WP15	7	12	Level of training in countries
MS67	Initial structural organisation, information and dissemination of training courses.	WP15	7	12	Initial structural organisation, information and dissemination of training courses.
MS68	Creation of a platform for communication and interaction with Pharmaceutical industry	WP16	6	24	Minutes of the first meeting (report)
MS69	Creation of an IPR committee	WP16	6	30	Annual activity reports of the Club of Industrial Interest.
MS70	Approval by the ENCCA general assembly of	WP16	6	60	Annual activity reports of the IPR committee.

WT4:
List of Milestones

Milestone number [59]	Milestone name	WP number [53]	Lead beneficiary number	Delivery date from Annex I [60]	Comments
	a strategy for collaboration with Industry				
MS71	Establish 1st full meeting European Steering Group for ENTYAC	WP17	14	12	Report / minutes
MS72	Trial availability and entry of TYA in Europe	WP17	14	36	First publication
MS73	Steering Group minutes and annual report.	WP17	14	12	Steering Group minutes and annual report.
MS74	Ongoing programme and reports.	WP17	39	12	Ongoing programme and reports.
MS75	Review on current practice of ethical issues during paediatric hemato-oncology clinical trials	WP18	16	16	Analytic results of literature survey on ethical issues during paediatric hemato-oncology clinical trials
MS76	Methodology and review on current practice of clinical trials in paediatric oncology	WP18	35	24	Analytic results of literature survey on clinical trials in paediatric oncology
MS77	Minutes of the workshop with tumour group representatives	WP18	35	24	Minutes of workshop with tumour group representatives
MS78	Minutes of roundtables on ENCCA guidelines (in a view of identifying local discrepancies and obstacl	WP18	16	36	Minutes of roundtables on ENCCA guidelines
MS79	Methodology and review on current practice of confidentiality issues regarding human tissues, cells	WP18	16	16	Analytic results of literature survey on confidentiality issues

WT5:
Tentative schedule of Project Reviews

Project Number [1]	261474	Project Acronym [2]	ENCCA

Tentative schedule of Project Reviews

Review number [65]	Tentative timing	Planned venue of review	Comments, if any

WT6:
Project Effort by Beneficiary and Work Package

Project Number [1]	261474	Project Acronym [2]	ENCCA

Indicative efforts (man-months) per Beneficiary per Work Package

Beneficiary number and short-name	WP 1	WP 2	WP 3	WP 4	WP 5	WP 6	WP 7	WP 8	WP 9	WP 10	WP 11	WP 12	WP 13	WP 14	WP 15	WP 16	WP 17	WP 18	Total per Beneficiary
1 - CCRI	62.00	2.50	0.00	2.50	8.50	15.00	0.00	38.50	20.50	62.00	0.00	0.00	0.00	13.00	0.00	14.00	0.00	0.00	238.50
2 - SIOPE	0.00	8.00	8.00	8.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	36.00	8.00	0.00	0.00	0.00	68.00
4 - UCL	0.00	3.00	0.00	1.00	8.50	1.00	0.00	5.00	0.00	0.00	27.84	0.00	0.00	6.50	3.50	0.00	0.00	0.00	56.34
5 - CAU	2.75	9.75	0.00	3.00	17.00	11.00	0.00	7.00	37.00	0.00	0.00	0.00	0.00	7.00	3.00	1.00	0.00	0.00	98.50
6 - IGR	6.50	6.00	0.00	6.00	6.00	5.50	7.50	7.50	0.00	0.00	0.00	6.00	0.00	0.00	0.00	4.50	10.50	0.00	66.00
7 - UCSC	0.00	2.00	0.00	0.00	0.00	0.00	0.00	2.00	0.00	0.00	0.00	0.00	0.00	0.00	60.00	0.00	0.00	0.00	64.00
8 - UKE	0.00	0.00	0.00	0.00	36.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	36.00
9 - UNIMIB	0.00	0.00	0.00	1.50	0.00	38.00	0.00	4.00	25.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	68.50
10 - EMC	0.00	0.00	0.00	0.00	5.50	0.00	1.00	7.70	5.50	0.00	0.00	0.00	0.00	0.00	0.00	5.45	0.00	0.00	25.15
11 - LaFe	0.00	0.00	0.00	2.00	0.00	0.00	0.00	0.00	0.00	26.00	0.00	0.00	0.00	2.00	0.00	0.00	0.00	0.00	30.00
12 - MUG	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	11.70	0.00	0.00	0.00	0.00	0.00	0.00	11.70
13 - UOB	0.00	0.00	0.00	5.00	0.00	8.00	0.00	32.50	0.00	0.00	0.00	17.00	0.00	0.00	2.20	0.00	0.00	0.00	64.70
14 - LTHTNHS	0.00	0.00	0.00	0.00	0.00	0.00	0.24	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	36.70	0.00	36.94
15 - IGG	0.00	0.00	0.00	4.40	28.00	2.10	0.00	3.50	0.00	0.00	30.00	0.00	31.00	0.00	0.00	0.00	0.00	0.00	99.00
16 - CURIE	0.00	0.00	0.00	2.00	4.70	0.00	5.00	2.80	0.00	2.80	0.00	0.00	2.80	1.75	0.00	0.00	0.00	34.75	56.60
17 - FORTH	0.00	0.00	28.00	1.00	2.00	0.00	0.00	0.00	5.00	0.00	28.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	64.00
18 - AIT	1.80	0.80	29.00	4.10	0.00	0.00	0.00	0.00	0.00	11.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	46.70
19 - CINECA	0.00	0.00	22.00	0.00	0.50	0.00	0.00	0.00	0.00	0.00	0.50	10.00	8.00	0.00	0.00	0.00	0.00	0.00	41.00
20 - ESQH	0.00	0.00	0.00	22.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	22.50
21 - AMC	0.00	0.00	0.00	0.00	96.00	0.00	0.00	2.00	0.00	0.00	0.00	1.20	0.00	0.00	0.00	0.00	0.00	0.00	99.20
23 - CLB	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.90	0.00	1.40	0.90	0.00	5.90	0.00	0.00	0.00	2.25	0.00	11.35

WT6:
Project Effort by Beneficiary and Work Package

Beneficiary number and short-name	WP 1	WP 2	WP 3	WP 4	WP 5	WP 6	WP 7	WP 8	WP 9	WP 10	WP 11	WP 12	WP 13	WP 14	WP 15	WP 16	WP 17	WP 18	Total per Beneficiary
24 - IARC	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	35.00	0.00	0.00	0.00	2.30	0.00	0.00	0.00	37.30
26 - LUMC	0.00	0.00	0.10	0.00	3.00	0.00	12.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	15.10
27 - KI	0.00	4.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.00	0.00	4.00	0.00	0.00	10.00
28 - UGent	0.00	0.00	0.00	0.00	0.00	0.00	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	5.00
30 - CHARITÉ	0.00	0.00	0.00	0.00	12.00	0.00	0.00	0.00	26.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	38.50
31 - AP-HP	0.00	0.00	0.00	0.00	0.00	0.00	0.00	12.00	12.00	0.00	0.00	0.00	0.00	0.00	11.80	0.00	0.00	0.00	35.80
32 - OLGA	0.00	0.00	0.00	2.00	0.00	0.00	21.50	2.70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	26.20
34 - ECCO	0.00	7.00	8.00	3.45	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	32.00	8.00	0.00	0.00	0.00	58.45
35 - ÖK	0.00	1.80	0.00	5.40	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	12.00	13.60	4.60	0.00	0.00	13.60	51.00
36 - UNIPD	0.00	0.00	0.00	0.00	7.50	0.00	0.00	0.00	11.00	0.00	0.00	3.00	0.00	0.00	0.00	0.00	0.00	0.00	21.50
37 - WWU	0.00	0.00	0.00	0.00	0.00	0.00	6.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	6.00
38 - SOUTHAMPTON	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	36.00	0.00	0.00	0.00	0.00	0.00	36.00
39 - UoL	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.12	0.00	0.00	3.12	0.00	3.24
Total	73.05	44.85	95.10	73.85	235.20	80.60	53.24	133.10	142.50	103.20	122.24	48.90	95.70	113.97	103.40	28.95	52.57	48.35	1,648.77

WT7:
Project Effort by Activity type per Beneficiary

Project Number [1]	261474	Project Acronym [2]	ENCCA

Indicative efforts per Activity Type per Beneficiary

Activity type	Part. 1 CCRI	Part. 2 SIOPE	Part. 4 UCL	Part. 5 CAU	Part. 6 IGR	Part. 7 UCSC	Part. 8 UKE	Part. 9 UNIMIB	Part. 10 EMC	Part. 11 LaFe	Part. 12 MUG	Part. 13 UOB	Part. 14 LTHTNHS	Part. 15 IGG
1. RTD/Innovation activities														
WP 8	38.50	0.00	5.00	7.00	7.50	2.00	0.00	4.00	7.70	0.00	0.00	32.50	0.00	3.50
WP 9	20.50	0.00	0.00	37.00	0.00	0.00	0.00	25.00	5.50	0.00	0.00	0.00	0.00	0.00
WP 10	62.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	26.00	0.00	0.00	0.00	0.00
WP 11	0.00	0.00	27.84	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	30.00
WP 12	0.00	0.00	0.00	0.00	6.00	0.00	0.00	0.00	0.00	0.00	11.70	17.00	0.00	0.00
WP 13	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	31.00
Total Research	121.00	0.00	32.84	44.00	13.50	2.00	0.00	29.00	13.20	26.00	11.70	49.50	0.00	64.50
3. Consortium Management activities														
WP 1	62.00	0.00	0.00	2.75	6.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total Management	62.00	0.00	0.00	2.75	6.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
4. Other activities														
WP 2	2.50	8.00	3.00	9.75	6.00	2.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
WP 3	0.00	8.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
WP 4	2.50	8.00	1.00	3.00	6.00	0.00	0.00	1.50	0.00	2.00	0.00	5.00	0.00	4.40
WP 5	8.50	0.00	8.50	17.00	6.00	0.00	36.00	0.00	5.50	0.00	0.00	0.00	0.00	28.00
WP 6	15.00	0.00	1.00	11.00	5.50	0.00	0.00	38.00	0.00	0.00	0.00	8.00	0.00	2.10
WP 7	0.00	0.00	0.00	0.00	7.50	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.24	0.00
WP 14	13.00	36.00	6.50	7.00	0.00	0.00	0.00	0.00	0.00	2.00	0.00	0.00	0.00	0.00
WP 15	0.00	8.00	3.50	3.00	0.00	60.00	0.00	0.00	0.00	0.00	0.00	2.20	0.00	0.00

WT7:
Project Effort by Activity type per Beneficiary

4. Other activities														
WP 16	14.00	0.00	0.00	1.00	4.50	0.00	0.00	0.00	5.45	0.00	0.00	0.00	0.00	0.00
WP 17	0.00	0.00	0.00	0.00	10.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	36.70	0.00
WP 18	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total other	55.50	68.00	23.50	51.75	46.00	62.00	36.00	39.50	11.95	4.00	0.00	15.20	36.94	34.50

Total	238.50	68.00	56.34	98.50	66.00	64.00	36.00	68.50	25.15	30.00	11.70	64.70	36.94	99.00

WT7:
Project Effort by Activity type per Beneficiary

Activity type	Part. 16 CURIE	Part. 17 FORTH	Part. 18 AIT	Part. 19 CINECA	Part. 20 ESQH	Part. 21 AMC	Part. 23 CLB	Part. 24 IARC	Part. 26 LUMC	Part. 27 KI	Part. 28 UGent	Part. 30 CHARITÉ	Part. 31 AP-HP	Part. 32 OLGA
1. RTD/Innovation activities														
WP 8	2.80	0.00	0.00	0.00	0.00	2.00	0.90	0.00	0.00	0.00	5.00	0.00	12.00	2.70
WP 9	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	26.50	12.00	0.00
WP 10	2.80	0.00	11.00	0.00	0.00	0.00	1.40	0.00	0.00	0.00	0.00	0.00	0.00	0.00
WP 11	0.00	28.00	0.00	0.50	0.00	0.00	0.90	35.00	0.00	0.00	0.00	0.00	0.00	0.00
WP 12	0.00	0.00	0.00	10.00	0.00	1.20	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
WP 13	2.80	0.00	0.00	8.00	0.00	0.00	5.90	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total Research	8.40	33.00	11.00	18.50	0.00	3.20	9.10	35.00	0.00	0.00	5.00	26.50	24.00	2.70
3. Consortium Management activities														
WP 1	0.00	0.00	1.80	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total Management	0.00	0.00	1.80	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
4. Other activities														
WP 2	0.00	0.00	0.80	0.00	0.00	0.00	0.00	0.00	0.00	4.00	0.00	0.00	0.00	0.00
WP 3	0.00	28.00	29.00	22.00	0.00	0.00	0.00	0.00	0.10	0.00	0.00	0.00	0.00	0.00
WP 4	2.00	1.00	4.10	0.00	22.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.00
WP 5	4.70	2.00	0.00	0.50	0.00	96.00	0.00	0.00	3.00	0.00	0.00	12.00	0.00	0.00
WP 6	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
WP 7	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	12.00	0.00	0.00	0.00	0.00	21.50
WP 14	1.75	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.00	0.00	0.00	0.00	0.00
WP 15	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.30	0.00	0.00	0.00	0.00	11.80	0.00
WP 16	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.00	0.00	0.00	0.00	0.00
WP 17	0.00	0.00	0.00	0.00	0.00	0.00	2.25	0.00	0.00	0.00	0.00	0.00	0.00	0.00
WP 18	34.75	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

WT7:
Project Effort by Activity type per Beneficiary

4. Other activities														
Total other	48.20	31.00	33.90	22.50	22.50	96.00	2.25	2.30	15.10	10.00	0.00	12.00	11.80	23.50

Total	56.60	64.00	46.70	41.00	22.50	99.20	11.35	37.30	15.10	10.00	5.00	38.50	35.80	26.20

WT7:
Project Effort by Activity type per Beneficiary

Activity type	Part. 34 ECCO	Part. 35 ÖK	Part. 36 UNIPD	Part. 37 WWU	Part. 38 SOUTHAM	Part. 39 UoL	Total
1. RTD/Innovation activities							
WP 8	0.00	0.00	0.00	0.00	0.00	0.00	133.10
WP 9	0.00	0.00	11.00	0.00	0.00	0.00	142.50
WP 10	0.00	0.00	0.00	0.00	0.00	0.00	103.20
WP 11	0.00	0.00	0.00	0.00	0.00	0.00	122.24
WP 12	0.00	0.00	3.00	0.00	0.00	0.00	48.90
WP 13	0.00	12.00	0.00	0.00	36.00	0.00	95.70
Total Research	0.00	12.00	14.00	0.00	36.00	0.00	645.64
3. Consortium Management activities							
WP 1	0.00	0.00	0.00	0.00	0.00	0.00	73.05
Total Management	0.00	0.00	0.00	0.00	0.00	0.00	73.05
4. Other activities							
WP 2	7.00	1.80	0.00	0.00	0.00	0.00	44.85
WP 3	8.00	0.00	0.00	0.00	0.00	0.00	95.10
WP 4	3.45	5.40	0.00	0.00	0.00	0.00	73.85
WP 5	0.00	0.00	7.50	0.00	0.00	0.00	235.20
WP 6	0.00	0.00	0.00	0.00	0.00	0.00	80.60
WP 7	0.00	0.00	0.00	6.00	0.00	0.00	53.24
WP 14	32.00	13.60	0.00	0.00	0.00	0.12	113.97
WP 15	8.00	4.60	0.00	0.00	0.00	0.00	103.40
WP 16	0.00	0.00	0.00	0.00	0.00	0.00	28.95
WP 17	0.00	0.00	0.00	0.00	0.00	3.12	52.57
WP 18	0.00	13.60	0.00	0.00	0.00	0.00	48.35

WT7:
Project Effort by Activity type per Beneficiary

4. Other activities							
Total other	58.45	39.00	7.50	6.00	0.00	3.24	930.08
Total	58.45	51.00	21.50	6.00	36.00	3.24	1,648.77

WT8:
Project Effort and costs

Project Number [1]	261474	Project Acronym [2]	ENCCA

Project efforts and costs

Beneficiary number	Beneficiary short name	Estimated eligible costs (whole duration of the project)						Requested EU contribution (€)
		Effort (PM)	Personnel costs (€)	Subcontracting (€)	Other Direct costs (€)	Indirect costs OR lump sum, flat-rate or scale-of-unit (€)	Total costs	
1	CCRI	238.50	1,000,520.75	109,890.67	239,906.18	744,256.16	2,094,573.76	1,643,402.80
2	SIOPE	68.00	251,587.50	84,563.88	149,011.84	80,119.87	565,283.09	550,080.40
4	UCL	56.34	477,350.35	4,000.00	95,353.28	343,622.18	920,325.81	739,313.60
5	CAU	98.50	491,061.08	1,371.24	46,777.31	322,703.03	861,912.66	695,664.50
6	IGR	66.00	561,950.29	20,000.00	34,384.71	357,801.00	974,136.00	830,002.00
7	UCSC	64.00	261,569.98	2,000.00	20,739.20	169,385.51	453,694.69	449,460.00
8 (TERMINATED)	UKE	36.00	98,191.09	756.36	19,064.81	70,353.54	188,365.80	146,970.36
9	UNIMIB	68.50	192,466.00	0.00	42,980.50	141,267.90	376,714.40	331,808.10
10	EMC	25.15	145,645.00	0.00	50,000.00	117,387.00	313,032.00	266,994.00
11	LaFe	30.00	164,500.00	0.00	47,163.33	126,998.00	338,661.33	263,128.00
12	MUG	11.70	43,808.00	0.00	80,289.00	74,458.20	198,555.20	148,915.60
13	UOB	64.70	211,805.32	0.00	42,928.65	152,840.38	407,574.35	327,319.60
14	LTHTNHS	36.94	212,204.39	0.00	65,025.60	166,338.00	443,567.99	344,450.71
15	IGG	99.00	244,925.00	2,000.00	82,348.67	196,364.20	525,637.87	438,014.40
16	CURIE	56.60	410,006.50	2,000.00	32,706.23	265,627.64	710,340.37	638,373.21
17	FORTH	64.00	191,617.77	0.00	40,000.00	155,069.17	386,686.94	339,621.00
18	AIT	46.70	275,299.01	2,000.00	71,081.86	197,249.25	545,630.12	504,788.95
19	CINECA	41.00	240,017.94	0.00	45,164.14	71,284.98	356,467.06	273,791.25
20	ESQH	22.50	62,975.00	0.00	7,000.00	41,985.00	111,960.00	111,960.00
21	AMC	99.20	307,957.50	2,450.00	18,590.00	195,928.50	524,926.00	519,307.00

WT8:
Project Effort and costs

Beneficiary number	Beneficiary short name	Estimated eligible costs (whole duration of the project)						Requested EU contribution (€)
		Effort (PM)	Personnel costs (€)	Subcontracting (€)	Other Direct costs (€)	Indirect costs OR lump sum, flat-rate or scale-of-unit (€)	Total costs	
23	CLB	11.35	96,864.82	0.00	11,721.04	65,151.52	173,737.38	130,152.00
24	IARC	37.30	188,300.00	12,000.00	7,593.41	117,536.05	325,429.46	257,763.29
26	LUMC	15.10	89,239.38	0.00	9,000.00	58,943.63	157,183.01	154,383.00
27	KI	10.00	9,815.00	0.00	7,960.55	10,665.33	28,440.88	27,860.80
28	UGent	5.00	0.00	0.00	34,439.60	20,663.76	55,103.36	54,480.40
30	CHARITÉ	38.50	256,953.14	3,000.00	49,140.37	183,656.11	492,749.62	370,372.14
31	AP-HP	35.80	43,051.00	0.00	8,213.00	30,758.40	82,022.40	69,304.80
32	OLGA	26.20	171,066.11	0.00	32,313.23	40,675.86	244,055.20	210,981.50
34	ECCO	58.45	237,131.00	0.00	30,423.10	53,510.82	321,064.92	320,723.20
35	ÖK	51.00	148,100.00	0.00	81,500.00	116,220.00	345,820.00	283,214.99
36	UNIPD	21.50	104,249.00	0.00	47,472.50	91,032.90	242,754.40	193,311.30
37	WWU	6.00	25,340.00	0.00	18,910.00	26,550.00	70,800.00	70,000.00
38	SOUTHAMPTO	36.00	135,682.00	0.00	42,724.00	122,114.00	300,520.00	225,389.50
39	UoL	3.24	50,218.50	3,500.00	0.00	30,131.10	83,849.60	66,656.50
Total		1,648.77	7,401,468.42	249,532.15	1,611,926.11	4,958,648.99	14,221,575.67	11,997,958.90

1. Project number

The project number has been assigned by the Commission as the unique identifier for your project. It cannot be changed. The project number **should appear on each page of the grant agreement preparation documents (part A and part B)** to prevent errors during its handling.

2. Project acronym

Use the project acronym as given in the submitted proposal. It cannot be changed unless agreed so during the negotiations. The same acronym **should appear on each page of the grant agreement preparation documents (part A and part B)** to prevent errors during its handling.

53. Work Package number

Work package number: WP1, WP2, WP3, ..., WPn

54. Type of activity

For all FP7 projects each work package must relate to one (and only one) of the following possible types of activity (only if applicable for the chosen funding scheme – must correspond to the GPF Form Ax.v):

• **RTD/INNO =** Research and technological development including scientific coordination - applicable for Collaborative Projects and Networks of Excellence

• **DEM =** Demonstration - applicable for collaborative projects and Research for the Benefit of Specific Groups

• **MGT =** Management of the consortium - applicable for all funding schemes

• **OTHER =** Other specific activities, applicable for all funding schemes

• **COORD =** Coordination activities – applicable only for CAs

• **SUPP =** Support activities – applicable only for SAs

55. Lead beneficiary number

Number of the beneficiary leading the work in this work package.

56. Person-months per work package

The total number of person-months allocated to each work package.

57. Start month

Relative start date for the work in the specific work packages, month 1 marking the start date of the project, and all other start dates being relative to this start date.

58. End month

Relative end date, month 1 marking the start date of the project, and all end dates being relative to this start date.

59. Milestone number

Milestone number:MS1, MS2, …, MSn

60. Delivery date for Milestone

Month in which the milestone will be achieved. Month 1 marking the start date of the project, and all delivery dates being relative to this start date.

61. Deliverable number

Deliverable numbers in order of delivery dates: D1 – Dn

62. Nature

Please indicate the nature of the deliverable using one of the following codes

R = Report, **P** = Prototype, **D** = Demonstrator, **O** = Other

63. Dissemination level

Please indicate the dissemination level using one of the following codes:

• **PU =** Public

• **PP =** Restricted to other programme participants (including the Commission Services)

• **RE =** Restricted to a group specified by the consortium (including the Commission Services)

• **CO =** Confidential, only for members of the consortium (including the Commission Services)

• **Restreint UE =** Classified with the classification level "Restreint UE" according to Commission Decision 2001/844 and amendments

• **Confidentiel UE =** Classified with the mention of the classification level "Confidentiel UE" according to Commission Decision 2001/844 and amendments

• **Secret UE =** Classified with the mention of the classification level "Secret UE" according to Commission Decision 2001/844 and amendments

64. Delivery date for Deliverable

Month in which the deliverables will be available. Month 1 marking the start date of the project, and all delivery dates being relative to this start date

65. Review number

Review number: RV1, RV2, ..., RVn

66. Tentative timing of reviews

Month after which the review will take place. Month 1 marking the start date of the project, and all delivery dates being relative to this start date.

67. Person-months per Deliverable

The total number of person-month allocated to each deliverable.

SEVENTH FRAMEWORK PROGRAMME

THEME [HEALTH.2010.2.4.1-3]
[Structuring clinical research in paediatric and adolescent oncology in Europe. FP7-HEALTH-2010-single-stage]

Grant agreement for: Network of Excellence

Annex I - "Description of Work"

Project acronym: ENCCA
Project full title: “EUROPEAN NETWORK for CANCER research in CHILDREN and ADOLESCENTS”

Grant Agreement no: 261474
Project Coordinator: Professor Ruth Ladenstein (CCRI, Austria)

Date of preparation of Annex I (latest version): 2012-10-15
Date of last change: 2014-06-16
Date of approval of Annex I by Commission:

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Part B- narrative information

B.1 Concept and objectives, progress beyond state of the art, s/t Methodology and workplan

B.1.1 Concept and objectives

Cancer is rare in children and has a distinct 'embryonal' biology that is very different from the typical epithelial cancers of adulthood. Cancer affects approximately 1 in 500 during childhood and adolescence. This represents only 1% of all cancers in humans, yet remains a significant health burden for our young citizens. While overall **survival rates** have doubled from 40% in the early 1970s to **nearly 80%** today (Gatta G, EJC, 2009)[1], cancer remains **the leading cause of death from disease beyond infancy in Europe** (Pritchard-Jones K, EJC, 2006)[2]. Almost 20,000 young people (aged up to-19 yrs) will be diagnosed with cancer this year in the EU. The majority can expect to be cured but survival rates are disproportionate across Europe and there are significant health problems in many survivors. This is a consequence of the long-term side effects of many current chemotherapy drugs and radiotherapy administered to the growing child. It is estimated that there are currently between 300,000 -500,000 adults in Europe will have survived a cancer treated in their youth. This number is set to grow as survival rates improve.

The improvement in survival **during the last 40 years** has been achieved through mainly **national and international collaborative clinical trial groups** setting the standards of care for these rare diseases and constantly seeking to improve outcomes through investigator-driven clinical trials (IDCT). To continue to improve survival rates, there is an increasing need for wider collaboration in order to enrol sufficient patients for properly powered studies. To date, the necessary multinational collaboration has developed on an 'ad hoc' basis, often dictated by geography, shared language or cultural values. The recent increase in resources and infrastructure required to IDCTs has placed further strains on these informal networks and highlighted the need for better integration and shared procedures. At the same time, it appears that progress in improving survival rates using current conventional chemotherapy agents has reached its limits and new approaches as well as new targeted therapies are needed.

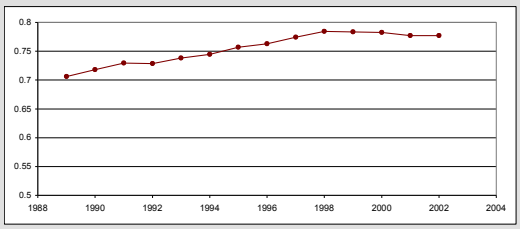


Figure 1: 5 year overall survival, all cancer, Europe EUROCARE_4 (1995-2002) Gatte G et al, EJC 2009

Despite the high cure rates achieved with current multimodality treatments, cancer remains the leading cause of death due to disease in children over the age of one year.
The challenge of the next decade will be to introduce the new generation of biologically targeted drugs to continue to make progress in improving survival rates and to improve the quality of cure of long-term survivors of childhood cancers.

Safe and effective **innovative therapies** are urgently needed to improve cure rates and the quality of cure in children. Advances in knowledge of the human genome, cancer cell biology and the development of high-throughput technologies have increased our knowledge of tumour biology. This has paved the way for identifying targets for the design of anticancer compounds with new mechanisms of action, new profiles of antitumour activity as well as new toxicity profiles.

[1] *Gatta G. et al., (2009).Survival of European children and young adults with cancer diagnosed 1995–2002. European Journal of Cancer.. 45 (6), 992-1005 ;*
[2] *Pritchard-Jones K, Kaatsch P, Steliarova-Foucher E, Stiller CA, Coebergh JW. (2006) Cancer in children and adolescents in Europe: developments over 20 years and future challenges. European Journal of Cancer. 42(13),2183-2190*

There has therefore been a dramatic increase in the number of new anticancer compounds under development worldwide, and oncology has become the leading area for drug development. However, the 'translational gap' between the basic scientific knowledge of paediatric tumour cell biology and defining the mechanisms that 'drive' these cancers remains wide.
Furthermore, **access for children to innovative compounds developed for adults** by pharmaceutical companies has been **extremely poor in Europe** in the last 20 years. This is in contrast to the USA, where many public programmes have provided easier access to new compounds to the paediatric oncology community. **ENCCA will speed up** and facilitate the **introduction of safe and effective innovative therapies** in the care of children and adolescents with cancer.

B.1.1.1 The need for new drugs for children with cancer

In light of the rapid expansion in new oncology drugs and the clear clinical need, it is **a societal issue to make new anticancer drugs available as soon as possible to children and adolescents** and to develop them in accordance with good clinical practice and ethical requirements. The most refractory paediatric diseases with an urgent therapeutic need are high-risk neuroblastoma, high-risk leukaemias, metastatic bone and soft tissue sarcomas, malignant brain tumours in particular brain stem tumours, and other metastatic tumour types, which together account for approximately one third of all paediatric cancers and for 80% of deaths.

The remaining two thirds are in need of efficacious alternatives to replace the chemotherapy drugs they currently need for cure, which confer risks of long-term side effects. **Prioritisation** of the plethora of molecularly targeted agents for clinical testing requires an improved level of knowledge of the biology of paediatric and adolescent cancers. Better preclinical model systems are needed to test-proof the mechanism and develop appropriate biomarkers for use in clinical trials. New statistical methodologies and designs are needed to make the most efficient use of the relatively small numbers of children available for clinical trials, especially early phase trials. Currently, this is fragmented activity and there is insufficient support within Europe to improve the preclinical and biological knowledge of childhood and adolescent cancers and to implement in an efficacious way the necessary clinical trials. Fortunately, the new regulatory framework in Europe has changed placing obligations and incentives on the pharmaceutical industry to develop paediatric investigation plans (PIPs) when an appropriate need is identified in the age group. While this should improve access to new drugs, industry will not have the capacity to test all of the possible paediatric oncology indications for their new products, in view of the small numbers of patients and resources required.

New drug development for children with cancer is therefore a shared responsibility; it can only be addressed by partnership with academia who provide access to the patients and knowledge of the disease subgroups, industry who can provide the new agents and initial knowledge of mechanisms of action and biomarkers, and regulators being sensitive to the need for innovation in trial design and endpoints. Parents and patients have an important voice too in this process, highlighting the clinical need and promoting high-quality trials that address relevant questions and are achievable. The recent EU Paediatric Medicine Regulation (entered into force on January 26th 2007, **Regulation (EC) No 1901/2006**) is a major initiative in favour of the development of safe and effective medicines for children and is already changing the landscape of new drug development for children with cancer significantly. It is crucial that this regulatory process meets the needs of children with cancer and is fully integrated into clinical and translational research to be run by or in partnership with the academic network.

ENCCA will contribute to making the European Paediatric Medicine initiative a success for children with cancer and to move on from the historical situation where standard treatments and recommendations for the commonly used anticancer drugs in children (dose, schedule, safety, toxicity profile, efficacy, pharmacokinetics) were established by the paediatric oncology community while 50% of these drugs remain unlicensed for paediatric use according to the pharmaceutical rules.

B.1.1.2 Tumour biology as the driver of therapeutic innovation in paediatric malignancies

Understanding the molecular and genetic mechanisms involved in tumour initiation, progression and metastasis is of crucial importance in order to develop **efficiently targeted drugs and therapeutic strategies** based on the tumour and patient characteristics. This is the promise of personalised medicine. This strategy is as relevant in paediatric malignancies as it is in adult cancers. There are already several examples of **biology-driven cancer care** in paediatric oncology. MYCN amplification and other genetic alterations are now routinely used for risk-adapted treatment of neuroblastoma. Molecularly-defined Minimal Residual Disease (MRD) is used daily to monitor the treatment of children with acute lymphoblastic leukemias. In the two clinical research groups, namely SIOPEN for neuroblastoma and IBFM for leukaemias, biologists, pathologists and cytologists have networked their activity to provide high-quality tests and to further develop additional biomarkers.

The development of innovative therapies needs to be based on a better understanding of tumour biology, especially identifying the 'drivers' of malignant behaviour and the influence of interactions between tumour and host factors. Since biology matters, there is a need to support and fund basic and translational research as well as the full development of compounds, infrastructure of clinical research and network of clinical centres.

There are numerous research teams in Europe working on the biology and genetics of paediatric malignancies that are internationally recognized for their skills and expertise. Several of these research teams have already joined their efforts in **EU-funded projects** under FP6, such as EET-pipeline, KidsCancerKinome and Childhope, in order to identify and validate potential new targets in paediatric malignancies and to generate biological databases. This research remains so far insufficiently linked to clinical research groups.

ENCCA will network biology and genetic research in the different paediatric tumours in order to mutualise databases and to achieve a critical mass of shared knowledge and expertise that will be exploited in to order to prioritise drug development and to develop a biology-based therapeutic strategy for each of the different paediatric malignancies.

B.1.1.3 Defragmentation of knowledge in Europe will increase efficiency in paediatric oncology clinical research

Current paediatric oncology clinical research in Europe is organised by a number of informal investigator –led groups, i.e.:

- The **different European leukaemia and tumour-type specific groups** (also known as EU disease groups) have been running clinical research in newly diagnosed patients (phase III trials) and in relapsed patients (phase II trials) for the last 30-40 years **(Tab. 1);** Some of these groups are well-organised and structured, such as SIOPEN and I-BFM while others are more informal, based on the commitment and willingness of European investigators to work together and develop prospective clinical research in paediatric malignancies whether they are frequent or rare.
- A network named **ITCC** (Innovative Therapies for Children with Cancer), an academic EU consortium was created five years ago to run early drug development across all of the paediatric tumour types and to serve as a "one-stop-shop" for drug development in Europe for pharmaceutical companies. This network, composed of 34 investigating centres, runs phase I and early phase II trials, both in leukaemias and malignant solid tumours, in collaboration with the EU disease groups. In addition, ITCC has expertise in biology, preclinical evaluation of relevant tumour *in vitro* and *in vivo* models, to identify relevant targets and prioritize anticancer compounds for their development in children.

- **Several groups** (e.g. SIOPEN, I-BFM) have also developed their capacity to run a **biology programme** (basic science, translational research and routine biology tests) in order to introduce biomarkers into the therapeutic decision making-process for each patient through prospective studies and to contribute to the prioritisation of new drugs to be studied in children.
- **Several academic institutions** have committed themselves to **sponsors and run investigator-led clinical trials** on behalf of the different disease groups. They have been facing major difficulties to run clinical trials since the implementation of the EU Clinical Trials Directive (Directive 2001/20/EC), as have many European academic institutions. All of them are ENCCA partners.
- EU-funded projects in the **FP6** include three STREP (Specific Targeted Research Projects) dedicated to innovative diagnosis and therapies for paediatric malignancies (**EET-Pipeline, KidsCancerKinome, Childhope**) and two networks of excellence for sarcomas in adults and children (**CONTICANET, EUROBONET**). (Tab. 1)
- EU-funded in the **FP7** include two STREPS on oncology products in the 'Off-patent medicines for children' call (**O3K, EPOC**). (Tab.1)

Therefore, European paediatric oncology clinical research has a strong track record of successful results as demonstrated by the current cure rate. However, it remains very fragmented with a fragile, voluntary infrastructure and an urgent need to strengthen inter-group collaborations.

ENCCA will network and integrate the different leukaemia and tumour groups in order to define and run a global strategy in Europe for the development of new drugs and biology-driven therapeutic strategies and to facilitate the implementation of clinical and translational research in all paediatric malignancies.

ENCCA will increase the critical mass of expertise and capacity to run trials and will ultimately spread 'know -how' to countries who are not currently major participants in clinical research. It will streamline the introduction of targeted compounds in standard care and thus facilitate the development of Paediatric Investigation Plans (PIPs), as requested by the European regulation (Art. 7 and Art. 8 of EU Paediatric Regulation (EC) No 1901/2006). This will also increase the likelihood for drug development to meet the needs of children and adolescents with cancer and thus ensure improvements in outcomes across Europe.

European Groups	Activity	Leader	Position	Institution	Country	ENCCA
IBFM	Haematological malignancies	Martin Schrappe	Chair	University of Kiel	Germany	ENCCA partner 5
EORTC Childhood Leukaemia Group	Leukaemias	Yves Benoit	Chair	University Hospital Ghent	Belgium	Member of the Council
Hodgkin's Lymphoma Inter-Group	Hodgkin disease	Judith Landman-Parker	Inter-group Chair	Hopital d'enfant Armand Trousseau, Paris	France	Member of the Council
		Dieter Korholz	Inter-group Chair	Halle University, Leipsig	Germany	Member of the Council
		Hamish Wallace	Inter-group Chair	Royal Hospital for Sick Children	UK	Member of the Council
EIC-NHL Inter-Group	Non-Hodgkin Lymphomas	Catherine Patte	Co-Chair	Institut Gustave Roussy	France	ENCCA partner 6
		Alfred Reiter	Co-Chair	University of Giessen	Germany	Member of the Council
SIOPE Brain group	Brain tumours	François Doz	Chair	Institut Curie	France	ENCCA partner 16
SIOPEN	Neuroblastoma	Ruth Ladenstein	President	CCRI	Austria	ENCCA partner 1
ITCC	Early drug evaluation (biology, phase I and II)	Gilles Vassal	Chair	Institut Gustave Roussy	France	ENCCA partner 6
EpSSG	Soft Tissue Sarcomas	Gianni Bisogno	Chair	University of Padova	Italy	ENCCA partner 36
		Odile Oberlin	Co-Chair	Institut Gustave Roussy	France	ENCCA partner 6
Euro-Ewings	Ewing's Sarcoma	Herbert Juergens	Chair	University of Mûnster	Germany	Member of the Council
EURAMOS	Osteosarcoma	Stefan Bielack	Chair	Olga Hospital, Stuttgart	Germany	ENCAA partner 32
SIOP RTSG	Renal tumours	Norbert Graf	Chair	University of Saarland, Homburg	Germany	Member of the Council
		Kathy Pritchard-Jones	Co-Chair	UCL Institute of Child Health	UK	ENCCA partner 4
SIOPEL	Hepatoblastoma	Piotr Czauderna	Chair	Academia Medyczna Gdansku, Gdansk	Poland	ENCCA partner 12
Histiocyte Society	Histiocytic disorders	Jan-Inge Henter	Chair	Karolinska Institute	Sweden	ENCAA partner 27

EU projects						
FP6-KidsCancerKinome	STREP biology to targets	Gilles Vassal Huib Caron	Co-ordinator Co-ordinator	Institut Gustave Roussy Amsterdam Medical Centre	France Netherlands	ENCCA partner 6 ENCCA partner 21
FP6- EET pipeline	STREP biology to targets	Angelika Eggert	Co-ordinator	Universitaetsklinikum Essen	German	ENCCA partner 8
FP6-Childhope	STREP biology to targets	Martin Pule	Co-ordinator	Great Ormond Street Hospital, London	UK	Member of the Council
FP6 - Eurobonet	NOE Bone tumours adults and children	Hogendoorn CW Pancras	Co-ordinator	Academisch Ziekenhuis Leiden - Leids universitair medisch centrum	Netherlands	ENCCA partner 26
FP6-Conticanet	NOE Soft Tissue Sarcomas adults and children	Jean-Yves Blay	Co-ordinator	Centre Léon Bérard, Lyon	France	ENCCA partner 23
FP-7 O3K	New oral formulation of off -patent drugs	Gilles Vassal	Co-ordinator	Institut Gustave Roussy	France	ENCCA partner 6
FP7-EPOC	Pharmacokinetics of off-patent drugs in infants	Alan Boddy	Co-ordinator	University of Newcastle	UK	Member of the Council
FP7 PanCareSurFup	Survivorship and QOL	Lars Hjorth Rod Skinner Riccardo Haupt	Chair Co-Chair Co-Chair	Lund University Newcastle University Instituto Gaslini	Sweden UK	Member of the Council associate partner
FP7 EurocanPlatform	A European Platform for Translational Cancer Research	Ulrik Ringborg (Per Kogner)	Co-ordinator	Karolinska Institute	Sweden	ENCAA partner 27
FP7 BBMRI	Biobanking and Biomolecular Resources Research Infrastructure	Kurt Zatloukal	Co-ordinator	Medical University of Graz	Austria	Member of the Council

Table 1: European leukaemia and tumour groups

B.1.1.4 The challenges of clinical research in children

Integration of research and care is a hallmark of paediatric oncology and has lead to the current cure rates with available multidisciplinary treatments. More than 80% of children are treated either within clinical trials from phase I to phase III or within prospectively-monitored therapeutic protocols that are applied in each paediatric malignancy and used by most paediatric oncology centres. These protocols standardise treatment and care across Europe, provide clinical information linked to biological samples, monitor the cure rate and provide the frame for the evaluation of long-term sequellae.

However, clinical trials involving children are amongst the most challenging types of studies performed from a scientific, ethical and medical perspective. The **current issues in paediatric oncology clinical research** are numerous:

- **Access to drugs** developed by industry remains so far **limited and difficult** even though the EU Paediatric Medicines Regulation has significantly changed the framework for drug development in children[1]
- There is a **lack of harmonisation of clinical research**. Moreover such research is **fragmented** across many informal groups with a lack of efficient communication between them. In addition, running paediatric investigator-driven clinical trials has become increasingly **difficult after the EU Clinical Trial Directive[2],** as well as for all academia-sponsored trials – this has dramatically increased the administrative burden and introduced new financial issues (insurance, free drug) as highlighted by ESF (www.esf.org), the European Science Foundation and a survey of the European Clinical Trial Groups undertaken by SIOP Europe, the European Society for Paediatric Oncology
- **Biological knowledge** is insufficiently linked to clinical research despite several internationally-recognised research laboratories dedicating their activity to paediatric malignancies in the field of biology, preclinical evaluation and pharmacology
- Available financial resources for clinical research are limited and fragmented; sources include national research funding programmes, charity donations and other private funders, with major differences between EU member states. Prioritisation of these resources for paediatric cancer trials is necessary to maintain quality of care
- **Many cultural differences exist** between European member states **in terms of ethics** and attitudes to experimental therapies and clinical research. There is a need to carefully address and monitor ethical issues in paediatric clinical research
- It is crucial that young oncologists and healthcare professionals are fully informed about clinical research in order to reinforce the capacity to integrate care and research for children in the long-term

Although the European Paediatric Medicines Regulation will greatly encourage pharmaceutical companies to develop paediatric drugs, it is unlikely that all efforts needed from basic science to clinical research will be funded by private industry alone. Indeed, a large part of the clinical research needed to introduce safe and effective targeted drugs into standard care and to set up prospective cohorts that will allow evaluation of long-term toxicity in paediatric cancer survivors needs to be run through investigator-driven clinical research, as highlighted by the European Science Foundation (ESF) Report (Investigator-Driven Clinical Trials report). A combination of EU and national public funding as well as charitable donations is necessary to deliver the research agenda that will improve the cure rate and quality of cure of children and adolescents with cancer.

[1] *Vassal, G., 2009. Will children with cancer benefit from the new European Paediatric Medicines Regulation? European Journal of Cancer, Volume 45, Issue 9, Pages 1535-1546*

[2] *Pritchard-Jones K; SIOP Europe. (2008) Clinical trials for children with cancer in Europe - still a long way from harmonisation: a report from SIOP Europe. European Journal of Cancer. 44(15),2106-2111*

Clinical Trials in FP7											
Project Acrom	Project Title										
ENCCA	European Network for Cancer research in children and adolescents.										
CT acronym	EudraCT	CT core of project?	Number of patients in CT	Single/multiple trial site(s)	Phases	Type of intervention	Disease area	Children involved?	Elderly involved?	Rare disease?	"Title" of the trial + comments, explanations
EWING 2008	2010-003658-13	CT is included in project	1383	multinational	phase III	pharmaceuticals (incl. therapeutic vaccines)	cancer	included	not included	main target	A randomised, international multicentre phase III clincial trial in localized and disseminated Ewing Sarcoma (EWING 2008)
HERBY	2010-022189-28	CT is included in project	120	multinational	phase II	pharmaceuticals (incl. therapeutic vaccines)	cancer	included	not included	main target	A phase II open-label, randomised, multi-centre comaprative study of bevacizumab-based therapy in paediatric patients with newly diagnosed supatentorial high-grade glioma.
BLINATUMOMAB	2010-024264-18	CT is included in project	51	multinational	phase I/II	antibody	cancer	included	not included	main target	A Single-Arm Multicenter Phase II Study preceded by Dose Evaluation to Investigate the Efficacy, Safety , and Tolerability of the BiTE Antibody Clinatumomab (MT103) in Pediatric and Adolescet Patients with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (ALL)
BORTEZOMIB	2009-014037-25	CT is included in project	24	multinational	phase II	proteasome inhibitor	cancer	included	not included	main target	Bortezomib (Vercade): a feasibility and phase II study in childood relapsed acute lymphobalstic leukemia.
AIEOP BFM ALL2009	2007-004270-43	CT is included in project	4750	multinational	phase III	pharmaceuticals (incl. therapeutic vaccines)	cancer	main target	not included	main target	Interantional collaborative tratement protocol for children and adolescents with acute lymphoblastic leukemia
LINES	2010-021396-81	CT is included in project	685	multinational	phase III	other	cancer	main target	not included	main target	European Low and Intermediate Risk Neuroblastoma Protocol (Phase III) - ES
BEACON	2012-000072-42	CT is included in project	120	multinational	phase II	pharmaceuticals (incl. therapeutic vaccines)	cancer	main target	not included	main target	A randomised phase IIbtrial of bevacizumab added to temozolomide +/- irinitecan for children with refractory/ralpsed neuroblastoma-Beacon-Neuroblastoma Trial
VIDAZA	2010-022235-10	CT is included in project	60	multinational	phase I/II	pharmaceuticals (incl. therapeutic vaccines)	cancer	main target	not included	main target	A Phase I/II study of Azacitidine (Vidaza®) in pediatric patients with newly diagnosed or relapsed high-grade pediatric MDS or JMML A collaborative EWOG-MDS and ITCC study Study ITCC-015/EWOG-MDS-Azacytidine-2010 or VZ-MDS-PI-0246)
NECTAR	2011-005923-42	CT is included in project	58	multinational	phase I	pharmaceuticals (incl. therapeutic vaccines)	cancer	main target	not included	main target	A phase I trial of NECTAR (Nelarabine, Etoposide and Cyclophosphamide) in T-ALL relapse: a joint study of TACL and POETC

ENCCA will establish and run a global strategy in Europe to address the challenge of cancer in children and adolescents, where it remains the number one killer from disease (or non-accidental cause of death) beyond one year of age. This strategy will implement harmonised therapy strategies that increase cancer cure, improve quality-of-life and reduce long-term side effects in children and adolescents.

ENCCA will cooperate with ongoing transnational EU-funded projects such as ECRIN (European Clinical Research Infrastructures Network**), PanCareSurFup, BBMRI, EuroCanPlatform and CONTICANET, EUROBONET** and will contribute to and profit from the ongoing European initiatives to facilitate academic clinical research.

ENCCA will streamline strategic efforts towards long-term sustainability through financial durability from the different public funding bodies and charities which will be asked to co-fund the clinical research agenda run at the European level.

B.1.1.5 High inequality of care in Europe

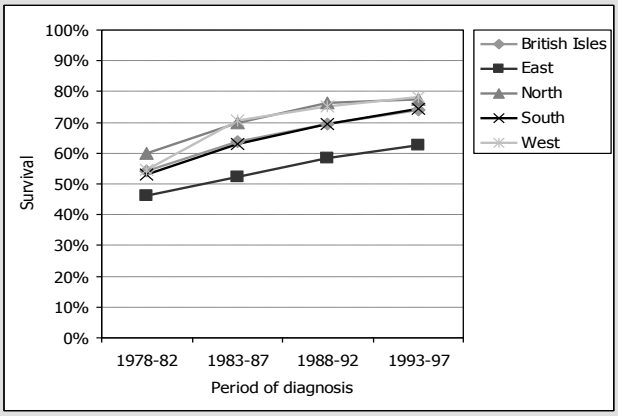


Figure 2: 5 year overall survival for all childhood cancers, by European region and period of diagnosis, the ACCIS project. Magnani et al, 2006, EJC 42:1981-2005

There are important differences in healthcare organisation between EU member states, resulting in significant inequity of access to appropriate specialist care and disproportionate outcomes for children and adolescents with cancer across Europe **(Fig 2)**.

The reasons for this are complex but include the need for current treatment protocols to be delivered by multi-disciplinary and multi-professional teams for successful outcomes. Such comprehensive care practices are not yet practised throughout Europe. Adolescents particularly are facing difficulties in accessing appropriate expertise for their condition.

Indeed **cancer in adolescents** raises particular issues: delays in diagnosis, low participation in clinical trials, difficulties accessing the best standard of care for their tumour type, and referral to clinical centres with the appropriate expertise. The main tumours observed in this population are sarcomas of the bone and soft tissues, germ cell tumours and lymphomas.

ENCCA will identify harmonised pathways for a more **equal, efficient and safe care** of children and adolescents with cancer and provide referral schemes for rapid access to the best standard of care.

B.1.1.6 The objectives of the ENCCA Network of Excellence

The **ENCCA vision** is to establish a durable, integrated clinical and translational research infrastructure for Europe that will define and implement its research strategy and will facilitate the necessary investigator-driven clinical trials to introduce the new generation of biologically targeted drugs into standard of care for children and adolescents with cancer. This will lead to more efficacious and less toxic therapies that will maximise the quality of life of the increasing number of survivors of cancer at a young age in Europe and allow them to assume their proper place in society. This biologically-driven research agenda will improve the training methods of clinical investigators and translational scientists of the future to spread excellence and increase the capacity to participate in research and monitor outcomes across Europe. Patients and their families will be full partners and will be better informed about the need for and processes of clinical research. They will be in a better situation to care for the long-term health risks for children and potential outcomes. Drug development for children will be accelerated in partnership with industry through improved access to young patients with cancer, to academic expertise in care, clinical and biological research. All of this will be achieved with respect for the highest ethical and patient safety standards.

These goals will be achieved by a new integrated strategy to bring all stakeholders to the table in a timely and efficacious manner. ENCCA will address the needs of all the current multinational clinical trial groups in the field and aims to create a **Virtual European Institute for Research in Childhood and Adolescent Cancers** for the benefit of all those suffering from these diseases in Europe and beyond. ENCCA will provide them with common tools and approaches to solve the bottlenecks in testing new therapeutic strategies for those rare diseases in a vulnerable age group and in running a competitive clinical research agenda. ENCCA will be led by the most active European research institutes in the field, recognised as being at the forefront of excellence. Ongoing efforts to coordinate European and US clinical research in the field will be reinforced through increased communication and implementation of collaborative studies when relevant

The ENCCA Network of Excellence aims to bring together the existing informal **European Clinical Trial Groups in Paediatric and Adolescent Oncology** towards a **European Virtual Institute** to reduce knowledge fragmentation and enhance their communication, collaboration and management of effective clinical research in Europe. The objective is to **restructure knowledge-sharing** through the integration of the whole chain of stakeholders (epidemiologists, biologists, clinicians, drug developers, statisticians, industrials, imaging developers and IT partners in electronic health records, parents and ethical and regular authorities) and to support the **acceleration of the development of innovative therapeutic strategies** for children and adolescents with cancer. This will in turn facilitate access to **efficient cure services** for children and adolescents throughout Europe and support **enhanced interest in scientific and clinical careers** for young European students. It will in addition contribute to better care and quality of life for children, adolescents and parents.

The **European Clinical Research Council for Paediatric and Adolescent Oncology (ECRC)** will be composed of the Chairmen of the different European disease groups and the Chairs of the national paediatric oncology societies and will contribute significantly to the political vision of creating a European Research Area (ERA). This Council will help to address common issues in paediatric oncology, facilitate access of the various groups to the ENCCA network and thus encourage the creation of the links between ENCCA and the paediatric and adolescent oncology community through the established disease-groups.

B.1.1.7 ENCCA Goals

1. Structure and integrate clinical and translational research for children and young people with cancer on a European scale and to create a long-term, sustainable operative platform.
2. Use the existing European research **tools and equipment** efficiently in paediatric oncology.
3. Promote **innovative methodology and designs for clinical trials**, as well as their implementation and integration to address the specific needs in rare diseases
4. Initiate **harmonised therapeutic strategies** by increasing significantly access to knowledge on paediatric tumour biology and interactions in between tumour and host. Facilitate strategic discussions and joint research between scientists and clinical investigators for prioritisation of drugs to be studied in the paediatric age range and the translation of this knowledge into biology-driven and risk-adapted treatments
5. Facilitate **the sharing of knowledge** and technologies across disciplines and the chain of all stakeholders in Europe (academia, parent and patient organisations, pharmaceutical companies and regulatory bodies) and improve the **career structure in paediatric and adolescent oncology** for clinical and translational medicine.
6. Eventually improve substantially the **quality of life of children and adolescents** with cancer, in particular the long-term side-effects of current and future treatments
7. Propose **common ethical definitions of issues and solutions** adapted to national and cultural requirements, while monitoring ethical issues in the implementation of the European agenda in clinical research.
8. **Streamline and facilitate funding of clinical research** from EU and national public bodies as well as from charities and other private funds.

It is crucial that ENCCA establishes strong links with all existing formal and informal groups in order to (a) implement its strategy, (b) raise the quality and efficiency of clinical research across Europe and (c) work on long-term sustainability towards a virtual institute.

As ENCCA will integrate pre-existing structures of institutions willing to work together it is not in need to be built from scratch ENCCA is created by **partners who are used working together for a long time** to run clinical research and who are willing to improve significantly their collaboration through a better integration and a shared research strategy in order to address the challenges of curing more children with cancer, in a cost-effective manner in terms of quality of survival.

The ultimate goals of the ENCCA Network of Excellence (NoE) are to

- **Increase cure for children and adolescents with cancer**
- **Improve quality of life during treatment and quality of survival**
- **Improve access to the best standards of care and increase the capacity to deliver this standard throughout Europe**

More specifically the objectives of the ENCCA NoE are presented in table 2 grouped in three types of activities:

1) Networking/ Integrating Activities
2) Joint Research Activities
3) Spread of excellence activities

Networking/ Integrating Activities	Common structure and sustainable integration of clinical trials in paediatric and adolescent oncology in Europe	Create a European Clinical Research Council in paediatric oncology Define a European Global strategy for clinical and translational research in paediatric and adolescent oncology Establish a European Virtual Institute Facilitate coordinated access of European researchers to biological and preclinical knowledge, relevant databases for research and to expert clinical facilities with easier mobility of staff and resources Ensure a balanced scorecard of enhanced coordination and performance indicators towards integration Prepare a sustainable approach for financial and legal durability
	Efficient sharing of clinical data and tools	Promote a common language among European databases and tools by reinforcing common standards and protocols Integrate data-sharing and common tools Optimizing availability of tissues for biology research Share and reinforce imaging tools Integrate biology into clinical trials
	Joint development in methodology for clinical trial integration and design	Develop new statistical approaches to clinical trial design in rare diseases Develop new methods for definition and validation of risk-based patient stratifications Develop a new approach for analysis of recurrent events and competing events and long-term outcomes
Joint Research Activities	Towards harmonized therapeutic strategies	Early evaluation/prioritization of drugs for childhood and ado cancers Run high-quality Paediatric Investigation Plans (PIP) and integrate them into the clinical research programmes for each paediatric malignancy, Introduce safe and effective innovative drugs into standard of care for all patients using a biology-driven approach Development and implementation of diagnostic standards Establishment of a harmonized pipeline for molecular diagnostics in a European virtual laboratory Harmonization and integration of clinical platforms for the introduction of molecularly targeted treatment in leukaemias Establish methods for prospective clinical studies using enhanced data collection through cancer registration and other data sources, to continually monitor outcomes Enable clinical research in very rare tumours Evaluate quality of life and quality of survival in children and adolescents treated for cancer
Spread of Excellence	Thorough sharing of knowledge	Implementation of a European paediatric and adolescent oncology Educational and Training Programme Advanced training in integrating biology into clinical research Contribute to a European dimension in research and clinical careers in childhood and adolescent cancer Improve information for parents and patients Intensify dialogue and interactions with industry and regulators as well as promoting citizen awareness Promote interactions with other pan-European networks and projects Use the integrated platforms to promote wider international cooperation for European researchers Make available to each cancer survivor a document summarizing treatments received and advice on follow-up treatment and care
	Improve access to care and research for adolescents	Promote cancer awareness to ensure timely diagnosis for children and adolescents with cancer Define and improve pathways of care Promote healthy behaviour in survivors of childhood cancer Define and improve referral schemes to provide patients with access to expert centres through networks to provide best standards of care
	Ethical issues	Understand cultural and practical differences in ethical issues Propose common guidelines for clinical trials and treatment standards Monitor ethical aspects of clinical research in children

Table 2: ENCCA Network of Excellence objectives

B.1.2 Progress beyond the state of art

B.1.2.1 Clinical trials for children with cancer in Europe – still a long way towards harmonisation

The majority of clinical trials for children and adolescents with cancer are investigator-driven with variable models of sponsorship by academic institutions. To date, there is a lack of co-ordination and inevitably much duplication of the massive efforts and resources invested by the Clinical trial groups to meet the requirements of the EU Clinical Trials Directive (EU CTD). The variable implementation of the EU CTD into national law in 2004 caused additional problems for clinical trials in children.[1] In particular, the high proportion of anti-cancer 'off-label' drugs used in the paediatric age group due to the lack of appropriately licensed drugs has led to highly variable definitions of Investigational Medicinal Products (IMPs) across Europe. This has had major implications for the bureaucracy and expense of pharmacovigilance and insurance requirements, which could be reduced by better harmonisation of procedures and a European-level dialogue with regulators and ethical approval boards. While the EU CTD aims to standardise the regulation and quality of trials, this has not yet been achieved in practice, while there has been no noticeable impact on the already excellent record for children's safety in research participation.

ENCCA NoE vision:
There is an urgent need to work with the clinical trial groups to define standard approaches that increase the efficiency of implementing Investigator-Driven Clinical trials (IDCT) and help define a pragmatic approach to risk-based assessment of trials in children. ENCCA expects to cooperate with ECRIN and BBMRI to contribute to the improvement and facilitation of academic clinical research in Europe.

B.1.2.2 Sharing data and tools

While there are increasing amounts of high-quality genomic and other biological data available on childhood cancers, sharing this data is challenging and affects the achievement of a higher level of understanding of the biology of cancer in this young age group. Reasons for this lack of cohesion include issues such as inappropriate 'architectures' (the format in which the data is stored and shared), the coding of data and its accessibility. It is often difficult to obtain data from drug manufacturers about their licensed drugs if a researcher wishes to investigate the product for the purpose of scientific research or to test the drug's effects on children for which the product was not originally licensed. Gaining access to data-sharing is a complex procedure, with numerous difficulties faced such as the curation and preservation of data, the ethical use of shared data, consent to use the data and regulatory mechanisms to ensure that the data is used appropriately. Sharing data is mandatory to integrate knowledge and information from the different trials in Europe and to effectively monitor outcomes, including long-term sequellae.

ENCCA NoE vision is to encourage data-sharing and facilitate and support this through a common knowledge management platform that will be established. ENCCA will permit to explicit European policy on data sharing and continue work to improve access to datasets, support data-sharing by installation of relevant architectures and harmonise data management.

B.1.2.3 Integrate Biology knowledge to guide innovative targeted therapy development for the management of childhood tumours

Biology plays a major role in identifying relevant therapeutic targets for safe and efficiently targeted drugs. Nearly all efforts in oncology are currently on the development of biology-driven approaches to treatment stratification towards personalized medicine in order to better adapt individual treatment to the risks (of the disease) by the use and validation of both prognostic and predictive biomarkers.

[1] *Pritchard-Jones, K., 2008. Clinical trials for children with cancer in Europe – Still a long way from harmonisation: A report from SIOP Europe European Journal of Cancer, Volume 44 pp. 2106 – 2111*

Improved technologies for more selective radiation therapy (proton therapy, IMRT, stereo radiotherapy) and more accurate imaging, including functional imaging can provide non-invasive biomarkers of prognosis that could enhance childhood tumour management.

ENCCA NoE vision:
There is a need to integrate and increase knowledge of paediatric tumour biology, to translate to drug development and to harmonise biological datasets and experimental data. In addition, it is necessary to develop virtual bio banking, establish relevant tumour models and improve access to high-technology platforms that are currently available. Furthermore, it is vital to improve collaboration between biology and clinical research teams. ENCCA will put in place the structures which will allow the uptake of functional imaging into clinical trials across the network for children with cancer.

B.1.2.4 Enhance innovative methodology and designs for clinical trials

The challenge in paediatric oncology research is to run trials in rare diseases. There is a need to make a distinction between studies whose risk is equivalent to standard (usual) care (including randomised trials that compare already marketed and labelled or 'tried and tested' treatments) and those that are aimed at innovation (e.g. testing a new drug). The current classification of trials does not make this distinction and has similar requirements for all the categories of interventional trials on medicinal products. A harmonised regulatory approach to clinical trials based on risk needs to be developed and the requirements of different types of clinical trials needs to be reviewed. Regulatory requirements need to be adapted depending on the risk, especially where the risk is similar to 'usual care'. EMA standards for approval of medicines for human use are not fully adapted to the paediatric population suffering from a life-threatening disease. For example, single agent Phase II or Phase III *versus* best supportive care in relapse which is a standard for regulatory approval in adults are neither feasible, nor acceptable nor ethical in children. In addition, it needs 5 to 7 years to run a phase III trial in the most « frequent » paediatric malignancies, due to the small numbers of patients available. It is even more difficult or impossible for the rarer paediatric malignancies. Thus it will not be feasible to run such single agent phase III trials for each drug of interest. Innovative designs and methodology are required to address drug development in paediatric malignancies which are rare and individually, very rare, diseases.

ENCCA NoE vision:
There is a need to create a virtual office of networked biostatisticians who will develop new methods for design and statistical analyses of clinical studies in paediatric and adolescent oncology with more sophisticated patient stratification. The increased complexity of biological studies where new targeted therapies need to be studied in often rare, molecularly-defined subgroups of patients necessitates more sophisticated statistical risk-based methodologies to be developed for collaborative trials at a European level. This virtual office will be accessible for the development of clinical trials within ENCCA as well as other trials run in the EU disease group programmes.

B.1.2.5 Create the conditions for financial sustainability and co-funding of the research agenda

Proper development and evaluation of innovative drugs and their introduction in children's cancer treatment will be supported only in part by pharmaceutical companies. This is illustrated by a preliminary analysis of PIPs in oncology that have been approved by EMA.[1] A large part of this research will be run through IDCT and public funding including charity donations is required. In addition, progress in paediatric oncology for higher cure rates and quality of cure will be achieved through large European academia trials and prospective studies. The introduction of innovative therapies into standard care for cancer in children should be considered as the priority for the next 15 years in order to improve child health in Europe.

[1] Vassal, G., 2009. *Will children with cancer benefit from the new European Paediatric Medicines Regulation?* European Journal of Cancer, *Volume 45, Issue 9, Pages 1535-1546*

As such, this research, beyond the strict drug development activity necessary for regulatory approval, needs to be supported by funding from the EU member states and charity organisations.

ENCCA NoE vision:
This project has prepared specific actions in order to provide a durable structure and financial sustainability for the network. One of the most important actions is the creation of a financing option assessment activity in order to streamline existing funding opportunities in EU member states, stimulate collaborations between academia and industry and improve visibility of the research agenda and goals for public and private funders. The creation of new mechanisms to facilitate the identification of funds is a high priority for ENCCA in order to provide a rapid introduction of new therapies and to develop high-quality and competitive clinical research that will meet the needs of children with cancer.

B.1.2.6 Improve access to new anticancer drugs for children in Europe through a biology-driven drug development strategy

There are not enough anticancer drugs in paediatrics in Europe momentarily in comparison to the US where a NCI (National Cancer Institute) programme has provided easy access to industry pipelines for many years. There are more than 600 anticancer compounds in clinical development each year in adults. Thus, the challenge is to select the best and most promising ones and introduce them into the standard care of children with cancer in a timely fashion. Effective prioritisation needs to be set up, and clinical development (for example the duration of trials and time for administrative processes) must be accelerated and facilitated through networks of qualified centres as well as the use of innovative designs that will reduce the number of patients required in the early phases of development. Indeed, there are more than 400 European clinical centres taking care of children with cancer in 27 member states. Early phase (I and II) drug trials require to be run in a limited number of qualified centres before their use in larger phase III trials. Referring patients to another centre for a specific treatment is not yet common practice in all member states. This limits access to innovative therapies for children across Europe.

ENCCA NoE vision:
There is a need to reinforce and develop existing cooperation between the Early Drug Development group and the EU disease groups in order to prioritise and streamline the development of innovative therapies in a comprehensive and coordinated programme. The goal is to run biology-based drug development programme in each of the main malignancies, within the regulatory frame set-up by the European Paediatric Medicines Regulation, through a strong partnership between the paediatric oncology community, the pharmaceutical industry and the regulatory bodies

B.1.2.7 Develop biology-driven treatments towards personalized medicines for both leukaemias and malignant solid tumours

With very few exceptions, the majority of children and adolescents with haematological neoplasms or solid tumours are treated on toxic multi-modality regimens including noxious non-specific anti-cancer chemotherapeutic agents which have been on the market already for decades. Although major improvements have been achieved over the last 40 years with three quarters of children and adolescents with cancer expected to survive their disease today, these advances are mainly based on clinical studies that have refined risk-adaptation of conventional treatment strategies to tailor treatment. The tremendous amount of biological and genetic information on cancer cells that has been gained during the same time period is has impacted on improved accuracy of diagnosis and, to a lesser extent, on clinical use for risk adaptation in a limited number of paediatric cancers.
However, this knowledge lacks a true translation into direct specific clinical treatment applications.

ENCCA NoE vision:
There is a clear need for a deeper integration of biological and genetic information with diagnostic and therapeutic strategies in clinical trials to develop clinically applied targeted therapies for children and adolescents with cancer. This will improve risk stratification for application of current therapies and identify subgroups that might benefit from specific targeted therapies. ENCCA will work with the major clinical trial groups within Europe to facilitate integration of evaluation of biological prognostic factors into phase III clinical trials. This will lead to improved therapeutic strategies by combining complex biological and genetic data with novel molecular and imaging measures of treatment response and risk group. This will lead to the timely introduction of personalized biology-driven treatment approaches based on molecular characteristics of each patient's malignant cells and hold the potential to minimise ineffective adjuvant therapy for those patients not in need of it. Thus, ENCCA will facilitate the practical translation of comprehensive molecular information into clinical application for children and adolescents with cancer to finally generate valuable patient-oriented output.

B.1.2.8 Reinforce integration of research and care for diseases with a good prognosis with current multimodality treatments

High rates of enrolment of children into phase III clinical trials have underpinned the continued improvements in survival in the last 40 years. However, availability of a comprehensive portfolio of phase III trials for all diagnostic groups is no longer sustainable with the administrative and financial resources required to run IMP-trials under the current regulatory framework. Hence the highly successful culture of close integration of clinical research and delivering the best standard of care is threatened. For diseases with an excellent prognosis with multi-modality treatments such as Wilms' tumour, and some leukaemias there is no rationale to run a phase III trial. Thus, there is an urgent need to solve the issue of prospective clinical studies that will generate clinical information, allow biological sampling, monitor outcomes and generate large cohorts of patients to improve risk stratification and adequately study long-term side effects.

ENCCA vision:
Every newly diagnosed child and adolescent with cancer in Europe should be offered registration in a relevant clinical trial or prospective clinical study, in order to properly monitor outcomes and efficacy of front line treatments. This can be achieved by working with the existing cancer registries and available national sources of health data to establish prospective clinical registries with enhanced detail of clinical information so that overall burden of therapy and relapse free survival can be continuously monitored and **quality of cure can be improved**. Wide participation in these studies will increase the expertise of their treatment centres through involvement in clinical research and structured outcome monitoring by centre, region or country. This should ensure excellent survival rates are achieved across Europe. This approach to data collection will provide a generic approach to monitoring for long term side effects of new agents and facilitate the implementation of clinical studies in tumour types with a good prognosis with standard therapies.

B.1.2.9 Solve the issue of running clinical research in very rare tumours

There are some very rare paediatric malignancies such as hepatoblastoma, malignant histiocytosis, GIST, medullary thyroid cancer, chronic myeloid leukaemia with less than 150 cases yearly in Europe, or even less. These patients should not be denied access to innovative therapies and improved multimodality treatments. New tools and designs to develop clinical research for these very rare patients must be invented, using the advantage of web-based technology and the experience gained by experts in the field of non-cancer rare diseases, such as Orphanet (portal for rare diseases and orphan drugs).

ENCCA vision:
There is a need to develop the technology to run clinical trials for limited cohorts of patients who are treated in a large number of centres, and to further develop international cooperation between Europe and, in particular the Children Oncology Group of North America.

B.1.2.10 Evaluation of long-term side-effects and quality of cure

As a result of the ever-increasing success rates achieved over recent decades in paediatric oncology, an increasing number of children and adolescents have successfully overcome their cancer experience and have or are about to become adults. It is estimated that one in every 750 persons in Europe is a survivor of childhood cancer and that between 300,000 and 500,000 individuals former childhood cancer patients are now living in Europe. Their median age is estimated to be 21 years and many are already well beyond the 50th year of age.
This cure, however, comes at a cost. Long-term side effects of chemotherapy or radiotherapy as of surgery given to treat the original cancer during childhood increase the risk of developing chronic health conditions and may affect Quality of Survivorship (QoS). Children with brain tumours or with tumours occurring at critical ages for psychological development are at an increased risk for poor QoS. Systematic assessment of QoS is an essential component of treatment trials in order to understand the consequences of new treatments for QoS, especially in brain tumours, and on-line methods promise a cost-effective way to achieve this at a European level. Childhood cancer long-term survivors (CCLTS) will eventually transfer from the paediatric to the adult setting.

Communication between the paediatric clinic who gave the cancer treatment many years earlier and the institutions where the adolescents or adult CCLTSs seek medical care is often insufficient, and lacking in important medical information. A standardised document for use by paediatric oncologists is required to provide each cancer survivor with an accurate therapeutic history and recommendations for preventative strategies and follow-up to allow early diagnosis of conditions that may be better treated if detected at an early stage. To address specific research questions on major health outcomes, under the 'HEALTH 2010.2.4.1-7' FP7 call, 'Predicting long-term side effects to cancer therapy" a research project **(PanCareSurFup)** has been funded. Based on a European cohort of about 100,000 CCLTS identified through different types of registries active in Europe, *PanCareSurFup* aims to provide unbiased and reliable measures of incidence and risk for some of the most serious and frequent adverse health outcomes. The same project will include the development of guidelines for harmonised long-term follow-up for childhood cancer survivors.
The PanCareSurFup project is complementary to the activities proposed by ENCCA in the present proposal, in particular WPs 11, 15 and this WP (13), with no duplication of effort.

ENCCA NoE vision:
ENCCA will interact with PanCareSurFup and in this framework will address the issue of QoS and methods for assuring effective long-term follow-up care. Detailed methods for assessing QoS using web-based instruments will be developed and translated into different languages. Medulloblastoma patients enrolled in standardised protocols will be involved in the pilot study.
ENCCA will also promote and pilot methods to ensure that each childhood cancer survivor will receive electronic and paper documentation of the cumulative doses of therapies received. On these premises a "survivorship passport" will be developed which will provide advice for follow-up and primary and secondary prevention strategies based on guidelines and previous medical history of each survivor.

B.1.2.11 Patient-oriented research as an attractive career for clinicians

The attractiveness of a career in clinical academic medicine has declined in recent years and this has resulted in a shortage of qualified researchers. Part of the problem has been ascribed to a lack of job security and uncertain future prospects and the absence of a clear well–defined and predictable career path for clinical investigators. Academic freedom appears to be diminishing with researchers being constrained by regulations and guidelines and an increasing demand for efficacy, which leaves less latitude for imaginative, innovative research. In addition there is a lack of mobility of researchers.

ENCCA NoE vision:
ENCCA project will encourage young people into clinical research as an attractive career option by improving career prospects and training in Europe though an accredited scheme and by creating optimal conditions for such careers at the European level. In order to increase mobility in Europe and make research more interesting and efficient through better knowledge, ENCCA proposes to support an e-mobility centre providing high-quality information and optimal facilities to prepare clinicians mobility and host them in different European countries. Moreover high-quality training sessions are programmed that will permit access to high-level information and motivate young researchers and physicians to attain these high-quality careers.

B.1.2.12 The European population is insufficiently informed about the need for paediatric clinical research, including evaluation of medicines

The discussion and debates that occurred at EU level during negotiations on the Paediatric Medicines Regulation as well as the EU CTD highlighted the need to better inform the European public about paediatric research. Better information should demonstrate that research is mandatory to improve child health and show that research in children, including evaluation of medicines, is ethical and is run ethically. A huge amount of information on medicine and research, including incorrect or misleading information, is easily available on the internet. It is crucial that health authorities along with health professionals, the pharmaceutical industry and all relevant stakeholders inform European citizens about paediatric research.
In addition there are cultural and ethical differences from one member state to another that need to be taken into account in order to improve access to new drugs for any child who may require it.

ENCCA NoE added value:
Citizen-awareness about the need for clinical research in childhood cancer is one of the important dissemination axes in ENCCA. The project is expected to provide information to the public at large through different actions: publication in popular scientific reviews, presentations in media, scientific seminars and through partnerships with parent/patient organisations. Moreover, ENCCA will participate in workshops attended by policy decision makers in an effort to accelerate decisions for clinical research in paediatric oncology and improve care of children with cancer.

B.1.2.13 Need for referral schemes to facilitate access to expertise in EU countries

Standardisation of care for rare diseases requiring complex treatments is critical to ensuring successful outcomes. National organisations have a major role in defining standards for initial training and accreditation of professionals working in the field of childhood cancer. Also, for those countries that have a national network of treatment centres, definition of the standards and accreditation of centres is a national responsibility.

ENCCA NoE vision:
ENCCA will initiate a move towards adopting European Standards of Care for children and young people with cancer. This emphasises the importance of networks of treatment centres with appropriate expertise and of defining referral pathways for access to expert centres, including clinical trials and innovative therapies. These standards will be disseminated and reinforced through specialist postgraduate training, which is increasingly at a European level. These multidisciplinary and multiprofessional courses need to be incorporated into the syllabus for training our young paediatric and adolescent oncologists to become the leaders of investigator driven trials in the future.

B.1.2.14 Most adolescents in Europe have no access

Nearly 65,600 adolescents and young adults (AYAs) aged 15–39 were diagnosed with cancer in 2005. The incidence of specific cancer types varies dramatically across the AYA age continuum. For example, leukaemias, lymphomas, and central nervous system (CNS) tumours are prevalent in younger AYAs; in those aged 20–39, these cancers decline in frequency while other cancers such as cervical, colorectal, and particularly breast cancer, comprise a growing share of AYA cancers. Compared with younger and older age groups, AYAs have experienced little or no improvement in cancer survival rates in more than two decades.

Several factors might account for the lack of improved outcomes in AYAs with cancer, including limited access to care and insurance coverage, delayed diagnosis of primary cancers, inadequate treatment practices and settings, poor understanding of the biology and etiology distinguishing the cancers in this population, inadequate collection of patients and patient data, low numbers of clinical trials and poor participation, unique psychosocial and supportive care needs, inconsistent treatment and follow-up care guidelines, and limited emphasis on prevention and early detection.

ENCCA NoE vision:
ENCCA aims to create a framework of professionals and centres who lead in teenagers and young adults (TYA) oncology to share practice, promoting development, interdisciplinary support and specific guidance of relevance to TYA. ENCCA will identify key TYA leadership and stakeholders from different disciplines centres and countries to establish a European Steering Group involving the paediatric and adult perspectives.

B.1.2.15 Training and education

The training in paediatric oncology despite the quality lacks of coordination of the course leaders to ensure comprehensive provision. Moreover there is a lack of provision to train together specialists in a multidisciplinary approach as well as trained research nurses to implement clinical trials for children and adolescents.

ENCCA NoE vision:
Implement the ESF (European Science Foundation) syllabus to train young investigators to safely lead investigator-driven clinical trials in the future. There is a need to promote multidisciplinary implementation of care and research. Also, joint training with paediatric research nurses should be run within ENCCA multiprofessional working and increase capacity for running IDCTs.
Specific training in adolescent oncology will then address the specific needs of teenagers and young adults with cancer.

B.1.2.16 Relevance to the topic of the project

Topic request	Relevance of ENCCA objectives to topic request
Integration and formalisation of translational clinical research (up to phase III clinical trials)	This proposal aims to integrate and network research activity among existing clinical research groups such as ITCC (new drug development), I-BFM (haematological malignancies), SIOPEN (Neuroblastoma), EpSSG (Soft tissue Sarcomas), SIOPE Brain, EuroEwing, ECNHL (non Hodgkin lymphoma), SIOP Renal Tumour Study Group and others. ENCCA will thus provide the framework for integrated translational and clinical research and relevant drug development up to phase III through both industry-sponsored clinical trials and investigator-driven clinical trials.
Harmonised therapy strategies	ENCCA aims to work with all the clinical trial groups to define standard approaches that increase the efficiency of implementing investigator-driven clinical trials (IDCT) and help define a pragmatic approach to risk-based assessment of trials in children. ENCCA will facilitate partnership between the paediatric oncology community, the pharmaceutical I-industry and EMA to assure that Paediatric Investigation Plans (PIPs) of targeted compounds meet the need in children with cancer and are implemented in a timely fashion.
Clinical epidemiology for early diagnosis	ENCCA will instigate prospective clinical registries to collect clinical and biological information for all patients who do not participate in a clinical trial, through collaboration with ongoing registries and epidemiology teams. Outcome comparisons between groups and countries will reveal those clinical factors important for successful outcomes. Public and patient awareness of cancer as a possible diagnosis will be raised through ENCCA's dissemination activities.
Effective sharing of data centres, standardised methodology, tools, equipment	ENCCA will create the conditions for data-sharing and cross-talk between existing clinical trial and biological databases. ENCCA will facilitate and support this through a common knowledge management platform that will be established. ENCCA will permit explicit European policy on data-sharing and continue work to improve access to datasets, support data-sharing by installation of relevant architectures and harmonise data management. Development of web-based tools like rapid radiology and pathology review, as well as electronic consultation service.
Joint training/ education	The project aims to establish a joint programme of education and training able to enhance the quality of clinicians in paediatric oncology and the quality of care for children with cancer in Europe. Continuous and effective joint professional training via in-built e-learning module. Educating patients and parents and facilitating their communication by a designated section of the internet platform. Training of clinicians in new ethical guidelines

Topic request	Relevance of ENCCA objectives to topic request
Referral schemes	ENCCA recognises the importance of networks of treatment centres with appropriate expertise and will define referral pathways for access to expert centres, including clinical trials and innovative therapies.
Long-term sustainability and durable joint structure	ENCCA NoE is a sustainable initiative to integrate the paediatric oncology clinical research that will take the necessary actions in order to create a virtual research institute. ENCCA will streamline existing and new funds from European and national public bodies, from charities and other private sources into an EU-coordinated clinical and translational research strategy.
Integration of a large number of informal, investigator-driven research networks.	All ENCCA partners are major stakeholders in paediatric oncology clinical and translational research. They participate in all European disease groups and even chair 8 of the 12 European groups. Each European group is expected to be represented by its Chair in the Clinical Research Council. In addition, ENCCA directly connects to 5 STREP and 2 Network of Excellence currently funded by FP6 and FP7 in the field of paediatric and adolescent oncology.

B.1.3 Long-term integration

B.1.3.1 A new sustainable European strategy to meet the needs of children and young people with cancer

The **overall strategy** of the network is to address the needs of **children and adolescents** with cancer in Europe by creating an integrated clinical and translational research platform that will facilitate the activities of all the existing and long-established multinational tumour groups and improve their dialogue with all necessary stakeholders. This will ensure safe, efficient and biologically relevant drug-development for children and young people with cancer. The ultimate aim is to build a sustainable **Virtual European Institute for Cancer** in young people that works with common tools and standards and shares knowledge and resources, to promote clinical trials and studies and training of the specialist workforce of the future (Fig 3).

1. This strategy will be achieved through a joint research programme that will encompass:
   The formulation of a biology-driven, drug development strategy by each of the tumour-specific trial groups and the facilitation of their abilities to introduce new compounds into care through investigator-led clinical trials that use novel methodologies adapted to the specific situation of children and adolescents with cancer.

2. The development and implementation of biology-driven, risk-adapted therapeutic strategies (tailored medicine) to harmonise 'standards of care' and improve cancer cure rates while reducing long-term side effects.

3. Establishing systems for evaluation of long-term outcomes (Quality of Life, Quality of Survival) that will include using clinical epidemiology to explore reasons for current inequalities in outcome, such as delays in diagnosis or access to clinical trials and relevant expertise.

4. Multi-disciplinary and multi-professional training of the clinical investigators of the future, to spread excellence in care, to reinforce integration of translational and clinical research and to increase the capacity of Europe to deliver world-class multi-national clinical trials for young people with cancer in partnership with all stakeholders.

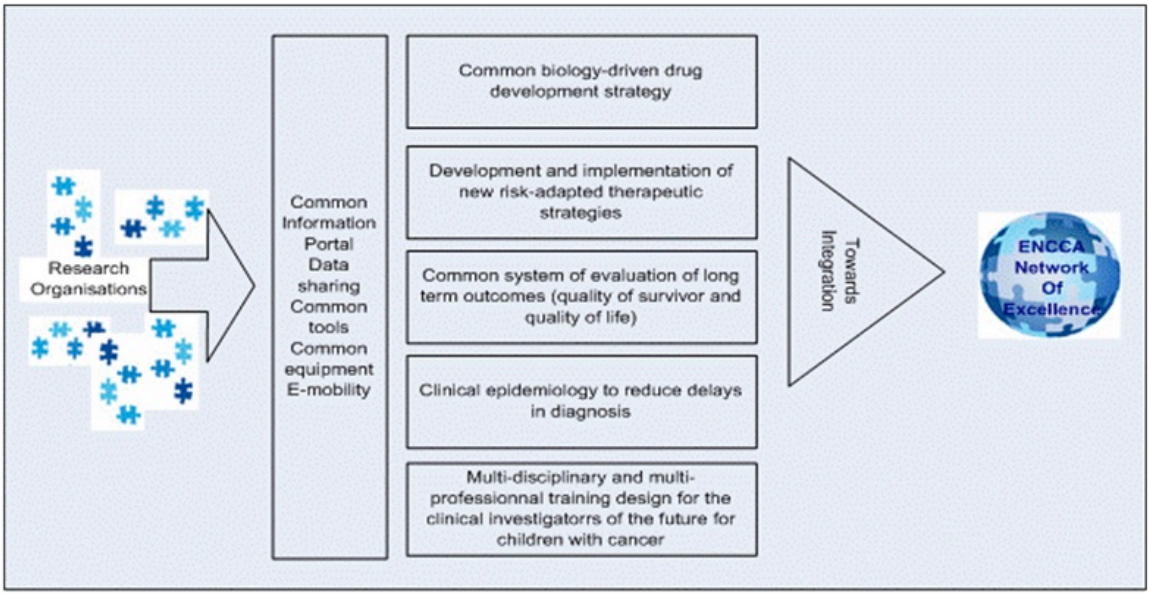
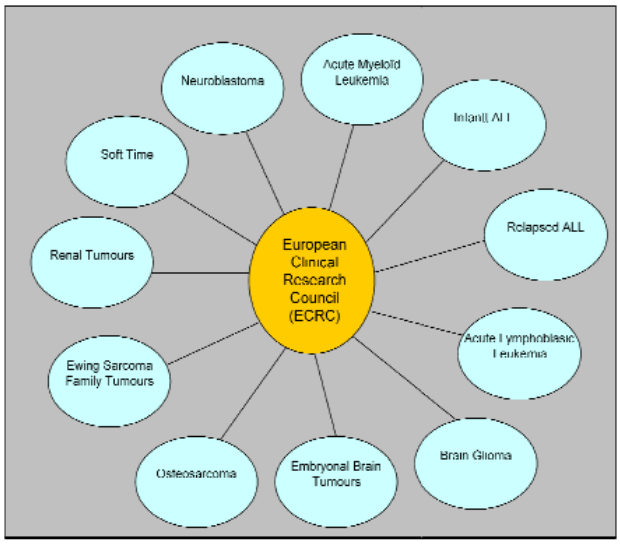


Figure 3: ENCCA NoE and the sustainable integration towards a European Virtual Institute in paediatric oncology clinical research.

B.1.3.2 An open network platform of all EU paediatric oncology disease groups for enhanced integration and a European Council to enhance co-ordination of clinical trials

The expertise and tools of the network's research platform will be open to all of the disease-specific and associated research groups involved in cancer research in young people, to facilitate and improve integration of their research efforts. It should be noted that most of these disease-specific groups are 'informal', comprising voluntary collaborations between researchers with a mutual interest and expertise in a particular cancer type. The clinical research activities of each group are hosted at major institutions in childhood and adolescent cancer research in Europe.

Many of these institutions are partners of the network, where they also act in a representative way on behalf of the needs of those disease-groups. The **European Clinical Research Council for Paediatric and Adolescent Oncology** (ECRC) will take into account the needs and expectations of the European disease groups in order to facilitate and streamline the coordination of the whole clinical research activity in paediatric oncology in a sustainable way with all academic stakeholders.



All the clinical groups will be represented by a Council composed of the Chairs of each tumour group and Chairs of the national paediatric oncology societies **(Fig. 4)**. This will be the first time that there is a European level of coordination for paediatric and adolescent cancer clinical research activities with the capacity to address the many common issues that cannot be solved by each group working in isolation. To date, only three groups (i.e. IBFM, NBL, and ITCC) are large and structured enough to have activities across all areas but even they have been unable to solve all of issues that the groups face, such as difficulties in implementing investigator-driven, multi-national trials.

Figure 4: Leukaemia and tumour groups represented

This sustainable and long-term coordination aims to better manage the needs and optimise the resources in Europe in order to obtain cost-efficient clinical trials for the benefit of the child but also the workload of clinicians and nurses.

B.1.3.3 A durable engagement of the consortium towards integration in paediatric oncology clinical research in Europe

A large number (33) of the eminent institutions in paediatric oncology from 11 countries in Europe representing different geographic regions and skills (clinicians, data analysis, epidemiologists, biologists, imaging analysis, parents associations) have committed by **letters from their institutions** to make the necessary efforts and adaptations in order to advance together towards a sustainable integration and eventually a new legal entity able to ensure a sustainable integration of paediatric oncology clinical research in a European Network of Excellence.

This large number of partners may be considered as a risk for running a successful Network. However all of the partners have a long-standing track record of successful collaborations in the field of clinical research (as stated by publications), that have been performed under the umbrella of SIOP Europe for malignant solid tumours and I-BFM for haematological diseases. SIOPE and I-BFM have decided to join their efforts into a single Network of Excellence, namely ENCCA, to streamline integration across all paediatric malignancies, to share and adequately address the challenges and to reinforce the voice of children and adolescents with cancer in Europe.

The ENCCA partner institutions and the many cooperating organisations that have aligned themselves with the project, represent a high-quality, critical mass of resources that are already committed to running the current European research agenda. It should be emphasised that the institutional partners will participate in ENCCA by bringing many more resources than those funded within the EU project.

Most of the funding will be used to finance specific tasks of integration (such as a virtual network, data sharing, dissemination, training and educational activities) and/ or Postdoctoral research projects. Most of the senior staff working for the project are supported by their institution's infrastructure and thus their expertise is provided free of charge to ENCCA. Overall, it is estimated that only 30% of the networking costs will be provided by EU funds.

It is noteworthy that the ENCCA clinical trials portfolio will be funded only partly by EU funds (from 10 to 30% of total costs) and that additional resources will be applied for through national public funding programmes, contributions from charity organisations, industry funding, other private funders as well as other calls at the European level.

Moreover ENCCA is an open structure that will integrate other partners in the future. Many cooperating organisations have already affiliated with ENCCA with the commitment to participate in the activities of ENCCA and the possibility to integrate into the network later. This demonstrates that the ENCCA project is already networking virtually with all the existing and high-quality clinical and translational research activities in the field. These cooperating organisations provide complementary expertise and skills that will be used by ENCCA to achieve the objective of long-term integration.
Pharmaceutical companies and other private enterprises will be integrated in the project and the joint activities that will be progressively integrated into ENCCA. More information about the ICI can be found in section B.2.1

Parents also have an important role to play and will be integrated in ENCCA through ICCCPO (ÖK) as a partner and the Parents/Patients Advocacy Committee in the project.
Equipments and materials of the different institutions are also expected to be integrated and shared in order o make efficient and less costly clinical research. An initial list of available material is presented in section B.2.4 but further commitments will be finalised at the consortium agreement stage.

B.1.3.4 Towards a durable financial autonomy

The current structure of the Network will put in place the necessary organisation and strategy in order to initiate ENCCA with a solid basis. Moreover a financing assessment 'office' will be created at the beginning of the ENCCA project. The aim of this office is to create favourable conditions that will lead to the financial autonomy of the Network. This Network of Excellence will develop the capacity to generate added value able to finance its research activities and its development at European and international level. A special office of financing options assessment will be created that will coordinate this financial integration.

This is made possible by:

- Efficiently managing the available (national or international) resources: The office will identify the current resources of the network (national or regional funding: bursaries for PhD students support to mobility and training) and examine the possibilities of integrating some of them in a new common ENCCA policy.
- Exploring and identify all the financial possibilities. Due to its achievements and notoriety it is expected that ENCCA will develop resources arising from charity, national research funding programs, industrial contracts and training inscription fees services. ENCCA will promote the academic/industrial cooperation and identify the possibilities of cooperation with financial contribution from public of private funds.
- The office will study the mechanisms of integration of new financing resources in the Network: ENCCA will imagine the common conditions able to integrate financial incomes from different resources and distribute equitably in labs in order to make clinical research more efficient.

B.1.3.5 Sustainable management and performance measurement to achieve lasting integration

To ensure that the new Network of Excellence (NoE) is successfully implemented, the partnership has decided to adopt a reinforced management process adapted to NoE.

- The **strategic management** of ENCCA is inspired by the principles of Quality Management. The NoE will establish an appropriate management system which will ensure the incorporation of pathways to Excellence and the consortium with any issues they may come across in order to simulate solutions
- The **integrative management** of activities and work packages is inspired by the ISO 10006 standard (guidelines for quality management) for the successful integration of the different actions.

The PDCA principles (Plan-DO-Check-Act) will be applied in the different levels of management in order to continuously enhance the consolidation capacity of the management system.

ENCCA will include a **quality measurement process** in its management system in order to:

- Support the strategic supervision for a sustainable integration and promotion of Excellence in Europe.
- Determine and improve the quality of the Network.

To support the quality and the vision a **balance scorecard** will be initiated that will:

- Align key **performance and integration measures** with strategy at all levels of the organisation
- Provide management with a comprehensive picture of NoE operations
- Facilitate communication and understanding of the NoE goals and strategies at all levels of the organisation
- Provide strategic feedback and learning

The balance scorecard will integrate key performance and integration indicators to ensure sustainable implementation of ENCCA. The efficient implementation of the whole system will be supported by a **coordination team** specialised in project management (CCRI; SIOPE). The team will be appointed by the NoE Manager hence enabling the Network to operate on a **long-lasting basis** as an integrated and self-sufficient high-level organisation even after the end of the EC contract. More details on the management organisation are given in section B2.1

B.1.4 S/T Methodology and associated work plan

B.1.4.1 Overall strategy of the work plan – Three types of activities towards integration

Three types of activities will be implemented in order to structure European clinical research for children with cancer and will ensure a high and durable integration visible to all stakeholders and of benefit to all of the tumour groups (Fig.5)

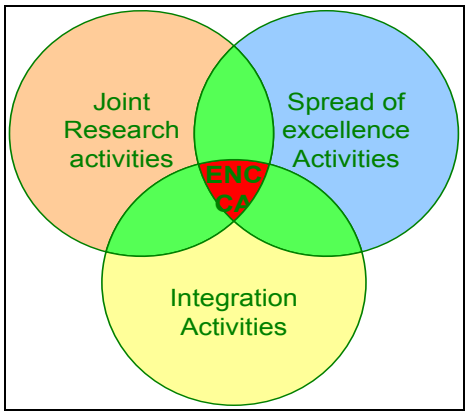


Figure 5: The three types of activities for establishment of the ENCCA Network of Excellence

B.1.4.1.1 The Integrating Activities

The Integrating Activities (WP1 to WP6) will ensure integration and standardisation of the infrastructure and tools for clinical trials, easier access to innovative methodology designs including innovative endpoints and will provide, in the longer term, solutions for better cross-platform working. There will be an immediate operational benefit in terms of implementation of clinical trials and standardisation of methods to integrate biological sample collections.

B.1.4.1.2 The Joint Research Activities

The Joint Research Activities (WP8 to 13) will illustrate the whole spectrum of approaches that the EU disease groups will consider in addressing the clinical needs of their patient group. They will 'field test' the tools and methods developed within the network. The EU disease groups will benefit from opportunities to define their strategy for new drug development and risk adaptation of current therapies, improved access to new drugs and the means to address their needs for long-term outcome research and monitoring. In formulating the joint programme of research, all groups were invited to identify a clinical trial or study at the development phase that exemplified the challenges they faced in implementing an area of therapeutic needs and for which a solution could be found by developing new common tools and strategies and/or by standardising methods and protocols.

A portfolio of **clinical trials** for drug development from different EU-disease groups will be chosed (examples in **Tab. 3**) will chosen and will be developed within the Network, as paradigms of the challenges to be overcome and the approaches needed to do so. This will help to find solutions on the long-term for running the comprehensive agenda of research in paediatric malignancies. The ENCCA resources available will support some key coordination efforts to design and launch these studies. Their full implementation will, of course, require co-funding additional resources to be provided by the relevant EU-disease groups, as described above.

Tumour type and clinical studies as exemplar	Type and Aim of Clinical Studies in the ENCCA network	Expected results	WP
MALIGNANT SOLID Tumours Ewing Sarcoma - (EWING 2005) Osteosarcoma - EURAMOS	Phase III trials - Development of xxx design and protocols - Improvement of professional cases for TYAs - Risk classification	- Improvement referral schemes - Improve case for TYAs	7
Leukemias and malignant solid tumours (in particular neuroblastoma, brain tumours)	Phase I and Phase II clinical trials Evaluation of new anticancer drugs	New effective drugs to improve prognosis selected on the bases of molecular pathways and preclinical models	8
LEUKEMIA 2 very-high risk ALL trials AEIOP-BFM ALL 2009 INTERFANT - 06	Phase III trials as infrastructure platforms to - Standardize common molecular diagnostic approaches - Identify predictive biomarkers - Use of preclinical models (cell lines, mice) for validation of identified targets	Identification of new risk profiles based on molecular analysis in prospective trials to adopt treatment intensity to maximize cue rates and to minimize late effects New insight for the use of most adapted drugs according to the molecular characteristics of leukemic cells	9
MALIGNANT SOLID TUMOUR Neuroblastoma: LINES Medulloblastoma: PNET 5& 6	Phase III trials - Implementing risk adopted treatments based on genetic tumour markers (notably, by genotyping) - Improved therapeutic strategies according to the aggressiveness of the tumour (less therapy intensity in presence of favourable genetic profiles whilst increased treatment intensity in case of unfavourable molecular risk profiles) - Key elements: o No or much less chemotherapy in LINES o No radiotherapy in medulloblastoma	Improved survival rates due to reduced treatment burden based on up-front tumour inherent risk evaluation Improved quality of life with less or no late effects	10
LEUKEMIAS AND MALIGNANT SOLID TUMOURS Population based cancer registries Wilms Tumour SIOP Wilms Tumour Study 2001	Evaluation of use of cancer registries for prospective collection of enhanced clinical data (histology/imaging/biology, toxicity, relapse, cause of death) obtained with standard care Phase III trial Implement a WEB based study tool for clinical and translational research	Use of ideally population based cancer registries for long term results of patients treated with standard treatments as opposed to patients treated on investigational trials Clarify the role potential of registries for enhanced long term follow up studies capturing in particular data on late effects Define a new risk factor stratification to optimize treatment approaches	11
MALIGNANT SOLID TUMOURS Hepatoblastoma: SIOPEL trial	Clinical research in very rare tumours Phase III trial Standardising international risk stratification of childhood liver tumours Improvement of data sharing Development of new trial design and treatment protocols	Improve outcome in very rare tumour types through international cooperation's Harmonisation of international clinical research efforts	12
Adolescent neuroblastoma: AYA Study	Phase II trial Cooperative effort of SIOPEN with the COG to reach sufficient patient numbers for an intensified treatment approach	Integration of WEB based trial management efforts to foster translational research in very rare tumours on an international bases	
MALIGNANT SOLID TUMOURS Study on long term survivors of Medulloblastoma	Development of methods to follow the survivors of medulloblastoma Establishment of a survivorship passport	Assessment of the of the quality of survivorship	13

Table 3: Clinical and other studies that the EU disease groups will consider within ENCCA Joint research Activities

B.1.4.1.3 The Dissemination ctivities

The dissemination activities (WP14-18) will spread excellence in standard care, build the capacity of Europe to implement clinical trials in children and adolescents with cancer and increase access of patients to research and centres of expertise.
A specific work package (WP17) will be dedicated to address the specific needs of adolescents. These activities will also increase the dialogue of academia with industry and regulators, to share their expertise in the needs of young patients with these rare diseases and the specificities of clinical research in this age group. This will result in a strong and durable partnership between all stakeholders, including the parents and patients themselves, to ensure that the introduction of novel therapeutic strategies into standards of care is always driven by the needs of the patients. The ethical dimension of performing clinical research in children with cancer will be addressed specifically with all stakeholders in the fields in WP18.

Through a common European strategy ENCCA will allow to advance towards a virtual sustainable institute that will permit major improvements for children with cancer. (Fig. 6)

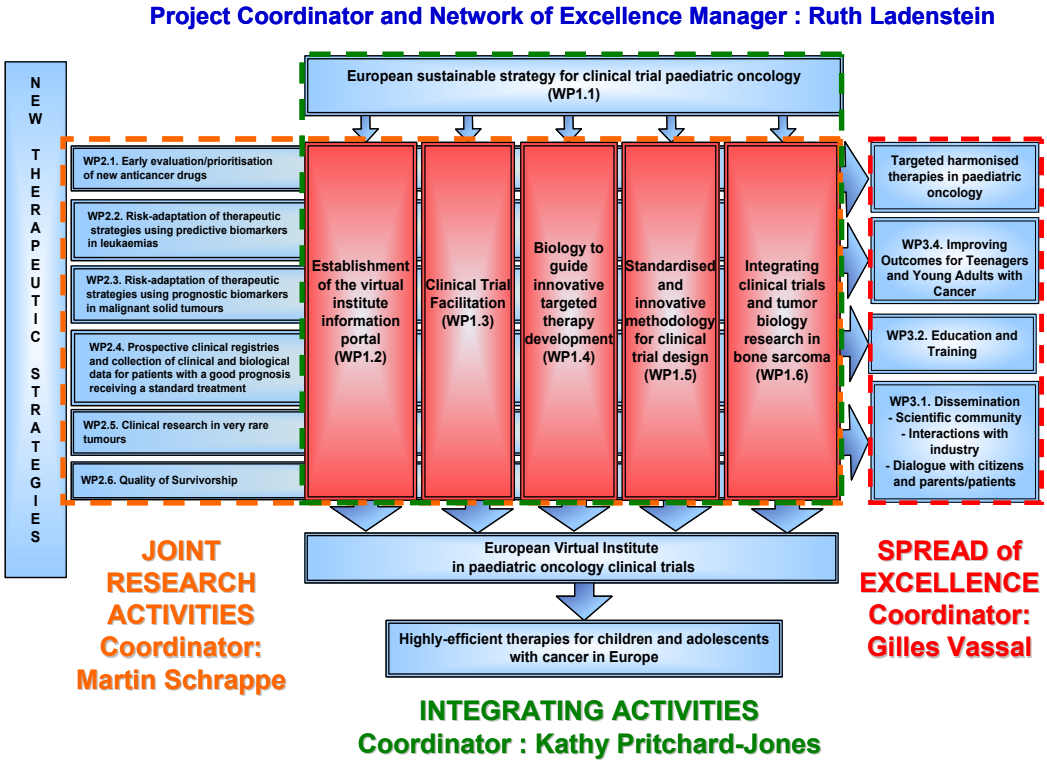


Figure 6: The Network methodology for clinical trials integration and coordination in Paediatric Oncology

B.1.4.2 Work package content of the 3 Activities

B.1.4.2.1 Integrating Activities (IA) towards a Virtual European Research Institute

This Virtual European Research Institute will increase the output of European paediatric oncology research through efficient communication and collaboration. Within the European Virtual Institute for Paediatric Oncology Research, supported by an integrated ICT infrastructure, **data** will be captured with higher quality and completeness, **information** will be used more efficiently and **knowledge** will be increased faster.

In order to reach this objective the ENCCA network will:

- Overcome geographical remoteness of the research teams by common policy of data and scientific information sharing;
- Convert a new organised Network into a European virtual platform by managing the generated knowledge in a common way in order to make European research more efficient;
- Manage new knowledge and its controlled diffusion at European and international level.

WP2: European sustainable strategy for clinical trial paediatric oncology
Through this Work Package the ENCCA network aims to establish an efficient strategy of coordination and integration of the existing paediatric oncology therapy platforms. The main objective is to provide accelerated answers and efficient results for children and adolescents diagnosed with cancer. In addition to the organisation of this platform and the definition of a common strategy, ENCCA will create actions that will ensure the financial and structural sustainability of the Network such as the creation of an Economic Interest Group (EIG) could be a possible option. Relationships with all the clinical actors of the paediatric oncology field will also be one or the priorities of the Network. Therefore, ENCCA will make sure that all the tumour/ leukaemia groups are represented to ensure better coordination and a higher integration of the actions allowing a reduction of research fragmentation.

WP3: Establishment of the virtual institute information portal
The information and communication technology (ICT) infrastructure for administration, treatment and research in paediatric oncology within Europe is widely characterized by heterogeneous systems and discontinuous process workflows. A number of planned and ongoing national and international activities have already helped in rising awareness on these issues. However, in order to establish a common technical framework and standard operation procedures ENCCA will encourage closer cooperation of medical facilities on a national and transnational level. Therefore this work package goal is to foster the design and establishment of a **common collaboration and research infrastructure**, interconnecting all stakeholders and applied ICT systems involved in research and trial management on a technical, semantic and process level. The development of such an infrastructure will ensure that each participating organisation will have real time and full - scale access to the knowledge that accumulates within the Network and also to the knowledge that will be generated by the Joint Programme of Activities.

WP4: Clinical trial facilitation
Investigator driven clinical trials are clinical trials that are instigated by academic researchers and are aimed at acquiring scientific knowledge and evidence to improved patients care. However, these studies deal with potential diagnostic and therapeutic innovations that do not attract commercial interest in particular as paediatric cancer is a typical orphan disease area. This WP will be reviewing the needs and elaborating solutions for the full scope of studies needed in paediatric and adolescent oncology enabling thus clinical research in this orphan disease segment. This encompasses the needs of early drug development studies (Phase I / II) supported by industry or driven by academia up to investigator-driven, academic phase III / IV settings with respect to ICH guidelines and EC directives.

This objective will notably be achieved by:

- Facilitating investigator driven trials (ICDT) through risk-based approaches;
- Reducing fragmentation and duplication through multinational clinical studies ensuring appropriate number of patients to produce statistically reliable results so that trials are correctly powered;
- Creating Clinical Trial templates and standardized data sets;
- Assuring improved informed consent approaches for the scope of studies and clinical research;
- Harmonizing data management systems by creating a European standard.

WP5: Biology to guide innovative targeted therapy development

The aim of this work package is to integrate and harmonise biological datasets and experimental data allowing therapy choices guided by biology and innovations to improve treatment outcome for children and adolescents with cancer. To achieve this central aim, the following seven goals have been defined:

- To set up and manage a network of pre-clinical research groups for high-risk childhood and adolescent cancers;
- To ensure integration and accessibility of high-quality, existing data on drug target, drug target validation and (targeted) drug testing for high risk childhood and adolescent cancers by building a common bio-informational data storage and analysis tool (incl. compiling a database with full profiling data from tumour series in ongoing clinical trials);
- To develop new analytical tools for molecular drug targets, biomarkers and drug efficacy testing, and to perform cross-platform and cross-tumour bioinformatics analysis;
- To move towards an integrated European biobanking solution for characterization, storage and distribution of clinical specimens, and information transfer about molecular data from paediatric cancer samples;
- To integrate and share profiling and experimental data accumulated as data packages providing the biological rationale for the clinical development of new treatment strategies based on algorithms for identification and prioritisation of molecular targets;
- To structure data-sharing and integration for the development of biological signatures to select patients for new treatment strategies ('predictive biomarkers');
- To structure data-sharing and integration for the development of biological signatures for risk stratification ('prognostic biomarkers').

WP5: Standardised and innovative methodology for clinical trial design

Paediatric oncology research faces an increasing complexity of biological and bio-molecular studies where new (targeted) therapies need to be studied in often rare subgroups of patients.
The objective of this WP is to enhance, within the network, the expertise in methodology for design and analysis of clinical studies in paediatric oncology. For this purpose, ENCCA will make sure to bring together, within a "virtual office", all biostatisticians already involved in the various areas of paediatric oncology or who have interest in related topics. Methodological support, with appropriate study design and statistical analysis, will be given to collaborative trials on new treatment options/strategies. It will also be provided to studies directed at investigating new prognostic/predictive factors and more sophisticated patient stratification, jointly with other work packages in the project. Information on projects, methods and software will be shared by the participants.

The main goals of these actions will be to develop:

- Methods of trial design for clinical research in rare diseases;
- Statistical approaches for the definition and validation of risk-based patient stratifications;
- Statistical approaches for the analysis of recurrent events (SAE) and competing events (composite endpoints) and long term outcome;
- Standardization and education in biostatistics.

In addition, the "virtual office" of biostatisticians will organise international workshops with four tumour groups to facilitate "meta-data" analyses for comparison of risk groups, overall burden of therapy and outcomes, including late sequelae, to improve treatment stratification and long term outcomes.

WP6: Integrating clinical trials and tumour biology research in bone sarcoma

The primary objective of this work package is to establish a platform for multinational, intergroup bone sarcoma trials (phase 2-4) with integrated tumour biology research questions by linking major bone sarcoma groups and networks such as EURAMOS, EURO-E.W.I.N.G. and EuroBoNeT. For this purpose, active collaboration with leading institutions and research groups from the aforementioned networks which are not formal members of the ENCCA platform will also be sought. Examples from EuroBoNeT would be the Universities of Oxford, Salamanca, and Bologna.

Secondary objectives are to use this platform to develop and implement specific clinical trials for osteosarcoma and Ewing sarcoma, to improve the infrastructure for the collection of bone sarcoma specimens for translational biology studies within these trials, and to improve the access to expert care for patients outside of established trial infrastructures.

B.1.4.2.2 Joint Research Activities (JRA) and harmonization of the therapeutic strategies

The goal pursued within the Joint Research activity is to implement the medical and scientific solutions identified in the "Concept and Objectives" of this proposal, in order to meet the unmet needs of children with cancer

In this purpose, a portfolio of 7 clinical trials, for different paediatric malignancies, will be performed in collaboration with the respective leukaemia and tumour groups in order to answer the questions to be raised in paediatric oncology in the next 10 years in order to increase cure rate and quality of cure.

The vast majority of those trials are planned, the content of the protocols has undergone discussion in the different groups are ready to start the process for final protocol writing, administration and regulatory authorisation process. It is likely that they will be launched within the first 2 years of the ENCCA project. However, for most of these studies recruitment will need more than two years and will not be complemented before the end of the ENCCA project.

Those trials, carried out within the WPs of this activity, will help to solve the specific issues and thus provide proof of principle for further dissemination to other clinical trials and disease groups.

WP8: Early evaluation and prioritisation of new anticancer drugs

The goal of this WP is to facilitate and increase the capacity of European disease groups (such as I-BFM, SIOPEN, EpSSG) to run early evaluations of new anticancer compounds (phase I, phase II trials) on children with leukaemia and malignant solid tumours. The prioritization of compounds to be studied in children will be based on tumour biology and target validation as accessible through WP5 A strategy for new drug development in the different paediatric malignancies will be established and discussed with EMA and the Paediatric Committee (PDCO). Disease-based strategies will be re-assessed on a yearly basis and discussions with pharmaceutical companies (facilitated by WP8 and WP16) will be held to have access to the relevant compounds. It will also enable the operation of phase I and II trials, in anticipation of the introduction of those targeted compounds in phase III trials and then in standard care. Four drugs will be studied independently and in combination in haematological malignancies and in solid tumours through investigator-driven clinical trials in order to demonstrate the proof of principle of the WP that will facilitate integration in between the existing groups and increase collaboration with both regulatory agencies and pharmaceutical companies.

Both industry-sponsored and investigator-led trials will be performed to facilitate the increase in the number of innovative drugs accessible for patients in Europe.

WP9 Improved therapeutic strategies using predictive biomarkers in leukaemia
Traditional clinical trials in childhood leukaemia have continuously improved long-term survival rates over the last four decades. However, refractory childhood leukaemias of lymphoid and myeloid origin still remain a challenging therapeutic problem. Despite a growing number of targeted therapies in clinical development, there are only a relatively small number of leukaemia patients eligible to be included in their clinical evaluation. Thus, there is an urgent need for a common harmonized approach to optimize evaluation of potentially valuable new targeted therapeutics and – at the same time – to overcome the diverse and fragmented activities related to refractory leukaemia in Europe. A second important issue relates to the timely introduction of new targeted therapeutics. Early introduction of these treatment approaches are likely to be highly beneficial due to the minimisation of unnecessary adjuvant therapy for those patients not in need of it and, thus, allow utilisation of optimised therapy already in the first treatment cycles. Therefore, a clear prerequisite to achieve timely introduction of new therapeutics is the early identification of adequate target populations for experimental treatment. To meet these needs, this WP will – as a proof-of-principle – develop standardised diagnostic approaches, as well as bio banking, and a common molecular diagnostic pipeline in a European virtual laboratory setting for leukaemia. Through developing algorithms for identification and prioritisation of molecular targets based on biological data, it will be possible to focus on the most promising molecularly-targeted treatments in preclinical model systems. In parallel, the international multicentre clinical trials AIEOP-BFM ALL 2009 and INTERFANT-06 will serve as infrastructural platforms and treatment backbones to prospectively validate the developed target identification approaches. The close association with the European Relapse trial in acute lymphoblastic leukaemia (INTREALL) will allow efficient clinical testing of molecularly-targeted treatment strategies, to finally prove their direct benefit to the paediatric patient population.

WP10 Risk adaptation of therapeutic strategies using predictive biomarkers in solid tumours
This WP will deal with two different studies regarding two solid tumour types, Neuroblastoma and Medulloblastoma.

Neuroblastoma is one of the most biological intriguing cancer diseases in childhood varying from poor survival in spite of intensive treatments to excellent ones with few or non-treatment. Aiming for risk-adapted therapies, the LINES (Low and Intermediate Risk Neuroblastoma SIOPEN) study is intending to stratify the patient's treatment according to biological and clinical biomarkers in order to:

- Minimise the burden of treatment in those low-risk patients who in previous studies have shown an excellent long-term outcome,
- Intensify treatment in those patients with biologically unfavourable non n-myc amplified neuroblastoma for survival improvement.

Medulloblastoma is the most common malignant brain tumour in childhood, treated with surgical resection followed by radiotherapy and chemotherapy. While this combined modality treatment has substantially improved the cure rate, survivors suffer from long-term toxic side effects related to therapy that often seriously affect their quality of life. Biological criteria for risk stratification are emerging: this is a heterogeneous disease at the molecular level and no diagnostic cytogenetic or molecular abnormality has been identified.Therefore, it becomes evident that risk-adapted therapies are an outstanding need in paediatric oncology since the final aim is to cure with minimal post-effects. Neuroblastoma and Medulloblastoma are diseases for which this approach can be undertaken in order to improve survival and quality of life.

The studies pursued within this WP will aim at reaching that goal through the following tasks:

- Implementation and evaluation of risk-adapted therapies in low and intermediate risk neuroblastoma;
- Assess data quality regarding therapeutic stratification;
- Use of tumour genotyping as a prognostic biomarker in low risk neuroblastoma patients;
- Assess molecular diagnostics as prognostic biomarkers in low risk medulloblastoma patients.

WP11 Clinical epidemiology and prospective registries for patients on standardised protocols.

Excellent survival rates approaching 90% can now be achieved for several good prognosis tumour types or subgroups (e.g. localised low and intermediate risk Wilms tumour, localised embryonal rhabdomyosarcoma at favourable anatomical sites, extra-cranial germ cell tumours, approximately one third of childhood acute lymphoblastic leukaemia and some lymphomas). However, this success has created its own problems and challenges. New approaches are needed for prospective clinical studies that will capture detailed clinical information on patients treated on standard protocols, allow biological sampling, monitor outcomes including relapse and generate large cohorts of patients to improve risk stratification and adequately study long-term side effects. This can be addressed by developing mechanisms to conduct prospective clinical studies that do not fall within the definition of a clinical trial testing an investigational medicinal product (IMP). Harmonisation is required here as the definition of what is considered a clinical trial or an IMP for off-label use in children still varies across Europe. This has a negative impact on the perceived need for a trial 'sponsor', the costs of this type of research and the ability to include all countries and hence all patients treated within the network, and ultimately, across Europe. There are also differing national attitudes to the need for patient/parent consent for such prospective data collection on treatment that is considered 'standard of care'. All of these issues will be addressed through links with WP 2 and 4

This WP proposes two tasks that will evaluate in parallel the possible approaches to running such studies according to the availability of population-based cancer registries. These will build on the long standing collaboration between cancer registries in the ACCIS and EUROCARE projects. A third task will pilot the EU-supported ACGT platform to collect and integrate clinical data with imaging and biological data using the current European Wilms tumour trial as an exemplar prospective study of an overall good prognosis tumour where risk stratification needs to be further improved. All three tasks will run in parallel throughout the duration of the project. The WP leader will work closely with WP 4 to ensure consistency in the definition of what is considered a prospective clinical study rather than a clinical trial requiring regulatory authorisation

WP12: Clinical research in very rare tumours

The objective of this WP is to improve quality of care for children with rare tumours, namely hepatoblastoma and adolescent neuroblastoma (AYA) as a template for international clinical research for rare childhood cancers.

Three major actions will be followed to reach the aforementioned objective:

- Improving E-RDE platforms and cross-talk / data sharing in order to make feasible global data sets for clinical research in very rare tumours;
- Standardising international risk stratification of childhood liver tumours;
- Improve molecular insight in poor risk adolescent neuroblastoma.
- Develop referral schemes across borders for special therapeutic approaches as high dose mIBG therapies needed in high risk neuroblastoma
- Design and implementation of a new and improved clinical trial for hepatoblastoma.
- Design and implementation of an innovative intensive clinical trial for adolescents and young adults with neuroblastoma known for a particular poor outcome

A model for organising care and structuring research in a very rare cancer in children will be developed through international global cooperation between SIOPEL, SIOPEN and major worldwide tumours study groups: the North American Children's Oncology Group (COG) and Japanese Paediatric Liver Tumours Study group (JPLT).

This in turn will generate new knowledge in the field of rare malignant tumours in children and adolescents, as well as lead to the harmonisation of international clinical research efforts.

WP13: Quality of Survivorship

Through this Work Package, ENCCA will evaluate the Quality of Survivorship (QoS) in a selected groups of subjects treated for particularly high-risk childhood cancers and/or at critical ages during psychological development. ENCCA will also address a critical issue for today and future long-term survivors: that is the availability of treatment details to be available well beyond the end of therapies in order to plan with their healthcare provider tailored prevention strategies.

One of the tasks will be to identify treatment-related risk factors for poor quality of survival. In particular, this WP will focus on long-term survivors of medulloblastoma treated with standardised protocols. This task will develop on-line method of quality of survival assessment which will be also adaptable for use in survivors of other childhood cancers. During the study saliva DNA samples will also be collected for future molecular genetic analysis of host factors relevant to neurological recovery. The ultimate goal of this WP will be that each cancer survivor will have access to a document on paper and electronically stored summarizing treatment history and providing patient specific advice on follow-up and primary or secondary intervention programmes.

B.1.4.2.3 Spreading of Excellence Activities (SEA)

WP14. Dissemination activities

The general objective of this work package will be to continuously monitor and provide the means for the ENCCA partners to share their knowledge within the consortium and to integrate the research activities as well as to disseminate and exploit the research results to the community at large.

This will be achieved through:

- Disseminating appropriate information to the scientific and clinical community to raise the awareness about the need to propose a virtual European research institute in paediatric and adolescent oncology;
- Finding potential industrial partners;
- Communicating to a wide audience the appropriate information on new breakthroughs and advances by the ENCCA network as well as outlining the numerous health and social benefits that have taken place due to the numerous partner projects;
- Communicating with patient and family support organisations to raise awareness about the positive outcome of creating a paediatric oncology European network on clinical trials;
- Fostering dialogue between clinical groups collaborating within the ENCCA network and clinical and research groups outside the Network;
- Disseminating information to long-term survivors of childhood cancer and on their needs. ENCCA will closely collaborate with parents and survivors to ensure that they can enjoy a healthy and independent life and are accepted in society, in the same way as their peers.

WP15: Education and training

Excluding a few nations, the recognition of Paediatric Oncology and Haematology, as well as the implementation of related educational and training activity, is still limited throughout Europe. A lower survival rate (from 10 to 20%) of children with solid tumours or leukaemia observed in some Europeans countries may be, at list in part related to lack of adequate training and educational programs. In addition the rapidly changing needs related to advancement of basic and clinical knowledge requires improvement and diffusion E and T activity able to adapt to the demanding new scenarios. A limited number of courses are available but for geographical and economical reasons not all the medical personnel can benefit from them. However, a comprehensive and accessible Educational and Training programme is essential for the success of the present proposal.

The objective of this WP will be to enable the recognition of Paediatric Oncology as a well-defined Paediatric sub-specialty which implies a training programme and a continuous medical education system keeping track with the rapid evolution of knowledge and the therapeutic use of new agents with the final goal of eliminating major differences in the quality of diagnosis and care of children with cancer throughout Europe. Our aim is not simply to increase the number of paediatric oncology courses available in Europe but to make them part of the NoE through exchange of programmes, exchange of faculties members and sharing written conclusions to be provided at the end of each course.
This work package will address the following points:

- Implementation of standards for subspecialist training in Paediatric Oncology in Europe;
- Training courses for clinicians and research nurses on new protocols and standards for clinical trials;
- Improving information for parents/patients;
- Collection, interpretation and use of population-based data on cancer in children and adolescent.

WP16: Facilitation of industry collaboration with pharmaceutical companies and SME for dissemination, exploitation and technology transfer

This WP will carry out two major objectives:

- Increase and facilitate the contacts and collaborations between the Network and pharmaceutical companies within the European Paediatric Medicines Regulation, in order to introduce well-studied, safe and effective targeted therapies in clinical research and then in standard care.
- Implement a sustainable survey of Intellectual Property Rights within the clinical trial environment and technologies, and increase awareness for the benefit of researchers, European industry and patients.

Thus the ENCCA Network aims to create the necessary mechanisms and links of communication with the European industry (Pharmaceutical companies, Diagnostic companies, SMEs) in order to find sustainable solutions for new drug development for children and adolescents.
Moreover, as a way to increase relationships between research centres and clinical tumour/leukaemia groups and industrials will be created.

WP17: Improving quality of survivor and quality of life for Teenagers and Young Adults (TYA) with Cancer

Outcome data for teenagers and young adults (TYAs) with cancer have not demonstrated the same level of improvement in survival reported over recent years for both older and younger cancer patients. Evidence shows that the TYA population has less opportunity to enter clinical trials than younger children, and has lower accrual rates even when trials are available. This group has been characterised as a ‘lost tribe’ in a ‘no man’s land’ between children and adults.
There are large gaps in our knowledge concerning these issues and how best to treat TYA patients with cancer. Relatively little is known about biological, genetic, epidemiological, therapeutic, psychosocial, and economic factors that affect the incidence, disease outcomes, and quality of life of TYA diagnosed with cancer.

The main objective of this Work Package will be to develop a European multi-professional network for TYA focussed on improving outcomes. This will include professionals from adult as well as paediatric base and will build on a successful national approach in one of the partner countries.

The group will:

- Create a network of centres to lead in TYA oncology by sharing practice, promoting service development, interdisciplinary support and by developing specific practice guidance of relevance to TYA cancer;
- Promote and develop TYA appropriate educational opportunities for professionals within Europe including the identification of relevant competencies;
- Promote and identify opportunities for TYA to receive treatment within high quality research trials;
- Start to develop research initiatives of relevance to TYA to address issues of TYA specific tumour biology; TYA epidemiology; delayed diagnosis; health service research related to best models of care; late effects.
- Promote healthy lifestyles in TYA cancer survivors;
- Link to relevant patient and charitable organisations to ensure that young people's voices are heard.

WP18: Ethical aspects of clinical trials

The objective is to formulate a general ethics guidance for clinical trials that will be reviewed by an Ethics Advisory Committee (EAC), composed of external experts and parents/patients representatives, not only in charge of ensuring respect of fundamental ethical principles but also to evoke continuous attention to aspects of ethical handling.

This objective will be achieved by:

- Pointing out the ethically sensitive issues and informing the clinicians about them. These issues are of course very different according to the phase (I, II or III) of the clinical trials and are also probably according to the cultural background. A study will be performed in order to analyse these differences;
- Discussing and establishing internal ethical questions and recommendations for the application of clinical trials in children and adolescents;
- Evaluating application and disseminating knowledge about all relevant existing regulations to the partners;
- Disseminating the rationale of the internal guidance within the European community;
- Interacting with an Ethical Advisory Group of external experts that will serve the project with an ethical review and screen for compliance with the network guidelines.

B.2. Implementation

B.2.1 Management structure and procedures

B.2.1.1 Project organisational structure and decision-making process

The project is divided into three activities (Integrating Activities IA, Joint Research Activities – JRA and Spread of Excellence Activities SEA) and its structure to ensure a global management is schematised in the following figure 7.

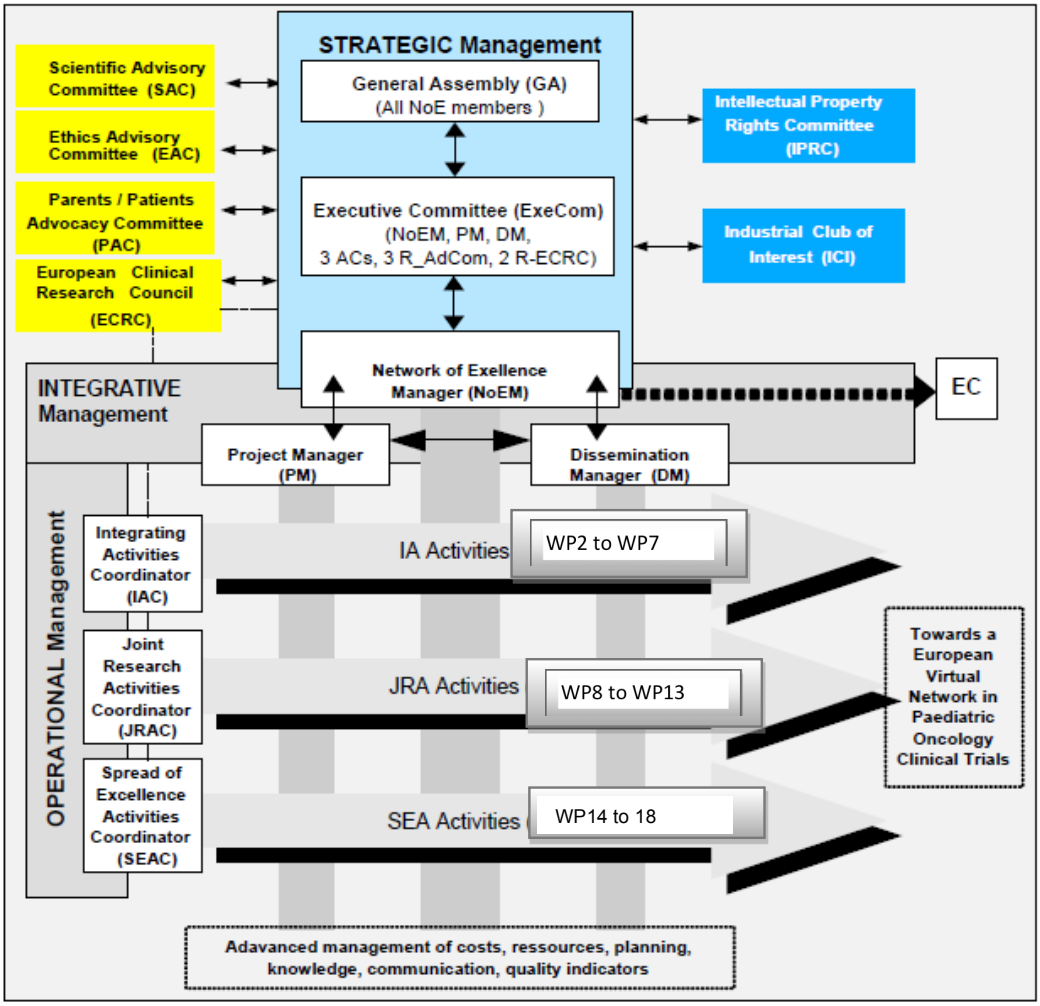


Figure 7: ENCCA management structure

The objective is to implement a management structure within the consortium which will give the possibility to take rapid and efficient decisions (avoid status-quo or blocking situation) whenever necessary and allow simultaneously to have each individual organisation represented, in order to anticipate and avoid the occurrence of disagreements/conflicts.

The chosen structure will:

- Ensure the possibility to take strategic decisions
- Allow a close collaboration between the strategic and operational level and the integration of external collaboration via integrative management of the Project Management Team
- Limit the use of veto power

The Network of Excellence Manager (NoEM) is the overall project co-ordinator, Associate Professor Ruth Ladenstein, who represents the legal entity (CCRI) in acting as the intermediary between the Parties and the European Commission. In addition to its responsibilities as a Party, the NoEM performs tasks assigned as described in the EC-GA and the Consortium Agreement. The CCRI will assume the responsibility of the technical, financial and administrative management of the project on a day-to-day basis, according to the contractual guidelines.

OPERATIVE MANAGEMENT

The Project Management Team takes responsibility for the operational management level and is ultimately accountable to the General Assembly. It consists of the **Project Manager (PM)** at the CCRI, the **Dissemination Manager (DM)** at SIOPE and the three **Activity Coordinators (AC)** at IGR, UCL and CAU together with the NoEM to implement the scientific & technical activities necessary to reach the goals of the project.

The Activity Coordinators are responsible to support the management of the three areas of activity and the corresponding work packages and work package tasks ensuring all parties within their Work Package are performing the tasks set out for them.

- Integrating Activities Coordinator (IAC) (Prof Gilles Vassal, IGR)
- Joint Research Activities Coordinator (JRAC) (Prof Martin Schrappe, CAU)
- Spread of Excellence Activities Coordinator (SEAC) (Prof K Pritchard-Jones, UCL)

The **Project Management Team** will together

- Survey the project progress and resources status
- Agree on the allocation of funds (received by the CCRI to be distributed by the PM)
- Be responsible for dissemination, standardisation as well as exploitation in accordance with the propositions of the corresponding committees
- Secure respect of IPRs when needed and involve the strategic management level
- Resolve conflict on technical, financial and strategic issues

The Project Management Team will take day to day decisions regarding the operative management tasks on the project (NoEM, PM, DM, ACs) with enrolment of advisory functions only when strategic management tasks need to be solved.

A **Project Office** will be set up for the Project Management Team at the CCRI to support the Work Package and Tasks Leaders in order to ensure an efficient day-to-day management of the project.

STRATEGIC MANAGEMENT

The Executive Committee (ExeCom) is a body with a total of 11 members responsible for the strategic management of the Project. It is **chaired** by the **Network of Excellence Manager (NoEM)** and composed of

- The Project Manager (PM)
- The Dissemination Manager (DM
- The three Activity Coordinators (AC)
- One representative each of the Scientific and Ethics Advisory Committee (SAC, EAC)
- One representative of the Parents/Patients Advocacy Committee (PAC)
- Two representatives from the European Clinical Research Council (ECRC) with one representing the the clinical trial groups and one representing the national pediatric oncology societies).

The Executive Committee has the responsibility to foster the interaction of European paediatric oncology clinical trial groups to develop the European Clinical Research Council as a vivid platform of interaction and future developments. It prepares high-level decisions for the General Assembly to facilitate integration of new coooperating organisations and institutions. The ExeCom will also prepare overarching ENCCA project decision making processes when needed with regards to technicalities, financial issues, work schedules, current and future partnerships, dissemination methods and exploitation. It will hence prepare all strategic decision making and inform about the respective suggestions and processes in a timely fashion prior to the annual General Assembly (GA) for the general assembly voting process, when needed.

Should an urgent need arise for an immediate major decision, the ExeCom may call an additional GA meeting to seek resolutions and approval by the GA (definition see below).

The General Assembly is the ultimate decision-taking body of the Consortium. The General Assembly consists of high-level representatives of all ENCCA partners. The General Assembly is responsible for strategic policy. The General Assembly has the right of a veto and to propose alternative solutions. Critical questions should be submitted in writing in a timely fashion to the General Assembly. When appropriate, such questions or proposals will be circulated prior to the meeting to allow coordination of the proposals to be voted on.

To allow the ENCCA project to address specific, highly relevant topics and issues of the Network of Excellence and to prepare for the future virtual European paediatric oncology research institute platform, a European Clinical Research Council, advisory and advocacy committees will be created.

INTEGRATIVE MANAGEMENT

Integrative management covers interface functions of NoEM, PM and DM and ACs to create win-win constellations between ENCCA project deliverables, milestones and external cooperating organisations and parties to establish the future virtual research platform /institute.

This management structure is justified by the rather large size of the consortium: the strategic and operational level will be closely related and, as a consequence, smooth communication and a structured **decision-making process** will be in place.

In particular, specific decisions will be taken according to the following rules:

- In general, matters concerning changes to the project budget and changes to the EU FP7 contract are expected to be decided upon on by a 75% majority.
- All other matters require a simple majority.
- In the case of a split vote, the Network of Excellence Manager (NoEM) will carry the deciding vote.
- Specific voting rights along these general principles will be detailed in the Consortium Agreement.

All the participants are used to collaborate with international groups to reach common ambitious scientific objectives; nonetheless it cannot be excluded that a conflict could occur during the life of the project. To resolve any conflicts that may arise, the following steps are proposed:

- Mediation via the Network of Excellence Manager representing the CCRI, with help of the PMT as needed within 1 month of being officially informed of the issue by letter.
- European Commission (EC) consultation
- Vote by the Executive Committee (if an extraordinary session is needed, at the expense of the parties).
- If no other solution is foreseen, exclusion of the party (-ies) may take place.

B.2.1.2 Project governance

The following information provides an overview of the governance of the project. More detailed modalities will be defined in the Consortium Agreement, under preparation, based on the DESCA model.

a. The Network of Excellence Manager (NoEM)

The Network of Excellence Manager, Assoc. Prof. Ruth Ladenstein at the CCRI will assume together with the PM the responsibility of the technical, financial and administrative management of the project on a day-to-day basis, according to the contractual guidelines. The CCRI will administer the Community contribution, regarding its allocation between contractors and activities, in accordance with the EC FP7 contract and the consortium agreement.

Assoc. Prof Ruth Ladenstein (MD, MBA, cP) has a high level of experience in management of clinical research and has been involved in many European and International projects as coordinator or participant. Assoc. Professor Ruth Ladenstein, has post-graduate studies in International Project Management (cPM) and in International Health Care Management (MBA) and has considerable experience in the management of academic concerted actions. She has previously managed the EC funded project SIOPEN-R-NET (SIOP European Neuroblastoma Research Network) which involves more than 200 clinics from more than 20 countries and is maintained successfully. She is Chairperson of the high risk neuroblastoma clinical trial (HR-NBL-1/SIOPEn) enrolling patients in 20 European countries (> 1500 patients up to date). She is president of SIOPEN (SIOP Europe Neuroblastoma Group) and since Sep 2009 president of SIOPE. She has 86 full article publications in peer-reviewed journals (31 as first, corresponding or senior author) and 8 published book chapters as first author. She has received 2 awards. In order to coordinate the consortium she will be assisted in her task by the Project Manager (PM) and the Dissemination Manager (DM) and the Activity Coordinators (ACs).

Within ENCCA, Assoc. Professor Ruth Ladenstein will be the Chair of the General Assembly and the Executive Committee, as well as the sole interface between the European Commission and the consortium. Professor Gilles Vassal, is elected Vice-Chair for both the GA and the ExeCom.

b. The General Assembly (GA)

ENCCA's **General Assembly** is responsible for strategic policy and decision-making. The General Assembly consists of high level representatives of all the ENCCA partners. Their main role is to oversee the strategy of European paediatric oncology clinical trial groups and the coordination of the participants' activities as well as to make high-level decisions in order to facilitate integration of the network members. Approval of technical re-orientations, validation of project review, IPR and exploitation issues as well as possible changes of the consortium are also some of the responsabilities of the General Assembly voting processes which will be detailed in the consortim agreement. Hence adopted strategies are approved and respected in order to reach excellence.

In order to facilitate the decision – making processes, the General Assembly is assisted by the ExeCom in-between meetings and a number of permanent Committees (such as Scientific Advisory Committee) .

- ✓ **Chair:** Assoc. Professor Ruth Ladenstein & Vice-Chair: Professor Gilles Vassal
- ✓ **GA representatives**: Representatives of all the ENCCA partners including administrative and scientific level.
- ✓ Meetings: The General Assembly meeting is held once a year

c. The Executive Committee (ExeCom)

The Executive Committee is a decision-making body with a total of 11 members supporting the execution of the Project. It is composed of the Project Manager (PM), the Dissemination Manager (DM), the three Activity Coordinators (AC) and the 2 representatives of the Advisory Committees (one each), one representative of the Parents/Patients Advocacy Committee (PAC) and the 2 representatives from the ECRC (one for clinical trial groups, one for national pediatric oncology societies). It is chaired by the Network of Excellence Manager.

The Executive Committee has the responsibility to oversee the strategy of European paediatric oncology clinical trial groups and the coordination of the participants' activities as well as to prepare high-level decisions in order to facilitate integration of the network members. It will prepare all-encompassing decisions concerning ENCCA such as technicalities, financial issues, work schedule, current and future partnership, dissemination methods and exploitation. It will prepare all strategic decision making and disseminate the respective suggestions and processes in a timely fashion prior to the annual General Assembly (GA) for the general assembly voting process, when needed.

- ✓ **Meetings:** The Executive Committee will meet at least once a year. Extraordinary meetings could be called for, should the need arise

d. The Committees & Council

1. The Scientific Advisory Committee (SAC)

This committee will be composed of a maximum of three internationally recognised specialists in paediatric and adolescent oncology from USA, Canada and Europe to be addressed when needed during the course of the ENCCA project. One representative of the SAC will be part of the Executive Committee. The list shows recognised people who already expressed their interest to participate in ENCCA initiative. The PMT will ultimately elect the SAC members.

Expertise/position	Contact Name	Organisation
Prof. and Chair in paediatric cancer & Director of Colorado Denver School of Medicine	Prof. Stephen P. Hunger	Un. Of Colorado Denver School of Medicine, USA
Prof. and Director of Institute for Cell and Molecular Pathology	Prof. Brigitte Schlegelberger	Hanover Medical School, Germany
Prof. and Chair, Depts. of Clinical Epidemiology & Biostatistics, Michael Gent Chair in healthcare Research	Holger J. Schünemann, M.D; PhD	McMaster un. Health Sciences Centre, Canada
Professor and CCRF Land Grant Chair Lab medicine/pathology and Paediatrics Blood and marrow Transplantation pr. Founding Director Emeritus	John H Kersey, M.D,	Masonic cancer Center, Un. Of Minnesota, USA
Professor in Paediatrics, Dir. Clinical Programs	Jim Nachman, M.D	Un. Of Chicago's Hospital, USA

Expertise/position	Contact Name	Organisation
Paediatrics	Professor Gregory H. Reaman, M.D.	The George Washington University School of Medicine and Health Sciences, Bethesda, USA
Paediatric Haematology-Oncology	Professor Katherine K. Matthay, M.D.	Transnational Cancer Research Department of Paediatrics San Francisco, USA
Current Chair of COG Neuroblastoma Group	John M. Maris, MD	Centre for Childhood Cancer Research Children's Hospital of Philadelphia, USA
Professor and Director, Paediatric Haematology/Oncology	Franco Locatelli, M.D.	San Matteo Hospital University of Pavia, Italy

Table 4: List of international recognised researchers and clinical experts (Potential SAC members)

2. The Ethics Advisory Committee (EAC)

- The EAC will be responsible for keeping the participants well-informed about ethical regulations relevant to the clinical trials.
- The EAC is a non-executive body addressing ethical issues raised by the Executive Committee (ExeCom)
- The EAC is also expected to act proactively by identifying further relevant issues.
    - The EAC may deal with a broad range of ethical matters connected with specific biomedical activities, including (but not limited to) clinical research in paediatric oncology and the use of knowledge and techniques derived from human genetics or biotechnologies.
    - The EAC may also study broader ethical and social issues, such as the protection of humans in research and the appropriate uses of biomedical technologies.
    - Moreover the EAC will also maintain contact with ECVAM (European Centre for the Validation of Alternative methods) in order to inform about new developments that could also initiate alternative experimental procedures.

Composition: External experts (approx. 5-7 EAG members) who will provide advice to the ENCCA consortium. Ideally external experts will be in contact on a twice yearly basis.

3. The Parent/ Patients Advocacy Committee (PAC)

ENCCA will establish a Parent/Patients Advocacy Committee to work closely with ENCCA in the design and implementation of its cooperative group clinical research strategy and access to clinical trials for patients.

- Aim is to assist in the development of clinical trials that advance prevention and cure of childhood cancer while responding to the medical, social and personal effects of cancer treatment.
- Seeks to continually improve the diagnostic, treatment and follow-up care of paediatric cancer patients.
- The PAC will enhance communication and increase understanding among childhood cancer patients, their families and the research community.

Composition: Members (indicated into the following table) will all be linked through ICCPO, the International Confederation of Childhood Cancer Parent Organisation and managed through the ENCCA project partner ÖKKH.

Proposed Parents association	Country	Person represented association
Österreichische Kinder-Krebs-Hilfe	Austria	Anita Kienesberger
SYLVA	Finland	Leena Vasankari-Vayrynen
Sdruží Šance	Czech Republic	Eva Dvořkáková
Floga - Parents Association of Children with Cancer	Greece	Xenia Botsoli
Európai Támogatási Egyesület a Rákos Gyermekekért	Hungary	Bert Fröbe
Federación Española de Padres de Niños con Cáncer (FEPNC)	Spain	Adelaida Fisas Armengol, Luisa Basset
Patient/parents advocacy committe Poland	Poland	Marzena Samardakiewicz

Table 5: List of Patient/Parents Groups and Potential PAC members

Meeting: The Committee will meet at lease once a year and interact with the Executive Committee of ENCCA

4. The European Clinical Research Council in Paediatric and Adolescent Oncology (ECRC)

Seeks the integration of the pre-existing major tumour and leukaemia therapeutic networks running clinical trials and will consist of all their respective chairs or their nominated representative. Through this pan-European effort, ENCCA aims to integrate aims and data across different cancer entities for higher translation of basic and preclinical research to clinical application. This council aims to welcome in addition the chairs of the European national paediatric oncology societies to better integrate and represent local expertise and infrastructures, needs and legal authority issues for clinical and translational research at the national level. This will permit better communication among groups and interaction with the ENCCA consortium to exchange new ideas, to identify new challenges and to accelerate the efforts for new therapeutic strategies for children and adolescent with cancer.

Composition:

- Chairs of all European tumour and leukaemia trial networks
- Chairs of all European national paediatric oncology societies
- The council will elect one representative each for both groups as outlined above presenting the two Council groups in the Executive Committee of ENCCA.

Meetings: The Council will meet twice per year and have input in the strategic decision and future direction of ENCCA.

5. Intellectual Property Rights Committee (IPRC)

An Intellectual Property Rights Committee (IPRC) is expected to brainstorm on the emerging results in the project. It will also keep the consortium updated on existing protocols, applications and patent databases which will reveal if and where patents can be submitted, and more importantly, potential methods and customers to generate incomes.

The IPRC proposes the exploitation and dissemination plan (including standardisation aspects) and it updates the ExeCom. All proposals by the IPRC to the ExeCom shall always be made in a consensual way, taking into account the combined members' interests.
The Intellectual Property Committee will be composed of one specialist from each partner organisation (the composition of which will be detailed in the Consortium Agreement) and is chaired by the project Exploitation Manager (IGR). The Dissemination Manager (SIOPE) will provide the necessary support in coordinating, recording and reporting on dissemination activities. The DM will in addition identify the most appropriate results, relevant publications and information outlets such as conferences and seminars that have not yet been identified.

e. The Activity Coordinators (ACs)

Each Activity Coordinator is responsible to follow closely the respective area of activity (IA, JRA, SEA) and to support the WP leaders to achieve their tasks as needed. The activity review meeting is conducted by a team made up of the Work Package Leaders (WPLs) involved in the activity and will be summarized in reports for the PMT.
Each Activity Coordinator (AC) is responsible for:

- Coordination and reporting on the progress in tasks and achievements of the respective area to the whole consortium via newsletters appearing in the forum section of the website
- Organising focused meetings in order to determine suitable measures to be taken.
- Ensuring that milestones and deliverables of the tasks are fulfilled and to eventually notify the ExeCom and to prepare alternative proposals and solutions, if such are needed, for approval by the GA.

The Activity Coordinators appointed are demonstrated in the following table.

Activity	WPs included in Activity	Activity Coordinator (AC)	Institution (AC)
Integrating Activities **(IA)**	WP1.1–WP1.5	**Prof. Gilles Vassal s**	UCL
Joint Research Activities **(JRA)**	WP2.1- WP2.7	**Prof. Martin Schrappe**	CAU
Spread of Excellence Activities **(SEA)**	WP3.1- WP3.5	**Prof. Kathy Pritchard-Jones**	IGR

Table 6: Overview Activity Coordinators

f. Work package leaders (WPLs)

The work package leaders (WPLs) defined their the objectives which were approved by the ACs and the NoEM. WPLs are committed:

- To control the progress of the scheduled work within the Work Package (WP) in terms of technical achievement planned deliverables and expenses in order to ensure the accomplishment of the technical objectives of the WP.
- To assess the quality of the outputs of their WP deliverables and milestones.
- To initiate and participate actively in the technical meetings necessary for the work progress, and to provide minutes of relevant meetings.
- To refer to the ACs for support in case of a major issue that affects the completion of the work foreseen.

Meeting: The WPLs will meet regularly according to given needs (phone conferences or meetings whenever possible) to follow the work in progress, in order to anticipate and resolve any issue that may arise.

WP	Leader	WP	Leader	WP	Leader
WP1	CCRI	WP7	OLGA	WP13	IGG
WP2	SIOPE	WP8	IGR	WP14	SIOPE
WP3	AIT	WP9	CAU	WP15	UCSC
WP4	CCRI	WP10	LAFE	WP16	IGR
WP5	UKE/CHARITE	WP11	UCL	WP17	UN. LEEDS
WP6	UNIMIB	WP12	MUG	WP18	CURIE

Table 7: Overview of the Work Package Leaders

g. Project management team (PMT)

The Project management team (PMT) is under the responsibility of the NoEM. The PMT will assist the NoEM in the management of administrative, contractual and financial aspects, organisation of inter-and intra-consortium communication, internal website, reporting, consortium management, in order to ensure an efficient project organisation towards EC requirements. A Quality Assurance Plan will be defined by the PM and approved by the PMT to secure high level quality within the consortium.

B.2.1.3 Internal project procedures and associated tools

In order to ensure the efficient launch of the project activities, dedicated management procedures and tools, fitting to the internal management requirements, will be created, under the responsibility of the Management Team. Further information may be found in dedicated work packages sections.

B.2.1.3.1 Decision-making mechanisms and conflict resolution

The objective is to implement a management structure within the consortium which will give the possibility to take rapid and efficient decisions whenever necessary and allow simultaneously having each individual organisation represented, in order to anticipate and avoid the occurrence of disagreements/conflicts.

The chosen structure will:

- Ensure the possibility to take strategic decisions
- Allow a close collaboration between the strategic and operational level (implementation of the scientific activities) represented by the Work Package Leaders.
- Limit the use of veto power

B.2.1.3.2 Dissemination and exploitation

As with all successful R&D projects, the consortium anticipates the generation of an important quantity of knowledge (foreground) and to associate it to appropriate dissemination and exploitation policies. Advisory bodies as well as dedicated managers will be nominated in order to track, protect and disseminate results and set the consortium strategies.

B.2.1.3.3 Risk management

Establish a management structure capable of dealing with a potential conflict of interest regarding the exploitation of the results.

B.2.1.3.4 Internal reporting

The project progress will be shared, presented, reviewed and analysed regularly on the following basis:

- Six-monthly basis: Internal activity reports and Executive Committee and Work Package leaders meeting
- Mid-term assessment (Meeting 24 month, could be the General Assembly):
  - All participants are expected to attend
  - The objective will be to assess the project progress on the basis of deliverables produced with a comprehensive risks analysis

B.2.1.3.5 Operational project coordinator

In recognition of the important management activities within ENCCA a Project Office will be created and will coordinate activities focusing on four main topics:

- **Contract management**: Co-ordinating the EC grant and consortium agreements and managing amendments.
- **Reporting management**: In order to track participants' activities, resources mobilised and results generated, adequate internal reporting procedures will be proposed.
- **Partnership management**: For a 4 year project, the internal evolution of each participant can have an impact on the project progress and success. Therefore, each participant's role in the history of the project will be recorded.
- **Quality management**: An internal quality policy (such as document standards, proofreading, validation workflow, project charter, quality indicators) will be proposed from the outset of the project.

B.2.1.3.6 Balanced scorecard

In order to efficiently lead the ENCCA with relevant measurements as regards the status of the activities, at the beginning of the project **adequate performance indicators**, such as Quality, Costs and Delay will be defined in order to establish a balanced scorecard. The balanced scorecard is a performance measurement system. The project manager will be responsible for implementing and monitoring the balanced scorecards together with the activity leaders. Any deviation between the ENCCA objectives and the indicator values will be timely addressed by the Executive Committee on the Network of Excellence Manager demand. Corrective actions to get back on track and meet the ENCCA goals will be promptly defined and implemented..

B.2.1.3.7 Communication and reporting

An efficient communication across the project will ensure that all the participants are fully informed of the project status, the planning and all other issues, therefore the synergy of the co-operation between them will increase. The following procedures and tools will be adopted:

- A web-based collaboration platform will be implemented. This website will be secure and will enable the consortium to have very efficient diffusion of the information relevant to the numerous WP deliverables and encourage exchanges between partners.
- The PMT will meet on a monthly basis from the beginning of the project and on an ad hoc basis if requested. Due to the size of the consortium, these meetings will be frequently technically-based. The meetings will be chaired by CCRI and SIOPE will assist in the organisation of such events. Additional specific technical meetings will be required and organised by the work package leaders, when judged necessary.

B.2.1.3.8 Mid-term assessment and review criteria

A mid-term assessment report is to be issued before the end of the 27th month of the project and prior to the Mid-Term assessment Project Management Team meeting .The goal of this meeting will be to assess the progress, to date, and to redefine (if necessary) the Project Programme for the remaining part of the contract. A GO/NO-GO decision, regarding the specific objectives and milestones for the technical / scientific progress and the partners' plans for future exploitation strategy, will be made with the relevant EC representative.

B.2.1.3.9 Consortium agreement

A Consortium Agreement (CAG) is being prepared on the basis of the DESCA model. It will be validated by the Executive Committee and signed before the contract starts. The CAG will include in particular provisions for the organisation of the consortium, grant distribution, management of IPR and dissemination and the exploitation of results.

B.2.2 Beneficiaries

Organisation	CCRI	Type	Research Organisation

General Description

The CCRI was founded in 1988 with the overall aim to improve the treatment options for children suffering from cancer. It has since then significantly contributed to the understanding of the pathogenesis of paediatric cancer diseases, to the development of therapy-optimization protocols and of novel, improved diagnostics that are nowadays implemented in different clinical studies across Europe. The scientific focus lies, on the one hand, on the translational science sector, specifically the development and refinement of diagnostics and the preparation, optimization and monitoring of bone marrow transplantation, and on basic research on the other hand. The close interaction with St. Anna Children's Hospital – the largest clinical haemato-oncological centre for the treatment of childhood cancer in Austria – is used as a platform to tackle patient relevant scientific problems. The CCRI is a non profit research Institution that is solely funded by volunteers' donations and competitive research grants.

Role within the project

Assoc. Professor Ruth Ladenstein, Head of the Studies and Statistics Department at the CCRI, will have the role of the **Network of Excellence Manager** and is the **leader of WPs 1 (management of the project), 2 and 4** where she will coordinate the investigator driven trial facilitation tasks on the European level. She will participate in tasks throughout the project and engage particularly with the parent's and patient's advocacy group.

The tumour biology group in the CCRI will i) initiate and direct all validation steps to allow implementation of genomic techniques newly developed for neuroblastoma for clinical routine; ii) organize online reviewing of uploaded genomic data before clinical use; iii) conduct quality control of the pan-/multigenomic techniques; and iv) stimulate and perform scientific projects based on well defined tumour samples and quality controlled genomic data.

Ulrike Pötschger, lead statistician within the CCRI, will collaborate in the WP 6 'Standardised and innovative methodology for clinical trial design' and will be task leader of task 6.3 'Statistical approaches for the analysis of recurrent events (SAE) and competing events (composite endpoints) and long term outcome that aims at reviewing, exploring and developing innovative approaches for the analysis of patient's safety, competing events and long-term outcome.

The molecular biological laboratory of the CCRI, will be participating in WP 5. on the Ewing´s sarcoma and related tumours tasks. The **i**mmunological diagnostics group at the CCRI will be participating in WP 9 in leukaemia specific tasks.

R&D Experience relevant to the project

Assoc. Professor Ruth Ladenstein, Head of the Studies and Statistics Department at the CCRI, has previously managed the EC funded project SIOPEN-R-NET (QLRI-CT-2002-01768; https://www.siopen-r-net.org) and is currently president of the European Neuroblastoma Group of the International Society for Paediatric Oncology (SIOPEN Association). She has a large experience in setting up and running investigator driven clinical trials (Phase I to III) on international platforms (as principal investigator and participant). She has managed also the antibody production of the ch14.16/CHO AntiGD2 Antibody from bench to bedside for the European Neuroblastoma High Risk Study (HR-NBL1/SIOPEN) facilitated through European fund raising.

The SIOPEN Biology Group started in 1994 by facilitating the implementation of FISH data on *MYCN* copy number as decision-making marker in neuroblastoma molecular diagnosis. Along this line, the group undertook major efforts to harmonize and standardise different techniques, to build up a uniform nomenclature, set up guidelines and, importantly, to work out a quality control system to minimise the error rate in molecular diagnosis.

The work, directed by the CCRI, was published in 2003 and forms the basis of the worldwide-accepted INRG guidelines, which were published in 2009. Furthermore, essential parts of these guidelines are now in use in different European protocols dealing with other solid tumours. Therefore, CCRI ensures that the expertise will help us to the multicentric validation of novel genomic diagnostics techniques, the related review of genomic data and the conduct the QC remains in good hands and will lead to cope with these new requirements, i.e. the up-to-date highest possible reliability and robustness of pan/multigenomic data for the decision making process., and will provide the basis for new scientific work.

Dr. Karla Valdés Rodrigues, grant manager in the CCRI, is experienced in the establishment of project management-documentation and -procedures and as deputy vice-president of cooperation contributed to negotiations with potential investors in the industry sector.

Ulrike Pötschger, statistician, has been working in the field of medical statistics since 1992 and since 1996 in the CCRI. She is the main responsible statistician of multiple international clinical studies in the field of paediatric oncology (since 2002 SIOPEN HR-NBL1 study, since 2004 ALL-SCT 2003, since 2007 ALL-SCT BFM International, since 1996 LCH-II-LCH-IV). Since 2008, she is Chairperson of the Information Management and Methodology Committee of the I-BFM-SG. In 2008, she started a collaboration with the Core Unit for Medical Statistics and Informatics of the Medical University Vienna in order to develop innovative approaches in the field of survival analysis focusing on long-term outcome.

Assoc.Professor Heinrich Kovar, head of the molecular biological laboratory of the CCRI, is studying the underlying genetic aberrations in this disease, tumour-specific mutations, in particular ESFT alterations of genes aiming at characterizing patterns of aberrant gene expression that are associated with distinct courses of disease. Monitoring of prognostic patterns at diagnosis may allow early stratification of therapy. Current studies seek to define the involvement of these genes in common pathways of cell growth and death and to reveal molecular interactions between them hoping to identify novel targets for therapeutic intervention.
The immunological diagnostics group at the CCRI has for main goal the development and evaluation of new diagnostic approaches for paediatric leukaemias and lymphomas based on flow cytometric immunophenotyping. Topics of the work are investigations into disease-associated peculiarities of protein expression which could in the future be exploited clinically for elaborate diagnostics, risk stratification and treatment tailoring to individual needs and development of new therapeutic approaches.

Description of key people involved in the project

Assoc. Professor Ruth Ladenstein
Associate professor, MD, MBA, cPM. She is Head of the Studies and Statistics Department at the CCRI and she has previously managed the EC funded project SIOPEN-R-NET. She is currently president of the European Neuroblastoma Group of the International Society for Paediatric Oncology (SIOPEN Association). She is president of SIOP EUROPE since September 2009, Group president of SIOPEN (SIOP Europe Neuroblastoma Group) since May 2007 and founder of the SIOPEN association. She is deputy Chair of the Solid Tumour Paediatric Working Party of EBMT (European Bone Marrow Transplantation Group) and head of the Austrian Paediatric Oncology Group (AGPHO). She has 86 full article publications in peer-reviewed journals (28 as first, corresponding or senior author) and 8 published book chapters as first author. She has received 2 awards.

Ulrike Pötschger
MSc. She is the lead statistician within the CCRI. She is a medical statistician with long lasting experience in clinical trials in paediatric oncology, and the main responsible statistician of 4 international randomised trials in paediatric oncology. She is chairwoman of the Information Management and Methodology Committee of the I-BFM-SG. She has 47 publications.

Assoc. Professor Peter F. Ambros
Associate professor. He is chairman of the SIOPEN-Biology Group, designing and conducting the technical requirements of the multigenomic test system, designing of quality control studies. 159 publications, 1 patent and 4 awards.

Assoc. Professor Michael Dworzak
MD, Associate professor. He is Research group leader since 1993 at the CCRI, Coordinator of the I-BFM-ALL-FLOW-MRD-SG since 2000, Coordinator of the Austrian AML-BFM studies since 2003, Austrian representative in the I-BFM Executive Board since 2006, Coordinator of the AIEOP-BFM ALL Trial Diagnostic Group – FLOW since 2009 performing quality control studies. He has 66 full article publications in peer-reviewed journals (24 as first, corresponding or senior author) and 4 national research awards received 1995 – 2009.

Participation in relevant National or European research projects
▪ Creation of the SIOP European Neuroblastoma Research Network (SIOPEN-R-NET) ▪ EC-projects: the FP6 projects PONT (STREP), CHIMERIC VACCINES (CRAFT), SARS/FLU VACCINE (STREP), FLUVACC (IP), Intranasal H5 Vaccines (STREP). ▪ ÖNB 13422 Cost effective multi-genomic technique allows risk evaluation in large scale neuroblastoma studies. ▪ FP6 STREP EET-Pipeline nr.037260 European Embryonal Tumour Pipeline. ▪ GEN-AU CHILD: Coordination of a 7 year long Austrian network devoted to the study of chromosome rearrangements characterizing childhood cancer. ▪ EWS-FL1 in post transcriptional regulation: Project funded by the FWF (national funding organisation)

Organisation	**SIOPE**	**Type**	**Non-Profit Organisation**

General Description

SIOP Europe (SIOPE) -with a membership of over 800 individuals- is a European organisation promoting research and optimal standards of care for children and young people with cancer. It is the only multidisciplinary, pan-European organisation dedicated to childhood cancer.

The aims of SIOPE include:

- Facilitate and increase professional medical, scientific and educational co-operation throughout Europe, in particular by supporting exchanges and meetings between doctors, nurses and other professionals involved in the care of children and adolescents with cancer;
- Optimise access to information and promote multi-centre and multinational clinical trials, forming a common platform for best practice guidelines in clinical research
- Promote better policies for children with cancer and raise awareness of the numerous challenges faced by paediatric oncology professionals to EU policymakers
- Participate in the development of European guidelines for, and standards of, training and care in paediatric oncology;
- Support better policies for children with cancer as well as their reintegration into education and employment and raise awareness of the numerous challenges faced by paediatric oncology professionals to EU policymakers, including support;
- Promote and develop collaborative relationships with organisations representing children and adolescents with cancer and their families.

Role within the project

SIOPE will within this project continuously monitor and provide the needed support to the ENCCA partners in order to facilitate knowledge-exchange and activity-integration within the consortium. Moreover, to ensure that information is exchanged across the paediatric oncology spectrum, the activities, outcomes and conclusions will be disseminated to the community at large. To ensure the successful establishment of the virtual research structure for paediatric oncology project additional managing capacity will be needed and shall be strengthened through the ENCCA project. A strategic decision was taken to place the central office in Brussels ensure and enhance close collaboration with European organisations and to create powerful links with all the actors. One of the outstanding SIOPE tasks will be to organise and implement a European Paediatric and Adolescent Tumour and Leukaemia Group Council that will be able to integrate all the paediatric oncology clinical trial platforms in Europe as well as to create the necessary synergies with all the clinical actors' clinicians, biologists, patient organisations, regulators, industrials, ethical committees participating in clinical trials.

In addition SIOPE will carry the responsibility to create the Patients/Parents Advocacy Group; the Scientific Advisory Group that will represent the groups in the ENCCA Activities and to maintain and elaborate these important structures beyond the mere project period. SIOPE will be the central access point and thus the virtual central hub and access point for standardised and quality controlled technologies, clinical facilities and tools. The final aim is to integrate the specific facilities in the Virtual Platform.

One major objective is to prepare the financial autonomy of the Network through the creation of a Financing Option Assessment Office. To ensure ENCCA's sustainable integration, it needs rely on a strong and durable structure able to efficiently manage the network activities in the future. This can only be achieved under the umbrella of a legal entity (European Economic Interest Group) and SIOPE will prepare the creation of a new legal entity.

SIOPE is leading WP1.1, the European sustainable strategy for clinical paediatric oncology and WP3.1, Dissemination activities.

R&D Experience relevant to the project
As many of the SIOPE tasks are already part of the day-to-day activities, SIOPE is the ideal point of dissemination of information towards members and all other relevant organisations and institutes involved directly or non-directly to Paediatric Oncology.
Description of key people involved in the project
Assoc. Professor Ruth Ladenstein: President of SIOPE and Associate Professor at the St. Anna Children's Hospital. Head of the Department, CCRI-SIRP "Studies & Statistics on Integrated Research and Projects", of the CCRI-Children's Cancer Research Institute. **Samira Essiaf:** She is Secretary General of SIOPE. Samira has a 9 years experience in the field of clinical trials where she was working as an Intercontinental Project Manager. **Edel Fitzgerald:** She is Public Affairs Administrator of SIOPE. She is experienced in marketing and communication and has an academic background in European legal studies. Achievements include an academic award from Queen's University, Belfast Northern Ireland and recognition of her contribution to student journalism from the University of Limerick, Ireland.

Organization	UCL	Type	Higher education

General Description

University College London (UCL) is one of Europe's largest and most productive centres for biomedical science. It employs over 4,000 academic and research staff working at the forefront of their fields, of whom 1,872 work in the biomedical sciences. In 2009, it was ranked 4th in the Times Higher Education World University rankings. UCL has extensive experience of working with EU funding (currently participating in over 200 projects, allocated a total of 104.5 million Euro). The UCL Institute of Child Health (ICH), where Prof. Pritchard-Jones is based, aims to define the scientific, epidemiological and clinical basis of childhood diseases to promote the health needs of children.

UCL has a formal academic partnership with Great Ormond Street Hospital for Sick Children (GOSH) and University College Hospital (UCH). These two hospitals function as a single specialist centre for the treatment of cancer in children and young people. The joint service is the largest in the UK, treating over 300 new cancer patients aged 0-18 each year.

Role within the project

Prof Kathy Pritchard-Jones will be one of the 3 Activity Coordinators, responsible for the oversight of progress of the WPs under "Spread of excellence acrtivities", hence UCL will be on the Executive Committee of the Network of Excellence. UCL will also lead WP 11 on Prospective Cohorts and contribute personal knowledge and skills to several other WPs. UCL (Jeremy Whelan) will contribute to 3 tasks and lead on develop a European platform for clinical trials in osteosarcoma in WP7.

R&D Experience relevant to the project

UCL ICH-GOSH has more than 30 years experience of clinical trials in children, including innovative early phase trials in very young children. UCH houses the largest teenage and young adult cancer unit in the UK and the London Bone Sarcoma service and is the largest recruiter to early phase trials in sarcomas in adolescents and young adults in the UK. GOSH has a dedicated clinical research facility that supports 'first in child' clinical trials of new, biologically targeted agents and pharmacokinetic and biomarker studies. There are several research groups within UCL and its partners with whom Prof Pritchard-Jones has research collaborations or established interactions of relevance to the ENCCA project. These include Professor Chris Boshoff (Director, UCL Cancer Institute) who has extensive experience of early phase trials in cancer and whose institute provides a GLP facility for molecular analysis of tumours treated in early phase trials; Professor Hilary Calvert, medical oncologist with a special interest in experimental therapeutics and drug development; Dr Mike Hubank, UCL Genomics, who support the full range of high resolution, whole genome analytical approaches; Prof Adrienne Flannagan, bone tumour pathologist. The UCL ICH Cancer Theme includes groups researching into the biology of renal tumours (Prof Pritchard-Jones) neuroblastoma (Dr Arturo Sala), medulloblastoma (Dr Jonathan Ham), rhabdomyosarcoma and immunotherapy (Dr John Anderson). In GOSH radiology, there are several active research projects in childhood tumours and several radiologists lead on response assessment for European paediatric clinical trials.

Description of key people involved in the project

Professor Kathy Pritchard-Jones

She is consultant Paediatric Oncologist and Professor of Paediatric Oncology at UCL and Programme Director for Cancer for UCL Partners. She is chief investigator for several phase I-III trials in childhood and adolescent cancer. She has published over 150 articles in the field.

Dr Jeremy Whelan leads a clinical research programme in bone sarcomas, including a role as chief investigator in the European-American collaborative phase III trial in osteosarcoma, EURAMOS 1. He chairs the UK National Cancer Research Institute Clinical Studies Groups for bone sarcomas and teenagers and young adults with cancer.

Professor. Hilary Calvert

Director of cancer drug discovery and development, UCL Partners. One third of his time is allocated to this activity for children and adolescents.

Participation in relevant National or European research projects

- **FP6 LSHC-CT-2006-037390 – "KidsCancerKinome"** – Selecting and validating drug targets from the human kinome for high risk paediatric cancers, (co-investigator)
- **FP7 collaborative project Health-F5-2009-223158 – "O3K"** – Oral Off-Patent Oncology Drugs for Kids. (co-investigator)
- **FP7 collaborative project Health-F5-2009-222910 – "EPOC"** – European Paediatric Oncology Off-Patent Medicines Consortium, (co-investigator)
- Cancer Research UK Translational Research in Clinical Trials Award C5066/A10399 (2007-2011) - Identification of prognostic markers and therapeutic targets for childhood rhabdomyosarcomas. (co-

investigator)
- Cancer Research UK Biomarker and Imaging Discovery and Development committee Award C1188/A11859 (2010-2012) - Molecular risk stratification to improve outcomes in Wilms tumour (Principal investigator)
- Cancer Research UK Clinical Trial grant C1188/A8687 (2002-2012) for SIOP Wilms tumour phase III trial in the UK (Chief investigator)

Organisation	**IGR**	**Type**	**Research organisation**

General Description

Institute Gustave-Roussy (IGR) is a large comprehensive cancer centre dedicated to care, research and education. In the 360 -bed hospital with 200 statutory physicians, annually over 11,000 new patients are recruited. 200 clinical trials recruit 1500 patients. IGR is currently sponsoring 44 clinical trials including 9 European trials, 1/3 of those trials are in paediatric oncology. The Paediatric Oncology department was created in 1957 by Odile SChweisguth, a SIOP Founder. Each year 350 new paediatric patients with malignant solid tumours are treated. IGR is a major stakeholder, deeply involved in clinical and translational research for children with cancer. A translational research team runs a biology and preclinical evaluation programme, using in-house made tumour models in paediatric brain tumours and neuroblastoma. A research team in statistics develops innovative methodology and trial designs and manages clinical trials.

The following department and teams will participate:

- Division of Clinical and Translational Research
- Department of Paediatric Oncology
- Paediatric Methodology and Statistics team within the Biostatistics and Epidemiology Department
- UPRES EA3535 – translational research team

Role within the project

Professor Gilles Vassal, director of Clinical and Translational Research at IGR will be member of the **Executive Committee and Activity Coordinator of the** Spread of Excellence activities, as well **Work Package leader of the WP8** (Early evaluation and prioritisation of new anticancer drugs) and **WP16** (Facilitation of Industry Collaboration with Pharmaceutical Companies and SME for dissemination)

IGR will also participate in WP2, WP6, WP8, WP12, WP17 as task leader, and will significantly contribute to the Joint Research Activity Programme as well as in training and education activities.

R&D Experience relevant to the project

IGR has been involved in paediatric oncology research for more than 50 years. The IGR paediatric oncology department has a large and internationally recognized experience in care and research for children and adolescents with malignant solid tumours (350 new patients yearly). A specific Adolescent program is run, the team is deeply involved in the development of innovative therapies as well as large phase III trials exploring therapeutic strategies. The team is a leader in the field of phase I and earl phase II trials of new anticancer drugs in children.

The IGR Clinical and Translational Research Division coordinates and sponsor IDCTs : phase I and II trials, the ongoing EUROEWING, the next EICNHL Burkitt lymphoma protocol, the French participation to HRNBL1 trials in high risk neuroblastoma and several French national studies. IGR has all the facilities and expertise to sponsor and run clinical trials at the European level (regulatory affairs, pharmacovigilance unit, statistics and trial management, on-site monitoring, contract negotiation, etc).

The UPRES EA3535 translational research team has established preclinical xenograft models of brain tumours and neuroblastoma, and develops preclinical evaluation of targeted compounds.

Description of key people involved in the project

Professor Gilles Vassal: MD, PhD, Professor of oncology at University Paris XI. He is currently Director of Clinical and Translational Research at IGR, Director of the Paediatric Translational Research team (U3535) and member of the Paediatric Oncology Department. He is Chair of the ITCC consortium since its creation in 2003 and an elected member of SIOPEurope Board since 2007. He is Coordinator of two FP6-STREPs and an EMA-expert member. He is a member of the European Academy of Cancer Sciences. He has 145 publications, and 2 patents.

Dr. Laurence Brugieres: MD. She is a Paediatric Oncology specialist with a Master Degree in Genetics. She is member of the Paediatric Oncology Department where she is head of the Adolescent unit. She is PI of the International trial in paediatric large cell anasplatic lymphomas, PI of the ongoing French osteosarcoma trial. She is author of 104 peer reviewed publications.

Dr. Marie Cécile Le Deley: MD, PhD. She is a paediatric oncologist and statistician. She is head of the Paediatric Statistical team in the IGR Biostatistics and Epidemiology Department. She is author of 26 peer-reviewed publications.

Participation in relevant National or European research projects
FP6- KidsCancerKinome : This project aims at identifying and validating kinases as druggable targets for 6 paediatric malignancies, and to run the preclinical proof of concept of therapeutic intervention on those targets and pathways using relevant in vitro and in vivo (xenografts) paediatric tumour models. **FP6- Conticanet :**Thi**s** large network is focussed on soft tissue sarcomas in adults and children. **FP7 – Oral Off-patent Oncology drugs for Kids:** This project aims at developing a liquid oral for formulations for two off-patent anticancer drugs, namely cyclophosphamide and temozolomide for children

Organisation	**CAU**	**Type**	**Research organisation**

General Description

The University of Kiel was formally inaugurated on October 5, 1665. Today there are at least 20,000 people studying in Kiel. The medical faculty is one of 8 faculties of the university, and the University Hospital Schleswig-Holstein one of the 5 largest in Germany. The Department of Paediatrics – which also includes paediatric haematology/oncology at our site – hosts the trial centre of the German ALL-BFM Study Group and the current office of the International BFM Study Group (I-BFM-SG). The ALL-BFM Study Group conducts multicentre clinical trials on the treatment of paediatric acute lymphoblastic leukaemia covering roughly 80% of the incident German population. TheI-BFM-SG is an informal collaborative international network of clinical trial networks from 25 countries worldwide – 20 of them being European. Work of the I-BFM is structured in 9 committees (ALL, AML, biology & diagnosis, bone marrow transplantation, early and late toxicity/education, information management and methodology, NHL, resistant disease, early clinical trials) and associated working groups. The activities under the umbrella of I-BFM cover a broad spectrum from basic research to standard clinical trials.

Role within the project

CAU will **coordinate WP9** with a focus on improving therapeutic strategies using predictive biomarkers in leukaemias. Through the application of algorithms for identification and prioritisation of molecular targets based on biological data, the activities in this WP will allow tofocus on the most promising molecularly targeted treatments in preclinical model systems. In parallel, the international multicentre clinical trials AIEOP-BFM ALL 2009 and INTERFANT-06 will serve as infrastructural platforms and treatment backbones to prospectively validate the developed target identification approaches. The close association with the International Relapsed trial in acute lymphoblastic leukaemia (INTREALL) will allow efficient clinical testing of molecularly targeted treatment strategies, to finally prove their direct benefit to the patient. In addition, CAU will be involved in several other WPs of this NoE (e.g., coordination of the tumour-subnet work leukemias in WP5). **Professor Martin Schrappe** will be **a member of the Executive Committee** and **Activity Coordinator of the Joint Research Activities.**

R&D Experience relevant to the project

The team from CAU has long standing experience in the design, conduct and analysis of national and international clinical trials. In addition, specific diagnostics and a broad spectrum of translational research activities mainly associated with ALL are conducted at CAU. The latter with a focus on the identification of clinically relevant biomarkers for important clinical endpoints. The team at CAU is part of the German National Genome Research Net (NGFN), where it uses genome-wide approaches for an extended molecular characterisation of ALL.

Description of key people involved in the project

Professor Martin Schrappe

Professor and Chair, Department of General Paediatrics, chairman of the German ALL-BFM Study Group and the I-BFM-SG. He has previous successful coordinating activities in the frame of national and international clinical trials. He has more than 200 publications, and several awards.

Professor Martin Stanulla

Professor of Molecular Paediatrics, scientific secretary of the ALL-BFM and the I-BFM-SG. He has previous successful coordinating activities for research in the frame of national and international clinical trials on ALL. He has 69 publications, three awards, and two patents.

Dr. Gunnar Cario

Paediatrician, working group leader expression analysis in the ALL-BFM laboratory at CAU. He has previous successful coordinating activities for research in the frame of national and international guideline development for gene expression analysis of leukemias. He has 32 publications, one award, and one patent.

Organisation	**UCSC**	**Type**	

General Description
Catholic University of Rome is a school of medicine with a 1600 beds University Hospital. Department of Paediatric Oncology is part of the Institute of Paediatrics. UCSC has teaching activities for students of medical school, specialty of Paediatrics, subspecialty for paediatric oncology (diploma supplement).

Role within the project
UCSC will organise training courses within WP 15 'Education and Training' and evaluate the level of recognition of paediatric oncology as a well defined paediatric subspecialty throughout Europe.

R&D Experience relevant to the project

Professor Riccardo Riccardi, Director of the department of paediatric oncology, is an experienced paediatric oncologist involved in a number of clinical and research activities and he's also involved in training and teaching activities focused on paediatric oncology. Professor Riccardo Riccardi has an extensive experience in teaching and training activities at Catholic University, Sacro Cuore and involved in the organisation of many courses in collaboration with ESO, SIOPE and ITCC.
Professor Riccardo Riccardi has been chairman of the following training activities:

- ESO-SIOPE Paediatric Oncology Masterclass (Editions 2006-2008-2010;
- ITCC Training Days (Editions 2008 and 2009)
- SIOPE Educational and Training Committee which contributed into the implementation of the training syllabus throughout Europe in cooperation with SIOPE
- ITCC Educational Task Force;

Description of key people involved in the project

Professor Riccardo Riccardi
Professor and director of the paediatric oncology. department and board member of SIOPE. member of ITCC (Innovative Therapies for Children with Cancer),member of AIEOP (Italian Association for Paediatric Haematology and Oncology),Member of the Flims workshop "Methods for Cancer clinical Research", Chairman of the ESO-SIOPE Paediatric Oncology Masterclass. He has over 200 publications in the field of paediatric oncology, laboratory and clinical reports.

Dr. Antonio Ruggiero
Assistant Professor at the department of paediatric oncology. He was involved in the preparation of national and International training courses in paediatric oncology. He has 60 publications.

Dr. Sonia Terella
Secretary at the department of paediatric oncology and has a degree in English and German Languages and Literatures. She liaises and manage with several European groups such as Innovative Therapies for Children with Cancer (ITCC), International Society of Paediatric Oncology – Europe (SIOPE), European CanCer Organisation (ECCO) for the organisation of training courses and for the conduction of the international phase I/II trials.

Organisation	**UKE**	**Type**	**Research organisation**

General Description

The UKE is a state-of-the art University Hospital hosting the WTZ, Germany's largest Comprehensive Cancer Centre consisting of 20 clinical departments and 16 research institutes. With a recruitment area of 8 million people in the densely populated Ruhr area, > 20,000 inpatients and > 70,000 outpatients are currently treated each year at the WTZ. The Dept. of Paediatric Oncology, directed by Prof. Angelika Eggert, is one of the largest Paediatric Oncology Centres in Germany with approx. 120 newly diagnosed paediatric cancer patients per year. The included paediatric oncology research institute has a major research focus in the field of embryonal paediatric tumours including neuroblastoma (NB), retinoblastoma (RB) and medulloblastoma (MB). Molecular biology and genetics research is focussed on genomic, transcriptomic, proteomic and epigenomic profiling of paediatric tumours and cell culture models.

Role within the project

UKE will coordinate WP5 until June 30th, 2013, in particular with the aim to build a strong, long-term and future-oriented novel European Paediatric Oncology Biology Network integrating existing, but currently more fragmented subnetworks. The major goals of this innovative network will be efficient data sharing, harmonisation of technological procedures and enhanced quality assurance to establish a well-functioning and fast pipeline from high-throughput bench work biology and genetics to the implementation of new findings within clinical studies. After June 30th, 2013, the role of UKE will be taken over by B30 CHARITE.

R&D Experience relevant to the project

UKE coordinated the EU FP6th STREP "E.E.T.Pipeline" (Co.# 037260), a consortium of leading European scientists with extensive expertise in paediatric oncology. The unique pipeline included the comprehensive development and validation of novel genomic and proteomic diagnostic tools in addition to efficient preclinical drug development for embryonal tumours. Involvement of clinical study centres ensured a direct link to the bedside. Additional R&D and successful networking expertise has been gained in the national consortium "ENGINE" focussed on genomics of neuroblastoma and funded within the NGFN (National Genome Research Net)-Program of the German Ministry for Education and Research (BMBF).
UKE is experienced in molecular and cellular biology of embryonal tumours research, especially neuroblastoma.

Description of key people involved in the project

Professor Angelika Eggert
She is Professor of Paediatric Oncology, Director, of the Dept. of Paediatrics III and Director of the WTZ (Comprehensive Cancer Centre). She published 61 publications, and has 7 scientific awards in the field of paediatric oncology.

Dr. Kathy Astrahantseff
She is Research Associate in Professor Eggert lab (Dept. of Paediatric Oncology). She has 6 publications in peer-reviewed journals.

Dr. Alexander Schramm
He is Eggert laboratory head (Dept. of Paediatric Oncology). He has 35 publications and 1 scientific award in the field of paediatric oncology.

Organisation	**UNIMIB**	**Type**	**Research organisation**

General Description
UNIMIB is a dynamic and multidisciplinary university especially oriented to research in medicine, biology and biotechnology. In particular, the department of clinical and preventive medicine is a research institution which brings together a wide range of knowhow and experiences: microbiology, molecular biology, genetics, physiology, biostatistics, epidemiology and internal medicine (in particular, cardiology, haematology and paediatrics). The department is the reference centre of: 3 doctorates, 4 Masters, 10 specialization schools, 5 research centres, 2 scientific consortia with other public and private institutions.

Role within the project
UNIMIB will contribute to the project mainly in the field of:
- Epidemiology and biostatistics for study design and analysis, both in applied research projects and in developing novel statistical methods;
- Translational medicine in paediatric oncology.

R&D Experien**ce relevant to the project**

UNIMIB has been working in the methodology of survival analysis and the design of clinical studies, with application to both clinical and epidemiological research, mainly in the field of oncology. These studies included a group of statisticians.

Description of key people involved in the project

Professor Maria Grazia Valsecchi
She is professor of Medical Statistics, and Head of the Center of Biostatistics for Clinical Epidemiology. She published 105 papers in peers-reviewed journals, 4 books, and 2 book chapters

Professor Andrea Biondi
He is professor of Paediatrics, and Director of Ph.D. Program in Translational and Molecular Medicine. He is the Scientific Director of "M. Tettamanti" Research Center for leukemic and haematological diseases of children, and head of "S. Verri" Cell Therapy Lab at S. Gerardo Hospital (Monza-MB). He is a world known expert in paediatric oncology and molecular biology. He published 319 papers in peers-reviewed journals, and 25 book chapters

Dr. Stefania Galimbert
She is Researcher of Medical Statistics. She collaborates routinely with clinical and laboratory researchers in various areas of research. She published 25 papers in peers-reviewed journals, and 2 book chapters

Participation in relevant National or European research projects

Associazione Italiana per la Ricerca sul Cancro (AIRC): 'Analysis of event-history data for modelling prognosis and safety with application in rare paediatric cancers' (MGV);
'Childhood ALL: from clinical studies to research questions to understand molecular history and pathogenesis' (AB).
Fondazione Cariplo: 'Understanding the pathogenesis of childhood ALL and development of innovative treatments' (AB).
MIUR-PRIN: 'Integrative genomics for understanding the pathogenesis and the response to treatment of childhood Acute Lymphoblastic Leukaemia' (AB)

Organisation	**EMC**	**Type**	**Research organisation**

General Description

Erasmus MC (EMC) is a University Hospital in the Netherlands. The Department of paediatric Oncology is the largest in the Netherlands and approximately 140 newly diagnosed patients with cancer are seen each year. EMC research is mainly focused on unravelling the genetic abnormalities driving paediatric malignancies, and developing targeted treatment options by translational research. Considering clinical research, EMC is an active phase I/II study centre with currently approximately 15 studies open, both in the field of new anticancer agents as well as in the field of supportive care. A trail bureau able to sponsor phase I/II studies at the European level has also been set up, and is in the process of implementing 3 phase I/II studies through this network.

Role within the project

EMC contribution will mainly consist of being principal investigator of several phase I/II studies to be performed in paediatric leukaemia. EMC will act as an international sponsor for these leukaemia-studies, and will be responsible for the trial management of the study. Moreover, by chairing the I-BFM New Agents Committee, EMC will be involved in selection and prioritization of new agent studies in paediatric leukaemia.
The group of Pathology led by Dr. Peter Riegman will set up a server for linking the different Biobanks using a so-called 'grid' as it was done for the EuroBoNeT (FP6 projecte) virtual Biobank.The server will be necessary to reache the following objectives of the task 7.2 (Optimizing the availability of bone sarcoma tissue for biobanks): - perpetuation and expansion of the virtual bone tumor biobank established within the EuroBoNeT FP6 NoE; - physical biobanks with the EuroBoNeT virtual bone tumor biobank

R&D Experience relevant to the project

EMC has currently initiated approximately 15 investigator-initiated and company-sponsored early clinical trials in Europe. 3 academia sponsored phase I/II studies were set-up at the European level for which the trial management is done at our paediatric oncology trial bureau, including all aspects such as protocol design, site selection, submission to regulatory authorities, pharmacovigilance, monitoring, etc.

Description of key people involved in the project

Associate Professor CM Zwaan

He is a paediatric oncologist, Associate Professor since 2008, Working Group leader of the Erasmus MC Molecular Medicine Postgraduate School. He is Chair of the I-BFM New Agents Group, and coordinator of the Paediatric oncology Trial Bureau at Erasmus MC. He is also national principle investigator in approximately 15 international phase I/II studies, and international principal investigator in approximately 5 of these studies. He is a member of the institutional review board committee in our hospital. He published more than 60 peer-reviewed publications, and 15 book-chapters.

Organisation	**La Fe**	**Type**	**Research organisation**

General Description

La Fe is an University Hospital. The paediatric oncology Unit covers an area of 4 million inhabitants, one of the biggest and best equipped in Spain (120 new paediatric cancer patients per year). Besides the clinical experience, La Fe has been responsible for conducting Neuroblastoma Clinical Trials in Spain since 1987 (Chairperson of the neuroblastoma Group of SEHOP: Dr. V.Castel, Vice-Chair person: Dr. A.Cañete). La Fe has been involved in all European neuroblastoma trials since 1995, responsible of the National Coordination, establishment of biological, pathological and minimal residual disease studies.

Role within the project

LaFe will be the WP leader or WP10 'Risk adaptation of therapeutic strategies using prognostic biomarkers in malignant solid tumours'.

R&D Experience relevant to the project

LaFe has been involved in low risk neuroblastoma studies and in all European neuroblastoma studies since 1995, and has strong experience related to neuroblastoma translational research.
La Fe has the expertise to run phase III clinical trials in paediatric oncology, in neuroblastoma as well as in other paediatric cancers. Last achievements are related to the developing of phase I and II trials, with special interest in paediatrics, mainly paediatric oncology. The paediatric oncology unit is an active member of these structures. Therefore, besides the experience of the paediatric oncology Unit in running phase III trials, participating in cooperative national and international studies, the University Hospital La Fe is supporting high-quality research.

Description of key people involved in the project

Adela Cañete

MD, PhD. She is a paediatric oncologist. and an active participant with research responsibilities in the Neuroblastoma Spanish Group since 1995, the European Neuroblastoma Group since 1995 and founder member of SIOPEN. Dr. Cañete has been responsible for the European Coordination of INES 99.4 since 1999-2004. She published 20 publications related to neuroblastoma in peer-reviewed journals.

Victoria Castel

MD, PhD. She is a paediatric oncologist. and since 1977 the head of the Paediatric Oncology Unit (Hospital La Fe, Valencia). She is also the National Coordinator of the Neuroblastoma Group (SEHOP). She was principal investigator in more than 20 clinical trials. She has 160 publications in peer review journals.

Yania Yañez

MSc in Molecular Biology and Biochemistry. She is a biologist and collaborator and / or coordinator of 3 clinical trials in paediatric oncology.

Organisation	**MUG**	**Type**	**Higher Education**

General Description
MUG is a main medical higher education body in northern Poland . Department of Surgery and Urology for Children and Adolescents of the MUG has been actively participating in the subsequent generations of SIOPEL group paediatric liver tumour trials from mid-90's. It is the national coordinating and referral centre for the treatment of paediatric liver tumours.

Role within the project
MUG will be the leader of WP12 'clinical research in very rare tumours'. MUG will be involved in steering of the global Liver Warehouse project and will take active part in the development of the new hepatoblastoma studies according to patients stratification developed.

R&D Experience relevant to the project

MUG is experienced in liver tumours as well as in very rare tumours. MUG has also been responsible for maintaining international bonds of the SIOPEL group, particularly including overseas colleagues (USA, Japan).

Description of key people involved in the project

Dr. Piotr Czauderna
He is a paediatric surgeon with 23 years of experience and profound interest in paediatric oncology. He is Chair of the SIOPEL group and department head, author of 300 publications, recipient of 8 awards.

Dr. Maciej Murawski
He is a paediatric surgeon in training with interest in paediatric oncology. and secretary of the Polish National Liver Tumours Group, member of SIOPEL, and author of 6 Medline-indexed publications.

Organisation	**UOB**	**Type**	**HE non profit**

General Description

Founded in 1900 by the citizens of Birmingham, the University of Birmingham is a well-established institution, both nationally and internationally, that offers high-standard teaching and research in all major academic disciplines. To facilitate research, researchers have access to top-class infrastructure and benefit from the support and expertise of the Finance Office and Research and Commercial Services, when involved in research projects.

Role within the project

UOB will be involved in several Work Packages : WP4 (Clinical Trial Facilitation), WP6 (Standardised and innovative methodology for clinical trial design and analysis), WP8 (Early evaluation and prioritisation of new anticancer drugs), WP12 (Clinical research in very rare tumours) and WP15 (Education and Training)

R&D Experience relevant to the project

UOB has well established collaborations with Electronic, Electrical and Computer Engineering at the University of Birmingham (Dr Arvanitis) and Medical Physics at University Hospital Birmingham which has led to developments in signal processing, data analysis using pattern recognition and clinical decision support systems as well as the development in Birmingham of a national database for functional imaging of childhood brain tumours. UOB has experience in the areas of biomedical imaging and health informatics, agent-based clinical decision support, clinical metabolics and bio-informatics.

Description of key people involved in the project

Dr. Andrew Peet

He is Clinical Senior Research Fellow and Honorary Consultant Paediatric Oncologist. He is Group Leader of the Brain Tumour Research Group. He is Chair of the UK Children's Cancer and Leukaemia Group's Functional Imaging Group. He has 40 paper publications, and received the National Clinician Scientist Award 2002.

Theodoros N Arvanitis

He is Reader in Biomedical Informatics, Signals and Systems. He has 18 years of academic expertise in medical imaging, eHealth, bioinformatics, and cancer informatics. He published 1 book, 4 book chapters, 2 Patent filings, 62 journal papers, and 94 conference papers.

Organisation	**IGG**	**Type**	**Public Body**

General Description

The Giannina Gaslini Institute (IGG) is the largest public paediatric research hospital in Italy, dedicated to the comprehensive health care of infants, children and adolescents. Its 500-plus beds accommodate nearly 20,000 hospitalizations per year, with its outpatient services performing more than 16,000 visits per year. Formally recognized by the Italian Health Ministry since 1959 as an *Istituto di Ricovero e Cura a Carattere Scientifico,* the IGG hosts 28 clinical/surgical units (15 with associated laboratories) and 4 independent experimental and translational research laboratories. The Epidemiology and Biostatistics Unit is part of the Scientific Directorate with 3 full time position for biostatisticians plus 4 contracts for data mangers and 1 epidemiologist. It has been performing clinical epidemiology studies in collaboration with the Department of Paediatric Haematology/Oncology. The laboratory of Molecular Biology has 4 tenure position for scientists dedicated to bio banking and 8 contracts 3 of which dedicated to bio banking and bioinformatics It has the responsibility of the Institutional Gaslini Tissue Biobank BIT together with the Pathology laboratory. It is responsible for the Microarray Unit of the Institution's Core Facility and for the Bioinformatics Unit.

Role within the project

IGG will be WP leader of the WP 13 'Quality of survivorship'. Within this project, Dr Haupt will collaborate providing data available through the Registries it is responsible of. Moreover, IGG will also participate in several other WPs, including 4,5,56,8,10,11,15. 2. Dr. Varesio will lead the task 5.3 in the bio banking activity and will organize the virtual bio bank for sharing material and data and harmonize operating procedures to be shared by the members of the consortium. Furthermore, Dr. Varesio will be involved in the Bioinformatics aspects connected with dissemination of the genomic results, and the analysis of the molecular profiling of the tissues and with the neuroblastoma related activities.

R&D Experience relevant to the project

Since its constitution in 1998, the Epidemiology and Biostatistics Unit (EBU) has been active in oncologic research in collaboration with colleagues of the Haematology Oncology Department of the Gaslini Institute as of colleagues of the Italian Association of Paediatric Haematology/Oncology (AIEOP). At the EBU the Italian Neuroblastoma Registry is maintained with updated information on almost 3000 NB patients. EBU is also the data centre for the SIOPEN Unresectable protocol (localized but unresectable neuroblastoma). Finally, dr. Riccardo Haupt is coordinating activities of the Italian off-therapy registry (OTR) which collects information on all cancer patients who completed treatment in continuous complete remission. The Registry was started in 1980 and at the last update more than 13,000 subject have been already registered.

The Department of Paediatric Haematology and Oncology is one of the largest in Italy with a mean annual recruitment of about 140 new cases. It is the national referring centre for neuroblastoma and besides this, has among the largest recruitment records for CNS tumours, non Hodgkin lymphomas, and soft tissue sarcomas. The transplant unit has performed more than 1200 transplants (400 allogeneic). The department has the largest long-term follow-up clinic in Italy with more than 1300 long-term survivors. The department is certified by the Italian Drug Agency f(AIFA) for phase I II and III trials.

Dr. Varesio worked for 18 years at the NCI, USA, where he became chief of the Macrophage Biology Section, NCI Frederick USA, before moving to Genova in 1995 to direct the Laboratory of Molecular Biology. Dr. Varesio has studied for about 30 years various aspects of tumour and mononuclear phagocytes cellular and molecular biology including the analysis of the tumour microenvironment and particularly of tissue hypoxia.. Dr. Varesio was responsible for the microarray facility at the Gaslini Institute and for the creation of the bioinformatics group dedicated to the analysis of the microarray results and to functional genomics. Dr. Varesio is responsible of the genomic aspects of the BIT, the tissue Biobank of the Gaslini Institute, namely the molecular characterization of the samples, the analysis and the dissemination of the results. Dr. Varesio is particularly active in neuroblastoma research and in promoting the collaboration of various laboratories through a network of Bio banks. Dr. Varesio served in Study Sections I and in scientific committees in the USA and in Europe and organized several scientific events. During the course of these activities he has acquired expertise in bio informatics particularly to deal with high throughput technology results. The team under the direction of Dr. Varesio has been active in the molecular characterization of tumours and infiltrating leukocytes and in the characterization of the tumour microenvironment. Dr. Varesio has set up the Microarray facility of the Gaslini Institute where genomic derivatives are extracted and characterized by high throughput technologies and the BIT, the Gaslini Tissue Biobank for storage and analysis of paediatric tumours.

Dr. Haupt has over 30 year experience in clinical oncology and has participated to many national and international clinical trials. He Has been involved in the Italian Registry of off-therapy patients since its constitution in 1980, and has been its coordinator since 1991. He spent more than 2 years at the Clinical Epidemiology Branch of the NIH-NCI in Bethesda analyzing a large cohort of leukaemia survivors. In the same period he received formal training in Epidemiology and Biostatistics at the Jons Hopkins University in Baltimore.

He is chairman of the Early and Late Toxicity Educational Committee of the I-BFM-SG, and of the Epidemiology and late effects study group of the Histiocyte Society. He was the organizer in 2006 of an international workshop in Erice that lead to the called "Erice statement" on the concept of cure and care in long-term survivor of childhood cancer. He is founder and member of the steering committee of PanCare, an European Network for research and patient care for childhood cancer long term-survivors. He coordinates activities of the Italian neuroblastoma Registry, and of the institutional cancer registry of the Gaslini Institute. He is collaborator of the hospital based registry of the Italian Association of Paediatric Haematology Oncology (AIEOP) . He has been involved either as PI or as collaborator in many National or International epidemiological studies (see below) focusing on long-term complications of cancer treatment or in cancer registries. As part of the above mentioned projects he has acquired expertise in record linkage analysis to merge individual data from different type of registries.

Description of key people involved in the project

Dr. Riccardo Haupt
He is a paediatric Oncologist with long lasting experience in clinical epidemiology. He is head of the Epidemiology and Biostatistics department and chairman of the Italian Registry of patient's off.-therapy after childhood cancer (OTR), coordinator of the Italian Registry of Neuroblastoma. He is chairman of the Early and Late Toxicity Committee of the I-BFM-SG, and founder and member of the Steering Committee of the PanCare network. He has more than 115 publications.

Dr. Luigi Varesio
Ph.D. Chief of the Molecular Biology Laboratory G. Gaslini Institute. He is a molecular biologist and pursues studies on the tumour microenvironment. He is Chairman of the Microarray facility of the institute and Co-Chairman of the Gaslini's paediatric Tissue Biobank. He served in several Study Sections and in the organisation of Scientific events in Europe and in the USA. He has more than 200 publications.

Dr. Maria Luisa Garrè
MD, head of neuro-oncology unit, Dept. Of Haematology/Oncology. She is a paediatric Oncologist with long lasting experience in neuro-oncology. Since 2001 she is coordinator of the neuro-oncology unit of the Gaslini Institute. She is Chairwoman of the Italian protocols for over 3 year old children with CNS tumours, and for CNS germ cell tumours. She is Head of the CNS sub-committee of the Italian Association of Paediatric Haematology/Oncology (AIEOP). She is member of the SIOP E brain tumours sub-committee. She has more than 60 publications.

Organisation	UNI LEEDS	Type	Research organisation

General Description

UNI LEEDS is acclaimed world-wide for the quality of its teaching and research. Leeds is one of the largest universities in the UK.

UNI LEEDS has a very strong track record in cancer research and network development. UNI LEEDS hosts the new Leeds Institute of Molecular Medicine (LIMM, 2006), is a designated Cancer Research-UK Clinical Centre, an NIHR/CR-UK Experimental Cancer Medicine Centre (ECMC) and hosts the National Cancer Research Network. Leeds Teaching Hospitals NHS Trust is one of the largest hospitals in the UK a comprehensive range of specialist medical services serving a local population of 750k and a regional population of 3.8 million. The combination of one of the largest and most research-powerful Russell group Universities with one of the largest hospital complexes in the United Kingdom has a central role in the drive to accelerate biomedical research.

Role within the project

Will be in charge of the WP17, 'Improving Outcomes for Teenagers and Young Adults with Cancer'.

R&D Experience relevant to the project

Our work on supporting randomised prospective trials in cancer and in general healthcare has been recently reviewed by external international independent panels as being of the highest quality. The Teenage and Young Adult Oncology service is recognised as an international exemplar in this field. UNI LEEDS has a lead national role in developing TYA services and research capacity in the UK and has acted as international advisor on TYA developments in the USA, Canada and a number of other countries. It has led the development of a special cancer register for TYA for Yorkshire and Humber. It also led the development of a national TYA register through National Cancer Intelligence Network. It has extensive international clinical trial experience and as a collaborator /lead in new agent development and translational research.

Description of key people involved in the project

Professor Ian Lewis

Consultant in TYA Oncology. He is full time NHS with Honorary University Chair/Contract. He is Chair of TYAC – UK National Professional group for Teenage and Young Adult Cancer. He is Principal Investigator of 3 International RCTs in bone sarcoma. He received the National Award for TYA service (DH 2003); He has over 110 publications.

Dr. Daniel Stark

Senior Lecturerin Cancer Medicine UNI Leeds. He is a medical oncologist who shared lead for TYA services. He is member of NCRI TYA Clinical Study Group; Chair NCRI Research Collaborative in structures of patient care; Member of the College of Physicians Oncology Training committee; TYAC Education committee member. He has 22 publications, and received Grant awards as applicant/co-applicant.

Susan Morgan

She is Nurse Consultant in TYA Oncology. She is full time NHS (Leeds THT) with Honorary University Lecturer Contract. She leads the Dept Health TYA Choices Project, she is member of the NICE Improving Outcomes Guidance for young people with cancer Implementation Group, she is organiser of 'Sense of Tumour' – annual national meeting for TYA with cancer – over 400 attendees at annual 3 day event. She has 20 publications on TYA cancer, and is a national award winner; she has a MBE for services to TYA cancer.

Participation in relevant National or European research projects

UK National Cancer Research Institute TYA Clinical Studies Group (since 2005)

TYAC (Teenagers and Young Adults with Cancer): multi-professional group formed in 2004 which has acted as a focus for developing an expert network in TYA cancer in the UK.

EuroEWING: UK Principal Investigator for this multinational study group that has now recruited close to 2500 patients.

Organisation	CURIE	Type	Foundation

General Description

Since its creation in 1909 and its state approval as a foundation in 1921, the Institut Curie has brought together scientists and physicians with a common goal: to defeat cancer. Marie Curie's legacy of the "Curie model" is defined by the seamless interface between cutting-edge basic research and innovative and quality healthcare. Its originality stems from its unique approach in a unique setting, the bringing together of scientists, nurses and patients so as to expedite access to diagnosis and new treatments. The Curie model benefits patients and inspires other institutes in France and beyond. Institut Curie therefore gathers a Research Center and an **Hospital.** The Institut Curie Hospital is a private organisation which contributes to the public health system. With its diagnostic (imaging, pathology, laboratory testing) and therapeutic (surgery, radiotherapy, medical treatments, support treatment) armory, it blends technology and care, and ensures national and international dissemination of medical innovations

.

A pioneer in a number of conservative treatments, the Hospital is a reference **centre** throughout the world for breast cancer, paediatric tumours, sarcomas, eye tumours and numerous advanced techniques such as oncogenetics and precision radiotherapy (curietherapy, proton therapy). Institut Curie's Hospital is one of the hospital sites of the University Paris Descartes, School of **Medicine.** The Department of Paediatric Oncology (DPO) has been created in 1977. The Institut Curie's DPO is a large department, taking care each year of 220 new patients with solid tumours. The DPO actively participates to clinical research at international (SIOP, ITCC) and national levels (SFCE); this work is conducted in close relationship with the research team INSERM U830.

Role within the project

Department of Paediatric Oncology (DPO)

- The DPO will coordinate the WP 3.5 'Ethical aspects of clinical trials', and will also be involved in the WP 10 'Risk adaptation of therapeutic strategies using predictive biomarkers in solid tumours' and in the W.P 2.6 'Quality of survivorship' in collaboration with Dr Colin KENNEDY, Southampton, for the follow-up of patients with medulloblastoma.
- The DPO will also be involved in the WP's related to clinical trials, in dissemination activities (WP 14), education and training (WP 15), in the field of rare tumours (WP 12), soft tissue sarcoma (WP 5), in the field of early clinical trials (WP 12), hepatoblastoma (WP12), and in the WP 17 'Improving Outcomes for Teenagers and Young Adults with Cancer'

INSERM U8300

- The laboratory entitled «Genetics and biology of cancer» hosts six different research groups. One of them is specifically dedicated to paediatric tumours. INSERM U830 will be involved in WP 5 'Biology to guide innovative targeted therapy development for Ewing sarcoma, neuroblastoma, soft tissue sarcoma and embryonal brain tumours', WP 10 'Risk adaptation of therapeutic strategies using predictive biomarkers in solid tumours, protocol LINES**'** and WP 11 **'**Prospective clinical registries and collection of clinical and biological data for patients with a good prognosis receiving a standard treatment'

Department of Imaging

- This department will participate in WP 2 'Establishment of the virtual institute information portal' and WP 4 'Clinical Trial Facilitation'.

Department of Biostatistics

- This department will be involved in the WP 6 "Common and innovative methodology for clinical trial design"

R&D Experience relevant to the project

The DPO has a large experience in clinical research within SIOP and SFCE in the last 20 years. François Doz, one of its members, is also the referring paediatric oncologist of several research projects devoted to the ethics of clinical research in paediatric oncology, focussed on the information and consent process during clinical trials. The first project was a general approach of clinical research, focussing on information of parents (Chappuy, Doz et al. Arch Dis Child 91:112-6, 2006) and children (Chappuy, Doz et al, Paediatric Blood Cancer 50: 1043-6, 2008). The following study was specifically devoted to phase III studies and the randomisation process (this work is submitted for publication). The ongoing national study is devoted to information and consent process during early drug development clinical studies (phase I and II). Currently, few investigators are working in this field in Europe.

One of the research groups of the laboratory entitled «Genetics and biology of cancer» is specifically dedicated to paediatric tumours. It has published seminal works on Ewing tumours, rhabdoid tumours ad neuroblastoma.

Hervé BRISSE, radiologist, has a large experience of participating to national and international networks of radiological reviews and has a large experience about DICOM image transfer organisation.
Paediatric oncology at Institut Curie is characterised by the narrow link between the Department of Paediatric Oncology (DPO) (Dr. Jean MICHON) and the INSERM U830 Research unit (Dr. Olivier DELATTRE). Both teams are together focusing their research on Ewing sarcoma, neuroblastoma, medulloblastoma, rhabdoid tumours and soft tissue sarcoma. Both teams are also involved in early drug development, from new target identification (INSERM U830, participating to the ITCC Biology Consortium and to the European project KidsCancerKinome) to early clinical research (DPO participating to ITCC early drug development clinical studies). Furthermore, Institut Curie is the national referring centre for patients with retinoblastoma: the DPO is working in this field with other Institut Curie's teams (Ophthalmology, Genetics, Radiotherapy and several research INSERM and CNRS units).

Description of key people involved in the project

Professor François DOZ
MD, he is Professor of Paediatrics, Paris Descartes University, Deputy Director for teaching and research at Institut Curie's Hospital and member of the Department of Paediatric Oncology. He is currently chairing the SIOPE Brain Tumour Committee and is one of the members of the ITCC Executive Committee. He has 137 international publications in peer reviewed journals an 2 awards.

Dr. Olivier DELATTRE
MD, PhD, he is the head of the INSERM U 830 which includes more than 70 staff scientists. He is heading the genetic and biology of paediatric tumours group. He is deputy director for biomedical research of the Curie research centre. International publications in peer reviewed journals: more than 200. Number of citations: 10 500 - H factor: 50.

Dr. Jean MICHON
MD, he has been appointed head of the Department of Paediatric Oncology since 2002. He was former chairman of the SIOP-E Neuroblastoma (SIOPEN) group (2001 to 2003), from which he is still active as advisory member and in the executive committee of SIOPEN. Chairman of the Paediatric Haemato-Oncology network of the great Parisian area since its creation in 2007. He has 70 international publications in peer reviewed journals and 1 award.

Participation in relevant National or European research projects

- KidsCancerKinome
- CONTICANET
- EET PIPELINE

Organisation	**FORTH**	**Type**	**Research centre**

General Description

The Foundation for Research and Technology – Hellas (FORTH) is one of the largest research centres of Greece. Two of its laboratories will be involved in the current proposal. Namely (a) the Biomedical Informatics lab of the institute of Computer Science (ICS) and (b) the Post-Genomics lab of the Institute of Molecular Biology & Biotechnology (IMBB). The Biomedical Informatics laboratory of the ICS is focusing on various computational aspects of biomedical informatics, such as (a) ontology based integration and analysis of genetic and medical information for health applications; (b) Grid-based approaches to demanding molecular-biomedical applications; (c) analysis, simulation and modelling of complex biomedical processes, and (d) design and development of novel and prototypical DM/KDD methods, techniques, algorithms, tools and systems. On the other hand the Post-Genomics laboratory of IMBB focuses its research activities on: (a) the development of advanced micro fabrication methods for biomaterials, (b) multianalyte technologies and gene expression profiling methodologies for the identification of molecular classifiers, and (c) bioinformatics solutions.

Role within the project

The relevant R&D groups of FORTH have an impressive track record in state-of-the-art R&D in the domain of biomedical informatics, i.e. on the application of innovative ICT technologies in healthcare, bioinformatics and translational research. These skills, experience and expertise will be brought into the project with the objective of developing a robust, legally compliant, secure and innovative technological infrastructure in support of the core project objectives.

R&D Experience relevant to the project

FORTH has an impressive track record in state-of-the-art R&D in the domain of biomedical informatics, i.e. on the application of innovative ICT technologies in healthcare, bioinformatics and translational research. Dr. Tsikanis from FORTH is currently the scientific coordinator of the FP6 integrated project ACGT (full title: Advancing Clinico-genomic Trials on Cancer – Open Grid Services for Improving Medical Knowledge Discovery – www.eu-acgt.org) which is delivering an ontology driven, semantic grid services technological infrastructure enabling efficient execution of discovery-driven analytical workflows in the context of multi-centric, post-genomic clinical trials and translational research. Dr. Tsiknakis has focused his research, amongst other areas, on security related issues and technologies. An indicative such example has been the EU funded CORAS project, which developed a framework for precise, unambiguous, and efficient risk analysis of security critical systems.

Description of key people involved in the project

Dr. Manolis Tsiknakis

He is a Principal Researcher at FORTH-ICS within the Biomedical informatics laboratory. Dr. Tsiknakis earned his Ph.D. in systems engineering from the University of Bradford, U.K. He is chairing the European Research Consortium on Informatics and Mathematics (ERCIM) Biomedical Informatics WG. Dr. Tsiknakis is the scientific and technical manager of the ACGT Integrated project and a key investigator in other flag-ship EU funded projects. He is a member of the PC in a number of conferences and am editorial board member in the Medical Informatics journal. He has published extensively in the domain of biomedical informatics and bioinformatics.

Dr. Dimitris Kafetzopoulos

He is Principal Researcher at FORTH-IMBB leading the Postgenomic technologies laboratory. He is awarded the doctorate degree in Applied Biology and Biotechnology from the Dept. of Biology of the University of Crete. His research interests include molecular classification with microarrays and multianalyte approaches in genotyping. He is actively involved in the ACGT, LOCCANDIA and Nano2Life projects.

Dr. Giorgos Potamias

Principal Researcher at FORTH-ICS within the BMI laboratory. For a number of years he was adjunct professor at the Dept. of Computer Science, University of Crete, Greece. He has been working in the field of machine learning and data-mining for over 15 years, with a number of publications to his credit. His current R&D interests focus on GRID-enabled integration of multi-level biomedical information, and on mining related biomedical data and information sources. Dr. Potamias has contributed to several R&D projects including, GEN2PHEN, ACGT, and LOCCANDIA.

Organisation	**AIT**	**Type**	**Non-profit body**

General Description

AIT is a government controlled non-profit and applied research & development organisation with 5 specialised departments researching the key infrastructure issues of the future. AIT develops technological innovations, methods and solutions for industry and customers from public institutions and has a long experience in conducting international research projects. An inter-disciplinary team of about 150 scientists and engineers work at the Safety & Security Department on future-oriented technologies along with innovative procedures and sophisticated processes fostering research, development and roll-out of national and international ICT-infrastructures. The eHealth research activities of the department focuses on biomedical and translational research issues addressing eTrial systems, telemedicine, bioinformatics, biosignal biosignal processing and knowledge-based systems. The Safety & Security Department has a long experience in the design, development and operation of ICT infrastructures – from rapid prototyping through feasibility studies to clinical trials and ICT applications for daily clinical use.

Role within the project

- AIT will establish the Virtual Institute interoperable ICT common infrastructure, including advanced trans-institutional image management, and central registry and follow-up concept as well as pilots
- AIT will realise Enhancement, interoperability and integration of pre-existing research infrastructures within the community (eTrial systems, image management...) built by AIT and others
- AIT will also build the Communication infrastructure (portal, secure & trusted communication tools, electronic patient reported outcomes ePRO)
- AIT will also take care of Secure & trustworthy concept & policy for communication, data exchange, responsibilities, regulatory affairs

R&D Experience relevant to the project

- AIT played leading roles in previous & on-going EU projects (SIOPEN-R-NET, CARE-MAN, RegIonCo)
- AIT has already designed, developed & operated research ICT infrastructures
- AIT has a highly skilled, inter-disciplinary team of scientists and engineers with particular skills for the given tasks
- AIT has long ICT experience in the healthcare and the biomedical/translational research domain as well as infrastructure, tools and skills for design, development and operation of ICT infrastructures – from rapid proto-typing through feasibility studies to clinical trials and ICT applications for daily clinical use.

Description of key people involved in the project

Dr. Guenter Schreier

Head of the AIT eHealth research group. He has 2 MSc (Electrical Engineering & Communications), 1 PhD (Biomedical Engineering), 1 Habilitation (Biomedical Informatics); 13 years applied research experience (4 years in a start-up company). He is lecturer. He is head of working group “medical informatics and eHealth” (Austrian Computer Society), member of Austrian Society of Biomedical Engineering, Austrian Scientific Society for Tele-medicine and eHealth, IEEE Engineering in Medicine and Biology Society. He has 250 scientific publications, 4 patents, 4 awards.

Dr. Guenter Rauchegger MSc (Telematics), PhD (Biomedical Engineering), MBA (intra- & entrepreneurship), ISO 27001 (Information security management). He is Lead Auditor, has 9 years applied research experience, is Work package leader in two EC-projects: CARE-MAN (www.careman.eu) & RegIonCo (www.regionco.eu), and chief operation officer (COO) of more than 15 web based EDC solutions.

Dr. Mario Drobics

PhD (Applied Mathematics), area manager for knowledge-based technologies at Software Competence Center Hagenberg, he is associate professor at Medical Statistics and Informatics of the Medical University Vienna, senior scientist at AIT focusing on applied data analysis, therapy management solutions, and medical informatics. He published 4 scientific publications and 1 book.

Organisation	**CINECA**	**Type**	**Consortium**

General Description

Cineca is a non profit Consortium, made up of 37 Italian universities, the National Institute of Oceanography and Experimental Geophysics, the National Research Council, and the Ministry of Education, University and Research. Today it is the largest Italian computing centre, ranked 46nd in the top 500 supercomputer site list, it operates in the technological transfer sector through high performance scientific computing, the management and development of networks and web based services, and the development of complex information systems for treating large amounts of data.

The Health Care Systems Department of Cineca deals with activities related to the design and development of IT systems and services in the health care and biomedical area, using advanced technologies and methodologies. The department's main activities are: monitoring and analysis of multicentric clinical trials, epidemiological registries/observatories, Web-based systems and IT infrastructure for management and monitoring and planning internal activities of Health Care Organisations and scientific associations.

Role within the project

CINECA will provide the technological infrastructure for the development of the new patients stratification based on retrospective database analysis with its correlation with pathology and biology findings, improvement in web based patients clinical trial management system – including centralised radiology and pathology review, as well as inbuilt e-learning module.

R&D Experience relevant to the project

The Health Care Systems Department has developed 190 systems (clinical trials and epidemiological registries) as of today gathering data of more than 250.000 patients across 25 years. Furthermore it has more than 20 years experience in paediatric oncology RDE systems and data analysis, and collaborates with different research group, in Italy (AIEOP: 64 studies, 3 registries, 35.000 patients), and abroad with Childhood Liver Tumours Strategy Group (SIOPEL: 3 protocols), International Research Consortium on childhood low grade glioma research (ICLGG: 1 protocol), European Paediatric Soft Tissue Sarcoma Study Group (EpSSG: 3 protocols), international trials on Leukaemia (EsPhALL, Interfant).

Cineca has the skills required since it has already managed a lot of systems with the same tasks requested by the project, and would be able to satisfy the project requirements. The department has already set–up one CTMS web system for the partners, which could be easily extended with additional modules to meet the global research tasks.

Description of key people involved in the project

Dr. Marisa De Rosa

Director of Health Care Systems Department. She has a degree in Pharmacy and is Lead Coordinator of the MEDISHARE project. She is Expert member of the National Board for Clinical Trials of National Medicines Agency (AIFA) and IT-Coordinator of the project “National Registry of Clinical Trials” of AIFA. She is contract professor at the School of Oncology at the University of Ferrara teaching the Course of Methodology of Controlled Clinical Trials. She is member of DIA (Drug Information Association), SCT (Society of Clinical Trials), SIFO (Italian Society of Hospital Pharmacies). She has more than 70 articles published in national and international scientific reviews.

Dr. Anna Covezzoli

Project Leader in paediatric oncology systems. She has a University Degree in Statistic and Demographic science (4 years), 17 years experience in clinical trials and epidemiological registries in internet, for national and international group. She has 45 publications.

Organisation	**ESQH**	**Type**	**Research Organisation**

General Description

The ESQH-Vienna Office is an independent entity for scientific and practice based decision-making and technical support in the health care and the social sector. It facilitates the cooperation between science, education, policy and industry. Aiming at sustainable solutions for our national and international partners it promotes health, social security, well-being and quality of life for all citizens through research, evaluation, training, technical assistance, advisory services and capacity development endeavours in strong conjunction with its local partners.

Role within the project

ESQH will be involved in WP4 'Clinical Trial Facilitation' and WP10'Risk adaptation of therapeutic strategies using prognostic biomarkers in malignant solid tumours'.

R&D Experience relevant to the project

The ESQH Vienna and its Department for interdisciplinary research law has in-depth experience for more than 18 years in legal research expertise, quality management and patient safety and knowledge and technology transfer. The main focus of the Department is Pharmacovigilance.

The department and the acting persons are the WHO Drug Monitoring Center for Austria assigned by the MoH Austria (AGES PHARM MED). For more than one decade it has been involved in educational trainings on national and international level in the field of Pharmacovigilance and signal detection where it currently trains Members of the Austrian, Serbian, Hungarian and Greek Ethic Commissions in the field of Research Law and Pharmacovigilance with a strong focus on EU Research Law and EU Medical Law.

The Department is acting as a contact point for Pharmacovigilance and Research Law between the EMA and the WHO in Austria.

Description of key people involved in the project

Professor Mag. Martina Gantschacher

She is legal practitioner with Diploma on Medical Law and more than 18 years experience in the field of research and medical law. She is Head of the Research Law Department of the Sigmund Freud University. She is Key Expert 2 for the ESQH Vienna Office

Dr. Roland Schlesinger

MBA, MPH. He is a Medical doctor with specialisation in Epidemiology and Director to the ESQH Vienna Office, Former Chief Medical Officer of the UNDP High Level Group, Head of the UN Knowledge and Technology Transfer Program. He is Key Expert 2 for the ESQH Vienna Office

Professor Peter Birner MSc

He is a Medical doctor with specialisation in Pathology, the Austrian Group leader of Hypoxia and Angiogenesis in Malignant Tumours. He is Head of the medical education Commission at the Austrian Medical Chamber. He has more than a decade of in depth experience in the field of Cancer Research and continuous medical education on national level. He is Key Expert 3 for the ESQH Vienna Office

Participation in relevant National or European research projects

- EUNet PaS
- Development of Food Safety Service in Montenegro / EU-Project
- HEALTH SYSTEM MODERNISATION PROJECT- Albania / WB Project
- Development of Quality Infrastructure in Montenegro EU Project
- Health Technology Transfer Program Bosnia and Herzegovina / Republica Srpska , Establishment of an Health Technology Education Center in Cooperation with The local MoH
- Health Technology Transfer Program Serbia - Establishment of an Health Technology Education Center in Cooperation with The local MoH
- Health Technology Transfer Program Albania - Establishment of an Health Technology Education Center in Cooperation with The local MoH

Organisation	**AMC**	**Type**	**Research organisation**

General Description

The Academic Medical Center (AMC) in Amsterdam, the Netherlands, is a general academic hospital with over 5000 employees, of which about 600 are working in research. Embedded in the AMC is the Emma's Children's Hospital (EKZ), which is the largest paediatric oncology center of the Netherlands, yearly ~180 new paediatric cancer patients are treated there. Over the years there has been a strong collaboration between the departments of Paediatric Oncology (headed by Prof Dr H. Caron) of the EKZ/AMC and the department of Human Genetics (headed by Prof Dr R. Versteeg) in the AMC with the overall aim to improve the treatment for paediatric cancer patients and to get a better understanding of the biological behavior of the tumours. Research at the Human Genetics department is directed to identify the genes and signaling pathways that play a crucial role in paediatric cancer.

Role within the project

AMC will participate in the WPs 2 'European sustainable strategy for clinical trial paediatric oncology', 5 'Biology to guide innovative targeted therapy development', 8 'Early evaluation and prioritisation of new anticancer drugs' and 12 'Clinical research in very rare tumours'.

R&D Experience relevant to the project

The Department of Human genetics, AMC, Amsterdam, has developed, first for internal use, a huge bioinformatics platform to analyse mRNA and miRNA expression profiles, CGH profiles and SNP profiles.

The relevant experience AMC is the following:

- Establishing for over 150 neuroblastoma tumours: microarray expression profiles, CGH profiles, SNP profiles and miRNA profiles. Establishing similar data for neuroblastoma cell lines and idem for cell lines after gene manipulation;
- Establishing the high throughput analyses for many tumour types studied in the ITCC-KCK network and for neuroblastomas in the NRC consortium ;
- Establishing a web-accessible bioinformatics storage and analysis tool for neuroblastoma data, for ITCC-KCK tumour series and NRC tumour series. Partners can access this network password-protected over the internet.

Description of key people involved in the project

Professor R. Versteeg

Molecular biologist, Professor in genetics, head dept. of Human Genetics, founding member of NRC, ITCC biology, KCK. He is lead-participant in Bioinformaticsworking group for data-integration. He has 86 peer-reviewed papers.

Professor H.N. Caron

Professor in paediatric Oncology, head department Paediatric Oncology EKZ AMC, molecular determinants of prognosis, founding chair KidsCancerKinome (EU-FP6), founding chair ITCC Biology. He is member of the AMC research Council, member of the scientific advisory board KWF, leading member of several scientific committees on paediatric cancer. He has 100 peer-reviewed papers.

Dr. J. Koster

Ph.D. in molecular biology; Bioinformatician. He is lead participant in Bioinformaticsworking group for data-integration. He is author on 32 peer reviewed publications.

Participation in relevant National or European research projects

NRC (Neuroblastoma Research Consortium): German-Dutch-Irish-Belgian-Swedish consortium for analysis of joint neuroblastoma series by high throughput technologies and bioinformatic data analysis.
KCK: Kids Cancer Kinome study. FP6 project with partners from Italy, France, Germany, Denmark, England to identify kinase drug targets in 6 childhood cancers by high throughput analysis, shRNA and drug testing.

Organisation	**ICCCPO (ÖK)**	**Type**	**Non profit body**

General Description

The "International Confederation of Childhood Cancer Parent Organisations" :

- Is an international network through which its member parents organisations may share information to build better links between parents and health care professionals;
- Promotes greater awareness and understanding of the issues and effects of childhood cancer on an international level with other health or child related organisations such as the International Society of Paediatric Oncology (SIOP), UNICEF and WHO;
- Creates opportunities to improve access to advances in the treatment and care of childhood cancer patients, particularly in underdeveloped nations where the best possible treatment and care are not available due to lack of medications, facilities, information or other resources.

Role within the project

ICCCPO (ÖK)´s focus is to improve the cooperation and sharing of information and experiences between parent and survivors 'groups around the world, so that all can benefit from it and become more effective in improving the treatment and care of children with cancer in their own countries.
ICCCPO (ÖK) will contribute its experience and knowledge to this project.

R&D Experience relevant to the project

ICCCPO (ÖK) has already participated in the following projects:
EPOC: European Paediatric Oncology OFF-Patent Medicines Consortium, Newcastle University & The Newcastle upon Tyne Hospitals NHS foundation Trust, Newcastle upon Tyne, United Kingdom.
O3K
CHILDHOPE: Chimaeric T-cells for the treatment of paediatric cancers, Centre Rérional Léon-Bérard, Lyon, France.
ITCC: Innovative Therapies for Children with Cancer, Institut Gustave Russy, Paris, France.

Description of key people involved in the project

Anita Kienesberger, EC member of ICCCPO (ÖK)

Dr. Gerlind Bode

Marianne Naafs-Wilstra

Organisation	**CLB**	**Type**	**Public body**

General Description

The « Institut d'Hématologie et d'Oncologie Pédiatrique » (IHOP) part of Léon Bérard Comprehensive Cancer Center (CLB) in Lyon, France, take treats 150 new children and adolescents with cancer (leukaemia and solid tumour) per year. IHOP has 54 beds (15 beds for bone marrow transplantation), 12 for outpatient clinic and 27 for convention al hospitalization.

Oncologist and haematologist from IHOP are involved in different steering committees of tumour group at European level (Rhabdomyosarcomas , Wilms tumour, Ewing sarcomas, Brain tumour, Leukaemia and LMNH, pain).

Role within the project

Dr Christophe Bergeron (MD, PhD), will participate in WP11 'Prospective cohorts for patients' with a good prognosis and in the WP13: 'Quality of survivorship', to build the "health passport " and will participate into the setup of "tumour tracker site" of the patients in order to have long-term data of sequelaes and long survival.

Dr Perrine Marec Bérard (MD) will actively participate to WP17 'Improving Outcomes for Teenagers and Young Adults with Cancer'.

Dr Cécile Conter (MD) will actively participate to WP13 'quality of survivorship'.

R&D Experience relevant to the project

Our experience in Léon Bérard comprehensive cancer centre is well suited as

a) Dr Perrine Marec Bérad, paediatrician oncologist is involved in a program that facilitates the "take charge" of teenagers and young adults

b)Dr Cécile Conter is already involved on this issue at the national level (SFCE)

c)Dr Christophe Bergeron is involved in Wilms tumour European group (SIOP RTSG) and Rhabdomyosarcoma group (EpSSG). He also developed at a regional level a "health passport" for our patients to facilitate the follow up in particular the following of the sequelaes.

The IT department of Centre Léon Bérard has a large skill in the IT files in health organisation. It has developed complete IT files to follow-up patients. It also developed with the Rhône Alpe area (5 million people) an IT file named DPPR (Dossier patient Partagé Réparti) which received in November 2009 a first price award from EU in a recent European contest.

Description of key people involved in the project

Dr Christophe Bergeron

MD, PhD, oncologist in IHO/CLB since 1996, and in charge of Wilms tumour (Chairman), Soft tissue sarcoma (co-Chairman) at national level (France). Member of the steering committee of EpSSG and RTSG at European level.

Dr Perrine Marec Bérard

MD, oncologist in IHOP/CLB since 1999 and in charge of Bone tumours, Pain and Organisation of "Adolescent/Young adult" She is involved in European Ewing Sarcoma group and has 44 publications.

Dr Cécile Conter

MD, post doc, oncologist in IHOP/CLB since 2005 and in charge of Germinal tumour, Brain tumour and late effect in SFCE in France and has 6 publications.

Participation in relevant National or European research projects

- EpSSG group for Rhabdomyosarcoma, randomised trial for high risk patients (IVA / IVADo)
- RTSG group for Wilms tumour, randomized trial for intermediate risk (VADo / VA)

Organisation	**IARC**	**Type**	**Non profit body**

General Description

The objective of the IARC is to promote international collaboration in cancer research. The Agency is inter-disciplinary, bringing together skills in epidemiology, laboratory sciences and biostatistics to identify the causes of cancer so that preventive measures may be adopted and the burden of disease and associated suffering reduced.

The IARC has an important role in describing the burden of cancer worldwide, through co-operation with and assistance to cancer registries and in monitoring geographical variations and trends over time, including in populations of children and adolescents. IARC has a special interest in studying cancer incidence and survival in the young population in collaboration with international partners. The European project "Automated Childhood Cancer Information System" (ACCIS), coordinated by IARC, demonstrated the importance of monitoring cancer burden in population of children and adolescents. IARC also contributes to international studies of childhood cancer aetiology.

Role within the project

IARC will lead the task "Evaluation of use of cancer registries for prospective collection of enhanced clinical data" in the WP11 "Prospective clinical registries and collection of clinical and biological data for patients with a good prognosis receiving a standard treatment". Using its expertise and established network of the cancer registries, IARC will assess the ways of incorporating selected information important for evaluation of clinical research into standard routines of population-based cancer registries, in a harmonised way suitable for international comparisons.

R&D Experience relevant to the project

IARC has expertise in the development of standards for data collection, coding and quality evaluation, which can be documented by many publications, including the International Classification of Diseases for Oncology and International Classification of Childhood Cancer. IARC also has a rich experience in coordinating the international collaborative studies involving population-based cancer registries, such as Cancer Incidence in Five Continents, International Incidence of Childhood Cancer and others. The European project "Automated Childhood Cancer Information System" (ACCIS), coordinated by IARC, demonstrated the importance of monitoring cancer burden in population of children and adolescents and created a sound basis for the proposed expansion of informative value of international population-based cancer data.

Description of key people involved in the project

Dr. Eva Steliarova-Foucher

Scientific coordinator of International Incidence of Childhood Cancer (IARC project), ACCIS, EUROCOURSE project IARC part) and some others. She is Executive secretary of International Association of Cancer Registries (2007), and Scientific coordinator of the European Network of Cancer Registries (ENCR). She has 80 peer-reviewed publications, several fellowships awards (IARC, UICC, French Government), Childhood Cancer Task Force (UICC).

Organisation	UNIPD	Type	Higher education

General Description

The foundation of the University of Padova goes back to the 13th century and the Padova Medical School had an early start in 1222. Today's Medical School comprises of 7 preclinical and 9 clinical departments the later forming an integral part of the hospital (University Polyclinic). The Department of Paediatrics, being part of the local hospital, allows for diagnostics and treatment as well as clinical, applied and basic research. The laboratory of Paediatric Onco-haematology provides Gold Standard (GS) diagnosis of leukaemia and MDS and performs bench to bed oriented research in the framework of national and international research projects. The laboratory of Onco-haematology is a central laboratory for paediatric acute leukaemia diagnosis of the AIEOP (Italian association for haematology and paediatric oncology) and analysis 3000 Bone Marrow samples (of which 600 newly diagnosed Acute Leukaemia) on a year's basis. The AOP-HOD is a clinical, research and teaching Institution and is part of the University Hospital of Padova and represents the reference centre for paediatric oncology in the north-east region of Italy.AOP-HOD is the coordinating centre for the national protocol for paediatric soft tissue sarcoma, lymphoma, very rare tumours and some CNS tumours.

Role within the project

Contribution to the project in WP 9 is in the first place on integration of novel diagnostic markers for leukaemia and MDS in current gold standard diagnostic work-up to create a back bone for Italian and European trials (AIEOP-BFM). Former experience in networking and coordination of large international studies will further contribute to strengthening collaborations within WP 9 and beyond that. The AOP-HOD and Dr. Bisogno will have a key role in the liaison with the E*p*SSG for the recruitment and data management of the patients with RMS and other soft tissue sarcoma. Similarly Dr. Bisogno can contribute to develop the part dedicated to very rare tumours in connection with existing national and international Groups.

R&D Experience relevant to the project

Dr. Bisogno is member of the EpSSG board and coordinator of the ongoing international trial dedicated to children with rhabdomyosarcoma. He has a leading role in the Italian TREP project dedicated to very rare tumours in infancy and is one of the promoters of the EXPeRT a recent European initiative aiming to build a multinational network dedicated to children with very rare tumours. AOP-HOD and Dr. Bisogno have a long standing collaboration with CINECA, an academic consortium that has developed an extensive experience in the preparation and managing of remote data entry system.

Description of key people involved in the project

Dr. Gianni Bisogno

Paediatric Oncology Consultant*,* coordinator of the clinical research in solid tumours at the AOP- HOD. He is coordinator of the AIEOP soft tissue sarcoma Committee, founding member and coordinator of the Italian TREP Project (Very rare paediatric tumour Group). He is member of the board of the European paediatric Soft tissue sarcoma Study Group (EpSSG) and Coordinating Investigator of the protocol for rhabdomyosarcoma. He has written over 80 scientific papers and 4 book chapters.

Professor Giuseppe Basso

MD, Head of the central diagnostic and research laboratory and full Professor in Paediatrics at the Medical School, Padova University. He is author of more than 200 peer reviewed publications, member of several scientific societies, national coordinator of the Acute Leukemias Phenotype AIEOP Study Group.

Dr. Geertruy te Kronnie

PhD, senior scientist of the Onco-haematology laboratory and head of the genomic unit. He is author of more than 80 peer reviewed scientific publications among which several invited reviews.

Dr. Rita Alaggio has recently been designated European Coordinator of the Pathology Panel of the SIOPEL Group. She will be in charge of collecting all the available histological tumor slides and upload these in the central pathology web platform according to objectives of WP12. Dr. Alaggio will be included as participant from UNIPD in WP12 for 2 p.m. from 1/6, 2014 -to the end of the project.

Dr. Rita Alaggio works in the Section of Pathology, Department of Medicine (DIMED) of the University of Padova. She has a long term experience in the diagnosis of pediatric rare tumors including liver tumors. She has been involved in the working Group for the new Hepatoblastoma International Classification (Modern Pathology 2014). Since 2009 she is the Coordinator of the Italian Pediatric Pathology Group. She is also member of the Pathology panels of the European pediatric Soft sarcoma Group and the Italian rare tumor in

pediatric age (TREP) project. As part of this activity she has published > 100 papers.

Prof. Giorgio Perilongo
MD, Full Professor of Pediatrics, Chairman of the Department of Woman's and Child's Health, University of Padova (since 2007). Member of the Board of Directors of the Italian Children's Hospitals Association. Participant of cooperative clinical trial groups: SIOPEL –1994/2007 and Childhood Low Grade Glioma Study Groups of the SIOP-Europe Brain Tumour Sub-Committee (co-chairmanship) – 2001-2012. Elected president of SIOP (2013-2015). He is author of 130 peer-reviewed publications in international scientific journals, 12 book chapters and co-editor of two scientific books.

Participation in relevant National or European research projects

Protocol EpSSG RMS2005: International Coordination and Data Management (Principal investigator)
The TREP Project - A comprehensive strategy for epidemiology, diagnosis and care of children with rare tumours (Principal investigator)
EPOC - European Paediatric Oncology off-patent medicines Consortium (FP-7HEALTH-2007-4.2-1)

Organisation	**LUMC**	**Type**	**Research organisation**

General Description
The LUMC hosts since 1952 the Netherlands Committee of Bone Tumours, one of the largest tumour bone registry with radiographs, clinical details and histology available of over 16.000 cases and is a major centre for treatment of primary bone tumours. Within the department research lines are directed at molecular pathology and biology of bone and soft tissue tumours, and more specifically osteosarcomas, Ewing Sarcomas and more rare histotypes. The aim is to develop new tools for diagnostics, to elucidate new targets for therapy, and working toward further understanding of tumour genesis. The department has a longstanding record in international collaboration in research and trials and the involved pathologist act as reference pathologist for the major bone and soft tissue tumour trials. The EuroBoNet consortium is coordinated by one of the P.I.'s.

Role within the project
LUMC will participate in WP1.4 'Biology to guide innovative targeted therapy development' and in WP17'Improving outcomes for teenagers and young adults with cancer'. LUMC will provide tissue banking, availability and production of tissue arrays, histopathological reference review, and molecular genetic analyses. LUMC will realise data analyses, and mouse and zebra fish models are available for Ewing sarcoma and osteosarcoma. Functional and genetic characterisation of Ewing (n = 12) and Osteosarcoma (n = 19) cell lines has been determined. Approved protocols are available to obtain bone marrow samples and pre-treatment biopsies from patients. Several new cell lines are established from this tumour tissue.

R&D Experience relevant to the project

LUMC is experienced in Zebra fish models for osteo and ewing sarcoma allowing high throughput drug screening, genomic profiling on decalcified paraffin embedded bone tumours, Transcription (mRNA and microRNA) and proteomic profiling on fresh frozen tumours.

Description of key people involved in the project

Professor Pancras CW Hogendoorn
Professor in pathology, specialised in bone and soft tissue tumours, leader of an active research group on bone tumours. He is a substantial contributor to the Working group of the World Health Organisation on classification of tumours of soft tissue and bone. He is Chairman of the Netherlands Committee on Bone tumours, reference pathologist EORTC Soft tissue and Bone Sarcoma Group, EOI, EuroEwing Consortium. He currently is the coordinator of EuroBoNeT, a FP6 network of excellence (LSHC-CT-2006-018814), dedicated to bone tumours. He has more than 200 original publications; several review articles and book chapters.

Dr. Judith V.M.G. Bovee
Associate professor in pathology, specialised in bone and soft tissue tumours, senior researcher on bone tumours. She is work package leader within the EuroBoNeT consortium. She is active in the Netherlands Committee on Bone Tumours (member), EMSOS (Board member), and working group molecular diagnostics in Pathology (Board member). She has more than 50 publications on bone tumours, including review articles with some additional book chapters.

Dr A.M. Cleton-Jansen
Associate professor in molecular, specialised in genetic and cellular biology of Bone-tumours. He is leader of the EuroBonet work package technology, and Chairman of the Dutch Cancer Society working community of tumour cell biology. He has more than 50 publications on molecular genetics of tumours.

Participation in relevant National or European research projects

- EuroBoNeT (FP6 network of excellence dedicated to bone tumours) (Hogendoorn)
- KWF on osteosarcoma (AM Cleton)
- NWO on chondrosarcoma (Bovee)
- KWF on vascular tumours of bone (Bovee)

Organisation	**KAROLINSKA**	**Type**	**Research organisation**

General Description

Karolinska Institute is a medical university, one of the highest ranked medical universities in the world specialised in research and education. The Childhood Cancer Research Unit at Department of Women's and Children's Health is the first and largest comprehensive research unit within Paediatric Oncology in the country including clinical research, population-based registries covering Sweden as well as all five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden), psychosocial and nursing research as well as laboratory basic and translational research with particular skill in developing novel therapeutic strategies based on biological targeting employing specific in vitro and in vivo models of clinical significance. The unit is involved in clinical studies of novel therapies, coordinating national and international clinical studies, performing biological studies identifying important mechanisms for cancer development and targets for therapy. Population-based epidemiological studies and controlled intervention studies on psychosocial issues are performed from the unit. Have particular expertise in translational studies on neuroblastoma, leukemias, histiocytoses and brain tumours.

Role within the project

Karolinska institute will be involved in the WP10, 'risk adaptation of therapeutic strategies using prognostic biomarkers in malignant solid tumours'.

R&D Experience relevant to the project

Karolinska Institute has a vast experience with excellent track record in the field of paediatric oncology research. It has well equipped lab, and provide availability of modern techniques and well-characterized clinical specimens as well as outstanding experience in vitro and in vivo therapeutic studies. Karolinska has experience in Cancer Stem Cell identification, In vivo models for human cancer cells in a human environment, and unique experience in Lipidomics and metabolomics. Moreover, it has a long experience in translational studies, clinical studies and biological characterization of novel therapeutic targets. It has a close link to clinical unit and international networks.

Description of key people involved in the project

Professor Per Kogner

MD PhD, professor of paediatric oncology, head of lab and research group. He has more than 100 publications, numerous awards including several NOPHO Prizes, Audrey Evans Prize three times, Schweisguth prize.

Participation in relevant National or European research projects

- NBCNS; Coordinator of a national research network on childhood brain tumours and neuroblastoma, funded with >9 million Euro/5 years, "Neuroblastoma and CNS tumour Network of Sweden". See www.nbcns.se
- SIOPEN; National coordinator and member of executive committee of the SIOP Europe Neuroblastoma Association and research network. See also www.siopen-r-net.org
- NOPHO; Neuroblastoma coordinator since 1994 in Nordic Society for Paediatric Haematology and Oncology (covering Denmark, Finland, Iceland, Norway and Sweden). Secretary General of NOPHO 2006-2008. See also www.nopho.org
- INTENT; Leader of a national research network funded by the Swedish Research Council, "Innovative Therapy for Embryonal Neural Tumours".
- KPON; Coordinator of "Karolinska Paediatric Oncology Network"
- ENQUA, SIOPEN-R-NET; Partner in two previous EU-funded research networks.
- ANR 2010; Organiser and president of the international neuroblastoma meeting "Advances in Neuroblastoma Research 2010" in Stockholm next year. See www.anr2010.com and www.anrmeeting.org

Organisation	**UGent**	**Type**	**Non-profit body**

General Description

The University of Ghent is a non-profit organisation who is actively involved in the education of students, the performance of basic and translational scientific research and also offers scientific advice to third parties. The Department of Medical Genetics Ghent, which is part of the University Hospital and the Ghent university, performs routine diagnostics as well as scientific research in the context of paediatric, adolescent and adult constitutional genetic conditions and malignancies. Since many years, our department is responsible for the cytogenetic and molecular work-up of constitutional genetic disorders and cancers.

Role within the project

Our department is the reference centre for neuroblastoma, paediatric MDS and ALL in Belgium and will be involved in the project in the gathering of samples from all over Europe and perform all necessary investigations, especially those related to the-omics field.

R&D Experience

Our department performs since more than 20 years active research on neuroblastoma, one of the most common solid tumours of childhood and is also the reference centre for Belgium, involved in the cytogenetic and molecular diagnostic work-up of these tumours. During the last years, we have build up significant experience in the –omics field, including genomic, trancriptomic and epigenetic analyses. We are one of the leading experts in the field of quantitative real-time PCR, data acquisition and normalization. We have international collaborations with other researchers working in the field of paediatric malignancies including leukaemia and neuroblastoma. We have always introduced the state-of-the-art technologies in the research of the above mentioned malignancies, including gene expression profiling by micro-array and real-time quantitative PCR, arrayCGH analysis, epigenetic analysis and very recently also the next generation sequencing technology.

Description of key people involved in the project

Dr. Franki Speleman

Head of department cytogenetics. He is involved in research of paediatric malignancies, is author or co-author of 231 peer-reviewed international articles and holder of 1 patent.

Dr. Nadine Van Roy

Supervisor of cytogenetics lab. She is biologist and cytogeneticist. She is involved in research of paediatric malignancies, is author or co-author of 117 peer-reviewed international articles and holder of 1 patent, Pfizer award for doctoral thesis and young investigator award in the field of genetic research on neuroblastoma.

Participation in relevant National or European research projects

- National projects: Translational research projects on paediatric ALL, neuroblastoma and paediatric brain tumours
- European projects: EET project on paediatric embryonal tumours

Organisation	**CHARITE**	**Type**	**Higher education**

General Description

In the Charité the scientists and physicians engage in state-of-the-art research, patient care and education. More than half of the German Nobel Prize winners in medicine and physiology come from the Charité, among them Emil von Behring, Robert Koch and Paul Ehrlich. The Charité also has an international reputation for excellence in training. It extends over four campuses with more than 100 clinics and institutes bundled under 17 CharitéCenters. The Charité has a turnover of nearly 1 billion euros per year, and it is one of the largest employers in Berlin with 14,500 employees.

IntReALL, hosted by Charité, is a consortium of all European and some non-European relevant study groups on treatment of childhood relapsed ALL, based on the Resistant Disease Committee of the I-BFM SG. After harmonisation of definitions, diagnostic procedures, and risk factors among national trials the group now plans a common trial on childhood relapsed ALL for 2010 with the aim to integrate new targeted agents on the basis of a common chemotherapy backbone. SCT is performed according to the international ALL BFM SCT trial. A biologic committee organises the routine and reference diagnostics as well as translational research with a rational distribution of patient material. IntReALL forms the largest study group on childhood ALL worldwide and allows to investigate drugs in specific subgroups such as T-ALL, or CD19 positive B-cell precursor ALL.

Role within the project

Charité will be involved in the WP5 'Biology to guide innovative targeted therapy development' and WP 2.2 'Improved therapeutic strategies using predictive biomarkers in leukaemias'. From July 1st, 2013, CHARITE will become WP 5 leader taking over the role of UKE, aiming at building a strong, long-term and future-oriented novel European Paediatric Oncology Biology Network integrating existing, but currently more fragmented subnetworks.

R&D Experience relevant to the project

The Charité is one of the largest university medical centres in Germany and experienced in sponsoring and conducting national and international clinical trials. The Clinical Trials Centre of the Charité provides all necessary experience on organizing clinical trials according to GCP on an academic level.

Members of the IntReALL Group are national and international experts on relapsed and refractory childhood ALL. They have experience in conducting clinical trials and scientific programmes over many years. Arend von Stackelberg is co-ordinator of the German/Austrian Study Group of Childhood Relapsed ALL ALL-REZ BFM and nominated for the chairmanship of the national group

Description of key people involved in the project

Dr. Arend von Stackelberg.

Arend von Stackelberg, MD, PhD, Otto-Heubner-Centrum für Kinder- und Jugendmedizin, Klinik für Pädiatrie m. S. Onkologie/Hämatologie. Chair of the IntReALL 2010 trial. He was coordinator of the ALL-REZ BFM Study Group, Chair of the Resistant Disease Committee of the I-BFM SG from 2001 until 2009. He is member of the EMA Paediatric Oncology Task Force. He is the PI of several phase I/II trials for development of new agents in childhood relapsed ALL.

Professor Dr. Vaskar Saha.

Co-Chair of the IntReALL 2010 trial. He is Professor of Paediatric Oncology, University Hospital of Manchester, Chair of the UK childhood relapsed ALL Study Group R3 protocol, Chair of the Resistant Disease Committee of the I-BFM SG since 2009. He is the PI of several phase I/II trials for development of new agents in childhood relapsed ALL.

Professor Peter Hoogerbrugge.

Chair the IntReALL Biologic Committee. He is Professor of Paediatrics at the Radboud University Nijmegen Medical Centre, chairman of the department of Paediatric Haemato- Oncology. He is Chair of the Dutch Study Group for Childhood relapsed ALL.

From July 1st, 2013:

Professor Angelika Eggert and her gorup (see B8 UKE) will start working in CHARITE and will contrinue the activities previously allocated to UKE.

Participation in relevant National or European research projects

- Innovative Therapies in Childhood Cancer (ITCC); performance of phase I/II trials in paediatric refractory ALL, drug development
- International Society of Paediatric Oncology/Europe (SIOP/E); umbrella for basic and clinical research in paediatric oncology in Europe
- EMA; Interaction and consultation in development of new drugs, PIP, and international phase III protocols.
- International BFM Study Group (I-BFM SG); umbrella for clinical research activities in childhood ALL in Europe; Resistant Disease Committee as basic group for the IntReALL trial.

Organisation	**AP-HP**	**Type**	**University Hospital**

General Description

AP-HP is the biggest teaching hospital in Europe, federating 39 different hospitals mainly located in Paris and its suburban area. It is also the largest employer in Paris region with 90,000 people working for this public institution representing more than 150 different jobs. With more than 19,000 medical staff, 3000 hospital physicians, including 1000 professors and more than 6000 interns and medical students, AP-HP's staff cover all the major medical specialties. As a public health institution, AP-HP pursues 3 main missions: healthcare delivery, medical and paramedical teaching and biomedical/clinical research. In particular, AP-HP is involved and/or coordinates more than 40 European research projects supported by the Research and Technological Development Research Programme from European Union. The department of Paediatric Haematology of the Robert Debré Hospital (chairman: **Pr André Baruchel**) is a new 38 in-patient bed- unit and 10 day-care beds. It has 4 major axis: malignant haematology (100 new pts/year), phase I-II trials (5 activated), allogenic stem cell transplantation (target: 100/year), severe benign haematology. The medical staff is composed of 2 university professors, 6 attending, 4 fellows and 4 residents. The non medical team is constituted by 150 persons including 2 CRAs. The Center for Clinical Investigation (chair **Pr Jacz-Aigrain**) is a professional structure dedicated to paediatric trials. **Pr Hélène Cavé** (department of Genetics) is very well known expert of biology of childhood acute lymphoblastic leukaemia (ALL) and its biomarkers (evaluation of minimal residual disease)

Role within the project

AP-HP will contribute to most aspects of WP2, moreover its expertise in the field of adolescent with leukaemia will make it contributor to WP 17

R&D Experience

The 3 participating teams have demonstrated their dedication to Paediatric leukemias in terms of Biology deciphering, generation of biomarkers, multicenter clinical trials, evaluation of new drugs, pharmacology and pharmacogenetics.

Description of key people involved in the project

Professor André Baruchel: Professor of Paediatrics, Head of Paediatric Haematology Department in St-Louis Hospital since 1998 and in addition in Robert Debré Hospital Since 2004. He is Chairman of the FRALLE group (ALL multicenter trials), Chairman of the Leukaemia Committed of the SFCE (French society for Paediatric Oncology), and member of the IBFM board. He is involved in the field of childhood and adolescent leukaemia since 20 years. He has 128 publications.

Professor Evelyne Jacqz-Aigrain: Paediatrician, Professor of Pharmacology, Head of the Clinical Investigation centre and department of Paediatric Pharmacology and Pharmacogenetics, Hopital Robert Debré – Inserm. She is member of French WG of clinical pharmacology and drug investigations in children, Inserm committee for trial evaluations, CENGEPS scientific committee. She has 135 publications.

Professor Hélène Cavé: Pharmacist, Professor of Biochemistry. She is Member of the Department of Genetics Hopital Robert Debré, Coordinator of Molecular biology studies of the EORTC-CLCG, Member of the European Study group for evaluation of Minimal residual Disease in Leukemias (ESG-MRD). She has 112 publications.

Participation in relevant National or European research projects

Professor André Baruchel is involved in all ALL and AML trials generated at the European or international level (INTERFANT- infant ALL-, Relapsed ALL trial –EUREAL-, Relapsed AML trials, Down syndrome AML trial, phase I-II trials – dasatinib, clofarabine, forodesine, PKC412, VANDEVOL, CLARA Daunoxome).

Professor Evelyne Jacqz-Agrain is Coordinator of the French Network of Paediatric Clinical Investigation Centres (Inserm and Hospitals), Coordinator of the FP7 project TINN (Treat Infections in Neonates), Member of the FP6 Teddy network and FP7 Penta LabNet.

Organisation	**OLGA**	**Type**	**Public body**

General Description

Klinikum Stuttgart is a consortium of four tertiary case hospitals owned by the city of Stuttgart capital of Baden-Württemberg. Academically, it is affiliated with the university of Tübingen. Pädiatrie 5 is the department of paediatric oncology, haematology and immunology, one of the largest paediatric oncology centres in Germany. Pädiatrie 5 offers comprehensive treatment for children, but also for adolescents and young adults up to approx. age 20 with all types of cancer and hematologic disorders, it is also home to the study centres of German Cooperative Soft Tissue and Osteosarcoma Groups (CWS and COSS).

Role within the project

OLGA will participate in the WPs 4 'Clinical trial facilitation', 8 'Early evaluation and prioritisation of new anticancer drugs', 17 'Improving the outcomes for teenagers and young adults with cancer'.

R&D Experience relevant to the project

Our department gained ample experience through previous successful European and even trans-Atlantic clinical trials in sarcoma, particularly osteo and paediatric soft tissues sarcoma.
The applicant is chairman of the German- Austrian-Swiss-Osteosarcoma Study Group COSS and Project Leader of the European and American Osteosarcoma Study EURAMOS1 within the European Science Foundation´s Pan European Clinical Trials European Collaborative Research Scheme (ECT-EUROCORES). He is also president of the European Musculo-Skeletal Oncology Society EMSOS. Pädiatrie 5 is host to the Cooperative Osteosarcoma Study Group COSS and the Cooperative Weichteilsarkomstudiengruppe CWS, both with three decades of successful multinational clinical trial organisation, implementation, and completion. With this background, we have ample experience in organizing international collaboration within a multidisciplinary framework and also access to the relevant clinical trial networks.

Description of key people involved in the project

Dr. Stefan Bielack

Specialist Paediatric and Adolescent Medicine, Subspecialty Paediatric Oncology/Haematology, Director, Klinikum Stuttgart – Center for Paediatric and Adolescent Medicine - Olga hospital, Department of Oncology/Haematology/Immunology. He has 94 publications.

Participation in relevant National or European research projects

- EURAMOS1: European and American Osteosarcoma Study Group, Pan-European Clinical Trials ECT-EUROCORES (Project Leader)
- TranSaRNet: Translational Sarcoma Research Network, "Rare Diseases" Funding Program of the German Federal

Organisation	**WWU**	**Type**	**University Hospital**

General Description

Muenster University Hospital (UKM) is part of Westfaelische Wilhelms-Universitaet (WWU) and with a capacity of over 1.300 beds one of the largest hospital complexes in Germany. Approximately 420.000 patients per year receive high-level inpatient or outpatient treatment in 33 clinics and polyclinics with more than 7500 people employees. Over 3.000 students and postgraduates are currently studying at the Medical Faculty. The top ranking fundamental research (no.1 in North Rhine Westfalia) is supported by more than 32 M Euro third party funds per year and has contributed largely to the prominent international reputation of the Muenster University Hospital.

Role within the project

WWU will contribute to WP1.6.and will fullfill as partner the following tasks

- Establish a virtual interdisciplinary Ewing tumour board between national reference paediatric oncologists, orthopaedic surgeons and radiotherapists
- Develop valid standards and guidelines based on meta-analyses of existing data banks
- Facilitate international, interdisciplinary workshops to assure an appropriate level of training
- Roll-out of referral schemes established by selected bone sarcoma groups to provide patients without access to such infrastructure with access to expert centres and networks of care
- Support the development of bone sarcoma groups in European countries currently without such groups, particularly in Eastern Europe
- Education of oncologists caring for teenagers, young and older adults about possibilities to enrol their patients into “pediatric” trials
- Increase the number of patients with access to an infrastructure which will allow future participation in biology driven clinical trials

R&D Experience

The Department is the largest Pediatric Hematology and Oncology Center in Germany and has a major research focus in bone tumors. Beside headquarter of the European Bone sarcoma studies TranSaRNet, a translational sarcoma research network of the German Federal Ministry of Education and Research (BMBF) and also a BMBF Bone Tumor late follow up project are being conducted and coordinated in Muenster.

Description of key people involved in the project

Prof. Dr. Heribert Juergens, Head of the Department, has a long standing experience in bone tumor translational and clinical research and is chairman of the German and co-chairman of the International Ewing sarcoma trial.

Prof. Dr. Uta Dirksen is involved in the coordination of the BMBF projects and the International Ewing Trials.

Participation in relevant National or European research projects

The department has a broad experience in Clinical Bone Tumor Studies and is the European headquarter of the EURAMOS Osteosarcoma Trial and as well as the EURO-EWING-Trials 1999 and 2008.

Organisation	**ECCO**	**Type**	**Non profit body**

General Description

ECCO is an International Non-Profit Association (aisbl) Following the philosophy that every cancer patient deserves the best, ECCO – the European CanCer Organisation is especially structured to respond to the needs of its Member Organisations, connect and serve all stakeholders in oncology Europe-wide. It exists to uphold the right of all European cancer patients to the best possible treatment and care, and promote interaction between all organisations involved in cancer research, education, treatment and care at the European level.

Role within the project

ECCO will look after the dissemination activities on the results of the project. It will use its existing platforms and tools to reach the oncology community.

R&D Experience

ECCO – through its Member Organisations - represents and connects with the entire spectrum of specialties and interests from basic, applied and translational research to practice, treatment, care and advocacy.
ECCO is therefore well positioned and placed to act as partner in this project for the dissemination activities.

Description of key people involved in the project

Amanda WREN

She is ECCO Communication Manager. Ms Wren founded Nature's Spanish bureau in 1998, and remained as bureau chief; she was later director of international communications at the Spanish National Cancer Research Centre (CNIO), also in Madrid. Amanda Wren is in charge of promoting all ECCO initiatives in multidisciplinary education as well as further ECCO's mission – that every cancer patient deserves the best.

Organisation	**SOUTHAMPTON**	**Type**	**Higher Education Institution**

General Description

The University of Southampton is one of the most prestigious in the United Kingdom. The University is truly international, drawing students from over 100 different countries and benefiting from a wide and varied culture. It is a dynamic, international community dedicated to scholarship, discovery and enterprise. This provides a very strong environment for collaborative research, enhanced by the close cross disciplinary links between the academic Schools.

In the 2001 UK Research Assessment Exercise, the School of Medicines was graded 5* and rated of international excellence and again has scored highly for its range and quality of research and staff at the forefront of their disciplines during the 2008 RAE.

The University is ranked in the top ten of research led Universities in the UK receiving over £88M in research grants and contracts in 2008/9. This includes over £39M from the UK Research Councils and £8.8M (2008/9) from the European Commission with the School of Medicine receiving almost £20M in research income in 2008/9 and the total value of its research portfolio being over £34 million Within the UK the University is the second most successful organization in terms of EC contribution for FP7 ICT projects.

Role within the project

Leading on task 2.6.1

R&D Experience

Research and Innovation Services is a central resource which provides support and expertise to Schools across the University of Southampton in the activities of contract negotiation, spin-outs, licensing, IP, funding opportunities and student placements as well as dedicated bid preparation support on major, strategic bids. Collaboration Support Managers provide the prime point of contact and support activity to Schools and three teams support business communications and events, knowledge management and company incubation support. The Research Funding Manager has extensive experience in the area of European Funding and in particular of the R&D Framework Programmes and offers guidance to participants and support staff.

Description of key people involved in the project

Dr Colin Kennedy, Professor in Neurology and Paediatrics

Participation in relevant National or European research projects

Chair of joint WHO-EPNS-EACD working group on improving care of children with neurological problems in the Commonwealth of Independent States and Task Leader within EC-funded WHO project to improve Maternal and Child Health in Kazakhstan (2009-2011)

Approx 90 peer reviewed publications, including original descriptions of 8 national or international research projects and first or last authorship on approx 30 original scientific studies, including publications in The New England Journal of Medicine, The Lancet (x5), The Journal of Clinical Oncology, and Paediatrics.

Board member, Trustee and Research Panel chair of United Kingdom Children's Neurological Research Campaign

Former board member, trustee and vice-chair of Medical Advisory Committee of Action Medical Research

Principal Investigator of three national or European collaborative group (CCLG) studies of outcome in childhood brain tumour survivors (PNET3 Quality of Survival study 2003-2006; PNET4 Quality of Survival Study 2005-2010; In depth study of survivors of cerebellar tumours 2005-2010.)

Lead for Quality of Survival aspects on current (PNET4) or planned (PNET5 & 6) European RCTs of treatment for childhood brain tumours.

Chair of UK (CCLG) and European (SIOP-E) CNS Tumour Committee Quality of Survival groups.

Organisation	UNIVERSITY OF LEEDS	Type	Research organisation

General Description

University of Leeds (UoL) is acclaimed world-wide for the quality of its teaching and research. Leeds is one of the largest universities in the UK.
UoL has a very strong track record in cancer research and network development. UoL hosts the new Leeds Institute of Molecular Medicine (LIMM, 2006), is a designated Cancer Research-UK Clinical Centre, an NIHR/CR-UK Experimental Cancer Medicine Centre (ECMC) and hosts the National Cancer Research Network.

Role within the project

Is in charge, together with LTHTNHS, of the WP17, 'Improving Outcomes for Teenagers and Young Adults with Cancer'.

R&D Experience relevant to the project

Our work on supporting randomised prospective trials in cancer and in general healthcare has been recently reviewed by external international independent panels as being of the highest quality. The Teenage and Young Adult Oncology service is recognised as an international exemplar in this field. UoL has a lead national role in developing TYA services and research capacity in the UK and has acted as international advisor on TYA developments in the USA, Canada and a number of other countries. It has led the development of a special cancer register for TYA for Yorkshire and Humber. It also led the development of a national TYA register through National Cancer Intelligence Network. It has extensive international clinical trial experience and as a collaborator /lead in new agent development and translational research.

Description of key people involved in the project

Dr. Daniel Stark

Senior Lecturerin Cancer Medicine UNI Leeds. He is a medical oncologist who shared lead for TYA services. He is member of NCRI TYA Clinical Study Group; Chair NCRI Research Collaborative in structures of patient care; Member of the College of Physicians Oncology Training committee; TYAC Education committee member. He has 22 publications, and received Grant awards as applicant/co-applicant.

Susan Morgan

She is Nurse Consultant in TYA Oncology. She is full time NHS (Leeds THT) with Honorary University Lecturer Contract. She leads the Dept Health TYA Choices Project, she is member of the NICE Improving Outcomes Guidance for young people with cancer Implementation Group, she is organiser of 'Sense of Tumour' – annual national meeting for TYA with cancer – over 400 attendees at annual 3 day event. She has 20 publications on TYA cancer, and is a national award winner; she has a MBE for services to TYA cancer.

Participation in relevant National or European research projects

UK National Cancer Research Institute TYA Clinical Studies Group (since 2005)
TYAC (Teenagers and Young Adults with Cancer): multi-professional group formed in 2004 which has acted as a focus for developing an expert network in TYA cancer in the UK.
EuroEWING: UK Principal Investigator for this multinational study group that has now recruited close to 2500 patients.

B.2.3 Consortium as a whole

B.2.3.1 Description and complementarities of the consortium

The ENCCA consortium aims to **structure clinical research in paediatric and adolescent oncology within Europe**. Altogether, the 33 members can provide the necessary taskforce to strengthen and optimise clinical studies in Europe, by joining research activities, sharing data, equipment and knowledge, joining training and education, and establishing referral schemes.
Their excellence was affirmed in previous European projects, as shown by the various publication and communication tasks they produce and their ability to spread scientific excellence throughout Europe. The ENCCA Network of Excellence has a large breadth of experience and involves multidisciplinary stakeholders:

- The **clinical partners** constitute a high European potential group of excellence representing all the tumours groups, from the most common tumours to the rarest. They share a wide range of complementary technical competencies, research specialities, as well as methodology **(Tab.8).**

- International **organisations representing clinicians and scientists** concerned with the issues of children and young people having cancer will be enrolled in the project, either as partners or cooperating organisations.

- **Parents associations (via ICCCPO (ÖK))** will work closely with ENCCA, with the aim to help in the development of clinical trials in order to advance prevention and cure of childhood cancer while responding to the medical, social and personal effects of cancer treatment. Data information system specialists, specialised in the biomedical and research area, will be included in order to establish the virtual institute information portal.

- Greater collaboration with the **international community** will enlarge the synergies and the influence of the network in an international context. Starting from and while developing their complementarities with other NoE and IPs, the network will aim to create a virtual research institute to help Europe restore its leadership in clinical research in paediatric oncology through the implementation of common standards and strategies.

The network comprises partners from 11 European countries that will execute the tasks foreseen to achieve the network objectives. These partners undoubtedly represent the EU's **nucleus of excellence** and have proven experience in the field of paediatric oncology clinical research. The number and type of institutions involved in the project brings a **unique combination of competencies and facilities** able to succeed in the ambitious task of providing technical support for the standardisation of clinical trials. Notably, the network brings together in the necessary skills required for **running early therapeutic development, epidemiology, biology, imaging, bioinformatics and biostatistics**. Furthermore, the consortium has a strong experience in **conducting clinical trials**. Such a combination of competencies and excellence could only be achieved at the European level in a coordinated fashion.

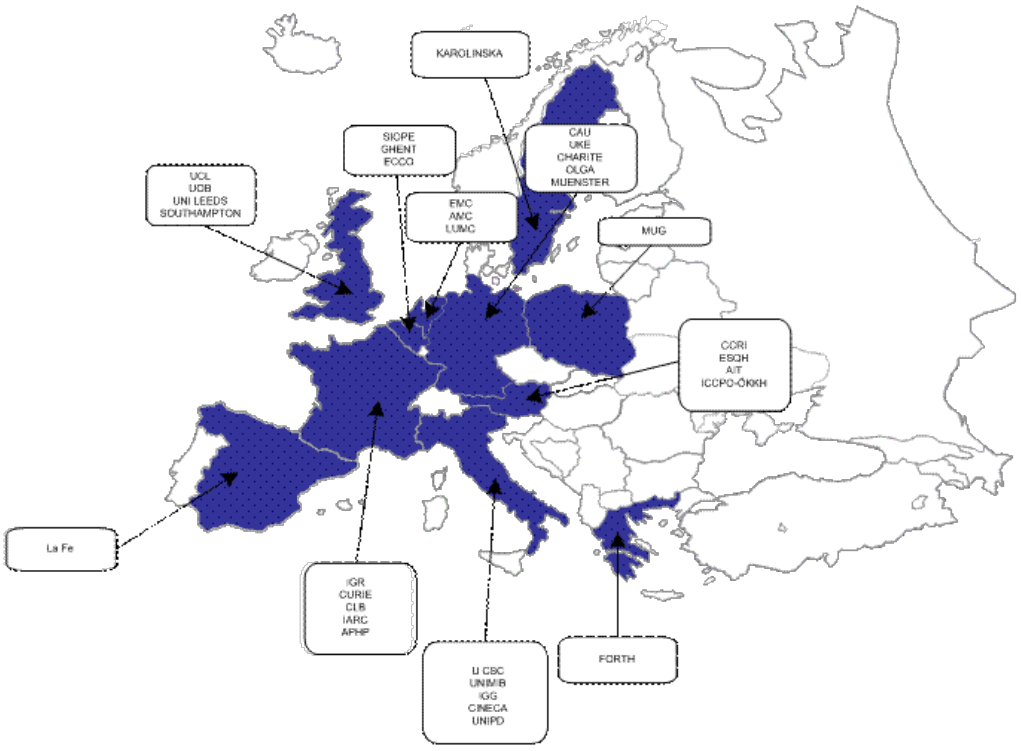


Figure 8: ENCCA partners in European regions

Indeed, **11 member states** are represented within the consortium (Austria, Belgium, United Kingdom, France, Germany, Italy, Netherlands, Spain, Poland, Greece, Sweden). All members of this consortium have extensive experience in collaborative work, through a high number of European projects and initiatives. A large part of the ENCCA members are also members of several groups of clinical research. The major competencies of the consortium are presented into the following table.

Partner	Competencies	Participation in WPs
CCRI	Management and communication, clinical trial design statistical approaches for analysis of recurrent events, Ewing's sarcoma and related tumour tasks	WP1, WP2, WP4, WP5, WP6
SIOPE	Management and communication, strategy of clinical research council, legal entity	WP1, WP2, WP4, WP5, WP14
UKE	Paediatric haematology, oncology and endocrinology Neuroblastoma cellular biology and genetic research	WP2, WP5, WP18
UNIMIB	Epidemiology and biostatistics Methodology of survival analysis Leukemic and haematological diseases	WP4, WP6
IGR	Clinical and translational research Early therapeutic development Early diagnosis New diagnosis and therapeutic strategies evaluation	WP2, WP6, WP7, WP8, WP12, WP13, WP17

Partner	Competencies	Participation in WPs
EMC	Phase I/II studies investigation in the field of leukaemia (protocol design, site selection, submission to regulatory authorities, pharmacovigilance, monitoring, etc)	WP8, WP16
CAU	Childhood acute lymphoblastic leukaemia	WP5, WP9
La Fe	Phase III clinical trials in Paediatric Oncology, mainly in neuroblastoma	WP2, WP10
ICR	Biology of childhood cancer Molecular genetics, paediatric kidney cancer (nephroblastoma, or Wilms tumour).	WP11
MUG	Paediatric liver tumours	WP12
UOB	Functional imaging for childhood tumours Brain tumour research	WP8, WP12
IGG	Epidemiology, long-term follow-up of patients Neuroblastoma, CNS tumours, non Hodgkin lymphomas, and soft tissue sarcomas	WP11, WP13
UCSC	Phase I trials Evaluation on new drugs Teaching and training	WP15
LTHTNHS UoL	Lymphoid malignancies Children and young adults clinical studies and epidemiology	WP17
CURIE	Etudes cliniques	WP2, WP10, WP18
FORTH	Track record in state-of-the-art R&D in the domain of biomedical informatics	WP4
AIT	Development and operation of research ICT infrastructures	WP3, WP4
CINECA	Design and development of IT systems and services in the health care and biomedical area	WP4, WP12
ESQH	Technology Transfer between Healthcare and Industry	WP4
AMC	Rare tumours Hepatoblastoma, neuroblastoma, nephroblastoma, sarcoma	WP2, WP5
ICCCPO (OK)	Parent's organisation	WP2, WP4, WP18
CLB	Rhabdomyosarcoma Teenagers and Young Adults cancer	WP6, WP 8, WP11, WP13, WP17
IARC	Development of standards for data collection, coding and quality evaluation	WP11
UNIPD	Off-patent medicines Rhabdomyosarcoma Very rare tumours	WP9, WP12
LUMC	Molecular pathology, bone tumours, soft tissue tumours, chondrosarcoma, paraganglioma	WP5, WP17
KI	Histocytic disorders	WP5, WP7, WP10, WP16, WP18
UGent	Neuroblastoma Leukemias Medical genetics, cytogenetic and molecular work-up of cancer	WP 5

Partner	Competencies	Participation in WPs
CAMPUS VIRCHOW-KLINIKUM (EUREALL)	Relapse and refractory cancers Clinical trials organisation and conduction	WP5, WP9
AP-HP	Biology deciphering Generation of biomarkers Multicenter clinical trials, evaluation of new drugs Pharmacology and pharmacogenetics	WP8, WP9
OLGA	Osteosarcoma	WP4, WP8, WP17
WWU	Bone sarcoma	WP7
SOUTHAMPTON	Quality of survivorship Medulloblastoma	WP13

Table 8: ENCCA competencies

B.2.3.2 The communication with industry.

ENCCA will strengthen its partnership with industries by creating a platform for communication and interaction with Industry. Its main objective is to gather industrial partners- SMEs, large companies, end users- in order to:

- Disseminate advanced scientific information and standards
- Create academic/industry synergies
- Favour the Establishment of new research partnerships in emerging topics
- Accelerate technology and/or knowledge transfer, when appropriate

The main interest of the proposed collaboration structure **(Fig. 9)** is to ensure and facilitate the needed synergies between ENCCA and industry as well as other stakeholders such as public authorities, regulatory bodies, patients and parents in order to create a long-term partnership in which clinical research and knowledge transfer are closely linked. A strong collaboration between the network and Industry will allow further achievement of the necessary coherence between clinical research and the regulatory framework in which clinical trial processes can be developed and harmonised. This platform will be created in collaboration with the Biotherapy Development Association (BDA) to address improvement in paediatric new oncology drug development, facilitating SMEs and Industrial groups (Pharmaceutical, Diagnostic and Equipment Companies) which are interested in being involved in Network activities will be involved. Only non-confidential information will be shared. Industry as well as ENCCA intellectual property and confidential information will not be released. If needed, Confidentiality Disclosure agreements between relevant parties will be used, when appropriate.

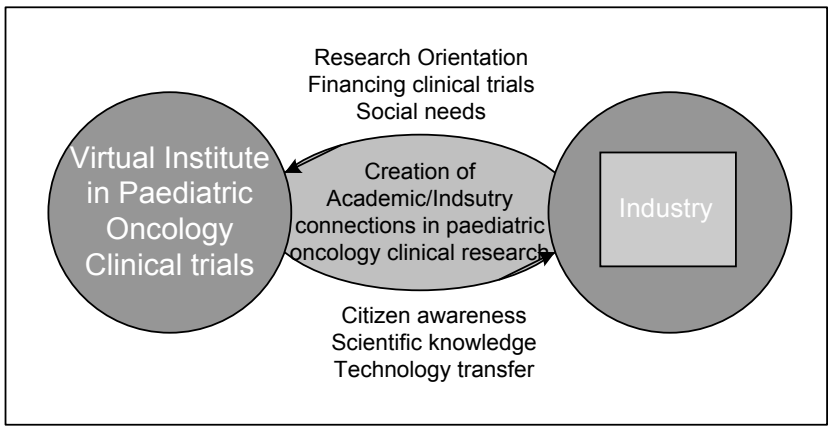


Figure 9: Interaction between industry and virtual network

The industry will then able to participate in common expertise working groups, to have access to expertise as well as to finance specific studies of common interests or even create synergies for collaborations.

Strong interaction between industry and the Network will:

- Provide access to a network of clinical and translational research experts for clinical trials in paediatric oncology representing excellence at European and International level
- Increase the collaboration between academia and industry - this will be measured by specific indicators throughout the life of the project with the final objective being to make efficient clinical trials in paediatric oncology
- Accelerate drug development and improve cure of children and adolescents. The objective is to enhance the contacts between academia and industry and create also new services for the private sector
- Participate in common research programmes and financing activities of common interest Provide opportunities for joint training programmes for young investigators to better understand the needs of industry in drug development;
- Boosting research and attracting research funding at regional, national and European level
- Be open to a market of trained engineers and clinicians able to supply highly-qualified resources for industrial careers
- Provide relevant information on the advancement of clinical trials via private newsletters and joint scientific workshops and visits. The information will enable industrials and clinicians to analyse and evaluate the newly-developed knowledge for their own purposes;
- Facilitate the identification of ENCCA results that can be converted either into economic, social or technical added value
- Contribute to the sustainability of the Network activity by creating services for the private and public sectors;
- Due to the expected creation of various innovative communication and dissemination tools, ENCCA's vital contribution to paediatric oncology coupled with its association and support from the pharmaceutical industry is likely to gain significant public awareness, as well as academic, scientific, corporate and political awareness

Industry	Type	Country	Activity –Interest in Network
ETIAM	SME	France	DICOM image transmission
MicroArt	SME	Spain	Medical informatics
MRC Holland	SME	Netherland	easy-to-use, high quality tools for genetic analysis
Biocrates Life Sciences AG	SME	Austria	Biotechnology focused on metabolomics
ITH icoserve technology for healthcare GmbH	SME	Austria	e-Health solutions
Bristol-Myers Squibb	IND	UK	Paediatric Oncology drug development
Merck & Co., Inc.	IND	UK	Experimental Medicine/Oncology
Sanofi-Aventis	IND	France	Oncology Division
Astra-Zeneca	IND	France	Oncology clinical development
Pfizer	IND	France	Oncology Division
GSK	IND	France	Oncology Medicine Medical Center
Pharmamar	IND	Spain	Clinical development
Hoffman Laroche	IND	Switzerland	Clinical development
BMS	IND	USA	Oncology Global Clinical Research
Lilly	IND	Germany	European Platform, Oncology

Table 9: List of SME and industries members already interested in collaborating with ENCCA

B.2.3.3 Collaboration with other Networks

We will integrate the currently active, strong preclinical research networks as well as their previously obtained extensive datasets and NoE's in paediatric and adolescent oncology, including the EET-Pipeline (EU-FP6 STREP), KidsCancerKinome (EU-FP6 STREP), IBFM (academia), CONTICANET,EuroBoNeT (EU-FP6 NoE), SIOPEN-R-NET (EU-FP5 NoE) and the NRC consortium (neuroblastoma profiling). However, an open structure is planned that is capable of integrating new networks established at a later date, which are relevant to paediatric oncology. This will ensure a stable network linking cutting-edge preclinical research to the clinic for stronger support in advancing treatment for childhood and adolescent cancer. A formal link will be established with the FP6 integrated project: 'Advancing Clinico-Genomic Trials on Cancer (ACGT)' to profit from their expertise and tools in integrating, sharing, exchanging and analysing tumour biology data together with clinical data.

B.2.3.4 Sub-contracting

Seven beneficiaries intend to make use of subcontracts as described below. In each case the subcontract selection has been done and will be done according to the best value for money (best quality/price ration) transparency and equal treatment, the availability of the place and services and according to the internal rules of the Beneficiaries, in agreement with the FP7 rules.

Partner sub-contracting task	**Task to be sub-contracted and Expected costs of sub-contracted task**
IGR	IGR&D, SME dedicated to the transfer of technology (e.g. filing and managing patents, dealing with Intellectual property matters, Consortium Agreement and Material Transfer Agreement issues, Research Collaborations, Services and License Agreements). IGR&D, already subcontracted in other EU projects, is in charge of the elaboration of all legal documents in IGR for: 1) identification and protection of foreground of the project, including patent searches, filing of intellectual property applications and management of joint ownership between the partners of the project, by negotiating and drafting joint ownership agreements; and/or 2) Access rights to existing property knowledge and innovative results of the project between the partners of the Consortium; and/or 3) Access rights to existing property knowledge of the partners and innovative results of the project beyond the consortium, such as to SME companies or industrial pharmaceuticals groups, who are interested in the exploitation of the results by the negotiation and drafting of a confidentiality agreement, material transfer agreement and/or commercial licence agreement. Total 20000 euro
CCRI	CCRI will subcontract for services related to the organization of meetings (General Assembly, Dissemination and Policy etc) and events (hotel, catering etc) and for website development. The budget expected for these subcontract is the following:

	Subcontract costs CCRI		
RTD	**85112,18**	**description**	
Y1	5805,5	kick off meeting	
	2885,91	1st general assembly	
Y3	10701,69	2nd general assembly	
Y3	1500	payment to SAC members (Ringborg, Schunemann, Adamson)	
Y4	15000	3rd general assembly	
	18500	Joint ENCCA-SIOPEL meeting session	
	1500	payment to SAC members (Ringborg, Schunemann, Adamson)	
Y5	12500	4th general assembly	
	1500	payment to SAC members (Ringborg, Schunemann, Adamson)	
	15219,08	5th general assembly/ final event	
MNG	**8984**	**description**	
Y1	5900	Law service for CA	
Y2	2000	certification of the costs	
Y3	1084	certification of the costs	
Other	**15794,49**	**description**	
Y1	8944,5	ENCCA website	
	1312	First EU sarcoma summit	
Y2	557,99	ENCCA website	
Y3	2064	ENCCA symposium	
Y4	2916	ENCCA symposium	
total	**109890,67**		

SIOPE

SIOPE will subcontract for services related to the organization of meetings and events (hotel, catering etc) and for website development. The budget expected for these subcontract is the following:

	Subcontract costs SIOPE		
RTD	**14563,08**	**description**	
Y1	7125,23	kick off meeting	
	7437,85	1st general assembly	
MNG	**5000**	**description**	
Y4	5000	certification of the costs	
Other	**65000,8**	**description**	
Y4	30000,8	ENCCA Long Term Sustainabiliyt disseminationeEvent	
	35000	ENCCA/SIOPE -ABCD4E portal development	
total	**84563,88**		

SIOPE: 14563.08 (RTD) 65000.8 euro (Other activities) 5000 EURO (MNG)

Total: 84563.88 euro

UKE	UKE has the following costs for minor subcontracts for meeting organization : Year 1 249.24 euro (RTD) Year 2 507.12 euro (Other activities)
UKSH (CAU´s third party)	UKSH has the following costs for minor subcontracts for meeting organization : Year 1 365 euro (RTD)
UoL	UoL will pay 500 euro to the following centres to conduct a pilot a study of the international variation in time from symptoms to diagnosis and treatment in teenagers and young adults with cancer : 1) Sheffield UK – Daniel Yeomanson Sheffield Children's Hospital, Western Bank, Sheffield, S10 2TH. 2) Arrhus- Denmark- Pia Olsen Aarhus University Hospital, Department of Oncology, Noerrebrogade 44 Building 5 8000 Aarhus C Denmark 3) Lund - Lars Hjorth and Daniel Relander Department of Paediatric and Adolescent Medicine Skåne University Hospital SE-221 85 Lund Sweden 4) Prof.dr. Winette T.A. van der Graaf, Nijmegen, Netherlands Dept. of Medical Oncology Radboud University Nijmegen Medical Centre Department of Medical Oncology PO Box 9101 6500 HB Nijmegen The Netherlands 5) Hannover, Germany - Dirk Reinhardt, Anika Mohr Department of Pediatric Hematology and Oncology Hannover Medical School Hannover, Germany 6) Madrid, Spain - Alvarro Lasaletta, Rosalia Lorenzo Servicio de Hemato-Oncología Pediátrica Hospital Universitario Niño Jesús Avda. Menendez Pelayo 65 Madrid 28009 7) Budapest, Hungary - Daniel Erdelyi 2nd Dept Paediatrics, Semmelweis University, Budapest, Hungary

IARC

IARC will pay 12000 EUR to 3 subcontractror for the taks 11.4

Subcontractors	Amount in €	Address	Director	Responsible person	EMAIL
National registry of Childhood Cancers, CRESS EQ7, INSERM UMR-S 1153, Paris-Descartes University	3.000	16 avenue Paul Vaillant-Couturier - F-94807 **Villejuif** Cedex - **France**	Philippe RAVAUD, PU-PH	Jacqueline Clavel, MD, PHD.	jacqueline.clavel@inserm.fr
UNIVERSITY MEDICAL CENTER at the Johannes Gutenberg-University Mainz German Childhood Cancer Registry (GCCR)	6.000	Institute for Medical Biostatistics, Epidemiology and Informatics (IMBEI) 55101 **Mainz, Germany**	Professor Maria Blettner	PD Dr Peter Kaatsch, University lecturer	kaatsch@uni-mainz.de
National Cancer Registration Service, Oxford, Public Health England	3.000	Oxford Cancer Intelligence Unit 4150 Chancellor Court Oxford Business Park South **OXFORD** OX4 2GX	Kellie Peters, Head of Registration	Charles Stiller, Anita Bayne	Kellie.Peters@PHE.gov.uk
TOTAL:	**12.000**				

B.2.3.5 Third parties

The **WWU** (Westfälische-Wilhems-Universität Münster) has as third party the **UKM** (Universitätsklinikum GmbH, Münster). The UKM is a spin-off company of the WWU Muenster and manages certain administrative tasks for the latter.The comments from the EC Financial Guide, Article II.14.2 of the GA, **"**A THIRD PARTIES MAKING THEIR RESOURCES AVAILABLE TO A BENEFICIARY Special cases, bullet 1**"** apply. The UKM handles the financial and administrative aspects of the WWU involvement in certain research projects with clinical perspective, including all issues relating to the employment and payment of additional personnel, purchase of equipment and consumables, etc. The UKM is entitled to do so by force of a long-standing, general cooperation-agreement. Further, the Director of the UKM is appointed authorised signatory of the WWU in such undertakings. The WWU has an agreement that foresees the handling of Community financial payments by the UKM. Therefore, the coordinator pays the EC contribution directly to the UKM (third party) and not to the WWU (beneficiary).

The UKM makes resources available to the WWU specifically the researchers of the WWU work on the premises managed by the UKM (ownership of the premises is with the Federal State of Nordrhein-Westfalen), and use equipment of the UKM, which is not free of charge.
The UKM does not charge the beneficiary for this activity; it is not reimbursed by it. The WWU will not include the cost of the third party as an eligible cost of the project. Since these contributions in kind are not made specifically for this project, but are at the management discretion of the WWU Muenster, they are not considered a receipt to the project. All declared costs within this project are completely incurred by the WWU the PIC of the WWU applies.The UKM carries out all tasks in

compliance with the consortium agreement and the grant agreement, including its annexes. Specifically, Articles II.14-II.17, II.22 and II.23 of the latter do apply.

The **CAU** (Christian-Albrechts-Universitaet zu Kiel) is obliged by national law to call upon the **UKSH** (Universitätsklinikum Schleswig-Holstein) for the implementation of externally funded research projects carried out by researchers of the university's medical faculty. This includes that a significant share of the CAU's project budget (technical staff, consumables, travel cost and any other direct cost) will be administered by the UKSH and the cost will incur to the accounts of the UKSH, whereas the scientific staff leading the project and performing the research are employees of the CAU and their cost will be reported by the CAU. The UKSH therefore should be included as a Third Party via Special Clause 10."

The **AMC (**Academic Medical Center) has a third party AMC Medical Research BV (AMR) which provides service as described hereunder to AMC (P21-AMC) in the capacity of affiliated third party providing resources for which AMR is reimbursed by AMC.

AMR is a commercial non-profit entity jointly owned by Academic Medical Centre (51%) and the University of Amsterdam (49%). AMC Medical Research BV (AMR) was created in order to manage the administrative tasks of the Academic Medical Centre(AMC). The statutes of AMR provide the legal basis for the services provided by AMR. AMR and AMC have concluded a specific agreement with regard to the ownership of intellectual property generated by AMR personnel. All intellectual property generated by AMR personnel is owned by AMC.

The tasks performed by AMR include the management of all financial and administrative aspects of the AMC involvement in research projects, including handling the Community financial payments, all issues relating to the employment and payment of additional personnel, purchase of equipment and consumables, as a special case of a third party making it's resources available to a Beneficiary (AMC).
Therefore the coordinator pays the EU contribution directly to AMR.
AMR does not perform scientific/technical work in the project.

The resources made available by AMR to AMC are research personnel and standard laboratory research consumables, necessary for AMC to perform its designated tasks in project. These resources are used in the premises of the beneficiary AMC and are under its direct responsibility. As such the flat rate of 60% is used by AMC for the calculation of the indirect costs.

The costs of AMR will be charged by AMC in its Form C but they are recorded in the accounts of AMR. The costs are reimbursed directly by the coordinator on behalf of AMC. Above mentioned is based on the general agreement made between Academic Medical Centre and AMC Medical Research BV for managing externally financed projects.

AMR shall manage AMC's project share, employ temporary staff, pay for project consumables and shall pay for travel costs linked to the project. Staff employed shall work at the premises of AMC and under supervision of the AMC project leader Martin Offringa, AMR has liability insurance schemes in place for its employees as well as for patients enrolled in clinical trials.

AMR has been already involved as third party in other EU funded project.The budget estimated for AMR is about € 240.000.

B.2.3.6 Other countries (Non EU countries)

Many people from other countries (USA, Japan, Australia, and Brazil) with international expertise in paediatric oncology will participate in the clinical research Advisory Councils and/or in training sessions in order to increase the impact of ENCCA in EU paediatric oncology knowledge.

B.2.3.7 Cooperating Organisations

The project comprises also a number of cooperating organisations that have expressed their interest to participate in activities of the NoE without funding by the EU. This interest show the great importance that gibe the paediatric oncology clinical research in the networking of the whole field in order to provide a more efficient care for children with cancer. The cooperating partners will participate in tasks according to their interest and experience and also in dissemination and training actions. The final aim is to integrate all the interested organisation into the ENCCA NoE in the long term.

Cooperating organisation name	Acronym	Country
European Science Foundation	ESF	France
European Forum for Good Clinical Practice	EFGCP	Belgium
Sigmund Freud University (Vienna)	SFU	Austria
Tettamanti Research Center	TRC	Italy
International Breast Cancer Study Group	IBCSG	Switzerland
The Netherlands Cancer Institute/ Antoni van Leeuwenhoek hospital	NKI	Netherlands
MicroArt	MicroArt	Spain
University of Koln	UKOLN	Germany
University of Nottingham	UNOT	UK
Cooperating organisation name	**Acronym**	**Country**
Great Ormond Street Hospital for Children NHS Trust	GOSH	UK
UCL Institute of Child Health	ICH	UK
University of Hamburg	UNIHAM	Germany
University Children's Hospital Zürich	BFM-CH	Switzerland
University Hospital Motol (Paediatric Haematology)	MOTOL	Czech Republic
Medizinische Hochschule Hannover (Committee)	I-BFM AML	Germany
Paterson Institute for Cancer Research (Resistant Disease Committee)	I-BFM	UK
University of Oxford	UNIOX	UK
University of Catania	UNICAT	Spain
Agia Sofia General Children's Hospital Dept. of Paediatric Haematology- Oncology	SOFIA	Greece
Dept. of Pathology Rikshospitalet	DPR	Norway

SIOPEN Institutions	SIOPEN	Austria
University of Saarland	SAAR	Germany
University of Valencia	UNIVAL	Spain
European Network of Cancer Registry	ENCR	France
University of Munich	UOM	Germany
Institute of Pathology, Bern	IPB	Switzerland
SIOPEL	SIOPEL	UK
Children's Oncology Group	COG	USA
Japanese Liver Tumours Study Group	JPLT	Japan
Adam's Hat (Charity)	ADAM	UK
University of Southampton	UNISOUTH	UK
University Hospital, Munzer	MUNZER	Germany
Hospital Nationale St. Maurice	HNSM	France
Istituto Scientific "Eugenio Medea"	MEDEA	Italy
University of Lund	ULUND	Sweden
University of Newcastle	UNEW	UK
ESO	ESO	
University of Muenster	UNIMUNS	Germany
Children's Hospital, BASEL	CHILDH	Switzerland
Cooperating organisation name	**Acronym**	**Country**
Teenage Cancer Trust London	TCTL	UK
London Institute of Child Health	LICH	UK
The European and American Osteosarcoma Study Group	EURAMOS	UK
European Ewing Tumour Working Initiative of National Groups	EURO-EWING	UK
EuroBoNet	EuroBoNet	NL

Table 11: Overview Cooperating organisations

B.2.4 Resources to be committed

ENCCA will group together 33 research organisations and associations in Europe representing the major clinical research in paediatric oncology. The strong commitment of the participants to build an integrated network is visible not only from the letters of high authorities addressed to the coordinator (letter joint with this proposal) by all the organisations but also from the quality of scientific expertise ,the management skills and the critical mass that is reached by all the institutions.

The critical mass is achievable through:

- **Integration of researchers and PhD or post doctorate students:** ENCCA partners will involve a critical mass of resources. The 34 partners will integrate 125 researchers and 38 PhD and post-docs to address the ambitious objectives of the network. Moreover cooperating organisations are also committed to be involved in the Network activities representing additional 18 researchers. However partners are committed to using the total number of their resources (more than 350) to achieve integration.
- **Integration of facilities:** Academic and industrial partners altogether have a large volume of facilities (equipments, tools, clinical facilities, training).
- **Integration of financial resources:** The European grant will be the first financial support for integrating facilities, clinicians and other competencies and organisation. The fund represents 12 MEuros. Partners in the project have already established relationships though the existing tumour and leukaemia groups and are able to be integrated rapidly. Moreover a strong management organisation with a very close quality plan organisation will allow achieving the objective towards a virtual institute in 4 years. In fact, each partner will use its own resources for financing research activities. The grant represents only a small part of the total efforts that will be integrated by partners in the Network implementation. Foundations and national funds in different countries (UK, France, Austria, Germany,..) represent also sources that will be used. More specifically it is estimated that the total budget of the participating organisations in activities related to the Network will be 110 M Euros

	Proposal for integration within ENCCA NoE	**Real participation for integration within ENCCA NoE**
Number of researchers	125	More than 300
Financial contribution	12 M Euros	More than 110 M Euros

Table 12: Integration of researchers and PhD students

When looking at the figures listed in table 12 we can see that the grant represents **only 15%** of the total effort for integration. Further external financing sources are also envisaged during the project such as participation in other projects, national funds, industrial financing.
Other sources will be also identified and exploited by a specific Financing Assessment option team (WP1) that will be implemented especially for increasing the Networks financing autonomy.

B.2.4.1 Integration of human resources

ENCCA has estimated an overall budget of € 13,189,166 which corresponds to a **requested grant** to the budget of **€ 11.998.000.** These 12 M€ of funds represent **less than 15%** of the total effort that will be provided by the partners to advance towards a Virtual Institute in Paediatric Oncology clinical trials for children with cancer.Figure 10 represents the initial distribution of the budget among the different activities of the project.

It can be seen that budget is well balanced among the different activities. **6%** of the total budget is dedicated to the **management**, **59%** of the budget is contributed to **Networking/Integrated activities and Spread of Excellence activities (others) and 35% to the Join research Activities**. It can be notified that **3%** of the funds (360,000 Euros) have been reserved for **unpredictable integrating situations** and eventually **integration of new partners**. This fund will be presented in the WP1.1 together with the budget of the Network of Excellence Manager. However only the Executive Committee can use these funds after approval of the General Assembly.

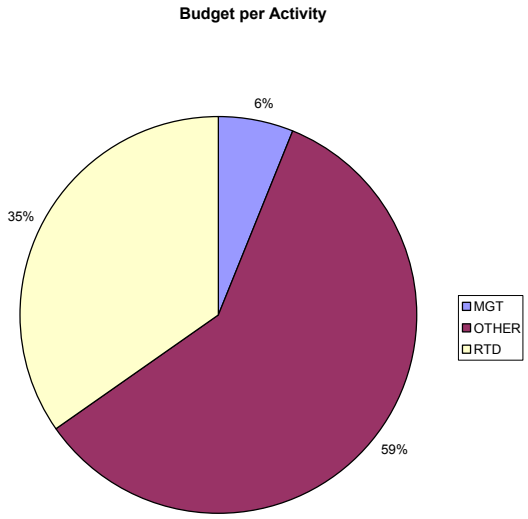


Figure 10: Distribution of budget per activity type
(MGT, JRA, Others- including Integration and spread of excellence activities).

Efforts will be shared between **17 Work Packages** of which 6 are dedicated to **Networking activities**, 6 to the Join research activities, 5 to the Spread of excellence and 1 to management activities. Additionally, ENCCA **budget** is **well-balanced** among the different European countries participating in the project as it can be seen in the figure 11. Austria, France, Germany, Belgium and Netherlands representing the core of the project and the most important clinical research have the most important participation on this project.
However all the European regions are represented (Sweden, Poland, Greece) in order to integrate in a long term all European clinical research in paediatric oncology.

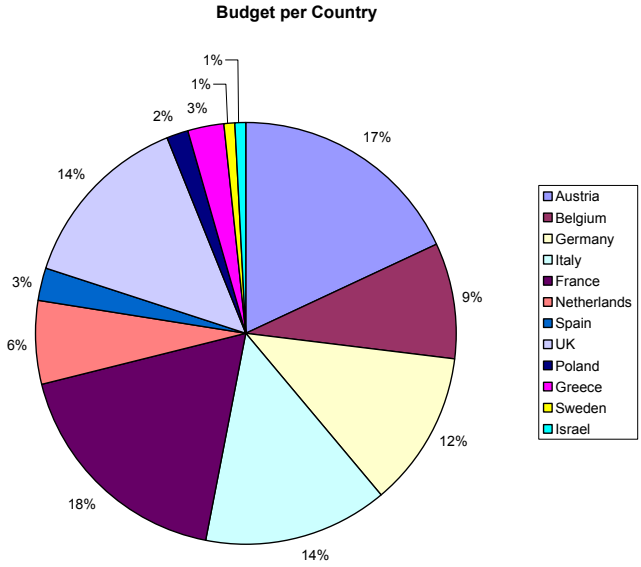


Figure 11: Distribution of the budget among the partners

Although the balance between the different **11 countries** was kept in mind, the major criteria for choosing the partners were their excellence in the domain, their proven commitment to the networking and equipment that are the intention to integrate.

Human resources

A critical mass of human resources is necessary to carry out the structured activities) needed to successfully achieve the project's objectives of ENCCA considering the main potential contexts. For the four-year project, the total effort for the **34** partners involved in ENCCA project is **1091 Person-months**. More precisely, **429** person-months are allocated to **Networking activities (**39.3%) **335** person/months to **join research activities** (30.7%), **253** person/months in spread of excellence activities (23.3%) and finally, **73 person/months** to **Management activities** (6.7%). For more accurate data we refer to the final budget overview of the ENCCA.

Nevertheless, it has to be accounted that this global effort only represents a part of the actual human resources devoted to the project. A rough assumption made on the basis of the partner declaration indicates that, the human resources proposed for a financial support by the EC only represents **15%** of the total commitment.

These efforts represent a **critical mass** of resources and means necessary to achieve one a very important networking activity in Europe and consequently a high quality improvement of dedicated clinical research in Europe for children with cancer. Regarding the management, an important effort is foreseen in order to launch activities such as, creation of the management structure and project follow up, virtual networking tools communication with the 33 partners through web and quality indicators will be defined at the beginning of the project and applied during the whole period of the project in order to establish a balanced scorecard for the efficient follow up of the activities and the successful networking of the European paediatric oncology clinical research for more efficient care of children and adolescents with cancer..

B.2.4.2 Integration of materials and equipment

In table 13 an overview is been given of the most important materials, equipment and facilities that ENCCA will integrate through the consortium

Partner	Available resources	Research facilities and infrastructures
CCRI	▪ Unit of studies en statistics ▪ Phase I/II/II clinical trial ▪ Licensed statistical software as SAS, SPSS ▪ Molecular genetic data on 100s of leukaemia, lymphoma, neuroblastoma and Ewing tumours	▪ Together with St. Anna Children's Hospital forms the only Austrian Comprehensive Cancer Centre for children and adolescents in Austria. 120 new patients/yr, including stem cell ▪ Epertise in standardising molecular biological assays for use in clinical practice ▪ Coordinates SIOPEN-R-Net(European Neuroblastoma group) ▪

SIOPE	▪ Primary communication tools
	  ▪ Website
	  ▪ Newsletter
	▪ Regular email news updates to both the paediatric oncology network in Europe and internationally as well as the EU health community.
		▪ SIOPE is the only pan-European society for childhood cancer. It is a founding member of ECCO, encompassing legally founded societies and organisations (EACR, ESMO, ESTRO, EONS, ESS) fully or substantially involved in day to day oncology in Europe.
		▪ The SIOPE office is located in Brussels in close proximity with the above European Cancer society's and has shared staff and resources with ECCO.
		▪ www.siope.eu

UKE/CHARITE	Genomic, transcriptomic, proteomic and epigenomic profiling of paediatric tumours and cell culture models.	▪ Germany's largest Comprehensive Cancer Centre. 120 new paediatric cancer patients/yr. Phase I-III trials and major focus on biology of embryonal tumours in the paediatric oncology research institute. ▪ Co-ordinates European Embryonal Tumours Pipeline project (EU FP6) ▪ www.uniklinikum-**essen**.de
UNIMIB	▪ Software: SAS, STATA, S-plus, R. ▪ methodology of survival analysis and the design of clinical studies. ▪ Clinical and epidemiological research. ▪ Large leukaemia sample repository with more than 5,000 specimens. ▪ Large panel of molecular data on leukemias at different level including genom-wide profiling data.	▪ The UNIMIB is multidisciplinary university especially oriented to research in medicine, biology and biotechnology. ▪ Major centre for research in biostatistics and clinical epidemiology ▪ Very large paediatric leukaemia/lymphoma practice (~100 patients/yr including 35 stem cell transplants). Phase I – III trials. ▪ Fully equipped leukaemia diagnostics and research facility. ▪ www.unimib.it
IGR	▪ Facilities and expertise to sponsor and run clinical trials at the European level (regulatory affairs, pharmacovigilance unit, statistics and trial management, on-site monitoring, contract negotiation, etc) ▪ A biology and preclinical evaluation programme (in-house developed tumour models in paediatrics brain tumours and neuroblastoma.) ▪ preclinical evaluation of targeted compounds.	▪ Largest comprehensive cancer centre in France. 350 new childhood cancer patients yearly. Referral centre for paediatric and adolescent patients with solid tumours to access early phase trials. Infrastructure to run early and late phase clinical trials including biomarkers and PD endpoint analysis in both adults and children. Teenage cancer unit ▪ Research team in statistics develops innovative methodology and trial designs and manages clinical trials. ▪ Coordinates Innovative Therapies for Children with Cancer consortium ▪ Website: www.igr.fr ▪ www.itcc-consortium.org

Partner	Available resources	Research facilities and infrastructures
EMC	▪ Infrastructure to sponsor phase I/II studies at the European level ▪ Large(1,000s) leukaemia sample repository ▪ Large panel of genome-wide microarray data at different levels.	▪ Erasmus MC is a University Hospital ▪ The Department of paediatric Oncology is the largest in the Netherlands ▪ Approximately 140 newly diagnosed patients/year, including phase I-III trials ▪ Research is mainly focused on unravelling the genetic abnormalities driving paediatric malignancies, and developing targeted treatment options by translational research. ▪ www.**erasmusmc**.nl/
CAU	▪ Access to German National Genome Research Net (NGFN), using genome-wide approaches for an extended molecular characterization of ALL. ▪ Large leukaemia sample repository with more than 10,000 specimens. ▪ Large panel of genome-wide microarray data at different levels (n > 700).	▪ Christian Albrechts Universität zu Kiel (CAU) hosts the Trial centre of the German ALL-BFM Study Group and the current office of the International BFM Study Group (I-BFM-SG). ▪ Large specialist childhood and adolescent cancer centre offering phase I-III clinical trials, broad spectrum of translational research activities mainly in acute lymphoblastic leukaemia. ▪ www.ilv.uni-**kiel**.de
LaFe	▪ Infrastructure to run phase III clinical trials in Paediatric Oncology ▪ Access to national neuroblastoma samples and diagnostics data through University of Valencia.	▪ University Hospital hosting a large paediatric oncology unit (120 new patients/yr) offering phase I-III clinical trials. ▪ Infrastructure necessary to run clinical trials and biological research projects. ▪ Coordinator of localised neuroblastoma phase III (LINES) trial. ▪ www.fundacionlafe.org
UCL	Access to groups researching in to biology of ▪ Renal tumours ▪ Neuroblastoma ▪ Medulloblastoma ▪ Rhabdomyosarcoma ▪ Immunotherapy	▪ Europe's largest and most productive centres for biomedical science ▪ Ranked 4th in the Times Higher Education World University rankings ▪ Largets teenage and young adult cancer unit in the UK
MUG	▪ Access to informal European network of paediatric oncology surgeons ▪ SIOPEL coordinator for links to international collaborators (USA, Japan).	▪ MUG is the main medical higher education body in northern Poland. Hosts large childhood cancer centre offering clinical trials. ▪ National coordinating and referral centre for the treatment of paediatric liver tumours. ▪ www.gumed.edu.pl
UOB	▪ Main clinical trial unit for the UK's Children's Cancer and Leukaemia Group ▪ Infrastructure to sponsor and run early and late phase trials at a European level. ▪ Hosts MRC methodology hub for statistical research in rare tumours ▪ Computing infrastructure, (hardware and software), to support functional imaging research, including developments in signal processing. Facilities for making test objects (phantoms). Also, data analysis using pattern recognition and clinical decision support systems	▪ Infrastructure to run early and late phase clinical trials including biomarkers and PD endpoint analysis in children. Specialist childhood cancer centre with ~200 new patients yearly. ▪ Access tot he National Institute for Health Research 3 Tesla Magnetic Resonance Research Facility ▪ Well established collaborations with Electronic, Electrical and Computer Engineering at the University of Birmingham (Dr Arvanitis) and Medical Physics at University Hospital Birmingham ▪ www.birmingham.ac.uk

Partner	Available resources	Research facilities and infrastructures
IGG	▪ Licensed statistical software as SAS, SPSS; Stata, Statistica, Epi info. ▪ Uni- and multivariable data analyses and Registries maintenance. ▪ Microarray Unit of the Institution's Core Facility and for the Bioinformatic Unit. ▪ A fully equipped structure for state of the art molecular biology: ▪ The microarray facility for CGH, ▪ The BIT Biobank structure for paediatrics tissues storage, processing and analysis for mRNA and miRNA profiling ▪	▪ The Giannina Gaslini Institute (IGG) is the largest public paediatrics research hospital in Italy (140 new patients/yr) and offers phase I-III clinical trials for children with cancer. ▪ Epidemiology and Biostatistics Unit ▪ Bio banking and bioinformatics. ▪ Expertise in neuroblastoma biology and genetics ▪ www.**gaslini**.org ▪
UCSC	▪ Access to training and teaching packages focused on paediatric oncology	▪ University Hospital with large paediatric and adolescent oncology unit (60 new patients/yr) and full facilities for stem cell transplant, MIBG therapy etc. Referral centre for access to phase I-III trials. Translational clinical research laboratory focussing on preclinical evaluation of targeted agents.
LTHTNHS UoL	▪ Experienced multi-professional team for research, teaching and care in adolescents and young adult cancers ▪ Interactive web platform for teenage and young adult cancer patients to share experiences (www.jimmyteenstv.com) ▪ Standardised molecular testing for sub-microscopic disease in Ewing's sarcoma and neuroblastoma	▪ Infrastructure to run early and late phase clinical trials including biomarkers and PD endpoint analysis in both adults and children. Large tertiary centre (160 new patients/yr). Referral centre for children and young people for early phase trials. Leading centre for research into adolescent and young adult cancer patients' needs. ▪ http://www.leeds.ac.uk/ ▪ www.leedsteachinghospitals.com
CURIE	Genomic profiling on 100 primary tumour samples (Ewing's, rhabdomyosarcoma, neuroblastoma)	▪ Institut Curie is a Comprehensive Cancer Centre that includes a very large paediatric oncology clinical unit (220 new solid tumour patients/yr). ▪ Research team INSERM U830, conducted by Dr. Olivier DELATTRE, specialising in molecular biology of several childhood solid tumours. ▪ www.curie.fr
FORTH	▪ A state-of-the-art computation infrastructure: national node of HellasGrid, which in turn is linked to the EGEE. ▪ Innovative solutions in the domain of eScience and scientific workflows ▪ Development of a Master Ontology on Cancer, for the semantic integration of heterogeneous, multi-scale biomedical data. ▪ Analytical tools and computational infrastructures to support innovative bioinformatics research.	▪ Postgenomics technologies laboratory of the Institute of Molecular Biology and Biotechnology is equipped with state-of-the-art research facilities, including DNA micro array scanner, DNA micro array spotter, DNA micro array hybridization station, automated workstation for multiple biochemical reactions, Real Time PCR. ▪ www.forth.gr/
AIT	▪ eHealth ICT platform, ▪ Clinical e-Trial system inclusive DICOM compliant image archive, advanced image management ActiveX plug-in with PACS functionality, rapid prototyping environment, simulated deployment environment (virtual server cluster), mobile eHealth monitoring platform for electronic Patient Reported Outcomes (ePRO), Patient Identifier Cross Referencing (PIX)	▪ AIT is a government controlled non-profit and applied research & development organisation with leading roles in previous & on-going EU projects (SIOPEN-R-NET, CARE-MAN, RegIonCo) ▪ The eHealth research activities of the department focuses on biomedical and translational research issues addressing eTrial systems, telemedicine, bioinformatics, biosignal processing and knowledge-based systems. ▪ The Safety & Security Department has a long experience in the design, development and operation of ICT infrastructures – from rapid prototyping through feasibility studies to clinical trials and ICT applications

	implementation, HL7 gateway.	for daily clinical use ▪ www.arcs.ac.at/

Partner	Available resources	Research facilities and infrastructures
CINECA	▪ CTMS web system for the partners, which could be easily extended with additional modules to meet the global research tasks. ▪ Centralized, integrated system for managing, analyzing, reporting and reviewing clinical research information, from the development of the clinical protocol to cross-trial Clinical Data Warehouse.	▪ Cineca is a non profit Consortium, made up of 37 Italian universities, the National Institute of Oceanography and Experimental Geophysics, the National Research Council, and the Ministry of Education, University and Research. ▪ The largest Italian computing centre, ranked 46nd in the top 500 supercomputer site list, it operates in the technological transfer sector through high performance scientific computing, the management and development of networks and web based services, and the development of complex information systems for treating large amounts of data. ▪ The Health Care Systems Department has developed 190 systems (clinical trials and epidemiological registries) as of today gathering data of more than 250.000 patients across 25 years. 20 years experience in paediatric oncology RDE systems and data analysis, and collaborates with different research group, in Italy with (AIEOP: 64 studies, 3 registries, 35.000 patients), and abroad with Childhood Liver Tumours Strategy Group (SIOPEL: 3 protocols), International Research Consortium on childhood low grade glioma research (ICLGG: 1 protocol) , European Paediatric Soft Tissue Sarcoma Study Group (EpSSG: 3 protocols), international trials on Leukaemia (EsPhALL, Interfant). ▪ www.**cineca**.it/
ESQH	▪ Expertise in transfer of quality tools from industry to healthcare and establishment of a web-based knowledge base. ▪ Expertise in clinical trial management , contracts, confidentiality agreements, informed consent and concise pharmacovigilance reporting	▪ ESQH is a not-for-profit organisation dedicated to the improvement of quality in European healthcare. It consists of 21 members, all of whom are National Societies for Quality in Healthcare (Austria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Lithuania, Luxembourg, The Netherlands, Norway, Poland, Portugal, Spain, Sweden, Turkey, The UK, Egypt). ▪ The ESQH Project Management is run through a Liaison Office in Brussels. ▪ ESQH is already involved in two EU research projects (MARQuIS, SIMPATIE Project) ▪ www.**esqh**.net

Partner	Available resources	Research facilities and infrastructures
AMC	▪ TRC-Broad Institute lentiviral shRNA library of 160.000 vectors targeting 16.000 human and 16.000 mouse genes, in individual vector 96 well format. ▪ A tumour bank of >250 neuroblastomas, with normal DNA of patients and parents. ▪ Web-accessible bioinformatics storage and analysis tool, R2 analysis platform, including microarray data of >15.000 tumours, including for neuroblastoma expression microarray data, miRNA expression data, SNP data, CGH data and all clinical data for over 145 patients.	▪ The Academic Medical Center (AMC) in Amsterdam, the Netherlands, is a general academic hospital which integrates the Emma's Children's Hospital (EKZ), (largest paediatric oncology centre in the Netherlands, ~180 new patients/yr), offering phase I-III clinical trials. ▪ Research at the Human Genetics department is directed to identify the genes and signalling pathways that play a crucial role in paediatrics cancer. ▪ Bioinformatics infrastructure with 3 bioinformaticians, ongoing development of high throughput analyses for many tumour types studied in the ITCC-KCK network and neuroblastomas in the NRC consortium ▪ Facilities for lentivirally infected cell culture, a mouse facility, standard lab facilities like (ultra) centrifuges, DNA, RNA and protein work and micro-array analysis. ▪ www.amc.nl/
ICCCPO (ÖK)	▪ Experience of patient/parental organisation of participation in five EU projects: (EPOC & O3K, Paediatric Off Patent Medicines, CHILDHOPE: Chimaeric T-cells for the treatment of paediatric cancers, ITCC: Innovative Therapies for Children with Cancer,	▪ The "International Confederation of Childhood Cancer Parent Organisations" provides access to an international network of childhood cancer parents' organisations to build better links between parents and health care professionals. ▪ Creates opportunities to improve access to advances in the treatment and care and information on the diseases and treatment including clinical trials. ▪ www.**ICCCPO (ÖK)**.org/
CLB	▪ Expertise in successful electronic health record linkage and remote record accessibility ▪ French Chief investigator for Wilms and soft tissue sarcomas	▪ Comprehensive cancer centre that includes basic, translational and clinical research. ▪ Large clinical activity in childhood and adolescent cancers. Facilities for early and late phase clinical trials ▪ www.lyon.fnclcc.fr/
IARC	Access to European-level population based cancer registry data in a standardised, quality-comparable format through the EU-supported ACCIS project Pre-existing educational courses on cancer registration processes – can be adapted for specific needs of paediatric cancers. Expertise in the development of standards for data collection, coding and quality evaluation Computer equipment for storage and management of expanded database as well as software to enable efficient and secure on-line networking.	▪ IARC has the necessary teams and infrastructure to describe the burden of cancer worldwide and, in co-operation with cancer registries, to monitor geographical variations and trends over time, including in populations of children and adolescents ▪ European project "Automated Childhood Cancer Information System" (ACCIS), coordinated by IARC, ▪ www.**iarc**.fr/

Partner	Available resources	Research facilities and infrastructures
UNIPD	▪ Established collaboration between clinical paediatric oncology and CINECA ▪ Broad spectrum of translational research activities on leukemias, sarcomas, lymphomas. ▪ Large leukaemia sample repository with more than 5,000 specimens and hundreds of genome-wide microarray data	▪ The AOP-HOD is a clinical, research and teaching Institution and is part of the University Hospital of Padova and represents the reference centre for paediatrics oncology in the north-east region of Italy. ▪ Coordinating centre for the national protocol for paediatrics soft tissue sarcoma, lymphoma, very rare tumours and some CNS tumours. ▪ Leader of the European paediatric Soft tissue sarcoma Study Group (EpSSG) hosting the coordinating and data collection centre. ▪ The Department of Paediatrics serves as a central leukaemia diagnostics facility in Italy and hosts cutting-edge diagnostic and state-of-the-art research facilities, including flow cytometers, cell sorter, DNA microarray scanner, DNA micro array hybridization station, Real Time PCR, etc ▪ www.unipd.it
LUMC	▪ Array CGH technology, automated "tissue micro array" marker, slide scanner, CoBRA FISH, Tissue banking, Expression array, Cloning facilities ▪ Bone tumour pathology expertise	▪ Childhood cancer clinical research centre ▪ Research and clinical expertise in novel therapies, especially bone tumours. ▪ Access to research infrastructure of EUROBONET through coordinator based in LUMC ▪ www.**lumc**.nl/
KI	▪ Well equipped lab ▪ Modern techniques and well characterised specimens ▪ In vivo models for human cancer cells ▪ Unique experience in Lipidomics and metabolomics	▪ Long experience in transnational studies, clinical studies and biological characterisation of novel therapeutic targets. ▪ Close link to the clinical unit and international networks. www.info.ki.se
UGent	▪ Robots for handling high-throughput DNA handling, quantitative real-time PCR, data acquisition and normalization ▪ Next generation sequencing technology ▪ Significant experience in the –omics field, including genomic, trancriptomic and epigenetic analyses	▪ The University of Ghent is a non-profit organisation who is actively involved in the education of students, the performance of basic and translational scientific research and also offers scientific advice to third parties. ▪ The Department of Medical Genetics Ghent, is responsible for the cytogenetic and molecular work-up of constitutional genetic disorders and cancers. ▪ www.u**gent**.be/
CHARITE	▪ Cutting-edge leukaemia diagnostics including immunophenotyping, MRD analyses, gene expression profiling. ▪ Preclinical models. ▪ Infrastructure to sponsor and conduct national and international clinical trials according to GCP on an academic level.	▪ Charité Campus Virchow Klinikum is one of the four campuses of Charite Berlin, the largest university medical centre in Germany. It hosts the IntReALL coordinating centre, a consortium of all European and some non-European relevant study groups on treatment of childhood relapsed ALL, based on the Resistant Disease Committee of the I-BFM SG. ▪ A biologic committee organizes the routine and reference diagnostics as well as translational research with a rational distribution of patient material. ▪ IntReALL forms the largest study group on relapsed refractory childhood ALL worldwide and coordinates investigation of drugs in specific subgroups such as T-ALL, or CD19 positive B-cell precursor ALL. ▪ www.charite.de/en/charite/.../**campus_virchowklinikum**_cvk/

Partner	Available resources	Research facilities and infrastructures
AP-HP	▪ Full facilities for molecular analysis of minimal residual disease in leukaemia, including large cell banks. ▪ All facilities for translational research in leukaemia and lymphomas	▪ University Hospital incorporating very large paediatric oncology centre for treatment of and research into leukaemia and lymphomas. Treats 250 new patients/yr, high level expertise in stem cell transplantation, innovative therapies and pharmacokinetic studies. Phase I-III clinical trials ▪ **http://robertdebre**paris.AP-HP.fr/
OLGA	▪ Project Lead of the European and American Osteosarcoma Study EURAMOS1 within the European Science Foundation´s Pan European Clinical Trials European Collaborative Research Scheme (ECT-EUROCORES). Prof Bielack is also president of the European Musculo-Skeletal Oncology Society EMSOS	▪ Klinikum Stuttgart is a consortium of four tertiary case hospitals with a department of paediatric oncology, haematology and immunology, one of the largest paediatric oncology centres in Germany. ▪ Home to the study centres of German Cooperative Soft Tissue and Osteosarcoma Groups (CWS and COSS) ▪ .host to the Cooperative Osteosarcoma Study Group COSS and the Cooperative Weichteilsarkomstudiengruppe CWS, both with three decades of successful multinational clinical trial organisation, implementation, and completion. With this background, we have ample experience in organizing international collaboration within a multidisciplinary framework, including with the USA and also access to the relevant clinical trial networks. ▪ www.**klinikum-stuttgart**.de/
WWU	▪ Research (BMBF) and also a BMBF Bone Tumor late follow up project are being conducted and coordinated in Muenster. • Major research focus in bone tumors. • Headquarter of the European Bone sarcoma studies TranSaRNet, ▪ Translational sarcoma research network of the German Federal Ministry of Education and	• The Department is the largest Pediatric Hematology and Oncology Center in Germany ▪ the top ranking fundamental research (no.1 in North Rhine Westfalia)
ECCO	▪ EU communications officer ▪ Communication and dissemination web platform ▪ E-learning ▪ Congress organisation	▪ Forum for dialogue with all European cancer society's to enhance research collaboration and identification of mutually beneficial research resources. ▪ Representation of cancer issues at a European level ▪ www.ecco.eu
SOUT HAMPTON	▪ Research and Innovation service ▪ Contract negotiation, spin-outs, licensing, IP, funding opportunities ▪ Business communication	▪ International university drawing students from over 100 different countries ▪ Provides very strong environment for collaborative research enhanced by close cross disiplincay links between te academic schools

Table 13: Integration of materials and equipment

B.3 Impact

B.3.1 Strategic impact

The European **N**etwork of **C**ancer research in **C**hildren and **A**dolescents (ENCCA) is a European 'Network of Excellence' comprising **33 partners including 27 eminent Paediatric Oncology Academic Institutions and ECCO** (the European Cancer Organisation) that will bring together the existing **informal Clinical Research Groups in Paediatric and Adolescent Oncology** towards a '**European Virtual Institute'** to reduce knowledge fragmentation and enhance the communication, collaboration and management of effective clinical research in child and adolescent cancer in Europe. A high coordination of clinical research in Europe will be established through the creation of the **European Clinical research Council in paediatric and Adolescent oncology** comprising the Chair of each European disease groups running clinical research in paediatric malignancies in Europe. The strong links between the Council and ENCCA Networking will permit to address the needs of all the current multinational clinical trial groups and to advance towards a more integrated and cost efficient clinical research in Europe.

It is expected to **restructure knowledge-sharing** through the integration of the whole chain of stakeholders (epidemiologists, imaging developers, biologists, clinicians, drug developers, industry, patient and parent groups, policymakers and ethical bodies) and to support the **acceleration of the development of innovative targeted drugs and biology-driven risk-adapted therapeutic strategies** for children and adolescents. This would in turn provide a great improvement in the **services** available for children and young people suffering from the burden of cancer in Europe and potentially encourage **interest in scientific and clinical careers** by young European students. In addition, it will also contribute to ameliorated standards of care and quality of life for our young patients and their families. Links with Industry need to be established and strengthened.

All these goals will be achieved by a **new integrated strategy** to bring all stakeholders to the table in a timely and efficacious manner. ENCCA will provide them with common tools and approaches to solve the bottlenecks in testing new therapeutic strategies for what are rare diseases in a vulnerable age group. ENCCA will be led by the most active research institutes in the field in Europe, recognised as being at the forefront of excellence.

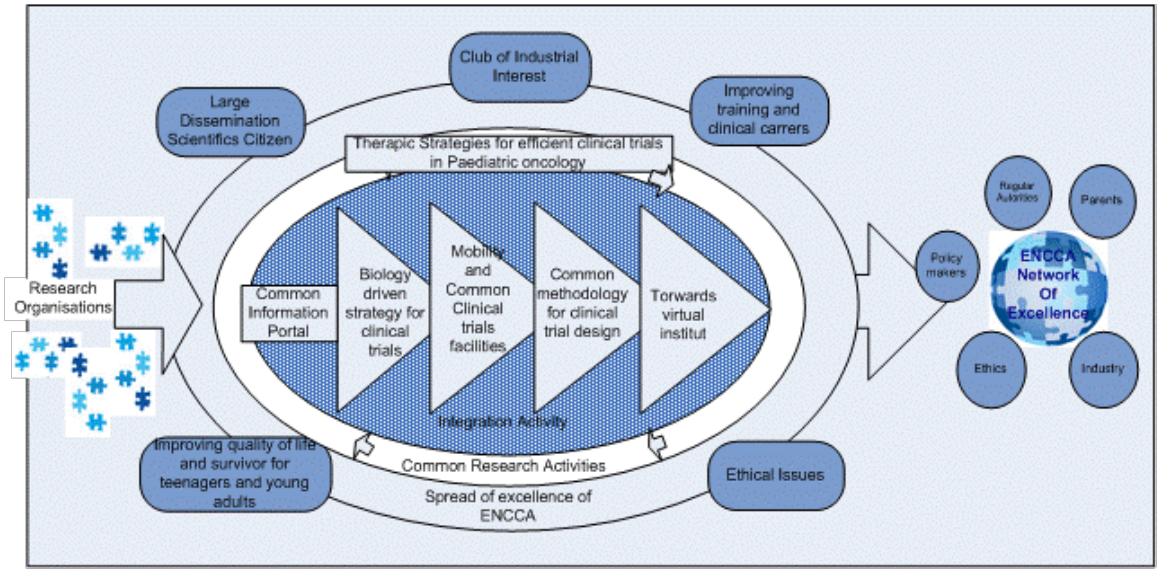


Figure 12: Integration of activities towards a virtual Institute within ENCCA project

Listed impact requested in the work programme	Expected impact of the project
Integration of a large number of informal investigator-driven research networks in paediatric and adolescent oncology	ENCCA will associate 34 partners including 27 Internationally recognised European Institutions in Paediatric and Adolescent oncology clinical research and a high number of associated institutions in A virtual open Network of excellence with the common aim to integrate durable the whole chain of stakeholders and accelerate drug development and care quality of children with cancer. Moreover a high coordination of existing tumour groups will be realised by the creation of European Clinical Research Council in Paediatric Oncology. This Council will permit a common political visions of address common issues as well as facilitate access to the mutual equipment and make research more efficient towards a long term integration of European research Area
Improve patient care and access to tailored medicine	New harmonised therapeutic strategies will be implemented thanks to ENCCA and will permit to accelerate new generation of biologically targeted drugs. Improved Referral schemes also will be implemented in EU in order to facilitate access to high quality care for children and adolescents with cancer
Structure European scientific excellence in paediatric and adolescent oncology	ENCCA is expected to create a new sustainable legal structure dedicated to paediatric oncology clinical research able to manage and coordinate clinical research in Europe and to create mechanisms for financing its own organisation but also to clinical trials for children and adolescents with cancer. This new Virtual Institute will permit to spread European scientific excellence in this area and attract young researchers for all over the world in European laboratories

Table 14: Expected impact of the project

B.3.1.1 Overcoming fragmentation towards a high integrated clinical research and education in paediatric oncology

Networking and European integration of the resources, facilities and knowledge at the different levels is required to bridge the gaps identified in this area. The proposal for a European Network for the advancement of children's cancer therapy is an important step forward in order to mobilise the efforts and expertises required. As the total number of cases of most types of childhood cancer is less than 100 per year in the average European country, such a multinational collaboration will then permit, and is the only way, to carry out successful clinical trials that will address the needs of children and introduce safe and effective targeted therapies in stand care..
There are many parallel activities in paediatric oncology, and ENCCA will enable them to be better coordinated. This will strengthen the European political position in improving care for children with cancer, and will also increase the optimal use of resources available for this area of medicine and spread the excellence of European research.

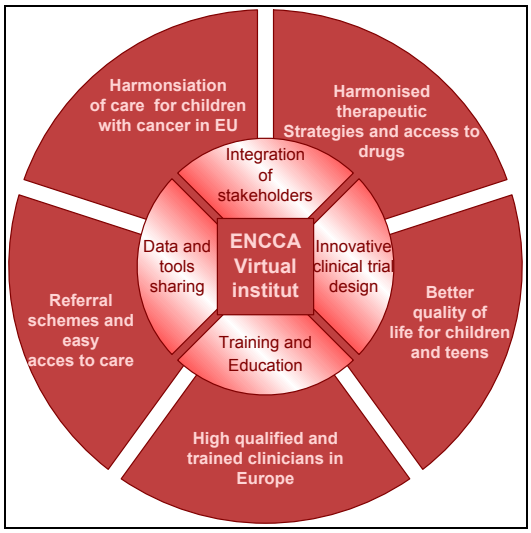


Figure 13: Towards the ENCCA Virtual Institute and fragmentation reduction in clinical and translational research in paediatric and adolescent oncology

The creation of this network of excellence will allow to reinforce liaisons and communication among the different pre-existing tumour and leukaemia groups in Europe through a Clinical Research Council in Europe in paediatric and adolescent oncology Through this new organisation and ENCCA NoE a more collaborating research and access to mutual equipment and personnel will be realised allowing a more efficient and safe clinical research and better care for children with cancer. Moreover ENCCA will bring together these European clinical groups and networks running early drug development and biology toward an increased collaboration.
The strengthening of the existing EU network for clinical research in paediatric oncology will guaranty that drug development will be performed in a timely fashion.

The development of the common patient's stratification will allow the coordination of testing of various therapeutic hypotheses in similar populations. Furthermore, the improved exchange of information on trials design, especially in the field of phase I and II trials on new agents will allow avoiding the research duplication and a more rapid selection of potentially interesting agents.
Moreover, the ENCCA NoE will permit to establish a stronger link between the biological knowledge and the clinical research, by bridging together internationally recognised research labs dedicating their activity to paediatric malignancies with the clinical centres running clinical trials.
ENCCA will also reinforce the link with the whole chain of stakeholders (clinicians, biologists, regulators, industrials, policy makers, parents/patients) by improving representation of all in ENCCA.
Another point in reducing fragmentation is that ENCCA will help to establish common definitions in the field of clinical trials, in order to improve the efficiency of the trials and to establish new standards of care. Indeed, the definition of an interventional clinical trial is being harmonised between the different member states of the EU through the ESF report while the definition of an investigational medicinal product (IMP) needs to be carefully address to allow the development of these IDCT.
Moreover, the network will contribute to reduce the still important differences in health care organisation between member's states, thereby reducing the inequity of access to care for children

across Europe, as well as the cultural differences in the field of ethics in between European member states. The network will liaise with the Council. This will be the first time that there is a European infrastructure for paediatric and adolescent cancer research activities, with the capacity to address the many common issues that cannot be solved by each group working in isolation. The results of such research, which will be increasingly diffused through the communication activities of the network, will at the end lead to an increased efficiency of childhood cancer treatment.

ENCCA will provide a new common **training and clinician's education strategy for European paediatric oncology research**, in particular with a reinforced specific training program for paediatric oncologists as a well-defined paediatric sub-speciality that is expected the reference in Europe. This will allow multi-disciplinary and multi-professional training of the clinical investigators of the future, to spread excellence in care. The network will thus build up **the best specialist's clinicians and good European careers to treat children cancer and will stop the clinician movement to US for better careers.**

ENCCA will also allow improve the **outcomes for adolescent's cancer**. This will permit to improve the important gaps in the knowledge of this particular population of patients, and to promote an increasing expertise in health professionals towards these issues.

B.3.1.2 Impact on research excellence

The strength of this programme is that it will coordinate clinical research and training in a European context of collaboration. The programme will involve already settled contacts with all stakeholders in the field of paediatric oncology in a broad transeuropean and international perspective. Indeed, all the groups and partner institutions are used to work together as illustrated by accomplished clinical trials and publications. With its intellectual excellence, broad expertise and capacity to establish reference platforms and standards, the ENCCA consortium will contribute to achieving durable integration in the European Research Area and fostering European competitiveness and excellence. It will dramatically increase the critical mass of expertise and capacity.

The joining of research efforts, as well as the sharing of data, and the mutual access to equipment, material and tools, will undoubtedly lead to a better and more efficient research as well as **better standards and protocols for children's cancer treatment**.

For example, **several clinical trials** have been planned together in the joint research programs (see also examples in **Tab. 3** for more details as well as **WP7, WP8 to WP12**). They represent the paradigms of the challenges to be overcome and the approaches needed to do so, and will demonstrate the proof of principle of the research activity. They should bring the short and long term impacts listed in the following chart, and thereby prove the **increased research capacities** brought by the ENCCA network.

Associated Work Package	Current Weakness and/or technological barriers to overcome	Main innovative scientific/technical partial outcomes of the project (methods, products, software, modelling)	Short and Long term impacts (new knowledge, new development opportunities, new applications, etc.)
WP 8 Early evaluation and prioritisation of new anticancer drugs	Insufficient access to relevant compounds in development. Insufficient contacts with Pharmaceutical companies which still perform most of their early phase clinical studies outside Europe	Access to new compounds will be enabled by reinforced contact with biology and industry A strategy for new drug development will be established and discussed with EMA and PDCO in order to meet the needs of children when developing Paediatric Investigation Plans	Clinical trials run with four new drugs will demonstrate the proof of principle of this WP for further dissemination to other clinical trials. The number of accessible innovative drugs for children will be increased in Europe
WP 9 Risk adaptation of therapeutic strategies using predictive biomarkers in leukemias	There is a need to further introduce biology knowledge in setting-up risk adapted therapeutic strategies based on predictive biomarkers, in the treatment of acute and chronic leukemias.	Early identification of adequate target populations for experimental treatment Development of standardised diagnostic approaches, bio banking, of a common molecular diagnostic pipeline. Development of algorithms for identification of molecular targets based on biological data	Identification of the most promising molecularly targeted treatments in preclinical model systems Clinical testing of molecularly targeted treatment strategies, to prove their direct benefit to the paediatric patient population
WP 10 Risk adaptation of therapeutic strategies using prognosis biomarkers in solid tumours	Prognostic biomarkers are used for only a limited number of malignant solid tumours Treatments have severe side effects, and there is a need to fine-tune therapeutic strategies to lower morbidity and toxicity in patients with a low-risk tumour	Implementation of risk-adapted therapies Use of tumour molecular portraits as a prognostic biomarker Assess molecular diagnostics as prognostic biomarkers	Identification of patients who will benefit from new drugs. Identification of patients that will benefit for decreasing intensity of treatment and avoid late effects.
WP 11 Prospective clinical registries of outcomes of patients on standardised protocols	Lack of prospective clinical epidemiology data on outcomes for children treated for a good prognostic tumour with standard protocols. Inequalities between different member states in terms of regulations to implement these prospective studies Lack of appropriate frame for systematic collection of biological samples.	Collection of data obtained with standard treatments (histology/imaging/biology, toxicity, relapse, cause of death) Implementation of record linkage procedures to administrative and clinical data for follow-up Implementation of data collection using an IT- platform	Establishment of methods for continuously evaluating the success of first lines therapies Improvement of the quality of care for children Increasing survival rates across Europe and dissemination of high quality standard of care Establishment of an important resource for clinical epidemiology studies.
WP 12 Clinical research in very rare tumours	Clinical research is extremely difficult to perform in very rare paediatric malignancies. Children suffering from these very rare diseases are denied access to innovative therapies. Moreover, there is an excessive defragmentation of patients subsets and a lack of coordinated clinical research approach.	Development of a model for organising care and structuring clinical research in a very rare cancer in children Strengthening the cooperation at the international level.	Generation of new knowledge in the field of rare malignant liver tumours Harmonisation of international clinical research efforts Dissemination of the model to other very rare paediatric malignancies in the various EU-disease groups.

Associated Work Package	Current Weakness and/or technological barriers to overcome	Main innovative scientific/technical partial outcomes of the project (methods, products, software, modelling)	Short and Long term impacts (new knowledge, new development opportunities, new applications, etc.)
WP 13 Quality of survivorship	Information on quality of survivorship in children with very rare diseases is difficult to have because of the little number of cases. A Psychological test need to be validated in different European countries/languages Guidelines on appropriate long-term follow-up are not available through Europe. After treatment completion, most childhood cancer survivors do not receive detailed documentation on treatment received. If they do, this is often on paper and not properly stored. This information might be very important later in life if any treatment related complication might occur and the long-term survivors is no more in contact with the paediatric clinic. Childhood cancer survivors may be affected by severe chronic health conditions that might occur late in life. Advice and guidance on long-term follow-up should be available to health care providers	An on-line package of questionnaires and direct on-line assessments will be developed, based on a new application of an existing secure, user-friendly on-line software system for delivery of low-burden assessments via personal computers. Application of this on-line package to assess QoS in survivors of three European studies of medulloblastoma. Linkage of the QoS information to baseline and therapy information. A bank of salivary DNA from participants in the above studies, all of whom have received CSI.Definition of minimal requirements to be included in "treatment abstracts" will be defined and methods for storage on electronic format will be implemented A "passport to survivorship" with treatment information and guidance for follow-up based on guidelines, available in an electronic format will be tested to be available to survivors and their health care providers	Availability of the QoS on-line assessment package to support low cost 'off the shelf' studies of QoS in other types of childhood CNS and non-CNS tumours. Information to inform tailoring of therapy according to individual susceptibility to late effects of CSI and other treatments. A means of identifying survivors with specific neuro-cognitive deficits that would be eligible for European intervention studies (e.g. drug or cognitive behavioural therapy for deficits of memory or executive function). Empowerment of survivors and their families by providing them with a systematic valid assessment of QoS to support them in accessing beneficial interventions and supportive care and in returning to normal life. Childhood cancer survivors will have a life-long available detailed information on cumulative doses of chem/radio therapy or surgery received. This will allow more accurate diagnoses and follow-up to health care givers, even when survivors will become adults.

Table 15: Impact on research excellence

B.3.1.3 Impact on durable integration towards building on ERA structure

ENCCA Network of excellence will substantially contribute to achieving the **European Research Area (ERA)** (COM (2000)6), as requested by the Lisbon European Council in March 2000. Indeed, ENCCA will implement a new "European Network of Excellence" that will gather centres specialised in paediatric oncology clinical trials able to promote European excellence and obtain high performances in children cancer therapy. This initiative will allow for a better use of therapy and research resources and facilities by sharing and using their potential in an optimum way.

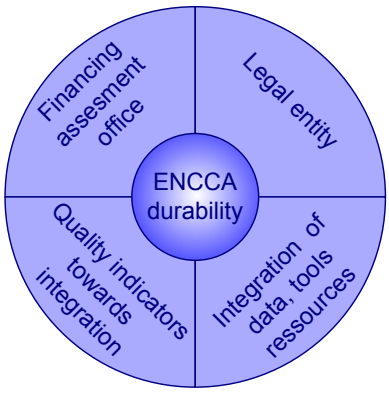


Figure 14: ENCCA mechanisms for a durable integration of Paediatric Oncology

The management of the funds obtained for this four years lasting project will eventually lead to the creation of a strong and sustainable structure. Indeed, to prepare the financial autonomy of the network, a **financing option assessment office** will be created. The objective of this office is to identify and structure the financial resources of the network and to provide the necessary funds for the future clinical trials.

The network will consider the creation of a **new legal entity** to provide a strong and durable structure able to efficiently manage the network activities, which will undoubtedly ensure a lasting integration.

Moreover, the establishment of a quality survey system within the network, with **quality indicators directed toward integration**, will also contribute to build a long-lasting structure.

The integration of resources (people and equipment) will also lead to a higher collaboration of organisations creating the condition for a sustainable integration. ENCCA will promote the mobility of clinicians in Europe. A successful project will contribute to increasing young people's awareness of the possibilities for pursuing high quality medical and scientific career in Europe and attracting clinicians from the rest of the world. This will be also an important contribution of ENCCA in a long term improvement of the education and training programmes in paediatric oncology clinical research.

B.3.1.4 Impact on European policies

B.3.1.4.1 European Health Policy and Strategy

ENCCA will contribute to supporting the **programme of community action in the field of public health** (decision No 1350/2007/EC). In fact, through the harmonisation of clinical trials and protocols in paediatric oncology, and through dissemination activities, education and training, and transfer to industry, this project will improve information and knowledge in this domain. This will permit to promote public health and health systems actions. By the way, this project will address key health priorities, aiming at reducing the high number of premature deaths caused by infant cancer.

B.3.1.4.2 The new strategic approach for health in EU

ENCCA will fit with **the new strategic approach to health for the EU (2008-2013)** (COM (2007) 630). Indeed, it will allow reducing inequalities by establishing the best common standards of care for children with cancer between the different member states, and will promote patient's right and advocacy by developing a deep work on ethical issues. Furthermore, ENCCA will dispose of the best scientific skills and expertise to structure the paediatric oncology field in Europe.

B.3.1.4.3The Clinical Trials Directive 2001/20/EC (EU CTD)

With its strengthened organisation and effectiveness, ENCCA will contribute to efficient clinical trials despite of the difficulties provided by the new clinical trials directive. Notably, it will make possible to overcome the problems of slowing of clinical trials, increasing in the cost of academic cancer trials, administrative burden, and requirement of sponsor. ENCCA will cooperate with ECRIN and contribute to the ongoing process to facilitate the implementation of Investigator-led clinical research in Europe.

B.3.1.4.4 European e-Health Area

By the establishment of an integrated communication platform, ENCCA will significantly contribute to the **European e-Health Area** (COM (2004) 356). Indeed, it will create a virtual institute information portal, allowing a better communication between paediatric oncology institutes, clinicians and patients, and a staff e-mobility centre.

B.3.1.4.5 Medicinal products for paediatric use (COM (2004) 599)

The paediatric population is a vulnerable group with developmental, physiological and psychological differences from adults which makes age and development related research of medicines particularly important. In contrast to the situation in adults, pharmaceutical companies were not committed to develop their drugs in the paediatric population and the medicines used to treat children's and adolescent's cancer have essentially been tested in the paediatric population by academia groups but are not authorised for use in children: the health and therefore quality of life of the children of Europe may suffer from a lack of testing and authorisation of medicines for their use. Clinical trials to establish valid safety are of crucial importance. In order to address concerns about the trials in children, the EU directive on clinical trials lays down specific requirement to protect children who take part in clinical trials in the EU.
ENCCA will facilitate the implementation of the EU Paediatric Medicines regulation through an increased collaboration with both EMA and the Pharmaceutical Company. ENCCA will significantly contribute to the design and development of Paediatric investigation plans that will meet the needs of children with cancer.

B.3.1.4.6 European Partnership for Action against Cancer

ENCCA will also take part to this European initiative proposed by the European Commission for the period 2009-2013 (COM (2009) 291). Indeed, it will allow to reduce the disparity between the best and worst performing member states in the fight against cancer, as well as to develop guidelines for models of best practice in children cancer.

B.3.1.4.7 Regulation of orphan medicinal products

The European joint efforts, together with the **European regulation** (EC No 141/2000) on **orphan medicinal products** and the set-up of market exclusivity, now enable European pharmaceutical companies to overcome the high risk of development and the problems of the low number of people affected with rare paediatric cancers by granting exclusive marketing rights for a ten-year period.

This will allow a greater contribution of the industry in the development of new anticancer drugs for children, as they will be involved in this process with the WP 2.1 of the ENCCA project, "early evaluation and prioritisation of new anticancer drugs". Indeed, each paediatric malignancy is a rare disease, according to the European definition, i.e. a prevalence less than 1 in 2000.

B.3.1.5 European Competitiveness and Scientific Knowledge Excellence

Europe publishes about the same **(about 1000 papers** for the 2005-2008**)** as the US/Canada**.** However **access** for children to **innovative compounds developed for adults** by pharmaceutical companies has been **extremely poor in Europe** in the last 20 years. This is in contrast to the USA, where many programmes have provided easier access to new compounds to the **paediatric oncology community**.

- ENCCA will enable to overcome the European fragmentation and bottlenecks presented in European research and allow the close collaboration of existing clinical groups and the whole chain of stakeholders in Europe tin order to provide easier and faster new drugs and therapies for children with cancer.
- ENCCA will be able to improve scientific position of Europe and competitiveness on scientific knowledge and transfer at international level, in particular comparing with **USA/Canada** and the rest of the World. This will permit Europe to maintain a high position in scientific and technological knowledge. Moreover ENCCA and the initiatives that will be taken will be able to improve the collaboration with industry and the percentage research outputs coming from the industry that represents only 0.25% of the research output supported by industry in paediatric oncology
- ENCCA will address key health priorities that are finally able to provide new drug development at reducing the high number of premature deaths caused by infant cancer improving also the Scientific Excellence of Europe.

B.3.1.6 Impact on social EU objectives

B.3.1.6.1 Impact on Quality of life, Health and safety

ENCCA will have a direct impact on the quality of life of the young European population.. As its shown in the table 16 the number of deaths for different type of tumour types remains important. This situation is expected to change substantially with the ENCCA integrated approach in paediatric oncology clinical research.

	Age at diagnosis (years)		
Diagnostic group	**0-14**	**15-19**	**20-24**
Leukaemias	3 700	700	600
Lymphomas	1 700	1 100	1 900
Brain tumours	2 660	635	500
Neuroblastoma	700	40	
Retinoblastoma	330		
Renal tumours (Wilms)	640	30	
Liver tumours (Hepatoblastoma)	100	30	
Bone tumours	440	500	350
Soft Tissue sarcomas	800	350	240
Germ cell tumours	380	750	1500
Epithelial (incl. Melanoma)	380	800	2800
Other	75	50	90
Total (approximate)	**12 000**	**5 000**	**8 000**

Table 16: Number of cases and deaths per type of tumour for children, adolescents and young adults*
*Adapted approximately for the EU of 27 from: Gatta G et al, Survival of European Children and Adolescents with Cancer diagnosed 1995-2002. (EUROCARE 4 study) European J Cancer (2009)

By setting up better pathways of care, promoting healthy behaviour in the young person and by increasing patients / parents access to information and advocacy, ENCCA will significantly contribute substantially in reduction of deaths and side effects for children and adolescent suffering from cancer. ENCCA will improve time diagnosis for children and adolescent cancer, access to clinical trials, pathways of care, and will also provide new drugs to set up better and more targeted therapies.
Therefore, it will have a considerable impact on health and safety for children and adolescent with cancer. The integrated approach proposed by ENCCA will greatly contribute to facilitating and reorganising the skills and facilities associated with clinical research. It will be performed through better structuring the training in paediatric oncology clinical research in Europe and improving sharing of data as well analysing and reporting general data. Introduction of new harmonised therapeutic strategies will also permit a high quality of care in Europe with lower inequalities. In terms, ENCCA will increase the likelihood that adults who are or will be survivors of a paediatric malignancy will have no late –effects of their treatment and will contribute to the socio-economic development of Europe.

B.3.1.6.2 Employment, working conditions and safety

ENCCA is expected to provide new knowledge, hence allowing defining new standards that will reinforce the implementation of new medical practices, and will promote the mobility of medical and clinical staff in order to increase knowledge sharing and skills. Additionally, ENCCA will establish a link between academic and industrialists able to stimulate and ensure career opportunities. The world leadership in paediatric oncology clinical development that the project will generate, will definitely attract young physicians from all over the world to come in Europe. In addition, the high-level training activities to be implemented within ENCCA will generate **highly–skilled groups of clinicians**, able to provide Europe with expertise through the different platforms and improve competitiveness and excellence of the European health care system. ENCCA will also greatly contribute to developing safe working conditions. Indeed, the quality of products will be ensured through the whole clinical trial process, from “bench to bed”. Standardisation of clinical trials will integrate the precautionary principle on bio safety as defined in the Cartagena Protocol. Moreover, by avoiding the administrative burden related to clinical trials thanks to simplification of procedures, ENCCA will improve the working conditions for clinicians, thus allowing them to concentrate mostly on children care.

B.3.1.6.3 Education and training

At present, personnel running clinical trials are not subjected to any kind of specific training and there is an increasing need to overcome this lack. ENCCA will allow recognition of Paediatric Oncology as a well-defined Paediatric sub-speciality by implementing European standards of quality identified by a specific European label. It will define and implement a **European Paediatric Oncology Educational and Training Programme**, with training courses for interns and post-graduates, as well as training for technicians / clinicians on new protocols and standards for clinical trials in paediatric oncology. Furthermore, e-learning methods will be utilised for a better, faster and more efficient training and higher impact in EU. Specific training programs will be utilised for countries who wish to establish structures for population-based cancer registration. ENCCA will increase mobility across Europe via a Mobility Center able to facilitate the exchanges among European countries and accelerate clinician careers through better and diversified training and experiences, Different exchange programs and geographically organised workshops will be also organised that will permit improvement of clinician competencies in local/regional level.
Moreover exchanges with industry will permit to multiply the experiences of academic staff and permit interaction with industrials towards an acceleration of new drug development for children with cancer. A great opportunity will be offered to 17 PhD and Post-doctoral degree in paediatric oncology clinical development process. ENCCA Is finally expected to increase career opportunities in biomedical sciences and clinical research hence making Europe more attractive to young graduates and researchers from all over the world.

B.3.1.6.4 Citizen awareness

To increase citizen awareness on the needs for clinical research in children and on the societal impacts of ENCCA network, this project will communicate within an open large audience on paediatric oncology clinical trials and paediatric tumours treatments by revealing the physical and social difficulties encountered by the patients, and will publish the aim of the ENCCA network to overcome patient's condition. The network will collect data and produce material to be used and submitted to citizens, such as science-oriented articles, overheads, and web-pages. It will also develop and disseminate new teaching tools, and organize events aimed at establishing the dialogue with citizen. Moreover, other initiatives will be initiated such as multilateral debates involving experts, sceptics, industry representative, policy makers and citizens.

ENCCA will also identify and quantify patients' concerns and expectations in terms of new therapeutic technologies, and inform patients and their organisations about the actions taken by the Network.

ENCCA is expected to foster the dialogue between scientists and citizens. In addition efforts will be made to strengthen education in Bio-Ethics in order to help the society become more ethically aware and make appropriate decisions, in particular considering the balance between benefits and risks.

B.3.1.6.5 Gender equality

It was widely recognised that a transition to a both gender-balanced and gender-sensitive organisation is needed to promote gender integration into research. It is worth pointing out that the **ENCCA NoEM and 5 WP leaders** in the proposed NoE structure are women. Moreover gender indicators will be created in order to measure progress toward s gender equality. ENCCA will promote gender equality in employment and participation of women in high level work positions and more generally in sciences.

B.3.1.7 Contribution to standards

ENCCA will ensure that all **quality and safety measures** established within the European Union are applied during the project. It will also contribute to the development of **protocols and guidelines** at the different phases of the project (pre-clinical and clinical phases). Among others, guidelines will be developed for efficient access in common facilities, for the analysis of safety data, and for validating risk groups stratification. Moreover, guidelines will be developed with EMA for the development of clinical and preclinical paediatric investigations plans in oncology. In order to follow the outcomes of the survivors, a data base template for storage of each survivor's medical history will be generated, as well as a template for end-of-therapy guidance for long-term follow-up. A 'passport' report of therapy and outcome data useable for individual survivors will be implemented.

In order to contribute to their inter-operability, the ENCCA partners will largely participate in the **definition and implementation of standards** for clinical trials by defining the pathway towards standard clinical protocols that will allow regulators to have all the data needed for standardisation. Standard templates for clinical trials developed through the WP 1.3 will enable facilitation of trials procedures. Moreover, the WP 1.5 will bring specific protocols for clinical trials, and methods of trial design for clinical research in very rare diseases.

In order to improve experimental protocols, ENCCA will increase the **level of standardisation and harmonisation in data collection and analysis procedures**, which in turn, will facilitate the compilation of data from different centres into the same analysis. This is particularly useful for diseases where patients are rare and disseminated throughout Europe. **Databases** on the different kinds of information (biology, epidemiology, imaging, patient's outcomes…) will be linked and established, as well as guidelines for data completion.

Common guidelines will be generated for several scientific and clinical purposes such as diagnostic approaches to specific tumours; target validation in preclinical model systems for molecular targeted treatments; image-defined-factors collections; collection and storage of biological material, bio banking; molecular diagnostics; minimal standards datasets for data collection of patients receiving standard treatments; minimal essential long-term follow-up of patients. Biology and integrated bio banking will be set-up and harmonised, and data sharing will be structured.

- ENCCA will define and / or upgrade **Standard Operating Procedures (SOPs)** on clinical trial design, data collection and storage in order to have a common point of reference across the multiple possible platforms used by the paediatric oncology community; wherever available existing internationally community standards will be used.

- ENCCA will also oversee the implementation of **Good Clinical Practices (GCP)** for paediatric clinical trials and common **ethical guidelines for clinicians,** notably regarding the involvement of children in clinical trials.

- ENCCA will also establish and disseminate successful **referral schemes**, in order to provide patients an access to expert centres and networks of care for standard care.

Finally new common standards in **EU education** will be established for the recognition of paediatric Oncology as a well defined Paediatric sub-speciality. A list of qualified training centres that fulfil the EUMS standards for training in paediatric oncology will be generated, and a uniform high standards of courses addressing the needs of paediatric oncology will be established. By this way, a **common programme for EU training** will permit to keep a high quality of clinicians in Europe.

B.3.2. Plan for the use and dissemination of foreground

B.3.2.1 Spreading of excellence and dissemination plan

B.3.2.1.1 Dissemination

In order to ensure a highly efficient dissemination of scientific information at European level, the ENCCA consortium will create and carry out key communication actions (WP 3.1) in order to examine and perform the best way to promote the project‘s results. To raise scientific and public awareness on ENCCA science, technology and clinical research progress, systematic public information will be disseminated through numerous communication channels, such as, through an innovative and interactive website dedicated to ENCCA dissemination, workshops, education and teaching tools and public debates and seminars.

The ENCCA consortium, as listed below, will participate in a wide range of national, European and international events for the development and **exchange of ambitious and interactive outcomes on paediatric oncology research**. An exchange forum (including an on-line forum) will be created in a coordinated fashion, taking into account the latest innovative audio-visual tools.

Comprehensive scientific information about the ENCCA project disseminated to a wide audience is already being carried out by many of the partners and will be more widely exploited through greater exchanges between the different organisations of the consortium, utilising ENCCA expertise and key contacts.

According to the ENCCA activities specific, focused and targeted attention will be paid to communication with the public and patient/parent organisations, through several communication channels such as conferences, seminars, networking events and interdisciplinary partner workshops, aware always that a patient-focused perspective is the best strategy to proceed, be successful and ensure a sustainable network.

- **Internal dissemination**

  The ENCCA infrastructure aims at guaranteeing that all the partners are informed about the progress and activity outcomes, network-planning and all other issues which ensure well-informed and well-briefed partners. This ensures the maximum efficiency of resources, consistency of results, and increases the synergy and integration of the partners. All management meetings and technical coordination meetings will play an important role in the communication strategy. All information generated within the project will be communicated to the Network of Exellence Manager who will be in charge of channelling this information to the other contractors, when appropriate. An **internet database** for all relevant ENCCA documentation (such as deliverables, publications, management procedures, strategies, research experimental data, progress reports and minutes) shall be created as a common tool for **e-communication and once again encourages partner interaction and activity integration**.

  The content of the database will be regularly updated and restricted by secure access control to project members and relevant EU bodies. The common database will be instrumental in ensuring all partners are kept well-informed of all events and in establishing consistent and productive contact between ENCCA and European Commission representatives.

- **External dissemination**

  Aims at communicating effectively with parties outside the consortium, as well as with other **European consortia**, **potential industrial users (industry)** and more generally with the **scientific community and its citizens.**

- **Scientific community:** All consortium members are encouraged to write public papers about the results obtained and the general efforts of ENCCA for harmonisation of clinical research, the presentation of the new therapeutic strategies and the efforts for better quality of care for children with cancer. ENCCA will organise specific events at EU level and will participate in international congresses in order to spread the excellence defined by this Network (see also WP3.1). The strategy for dissemination to the scientific community, including knowledge-sharing through **presentations**, active participation at relevant **conferences**, web content and press publications will be planned and approved by the dissemination managers within the limits of the **Consortium Agreement** and with respect of the restricted and confidential information.

- **Citizen awareness**: Dissemination to the citizen is a high priority for ENCCA in order to inform people about paediatric oncology and the specificity of clinical research in this area. European citizens will be informed through media, popular scientific reviews, and potentially presentations to policymakers of the importance of this research for drug development for children and adolescent with cancer as well regulators. High-quality, all-encompassing information and resources on results, as well as links to relevant bodies will be shared on the general **public section of the ENCCA website**.

- **Parents/patients**: ENCCA has prepared particular actions for parent/patient information. The presence of ICCCPO (ÖK) and a parent/patient advocacy group indicates ENCCA's recognition of the important of the involvement in this important initiative of patients, parents and families. Essentially, the objective is to provide them with all the necessary information and guidance they may need; a 'one-stop-shop' and the first point of contact to discover more about paediatric oncology in Europe, Moreover, it can provide the necessary expertise and insight into life for a patient on a clinical trial and how the network is endeavouring to improve that. This will take place in consultation with ICCCPO (ÖK) to ensure patients concerns are always addressed.

- **Industries:** The creation of the platform to collaborate with the industry is an important initiative. ENCCA will disseminate the latest developments and the key messages from the projects to their own affiliations and interested networks.

B.3.2.1.2 Dissemination plan

Greater public engagement, raising awareness and education is an important component of the communication and dissemination strategy of this NoE. Specific actions will be taken to ensure greater visibility and understanding of EU paediatric oncology. SIOPE as the Work Package leader for dissemination due to its broad membership base and its interaction with the oncology and political domains will create a strategic plan of action to ensure efficient and timely information announcements and will create the means to ensure greater communication, interaction and integration of activities through the online tools it will create and manage. ENCCA partners will utilise a wide range of effective communication to **guarantee proper diffusion of knowledge and project results**. The dissemination process will also be handled in a way that ensures information is spread amongst all concerned including all levels of policy-makers: such as standardisation and regulatory bodies, European and national policy-makers, third-level institutions, relevant NGOs and so on. Table 17 presents the activities that will be used to disseminate ENCCA results:

Dissemination to the scientific community	
Communications: **Symposia, meetings & congresses**	Within the ENCCA project, one of the communication tools that will be used to disseminate all relevant information obtained from the different ENCCA partners will be the scientific workshops, seminars and forums namely: ▪ SIOP Congress, 2010 (Boston, USA) ▪ ECCO 16 – ESMO 36 Multidisciplinary Congress, 2011 (Stockholm, Sweden) ▪ SIOP Congress, 2011 (Auckland, New Zealand) ▪ ASCO 2011, Annual meeting (Chicago, USA) ▪ SIOP Congress, 2012 (London, UK) ▪ ASCO 2012, Annual meeting (Chicago, USA) ▪ ECCO 17 – ESMO 38 Multidisciplinary Congress, 2013 (Amsterdam, The Netherlands)
Scientific Publications	Aiming to have some articles published in scientific journals about the experiences, methodologies and results gathered and developed within ENCCA project.
Teaching courses for students and technical staff	The following range of intensive crossover training programmes will be foreseen within the ENCCA project for students as well scientific and technical staff: Clinically-oriented educational programme for young paediatric oncologists to improve their skills in clinical management of common childhood tumours (Biennial): ▪ ESO-SIOPE Paediatric Oncology Master class June 2010, Italy ▪ ESO-SIOPE Paediatric Oncology Master class TBC 2012, Poland Clinically-oriented educational programme for paediatric oncologists who wish to improve their skills in the conduct of early clinical trials (Annual) ▪ ITCC Training days, December 2010, Italy ▪ ITCC Training days, 2011, TBC Joint- ECCO-ACCR-ASCO Workshop: Methods in Clinical Cancer Research (Annual) ▪ FLIMS workshop, 2010, Switzerland ▪ FLIMS workshop, 2011, Switzerland Advanced courses for leukaemia "state-of-the-art and future directions in childhood leukaemia" organised by I-BFM group (Annual)
Links with other projects/ networks	Within the ENCCA project several partners are linked to other projects and networks namely: ▪ EET pipeline (EU-FP6 STREP): comprehensive, multi-team approach for improving embryonal tumour diagnostics and treatment by the

	integration, assessment and validation of information generated by basic research utilising high-throughput technologies. ▪ KidsCancerKinome (EU-FP6 STREP): aims at selecting and validating drug targets from the human kinome for high-risk paediatric cancers. ▪ I-BFM study group (academia): aims to support fast clinical application of new diagnostics and risk-adapted therapies through excellent clinical research, to develop standards for state of the art diagnostics and best clinical care, to support translational research ▪ EuroBoNeT (EU-FP6 NoE): aims to increase and disseminate knowledge of primary bone tumours at the molecular level for the development of new tools for patient care and cure and technology. ▪ SIOPEN-R-NET (EU-FP5 NoE): aims to build a European Neuroblastoma Research Network to ultimately improve the survival in children suffering from neuroblastoma ▪ Childhope (FP6 LIFESCHEALTH): represents an innovative approach in paediatric cancer treatment ▪ NRC consortium (neuroblastoma profiling). (see Appendix 1 for listing of European lab. networks) ▪ A formal link will be established with the FP6 integrated project: 'Advancing Clinico-Genomic Trials on Cancer (ACGT) ▪ EUROCANCERCOMS project (FP7 science in Society): establishing an efficient network for cancer communication in Europe
Links with International Community	Links with the international community will be established and maintained via several dissemination channels including the following: Links with ICCCPO (**International Confederation of Childhood Cancer Parent Organisations**) ▪ Latin American Regional Parent Meeting, 2010 (Guadalajara, Mexico) Links with SIOP (**International society for Paediatric Oncology**) ▪ SIOP Congress, 2010 (Boston, USA) ▪ SIOP Congress, 2011 (Auckland, New Zealand) ▪ SIOP Congress, 2012 (London, UK) **"February Campaign"** to coincide with: International Childhood Cancer Day (15th February) ▪ European Rare Disease Day (28th or 29th February, depending on the year).

Dissemination of ENCCA NoE results to a wider range of potential users	
Industrial Dissemination	The dissemination of information to and from the pharmaceutical industry will occur via targeted workshops, forums and publications in order to exchange knowledge, expertise, challenges and obstacles experienced by the different ENCCA partners. In addition, dissemination actions will occur in collaboration with industry, non-governmental organisations (NGOs) and patient/parent organisations, in order to answer concerns and expectations from the stakeholding public. Two such communication outlets are: ▪ ECCO 16 – ESMO 36 Multidisciplinary Congress, 2011 (Stockholm, Sweden) ▪ ECCO 17 – ESMO 38 Multidisciplinary Congress, 2013 (Amsterdam, The Netherlands)
Citizen awareness	In order to make the public aware of the difficulties that paediatric oncologists and parents are encountering in childhood and adolescent cancer as well the progresses made by the ENCCA project, the consortium will organise events in particular as part of the "February Campaign", to raise awareness. Web Newsletter, interactive website and other communication tools, such as publication on the ENCCA partner websites and Cordis website of DG Research, will be explored and developed, in order to attract a wide range of visitors, including young researchers.
Parents/patients dissemination	The ENCCA project aims to promote multidisciplinary interaction between ENCCA partners and the established links with national, pan-European and international patient and family support organisations as well the comprehensive dissemination of the ENCCA project outcomes. Outlets for dissemination include: ▪ ICCCPO Latin American Regional Parent Meeting, 2010 (Guadalajara, Mexico) ▪ 'February Campaign' to coincide with - International Childhood Cancer Day (15th February) - European Rare Disease Day (28th or 29th February, depending on the year).
Specific dissemination tools	A specific ENCCA logo and documents for dissemination (such as brochures, flyers and other related communication material) will be developed and distributed to our scientific partner institutions and companies. A website dedicated to ENCCA will be implemented and, inter alia, will regularly publish news updates about the ongoing activities of the project.

Table 17: The dissemination actions of ENNCA NoE towards the whole chain of stakeholders

Training actions

- **Training in population-based cancer registration** development of a training module tackling the specific topics of paediatric oncology for epidemiologists and clinical oncologists. The target audience will be the staff of cancer registries with specific interest in childhood cancer and paediatric oncologists with interest in epidemiology. The training and education will comprise of three complementary phases: (1) training course, (2) individual mentoring, (3) on-site consultation. The training course will be developed in IARC in cooperation with the European Network of Cancer Registries (ENCR).
- **Label for standards** in training for paediatric haematology and oncology will be defined approved by the European Union of Medical Specialists (EUMS)
- Development of **courses for clinicians and research nurses** to address the gaps with multi-disciplinary training approach"

For more details about the whole training program see also in WP3.2

B.3.2.2 Exploitation plan

Most of the outputs of ENCCA will common procedures and protocols that will be susceptible to be standardized. However some of the research outputs (soft wares and other, tools) will be developed in common and will be necessary to protect and define rights. According to the Consortium Agreement that will be signed the same time with European contract, **knowledge** shall be the **property** of the contractor generating it. Where several contractors have jointly carried out work generating the knowledge and where their respective share of the work cannot be ascertained, they shall have **joint ownership** of that knowledge and shall be entitled to use and license it without owing any financial compensation to each other. In such a case, the dissemination manager and project management team shall propose the relevant allocation and terms of exercising ownership of that knowledge.

Those activities will be ruled by the European contract as well as the Consortium Agreement. Main rules are listed below:

- **Confidentiality**: during the project execution, the partners shall treat as confidential any information, which is designated as such by a disclosing partner. The partners shall impose the same obligations to their employees.
- **Dissemination**: any publication or communication proposed by one of the parties, regardless of the media, in connection with all or part of the project and of the knowledge is required to be submitted for the prior written consent of the Steering Committee.
- **Pre-existing know-how**: each partner is and remains the sole owner of its intellectual and industrial property rights over its pre-existing know-how. The partners shall identify and list in the Consortium Agreement the Pre-Existing Know-How over which they may grant access rights for the Project. The partners agree that the Access Rights to the Pre-existing Know-How needed for carrying out their own work under the Project shall be granted on a royalty-free basis.
- **Ownership and protection of knowledge**: knowledge shall be the property of the partner generating it. Joint ownership is possible but should be avoided.

B.3.2.3 Management of Intellectual Property (IP)

The intellectual property monitoring and patent survey is an indispensable prerequisite to ensure that the research and developments are driven properly. It consists in a continuous identification, monitoring and qualification of tangible and intangible results that should be either kept confidential, legally protected, disseminated or transferred to third parties. Dissemination Manager and the Project Management Team will work in close liaison with the Network of Excellence Manager. They will ensure that the issues related to Intellectual Property Rights are properly assessed and managed. The IPR management shall cover milestones and deliverables of ENCCA to identify any commercial potential of generated knowledge and information.

The Dissemination Manager and the Project Management Team will prepare an **Exploitation plan** in order to show the potential developed by the project and the possible exploitation routes of results. The exploitation plan will carefully **separate** the project **innovative elements** that are potentially to be **protected** and **elements** that could contribute in **future standards**.

The Dissemination Manager and the Project Management Team will be responsible for monitoring the effect of ENCCA achievements (e.g. any adjustments that will be necessary to make according to the results of the research and the effect on prospective applications) in terms of knowledge dissemination and further industrialisation/ commercialisation of results. Academic partners will increase their expertise in their respective scientific area and industrial partners will benefit from transfer of knowledge and develop their research and development portfolio.

B.4. Ethical Issues

B.4.1 General considerations

B.4.1.1 Respect of fundamental principles:

Europe's democratic societies should offer the necessary safeguards and channels of dialogue to ensure that the development and application of science and technology respects certain fundamental values. A Charter of European Fundamental Rights has established the general ethical principles as fundamental rights in Europe. These values are based on the following criteria such as: the inviolability of human dignity, freedom of research, protection of public health, non discrimination on account of genetics features, gender or age, protection of personal data, procedures performed on the human genome, non financial gains, intellectual property and patentability. This variety of ethical principles is guiding the human behaviour and decision making in the consortium. The implementation of the ENCCA project will be explicit and transparent for evaluating experts.

B.4.1.2 Precautionary principle

ENCCA consortium also aim to highly protect the human health and the environment for both the present and future generations and are committed to anticipating problems of dangerous and new research results or new substances and to applying the precautionary principle. Whenever reliable, scientific evidence is available to show that a result may have an adverse impact on human health and the environment. However, there is still scientific uncertainty about the precise nature or the magnitude of the potential side effects. Decision-making must be based on precaution in order to prevent human health and the environment from being damaged. Another important objective is to encourage the substitution of dangerous by less dangerous substances where suitable alternatives are available. The ENCCA consortium will ensure through WP18 and its Ethical Advisory Committee that the principle is applied through the steps of the project.

B4.1.3 Conflicts of interest

Conflicts of interest often arise at the intersection of two fundamental missions: to push the boundaries of knowledge and to transfer that knowledge to the private sector for the benefit of the public. The tension between science and medicine can also generate conflict. Considerations of personal gain however must not influence the decisions or actions of individuals in carrying out their responsibilities. Such incentives might harm research objectivity, or the protection of human subjects, or others whose work and need to be identified, and then managed, mitigated or eliminated, by the Ethical Advisory Committee.

B.4.1.4 Ethical Advisory Committee

In order to implement actions concerning ethical issues related to the research activities specific to the ENCCA project, an Ethical Advisory Committee will identify the ethical issues at stake with regards to patients as well as preclinical experimentation in primates. Then, the Ethical Advisory Committee will advise the consortium on the nature of the research activities, in order to anticipate the ethic issues and take actions with a view to making researchers fully aware about these issues. All clinical intervention will be conducted according to European and local guidelines, as detailed further in this document.

The Ethic Advisory Committee will be made up of partner representatives, external experts in particular in the fields of Ethics, and parents groups. Therefore, parents have an informative role to play in the dialogue on issues such as the precautionary principle, ethical issues related to clinical trial protocols and risk management. Adolescents and their representatives will be encouraged to actively participate in the debate on ethical issues both at the national and European levels.

The Ethical Advisory Committee will be responsible for keeping the participants well-informed about the new ethical regulations relevant to the ENCCA project. It will also ensure that the **existing ethical rules** are met. Actions will be taken in order to increase researchers' awareness of ethical issues. The Ethical Advisory Committee will monitor the work performed by the Clinical Research agenda in the respective WPs and advise it when necessary. Furthermore, it will ensure that the European Commission is informed by the Executive Committee and the Network of Excellence Manager that local, regional or national ethics approval has been obtained before the research (preclinical research on animals and clinical phase 1 trials) to which it relates is carried out.

B.4.2 Human biological samples & Patients

B.4.2.1 Human biological samples

During the ENCCA project, tumoural samples and blood from the patients will be studied. The samples will be taken according to GCP practice and Confidentiality Agreements as per current practice. Informed consent will be asked previously. Samples will be stored according to National Laws of the project participants.

B.4.2.2 Ethical issues regarding the use of human material

The integration of data is aimed at obtaining a combination of biological results with all available clinical data of the patients. This also includes follow-up data, because the outcome of disease is important information when investigating prognostic parameters. This valuable information is protected by strict regulation ensuring protection of personal privacy and prohibiting spreading of data to other sources through national codes. The following measures are operable to prevent incorrect use of privacy data:

1. An Ethical Advisory Committee, composed of independent experts will be established to oversee in the ENCCA Network the respect of ethical protocol guidance developed in WP 18. If and when necessary the committee will be extended with additional members with expertise on ethical issues.
2. The clinical trials which will be conducted by the EU-disease groups and ENCCA partners will be regulated by international standardized protocols.
3. All participants will act under national codes regarding the use of patient data, which may not be completely uniform, but definitely directed at protecting the patient's privacy and prohibiting misuse of data. All data will be handled in a coded fashion and following the "Use of Human Tissue" established by the Dutch Federation of Medical Sciences.

B4.2.3 Ethical issues regarding the involvement of children in the investigations

Implementation of the ENCCA clinical research agenda will follow the recommendations of the EMA ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use as well as the ICH Topic E11 on clinical investigation of medicinal products in the paediatric population (CPMP/ICH2711/99).

The context of clinical research in paediatric cancer raises numerous ethical issues:

- These studies are devoted to life threatening diseases during childhood;
- The access to care and new treatments is not homogeneous within Europe;
- Parents take the responsibility of accepting or refusing their child's participation to a clinical trial; the issue of child's information and consent/assent, according to the age, is also crucial
- It would be unethical not to do research in order to improve cure rates as well as quality of survival but the rarity of the disease should not imply that clinical research could be imposed to children and their parents.

- To follow E. KANT' s recommendation ("Act in such a way that you treat humanity, whether in your own person or in the person of any other, always at the same time as an end and never merely as a means to an end") (Grundlegung zur Metaphysik der Sitten, 1785), no child should ever be considered only as a mean to know a recommended dose of a new drug, a mean to know the response rate to a new drug or combination or a mean to know a best treatment arm.

The ENCCA Network will seek to answer those issues by performing research and protocols, including the manipulation and use of human material of children, according to the codes of conduct such as the ones published by the Central Committee on Research Involving Human Subjects (CCMO). Besides this, all organisations will have to have their research plans examined by the ethical board of their organisation to ensure that the local ethical guidelines are met.

The objective of our project is to formulate general guidance for clinical trials and to set up a ENCCA ethical committee, not only in charge of ensuring respect of fundamental ethical principles but also to evoke continuous attention to aspects of ethical handling and to monitor ethical aspects in implementing the ENCCA clinical research agenda. In addition, there is an entire work package WP18dedicated to Ethics aiming at understanding the cultural differences in between EU member states and providing guidelines for better information. A Philosophy Post-doctorate will be in charge of meeting with SIOPE tumour group and parent national representatives and of collecting the current practices in the different countries in the specific field of paediatric cancer clinical trials (Comparison of the implementation of the European Directive in the different EU countries, focussing on paediatric research has already been performed and these documents will be used for our project). A special attention will also be given to the use of new anti-cancer drugs outside a clinical trial. After the initial 2 years of the project, a first workshop will be organised in order to present the current situation and propose guidelines for improvement. In the last two years of this program, the Post-doctorate will meet again the professional and parent representatives to evaluate the implementation of these guidelines. A second workshop will is foreseen at the end of the program, in order to present this implantation and improve the initial

B4.2.4 Patients information issues

Patients who take part in clinical research may have concerns especially about inadequate information before, during and after research and clinical trials. They sometimes feel that researchers and clinicians do not always treat them as equal and respected partners in the research enterprise but rather as instruments of the scientist and medical teams' own purposes.

Children, particularly young children, have limited decision-making ability and do not have the legal capacity to provide informed consent. Thus parental permission for a child to participate in research is required. Because children are considered a vulnerable patient population, we need to make sure that parents and older children and adolescents understand well the clinical trial before they agree to research participation and that they have appropriate support in adhering to the protocol during the course of the study.

ENCCA, through the establishment of internal ethical guidelines regarding the application of clinical trials for children and adolescents, will offer practical details guidance to clinical researchers to let parents and patients know what they should expect when they take part in the trial protocols. Moreover, the Network will identify and facilitate the dialogue of the patients being able to integrate clinical trials at the European level. ICCCPO (ÖK) is a full partner of the project and will facilitate participation of parents to the research programme. The purpose will be to inform them on the progress made and difficulties still present on the road to clinical efficacious and safe trials for fighting children and adolescent cancer. The ENCCA will also try to respond to their concerns, their eagerness for trials and other requests, especially regarding security and safety.
Thus, it is critical that the information sheet provides useful and fair information on the research and that it is easily understandable by parents and children. This will be carefully addressed in all trials run within ENCCA and parents, through the ÖKKH_ICCCPO partner and from national parents organisations, will be asked to review the information package for those trials.

B4.2.5 Patients consent

Local and national ethical committees will be consulted to discuss the issues relative to clinical trials in children with cancer. Parent's (or legal guardian's) informed consent and patient assent will be obtained after adequate and understandable information, in accordance to EU directives. The ENCCA will collect reliable information using questionnaires. Patients or parents will be guaranteed that declining to participate at anytime during the clinical trials will not affect their subsequent care.

B4.2.6 Confidentiality, data protection and samples storage

There is an increasing link between clinical and biological studies and the high throughput technology leads to more and more possibly identifying data, making still more complex the issue of confidentiality. Therefore, analyses of biological samples will be strictly limited to the research purposes presented in this proposal and the results will not be communicated outside the ENCCA project without proper precaution to ensure patient confidentiality.

Data will be maintained within an allocated network server space dedicated to this purpose and access will be reserved to authorized personnel only. For the clinical trials to be launched within the project, the patient's personal data and Investigator's personal data which may be included in the databases will be treated in compliance with all applicable laws and regulations. All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Study findings stored on computers will be stored in accordance with local data protection laws. Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The Clinical Trial Groups as well as the laboratories, with which they will collaborate in terms of sample collection, will implement strict precautions and routines regarding the storage, recording, and disposal of biological samples and waste and follow good laboratory working practices.

B.4.3 Protection of animals and experimentation

B.4.3.1 Protection of animals

The challenge for the research community is to drastically increase the expectations in science to develop alternatives to animal-based tests. The ENCCA project is committed **to better organizing research** and development and to promoting and applying the "Three Rs" (Reduction, Refinement and Replacement) concept in order to **find alternatives** to animal experimentation.

Even though the ENCCA project will not directly involve animal-based tests, it will take initiatives to:

- **Reduce** animal experimentation. This will be possible by coordinating animal experimentation at Network level in order to reduce the number of experiences and improve knowledge communication. Indeed, the likelihood to use animals will be only in WP1.4 biology work package, where the vast majority of studies and experiments will be performed without the use of animals.
- **Refine** animal experimentation by using best practices which alleviate or minimise potential pain, suffering and distress and enhance animal well being. Discomfort and pain can be treated by specific protocols with anti-inflammatory or analgesic treatment. Some non traumatic protocol employed in human can now be used with animal. If mobility of animal is reduced, their living space will be accommodated. A number of refinements to toxicity testing have been developed and have become accepted as OECD guidelines. In addition, recommendations from ICCVAM have been published describing how in vitro data may be used to select the starting dose for the test, further limiting the numbers of animals needed and increasing the predictivity of the data.

- **Replace** animal experimentation, when possible, with methods that do not require experimentation or other scientific procedures on animals. Additionally, at the beginning and during the project, the Ethic Committee will be in contact with the ECVAM (European Center for the Validation of Alternative Methods) to find new protocol avoiding animal experimentation.

If animal experimentation is required, all protocols will be reviewed by Institutional Animal Care and Use Committees, established in all the institutions involved in the project and will adhere to EU and national regulations for animal research, such as Directive 86/609 EC. Moreover, all experimental establishments where experiments are conducted on living vertebrate animals must be accredited for the types of experiments actually carried out. Experiments will only be conducted by authorized competent personnel, or under their direct responsibility. People conducting experiments or taking part in them as well as people taking care of animals used in experiments, including people in charge of supervising, will have received the appropriate training and education (Directive no. 86/609/EEC).

A procedure will only be carried out by authorized personnel or under their direct responsibility. This authorization will only be granted by people deemed competent by the authority in charge. One of the conditions to be fulfilled for an experiment to be legal is the requirement that it is conducted by or under the supervision of a person with nominative authorization to experiment on living animals assisted by a sufficient number of qualified personnel working in an accredited animal experimentation establishment.

B.4.3.2 Protection of welfare of the animal

The guidelines underlying the conception and use of pathogen free animal facility have been drawn up so as to cope with emerging and forthcoming needs and challenges enacted by the scientific community throughout the world, both to practical and ethical ends. Not only is this reflected in the way the regulatory and operating processes are implemented and justified, but also in the dedication towards animal welfare rules. Accordingly, all the activities carried out with mice during the project will be respectful of the different standards stemming from our “quality-insurance” policy, promoting awareness of best practice in the care of laboratory animals, as recommended by EU legislation. All necessary measures will be taken during experiments, in accordance with our current veterinary practices, to ensure minimum discomfort, distress and pain, and using appropriate methods for sedation, analgesia or anaesthesia. Moreover, research work will be carried out only by individuals trained in the proper care, handling and use of animals, and fully authorised by national veterinary agencies to perform these animal experimentation studies.

B.4.3.3 Animal experimentation in ENCCA project

B4.3.3.1 Description of research activities with animal experiments

There is no direct relationship of ENCCA with animal-based projects. However, there are two work packages within ENCCA which may involve animal-based tests performed in ENCCA-associated institutions without funding through the EU.

WP 5 : Biology to guide innovative targeted therapy development
The recruitment of labs into the tumour subnetworks foreseen in WP5 will be based on scientific quality and commitment to contribute and share data within the tumour subnetwork. This activity to better support integration of biological data and ideas interesting across different cancer entities to support better translation of basic and preclinical research to clinical application may also involve laboratories performing animal-based tests as part of their algorithm development for identification and prioritisation of molecular targets based on biological data.
While data that have been derived through animal experimentation may be used in this activity, no potentially animal-based project will be directly funded through ENCCA.

WP 2.2: Improved therapeutic strategies using predictive biomarkers in leukaemias
Task 9.3 of WP9 aims at integration of a molecular diagnostic pipeline with preclinical model systems for molecular targeted treatment and application of algorithms for identification and prioritisation of molecular targets in very high-risk acute lymphoblastic leukaemia (VHRL) patients. This WP will indirectly employ preclinical models including cell lines (existing and newly established ones) as well as ALL xenograft models using NOD/SCID mice for the amplification of VHRL patient samples and validation of identified targets. Access to these ALL xenograft models is guaranteed through an associated partner (Children's Hospital Zurich) hosting the I-BFM xenotransplant bank of VHRL phenotypes, but not funded through this proposal. The I-BFM xenotransplant bank for VHRL diagnostic specimens has been previously established and will only provide data to this task as an associated institution.

B4.3.3.2 Justification of the use of animals in the research work or in the WP / task

The experiments associated with WP9/task 9.3 are necessary to model very high-risk acute lymphoblastic leukaemia phenotypes, for which no true preclinical model systems are available. These studies will explicitly pay attention to the following points:

- The number of animals used will be minimised whenever possible. Exact numbers cannot be given because of the attempts that will be made to minimise the numbers.
- In vitro tests are carried out in parallel whenever possible. As a result of this project, it is expected that instances will be identified where animal tests can be replaced by in vitro tests.
- Imaging methods will be favoured as a non traumatic and non invasive method for result evaluation.
- Similarly, mathematical models will be used and further developed to reduce the need for animal experiments.
- Animals that are involved in testing associated with WP9/task 9.3 will be taken care of in the professional and licensed facilities of the Medical Faculty of the University of Zurich.

B.4.3.3.3 Animal Models for research on cancer

Animal models of human pathologies, and particularly rodents, are increasingly used in pre-clinical research, allowing the description and understanding of human diseases and the evaluation of potential treatments. As an example related to the project, xenograft models of very high-risk acute lymphoblastic leukaemia patients associated with WP2.2/task 2.2.3 allow for preclinical validation of identified target pathways in a disease phenotype for which no other model systems are currently available.

Also, in-vivo imaging allows the follow-up of single animals, making the analysis of the time course of pathology and potential treatments more effective than the use of mice cohorts with multiple sacrifice times.

B.4.4 Fields of research which are excluded from the program

ENCCA partners confirm that the proposed research project does not involve:

- Research activity aiming at human cloning for reproductive purpose;
- Research activity intended to modify the genetic heritage of human being which could make such changes heritable;
- Research activities intended to create and / or destruction human embryo solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer.

ETHICAL ISSUES TABLE

	YES	PAGE
Informed Consent		
Does the proposal involve children?	x	83-107
Does the proposal involve patients or persons not able to give consent?	x	83-107
Does the proposal involve adult healthy volunteers?		83-107
Does the proposal involve Human Genetic Material?	x	83-107
Does the proposal involve Human biological samples?	x	83-107
Does the proposal involve Human data collection?	x	83-107
Research on Human embryo/foetus		
Does the proposal involve Human Embryos?		
Does the proposal involve Human Foetal Tissue / Cells?		
Does the proposal involve Human Embryonic Stem Cells?		
Privacy		
Does the proposal involve processing of genetic information or personal data (eg. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)	x	
Does the proposal involve tracking the location or observation of people?		
Research on Animals		
Does the proposal involve research on animals?	x	66, 83-107
Are those animals transgenic small laboratory animals?		
Are those animals transgenic farm animals?		
Are those animals cloning farm animals?		
Are those animals non-human primates?		
Research Involving Developing Countries		
Use of local resources (genetic, animal, plant etc)		
Benefit to local community (capacity building ie access to healthcare, education etc)		
Dual Use		
Research having potential military / terrorist application		
I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL	**No**	

B.4.5 National and international regulations

The fundamentals of research with human materials are contained within the Declaration of Helsinki. ENCCA intend to wholly support and actively promote the principles established within this declaration. Non-exhaustive lists of major EU directives, which are relevant to the ENCCA project, are listed hereafter:

- The Charter of Fundamental Rights of the EU, conventions of the Council of Europe on human rights and biomedicine, and the UNESCO Declaration on the human genome.
- Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.
- CPMP/ICH/295/95 "Note for Guidance on quality of biotechnological products: viral safety evaluation of biotechnology products derived from cell lines of human and animal origin".
- Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the member states regarding the protection of animals used for experimental and other scientific purposes;

- European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes CETS No.: 123 Strasbourg, 18.03.1986. Treaty open for signature by the member states and by the European Community and for accession by non-member states.
- Directive 95/46 on the protection of personal data,
- Directive 2001/20/EC on good clinical practice,
- Directive 2001/83/EC on medicinal products for human use,
- COMMISSION DIRECTIVE 2003/63/EC amending Directive 2001/83/EC,
- COMMISSION REGULATION (EC) No 1084/2003 on the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State,
- COMMISSION REGULATION (EC) No 1085/2003 the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93,
- Directive 98/44/EC on the legal protection of biotechnological inventions,
- Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes,
- Protocol on Protection and welfare of animals (Protocol to the Amsterdam Treaty),
- Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work,
- Ethics and EU funded research,
- Council Decision 1513/2002/EC on FP6,
- EU research on ethics in science,
- Convention for the protection of Human Rights and dignity of a human being with respect to applications of biology and medicine: Convention on the rights of human beings and biomedicine;
- Council Decision 2002/835/EC adopting a specific programme for research, technological development and demonstration: 'structuring the European Research Area' (2002–2006).

In addition, each partner will comply with its relevant national legislation. A list of applicable laws and regulatory texts follows for each country involved.

B.4.5.1 Austria

Bundesgesetz vom 2. März 1983 über die Herstellung und das Inverkehrbringen von Arzneimitteln (Arzneimittelgesetz - MUG) StF: BGBl. Nr. 185/1983

B.4.5.2 Belgium

- Loi du 7 mai 2004 relative aux expérimentations sur la personne humaine. Wet van 7 mei 2004 inzake experimenten op de menselijke persoon.
- Arrêté royal du 6 juin 1960 relatif à la fabrication et à la distribution en gros des médicaments et à leur dispensation. Koninklijk besluit van 6 juni 1960 betreffende de fabricage en distributie in het groot en de terhandstelling van geneesmiddelen.
- Version coordonnée (août 2003) de la loi relative à la protection des données à caractère personnel du 8 décembre 1992. Gecoördineerde versie (augustus 2003) van de wet van 8 december 1992 tot bescherming van de persoonlijke levenssfeer ten opzichte van de verwerking van persoonsgegevens.

B.4.5.3 France

Regarding the Ethical issues on clinical trials and the use of human material the following legislations will be respected:

France has established two decrees for the protection of animal:

- Décret n° 87-848 19/10/1987.
- Décret n° 2001-464 29/05/2001.
- According to the Decret n° 87-848, all persons involved in animal experimentation have been formed to the manipulation and use of laboratory animals (level I – cadres biologistes or level II- technicians).
- Décret 87-848 du 19 octobre 1987 pris pour l'application de l'article 464 du code pénal et du troisième alinéa de l'article 276 du code rural et relatif aux expériences pratiquées sur les animaux.
- Circulaire du 16 avril 1996 relative aux utilisations confinées d'organismes génétiquement modifiés à des fins de recherche, de développement ou d'enseignement.
- Décret n°2001-131 du 6 février 2001 portant publication de la Convention européenne sur la protection des animaux vertébrés utilisés à des fins expérimentales ou à d'autres fins scientifiques, adoptée à Strasbourg le 18 mars 1986 et signée par la France le 2 septembre 1987.
- Décret n° 2001-464 du 29 mai 2001 modifiant le décret n° 87-848 du 19 octobre 1987 pris pour l'application de l'article 454 du code pénal et du troisième alinéa de l'article 276 du code rural et relatif aux expériences pratiquées sur les animaux.
- Arrêté 0321919A du 21 mai 2003 relatif à la délivrance et à l'utilisation de médicaments employés par les établissements disposant d'un agrément pour pratiquer l'expérimentation animale.
- Décret no 2005-264 du 22 mars 2005 modifiant la partie Réglementaire du livre II du code rural et portant création d'un Comité national de réflexion éthique sur l'expérimentation animale.
- Décret no 2007-1220 du 10 août 2007 relatif au prélèvement, à la conservation et à la préparation à des fins scientifiques d'éléments du corps humain et modifiant le code de la santé publique (dispositions réglementaires).

B.4.5.4 Germany

- Gesetz über den Verkehr mit Artzneimitteln (Artzneimittelgesetz), Stand: August 2004.
- Arzneimittelnovelle vom 30.07.2004 (BGBl. I S. 2031), in Kraft getreten am 06.08.2004.

B.4.5.5 Italy

- Decreto Legislativo n. 211 del 24 giugno 2003: Attuazione della direttiva 2001/20/CE relative all'applicazione della buona pratica clinica nell'esecuzione delle sperimentazioni cliniche di medicinali per uso clinico.
- Decreto Ministeriale 8 maggio 2003: Uso terapeutico di medicinale sottoposto a sperimentazione clinica.
- Decreto del Presidente dell'Istituto Superiore di Sanità del 26 aprile 2002 : Accertamento della composizione e innocuità dei farmaci di nuova istituzione prima della sperimentazione clinica sull'uomo. Individuazione della documentazione da sottoporre all'Istituto superiore di sanità ai sensi dell'art. 4, comma 2, del decreto del Presidente della Repubblica 21 settembre 2001, n. 439.
- Circolare Ministeriale n. 6 del 2 settembre 2002: Attività dei comitati etici istituiti ai sensi del decreto ministeriale 18 marzo 1998.
- Decreto del Presidente della Repubblica n. 439 del 21 settembre 2001 : Regolamento di semplificazione delle procedure per la verifica e il controllo di nuovi sistemi e protocolli terapeutici sperimentali.

- Decreto Ministeriale del 23 novembre 1999: Composizione e determinazione delle funzioni del Comitato Etico Nazionale per le sperimantazioni cliniche dei medicinali, ai sensi del decreto legislativo n. 229 del 19 giugno 1999.
- Decreto Legislativo n. 196 del 30 giugno 2003: Codice in materia di protezione dei dati personali.
- Decreto Legislativo n. 206 del 18 aprile 2001.
- Decreto n° 493 (Gazzetta Ufficiale n. 294, 19 dicembre 2001) “Regolamento di semplificazione delle procedure per la verifica e il controllo di nuovi sistemi e protocolli terapeutici sperimentali” e decreto di 26 aprile 2002 (Gazzetta Ufficiale n°105 di 7 maggio 2002).
- Istituto Superiore di Sanità ottobre 1996 vol 9, n10 "Documentazione richiesta per l'avvio degli studi clinici con prodotti per terapia genica: proposta di linee guida e richiesta di commenti".
- Istituto Superiore di Sanità maggio 1997 vol 10, n5 "Linee guida per l'avvio degli studi clinici di fase I/II con cellule umane per la terapia cellulare somatica".
- Istituto Superiore di Sanità maggio 1999 "Linee guida per l'ingegneria dei tessuti e la terapia cellulare".
- Circolare di 5 ottobre 2000, n. 15, Ministero della Salute “Sperimentazione clinica dei medicinali”

B.4.5.6 Netherlands

- Wet Medisch–wetenschappelijk Onderzoek met mensen (WMO), 1 december 1999.
- Besluit Immunologische Farmaceutische Producten (BIF), augustus 2001.
- Wet op de Geneeskundige Behandelingsovereenkomst (WGBO), 1 april 1995.
- Wet Bescherming Persoonsgegevens (WBP), 6 juli 2000.
- Wet veiligheid en kwaliteit lichaamsmateriaal (WVKL), 6 februari 2003.
- Wet op de dierproeven, 11 januari 1977.

B.4.5.7 Spain

- Law 25/1990 on Medicines
- Convention on Human Rights and Biomedicine (2000)
- RD 223/2004
- Ley 14/2007 de Investigación Biomédica
- Orden SCO 256/2007
- Ley Orgánica 15/1999 de Protección de Datos.

B.4.5.8 Sweden

- Act (2003:460) on Ethics Review of Research Involving Humans- in Swedish
- Ordinance (2003:615) on Ethics Review of Research Involving Humans supplements the Act on Ethics Review
- Ordinance (2003:616) with Instruction for Regional Boards for Ethics Review
- Ordinance (2003:617) with Instruction for the Central Board for Ethics Review
- Medical Product Act (1992:859)
- Medical Products Agency's provisions and guidance (LVFS 1996:17) on the clinical trials of medicinal products
- Act (2002:297) on Biobanks in Health Care
- Ordinance (2002:746) on Biobanks in Health Care.
- National Board of Health & Welfare provisions and general advice (SOSFS 2002: 11) on biobanks in Health Care
- Research ethics guidelines for using biobanks. Adopted by the Swedish Medical Research Council (MFR) in June 1999, (Dnr 1999-570)
- CODEX The Swedish Research Council's gateway to various research ethics and professional guidelines

B.4.5.9 United Kingdom

- Anatomy Act (1832)
- Cruelty to Animals Act (1876)
- Animals (Scientific Procedures) Act (1986)
- Data Protection Act (1998)
- Health and Social Care Act (2001)
- Human Tissue Act (2004)
- Health Service (Control of Patient Information) Regulations 2002

B.5 CONSIDERATION OF GENDER ASPECTS

Several documents released by the European Commission[1] highlight the importance of taking into account the gender dimension for the execution of research programmes. The ENCCA will make **great efforts to employ more women among the research staff** in particular for the top decision-making positions, with efforts to consider gender issues in recruitment practices. Particular attention will be given in **sensitisation about the gender equality** in research structures. Incentives will be given to employ more women in laboratories. In the scheme to raise awareness in science, scholars will be invited to visit laboratories. This activity will put emphasize in raising interest among young women. Besides, flexible working hours and other family-friendly policies will be initiated in research organisations. A set of gender indicators will be produced during the ENCCA realisation in order to measure progress towards gender equality in design and engineering research. The topic of this project does not involve expected differences between genders so that both will be considered equally during the experimentation and both should benefit equally from the results. The ENCCA project proposes to address the lack of gender equality by promoting the participation of women.

A **gender action plan**, improving gender equality will be implemented which aims to:

- Recruiting: there will be no women discrimination, in particular in the management of the project (specific job opportunities) and in the innovation related activities (PhD). Partial time contract will be also used if necessary. Flexible working hours will be considered as well as family-friendly policies. The rate of women employed at different positions will be monitored all along the project.
- Creating specific measures for women when the equality of treatment indirectly favors men.
- Establishing a system for monitoring gender equality in mobility schemes such as equality of access and participation and subsequent impact on professional careers.
- Measure efforts made to employ **more women** among the research staff, at all hierarchy levels, and especially at **key positions** and take necessary measures against organisations which do not meet their commitment. To achieve this, gender **sensitive indicators** are defined.
- Each WP leader will be adequately briefed on gender-related issues so that if any gender-related issue should arise, they could take adequate actions to give adequate consideration to both men and women interests, needs and life patterns.
- Participate in a series of **public events** dedicated to promoting gender integration.

If the project succeeds in attracting a larger proportion of women students to the project, the result will be more qualified female personnel for work in the European medical, pharmaceutical and biotechnology fields and general more qualified women in the European society.

[1] ETAN Report on Women and Science: Science Policies in the European Union: Promoting excellence through mainstreaming gender equality, 2000; Gender Impact Assessment Studies - Synthesis Report, 2001, National Policies on Women and Science in Europe, 2002[1])

ANNEX 1

Publications

Partner	References (publications), and patents related to the project
CCRI	▪ Vermeulen J, De Preter K, Naranjo A, Vercruysse L, Van Roy N, Hellemans J, Swerts K, Bravo S, Scaruffi P, Tonini GP, De Bernardi B, Noguera R, Piqueras M, Cañete A, Castel V, Janoueix-Lerosey I, Delattre O, Schleiermacher G, Michon J, Combaret V, Fischer M, Oberthuer A, Ambros PF, Beiske K, Bénard J, Marques B, Rubie H, Kohler J, Pötschger U, **Ladenstein R,** ***Hogarty MD, McGrady P, London WB, Laureys G, Speleman F, Vandesompele J.*** Predicting outcomes for children with neuroblastoma using a multigene-expression signature: a retrospective SIOPEN/COG/GPOH study. **Lancet Oncol.** ***2009 Jul;10(7):663-71.*** ▪ Schreier G, Messmer J, Rauchegger G, Modre-Osprian R, **Ladenstein R**. A Web-based platform for interdisciplinary biomedical research. **Front Biosci.** 2009 Jan 1;14:2738-46. ▪ **Ladenstein R,** Pötschger U, Hartman O, Pearson AD, Klingebiel T, Castel V, Yaniv I, Demirer T, Dini G; EBMT Paediatric Working Party. 28 years of high-dose therapy and SCT for neuroblastoma in Europe: lessons from more than 4000 procedures. **Bone Marrow Transplant.** 2008 Jun;41: 18-27 ▪ Matthes-Martin S, **Pötschger U,** Bergmann K, et al. Risk-adjusted outcome measurement in paediatric allogeneic stem cell transplantation. **Biol Blood Marrow Transplant.** 2008, Mar;14(3):335-43. ▪ Gadner H, Grois N, **Pötschger U,** et al. Histiocyte Society. Improved outcome in multisystem Langerhans cell histiocytosis is associated with therapy intensification. **Blood.** 2008, Mar 1;111(5):2556-62. ▪ Kager L, Zoubek A, **Pötschger U,** et al. Cooperative German-Austrian-Swiss Osteosarcoma Study Group. Primary metastatic osteosarcoma: presentation and outcome of patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. **J Clin Oncol.** 2003 May 15;21(10):2011-8. ▪ **Dworzak M.N.,** Fröschl G., Printz D., et al. Prognostic significance and modalities of flow cytometric minimal residual disease detection in childhood acute lymphoblastic leukemia. **Blood.** 2002, 99(6):1952-1958. ▪ Langebrake C., Creutzig U., **Dworzak M.,** Hrusak O., Mejstrikova E., Griesinger F., Zimmermann M. and Reinhardt D. Residual disease monitoring in childhood acute myeloid leukemia by multiparameter flow cytometry: The MRD-AML-BFM Study Group. **Journal of Clinical Oncology.** 2006, 24(22):3686-3692. ▪ **Dworzak M.N.,** Schumich A., Printz D., Pötschger U., Husak Z., Attarbaschi A., Basso G., Gaipa G., Ratei R., Mann G., Gadner H. for the AIEOP-BFM-ALL-FCM-MRD-Study Group CD20 up-regulation in paediatric B-cell precursor acute lymphoblastic leukemia during induction treatment: setting the stage for anti-CD20 directed immuno-therapy. **Blood.** 2008, 112: 3982-3988.
UCL	▪ **Pritchard-Jones K**, Kaatsch P, Steliarova-Foucher E, Stiller CA, Coebergh JW. Cancer in children and adolescents in Europe: developments over 20 years and future challenges. **Eur. J. Cancer**, 42(13):2183-90, 2006. ▪ **Pritchard-Jones K**; SIOP Europe. Clinical trials for children with cancer in Europe - still a long way from harmonisation: a report from SIOP Europe. **Eur J Cancer**. 2008 Oct;44(15):2106-11. ▪ Ladenstein R, Potschger U, Le Deley M-C, **Whelan JS**, Paulussen M, Oberlin O, van den Berg H, Dirksen L, Hjorth L, Michon J, Lewis I, Craft A, Jurgens H. Primary Disseminated Multifocal Ewing Sarcoma: Results of the Euro-EWING 99 Trial. J Clin Oncol 2010 doi 10.1200/JCO.2009.22.9864 ▪ Fern L, Davies S, Eden T, Feltblower R, Grant R, Hawkins M, Lewis I, Loucaides E, Rowntree C, Stenning S, **Whelan JS**. Rates of inclusion of teenagers and young adults in England into National Cancer Research Network Clinical Trials: Report from the National Cancer Research Institute (NCRI) Teenage and Young Adult Clinical Studies Development Group. Br J Cancer 2008;19:1967-74 ▪ Paulussen M, Craft A, Lewis I, Hackshaw A, Douglas C, Dunst J, Schuck A, Winkelman W, Kohler G, Poremba C, Zoubek A, Ladenstein R, van den Berg H, Hunold A, Cassoni A, Spooner D, Grimer R**, Whelan J**, McTiernan A, Jurgens H for the European Intergroup Cooperative Ewings Sarcoma Study Group. Results of the EICESS-92 study: two randomised trials of Ewing's sarcoma treatment. J Clin Oncol 2008:20:4385-93

	▪ Lewis I, Nooij M, **Whelan JS**, Sydes M, Grimer R, Hogendoorn P, Memon M, Weeden S, Uscinska B, van Glabbeke M, Kirkpatrick A, Hauben E, Craft A, Taminiau on behalf of MRC BO06 and EORTC 80931 collaborators and European Osteosarcoma Intergroup. Intensified chemotherapy improved histological response but not survival in patients with operable osteosarcoma of an extremity: results of a randomised phase III study of the European Osteosarcoma Intergroup (MRC BO06 EORTC 80931 ISRCTN86294690). JNCI 2007;99:112-28
IGR	▪ Puget S, Grill J, Valent A, Bieche I, Dantas-Barbosa C, Kauffmann A, Dessen P, Lacroix L, Geoerger B, Job B, Dirven C, Varlet P, Peyre M, Dirks PB, Sainte-Rose C, **Vassal G**. Candidate genes on chromosome 9q33-34 involved in the progression of childhood ependymomas. **J Clin Oncol.** 2009 Apr 10;27(11):1884-92. ▪ Geoerger B, Doz F, Gentet JC, Mayer M, Landman-Parker J, Pichon F, Chastagner P, Rubie H, Frappaz D, Le Bouil A, Gupta S, **Vassal G**. Phase I study of weekly oxaliplatin in relapsed or refractory paediatric solid malignancies. **J Clin Oncol.** 2008 Sep 20;26(27):4394-400. ▪ Le Deley MC, Reiter A, Williams D, Delsol G, Oschlies I, McCarthy K, Zimmermann M, **Brugières L**. European Intergroup for Childhood Non-Hodgkin Lymphoma Prognostic factors in childhood anaplastic large cell lymphoma: results of a large European intergroup study. **Blood.** 2008 Feb 1;111(3):1560-6. ▪ Perilongo G, Maibach R, Shafford E, **Brugieres L**, Brock P, Morland B, de Camargo B, Zsiros J, Roebuck D, Zimmermann A, Aronson D, Childs M, Widing E, Laithier V, Plaschkes J, Pritchard J, Scopinaro M, MacKinlay G, Czauderna P. Cisplatin versus cisplatin plus doxorubicin for standard-risk hepatoblastoma. **N Engl J Med.** 2009 Oct 22;361(17):1662-70. ▪ **Brugières L, Le Deley MC,** Rosolen A, Williams D, Horibe K, Wrobel G, Mann G, Zsiros J, Uyttebroeck A, Marky I, Lamant L, Reiter A. Impact of the methotrexate administration dose on the need for intrathecal treatment in children and adolescents with anaplastic large-cell lymphoma: results of a randomized trial of the EICNHL Group. **J Clin Oncol.** 2009 Feb 20;27(6):897-903. ▪ **Le Deley MC**, Suzan F, Cutuli B, Delaloge S, Shamsaldin A, Linassier C, Clisant S, de Vathaire F, Fenaux P, Hill C. Anthracyclines, mitoxantrone, radiotherapy, and granulocyte colony-stimulating factor: risk factors for leukemia and myelodysplastic syndrome after breast cancer. **J Clin Oncol.** 2007 Jan 20;25(3):292-300.
UCSC	▪ Smith M, Bernstein M, Bleyer WA, Borsi JD, Ho P, Lewis IJ, Pearson A, Pein F, Pratt C, Reaman G, **Riccardi R**, Seibel N, Trueworthy R, Ungerleider R, Vassal G and Vietti T. Conduct of phase I trials in children with cancer. **Journal of Clinical Oncology**, 1998, Vol 16, 966-978 ▪ Di Francesco A.M., **Ruggiero A**., and **Riccardi R.** "Cellular and molecular aspects of drugs of the future: oxaliplatin". **Cellular and Molecular Life Science.** 2002, 59, :1914-1927. ▪ Barone G., Maurizi P., Tamburrini G., **Riccardi R**. Role of Temozolomide in paediatric brain tumours. **Childs Nerv Syst**. 2006, July: 22(7). 652-61. Epub 2006 Mar 25.
UKE	▪ Sitek B, Apostolov O, Stuhler K, Pfeiffer K, Meyer HE, **Eggert A, Schramm A.** Identification of dynamic proteome changes upon ligand-activation of Trk-receptors using two-dimensional fluorescence difference gel electrophoresis and mass spectrometry. **Mol Cell Proteomics.** 2005;4:291-9. ▪ Schulte JH, Horn S, Samans B, Heukamp L, Eilers UC, Otto T, Krause M**,** **Astrahantseff K**, Buettner R**,** **Schramm A**, Christiansen H, Eilers M**,** **Eggert A**, Berwanger B. N-Myc regulates oncogenic microRNAs in neuroblastoma. **Int. J. Cancer** 2008;122:699-704. ▪ Cimmino F, Schulte JH, Zollo M, Koster J, Versteeg R, Iolascon A, **Eggert A, Schramm A**. Galectin-1 is the major effector of TrkB-mediated neuroblastoma aggressiveness. **Oncogene.** 2009;28:2015-23.
UNIMIB	▪ Pieters R, Schrappe M, De Lorenzo P, Hann I, De Rossi G, Felice M, Hovi L, LeBlanc T, Szczepanski T, Ferster A, Janka G, Rubnitz J, Silverman L, Stary J, Campbell M, Li CK, Mann G, Suppiah R, **Biondi A**, Vora A, **Valsecchi MG**. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. **Lancet.** 2007 Jul 21;370(9583):240-50. ▪ Aiuti A, Cattaneo F, **Galimberti S,** Benninghoff U, Cassani B, Callegaro L,

	Scaramuzza S, Andolfi G, Mirolo M, Brigida I, Tabucchi A, Carlucci F, Eibl M, Aker M, Slavin S, Al-Mousa H, Al Ghonaium A, Ferster A, Duppenthaler A, Notarangelo L, Wintergerst U, Buckley RH, Bregni M, Marktel S, **Valsecchi MG,** Rossi P, Ciceri F, Miniero R, Bordignon C, Roncarolo MG. Gene therapy for immunodeficiency due to adenosine deaminase deficiency. **N Engl J Med**. 2009 Jan 29;360(5):447-58. ▪ Basso G, Veltroni M, **Valsecchi MG**, Dworzak MN, Ratei R, Silvestri D, Benetello A, Buldini B, Maglia O, Masera G, Conter V, Arico M, **Biondi A**, Gaipa G. Risk of relapse of childhood acute lymphoblastic leukemia is predicted by flow cytometric measurement of residual disease on day 15 bone marrow. **J Clin Oncol**. 2009;27:5168-74.

EMC	▪ **Zwaan CM**. An open label phase II trial of gemtuzumab ozogamicin in children with relapsed/refractory acute myeloid leukemia: results of study Relapsed AML 2001/02. **BrJHaematol.** 2009, in press. ▪ Porkka K, Koskenvesa P, Lundan T, Rimpilainen J, Mustjoki S, Smykla R, Wild R, Luo R, Arnan M, Brethon B, Eccersley L, Hjorth-Hansen H, Hoglund M, Klamova H, Knutsen H, Parikh S, Raffoux E, Gruber F, Brito-Babapulle F, Dombret H, Duarte RF, Elonen E, Paquette R, **Zwaan CM**, Lee FY. Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. **Blood**. 2008;112:1005-12. ▪ **Zwaan CM**, Rizzari C, Van der Velden VHJ, Beverloo B, den Boer ML, Baruchel A, Mechinaud F, Lancaster D, Matloub Y, Derreumaux D, Pieters R, and Kearn P. Dasatinib in Children and Adolescents with Relapsed or Refractory Leukemia: Interim Results of the CA180-018 Phase I Study from the ITCC Consortium. **Blood** (ASH Annual Meeting Abstracts). Nov 2008; 112: 3241.
LaFe	▪ **Cañete A,** Gerrard M, Rubie H et al. Poor survival for infants with MYCN-amplified metastatic neuroblastoma despite intensified treatment: the International Society of Paediatric Oncology European Neuroblastoma Experience. **J Clin Oncol**. 2009 Mar 1;27(7):1014-9. Epub 2009 Jan 26. ▪ De Bernardi B, Gerrard M, Boni L, Rubie H, **Cañete A**, Di Cataldo A, Castel V, Forjaz de Lacerda A, Ladenstein R, Ruud E, Brichard B, Couturier J, Ellershaw C, Munzer C, Bruzzi P, Michon J, Pearson AD. Excellent outcome with reduced treatment for infants with disseminated neuroblastoma without MYCN gene amplification. **J Clin Oncol.** 2009 Mar 1;27(7):1034-40. Epub 2009 Jan 26 ▪ **Cañete A**, Navarro S, Bermudez J et al. Angiogenesis in neuroblastoma: relationship to survival and other prognostic factors in a cohort of neuroblastoma patients". **J Clin Oncol.** 2000; 18(1): 27-34.
MUG	▪ Perilongo G, Maibach R, Shafford E, Brugieres L, Brock P, de Camargo B, Zsiros J, Roebuck D, Zimmermann A, Childs M, Widing E, Lathier V, Plaschkes J, Mackinlay G, Pritchard J, Scopinaro M, Aronson D, **Czauderna P**. Cisplatin versus Cisplatin-Doxorubicin for Standard Risk Hepatoblastoma. **N Engl J Med.** 2009 Oct 22;361(17):1662-1670 ▪ Neuwelt AJ, Wu YJ, Knap N, Losin M, Neuwelt EA, Pagel MA, Warmann S, Fuchs J, **Czauderna P**, Wozniak M:. Using acetaminophen's toxicity mechanism to enhance cisplatin efficacy in hepatocarcinoma and hepatoblastoma cell lines. **Neoplasia.** 2009 Oct;11(10):1003-11. ▪ **Czauderna P**, Otte JB, Aronson DC, Gauthier F, Mackinlay G, Roebuck D, Plaschkes J, Perilongo G. Guidelines for surgical treatment of hepatoblastoma in the modern era--recommendations from the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). **Eur J Cancer.** 2005 May;41(7):1031-6.
UOB	▪ Harris LM et al. Magnetic Resonance Spectroscopy in the assessment of Pilocytic Astrocytomas. **Eur J Cancer**, 2008; 44: 2640-7. ▪ González-Vélez H et al., Health Agents: Distributed Multi-Agent Brain Tumour Diagnosis and Prognosis. **Applied Intelligence**, 2009; 30: 191–202. ▪ **Peet AC** et al. Magnetic Resonance Spectroscopy suggests key differences in the metastatic behaviour of medulloblastoma. **Eur J Cancer**, 43, 1037-44, (2007).
IGG	▪ **Haupt R,** Spinetta JJ, Ban I, Barr RD, Beck JD, Byrne J, Calaminus G, Coenen E, Chesler M, D'Angio GJ, Eiser C, Feldges A, Gibson F, Lackner H, Masera G, Massimo L, Magyarosy E, Otten J, Reaman G, Grazia Valsecchi M, Veerman AJ, Penn A, Thorvildsen A, van den Bos C, Jankovic M. the International Berlin-Frankfurt-Munster Study Group Early and Late Toxicity Educational Committee (I-BFM-SG ELTEC). Long term survivors of childhood cancer: Cure and care The Erice Statement. **Eur J Cancer.** 2007;43:1778-1780 ▪ Fardin P. Barla A, Mosci S, Rosasco L., Verri A. and **Varesio L**. The L1-L2 regularization framework unmasks the hypoxia signature hidden in the transcriptome of a set of heterogeneous neuroblastoma cell lines. **BMC genomics.** 10:474, 2009 ▪ **Haupt R**, Fears TR, Robison LL, Mills JL, Nicholson HS, Zeltzer LK, Meadows AT, Byrne J. Educational attainment in long-term survivors of childhood acute lymphoblastic leukemia. **JAMA.** 1994 Nov 9;272(18):1427-32.

LTHTNHS &UoL	▪ Rodriguez-Rodriguez L, **Lewis I**, Somkin C. 'Clinical Care Models' in Closing the Gap: Research and Care Imperatives for Adolescents and Young Adults with Cancer. Report of the Adolescent and Young Adult Oncology Progress Review Group. pages B23 – B26, US Department of Health and Human Services. An National Institutes of Health, National Cancer Institute and Livestrong Young Adult Alliance Report, Washington DC (2006) ▪ Fern L, Davies S, Eden T, Feltbower R, Grant R, Hawkins M, **Lewis I,** Loucaides E, Rowntree C, Stenning S, Whelan J. National Cancer Research Institute (NCRI) Teenage and Young Adult Clinical Studies Development Group. Rates of inclusion of teenagers and young adults in England into National Cancer Research Network clinical trials: report from the National Cancer Research Institute (NCRI) Teenage and Young Adult Clinical Studies Development Group. **Br J Cancer**. 2008 99:1967-74 ▪ Paulussen M, Craft AW, **Lewis IJ**, Hackshaw A, Douglas C, Ahrens S, Dunst J, Schuck A, Winkelmann W, Köhler G, Poremba C, Zoubek A, Ladenstein R, van den Berg H, Hunold A, Cassoni A, Spooner D, Grimer R, Whelan J, Mc Tiernan A, Jürgens H. European Intergroup Co-operative Ewings Sarcoma Study-92. Results of the EICESS-92 Study: two randomized trials of Ewing's sarcoma treatment--cyclophosphamide compared with ifosfamide in standard-risk patients and assessment of benefit of etoposide added to standard treatment in high-risk patients. **J Clin Oncol.** 26: 385-93 (2008)
CURIE	▪ H. Chappuy, **F. Doz**, S. Blanche, J.-C. Gentet, J.-M. Tréluyer. Children's views on their involvement in clinical research. **Pediatr Blood Cancer.** 50 : 1043 – 1046, 2008 ▪ S. Fattet, C. Haberler, P. Legoix, P. Varlet, A. Lellouch-Tubiana, S. Lair, E. Manie, M.-A. Raquin, D. Bours, S. Carpentier, E. Barillot, J. Grill, **F. Doz,** S. Puget, I. Janoueix-Lerosey, **O. Delattre.** Beta-Catenin Status in Paediatric Medulloblastomas : Correlation of Immunohistochemical Expression with Mutational Status, Genetic Profiles and Clinical Characteristics. **J Pathol**. 218:86-94, 2009 ▪ P.Frange, C.Alapetite, G.Gaboriaud, D.Bours, J-M.Zucker, M.Zerah, H.Brisse, V.Mosseri, E.Bouffet, **F.Doz.** From childhood to adulthood: long-term outcome of medulloblastoma patients. The Institut Curie experience. **J Neuro-Oncol.** 95:271-279, 2009 ▪ Janoueix-Lerosey I, Schleiermacher G, Michels E, Mosseri V, Ribeiro A, Lequin D, Vermeulen J, Couturier J, Peuchmaur M, Valent A, Plantaz D, Rubie H, Valteau-Couanet D, Thomas C, Combaret V, Rousseau R, Eggert A, Michon J, Speleman F, **Delattre O**. Overall genomic pattern is a predictor of outcome in neuroblastoma. **J Clin Oncol.** 2009 Mar 1;27(7):1026-33. ▪ Janoueix-Lerosey I, Lequin D, Brugières L, Ribeiro A, de Pontual L, Combaret V, Raynal V, Puisieux A, Schleiermacher G, Pierron G, Valteau-Couanet D, Frebourg T, Michon J, Lyonnet S, Amiel J, **Delattre O**. Somatic and germline activating mutations of the ALK kinase receptor in neuroblastoma. **Nature**. 2008 Oct 16;455(7215):967-70. ▪ Vermeulen J, Ballet S, Oberlin O, Peter M, Pierron G, Longavenne E, Laurence V, Kanold J, Chastagner P, Lejars O, Blay JY, Marec-Berard P, Michon J, Delattre O, Schleiermacher G. Incidence and prognostic value of tumour cells detected by RT-PCR in peripheral blood stem cell collections from patients with Ewing tumour. Br J Cancer. 2006 Nov 20;95(10):1326-33. ▪ Tirode, F., Laud-Duval, K., Prieur, A., Delorme, B., Charbord, P., Del**attre, O.** Mesenchymal features of Ewing tumours. **Cancer Cell.** 11, 421-129, 2007 ▪ **Delattre, O.**, Zucman, J., Plougastel, B., Desmaze, C., Melot, T., Peter, M., Kovar, H., Joubert, I., De Jong, P., Rouleau, G., Aurias, A. and Thomas, G. Gene fusion with an ETS domain caused by chromosome translocation in human tumours. **Nature.** 359:162-165, 1992. ▪ Versteege, I., Sevenet, N., Lange, J., Rousseau-Merck, MF., Ambros, P., Handgretinger, R., Aurias, A., **Delattre, O**. Truncating mutations of hNF5/INI1 in aggressive paediatric cancers**. Nature.** 394:203-206, 1998. ▪ **Patents** ▪ Patent n° 92/06123 du 20/05/92 « Séquences d'ADN des produits de fusion résultant de la translocation chromosomique t(11 ;22) associée au développement d'un groupe de tumeurs cancéreuses ». Alain Aurias, Olivier Delattre, Chantal Desmaze, Thomas Melot, Martine Peter, Béatrice Plougastel, Gilles Thomas, Jessica Zucman

FORTH	▪ Zervakis M, Blazadonakis M.E., Danilatou V, Tsiliki G., **Tsiknakis M., Kafetzopoulos D**. Outcome Prediction Based on Microarray Analysis: A Critical Perspective on Methods. **BMC Bioinformatics.** 2009, 10:53. ▪ Graf N., Hoppe A., Georgiadi E, Belleman R., Desmedt C., Dionysiou D., Erdt M., Jacques J., Kolokotroni E., Lunzer A., **Tsiknakis M**., Stamatakos G. The impact of 'in silico' oncology on clinical decision making in the context of nephroblastoma, Clinical Paediatrics. **Klin Padiatr**. 2009; 221: 1– 9. ▪ **Tsiknakis M.,** Brochhausen M., Nabrzyski J., Pucaski J., Sfakianakis S., Potamias G., Desmedt C. and **D. Kafetzopoulos**. A semantic grid infrastructure enabling integrated access and analysis of multilevel biomedical data in support of post-genomic clinical trials on Cancer. **IEEE Transactions on Information Technology in Biomedicine**, Special issue on Bio-Grids, 2008, vol 12, no 2, pp. 191-204.
AIT	▪ **Schreier G**, Messmer J, Rauchegger G, Modre-Osprian R, Ladenstein R. A Web-based platform for interdisciplinary biomedical research. **Front Biosci.** 2009 Jan 1;14:2738-46. ▪ Kollmann A, Hayn D, García J, Trigo JD, Kastner P, Rotman B, Tscheliessnigg K, **Schreier G.** Feasibility of a telemedicine framework for collaborative pacemaker follow-up. **J Telemed Telecare**. 2007;13(7):341-7. ▪ Morak J, Schwetz V, Hayn D, Fruhwald F, **Schreier G**. Electronic data capture platform for clinical research based on mobile phones and near field communication technology. **Conf Proc IEEE Eng Med Biol Soc**. 2008;2008:5334-7.
CINECA	▪ Web-based international studies in limited populations of paediatric leukemia. **Paediatric blood & cancer** 2008;50(2):270-3. ▪ Survival of children with cancer in Italy, 1989-98. A report from the hospital based registry of the Italian Association of Paediatric Haematology and Oncology (AIEOP). **EJC European Journal of Cancer**. volume 44, No. 9, June 2008. ▪ Moving towards information Based Medicine in paediatric oncology. **Italian Journal of Paediatrics**. 2006; n. 32:14-18
AMC	▪ Molenaar, JJ, Ebus, ME, Geerts, D, **Koster J**, Lamers, SGM, Valentijn, LJ, Westerhout, EM, **Versteeg, R**, **Caron, HN**. CDK2 targeting is synthetically lethal to MYCN over-expressing cancer cells. **Proc Natl Acad Sci U S A.** 2009, 106(31):12968-73. ▪ Huang S, Laoukili J, Epping MT, **Koster J,** Holzel M, Westerman BA, Nijkamp, Hata A, Asghazadeh S, Seeger RC, **Versteeg R,** Beijersbergen RL, Bernards R. ZNF423 Is Critically Required for Retinoic Acid-Induced Differentiation and Is a Marker of Neuroblastoma Outcome. **Cancer Cell.** 2009, 15(4):328-40.
CLB	▪ **Marec-Berard P**, Azzi D, Chaux-Bodard AG, Lagrange H, Gourmet R, **Bergeron C.** Long-term effects of chemotherapy on dental status in children treated for nephroblastoma. **Pediatr Hematol Oncol.** 2005 Oct-Nov;22(7):581-8. ▪ Oberlin O, Fawaz O, Rey A, Niaudet P, Ridola V, Orbach D, **Bergeron C**, Defachelles AS, Gentet JC, Schmitt C, Rubie H, Munzer M, Plantaz D, Deville A, Minard V, Corradini N, Leverger G, de Vathaire F. Long-term evaluation of Ifosfamide-related nephrotoxicity in children. **J Clin Oncol.** 2009 Nov 10;27(32):5350-5. ▪ Ridola V, Fawaz O, Aubier F**, Bergeron C**, de Vathaire F, Pichon F, Orbach D, Gentet JC, Schmitt C, Dufour C, Oberlin O. Testicular function of survivors of childhood cancer: a comparative study between ifosfamide- and cyclophosphamide-based regimens. **Eur J Cancer.** 2009 Mar;45(5):814-8.
IARC	▪ **Steliarova-Foucher E**, Stiller CA, Lacour B, Kaatsch P. International Classification of Childhood Cancer. Third Edition. **Cancer.** 2005; 103: 1457-67. ▪ **Steliarova-Foucher E**, Coebergh JW, Kaatsch P, Pritchard-Jones K, Stiller C. (Eds.) Cancer in Children and Adolescents in Europe. **Eur J Cancer**. 2006, 42(13), 1913-2190. ▪ **Steliarova-Foucher** E, Arndt V, Parkin DM, Berrino F, Brenner H. Timely disclosure of progress in childhood cancer survival by period analysis in the Automated Childhood

	Cancer Information System. **Ann Oncol.** 18: 1554–1560, 2007.

UNIPD	▪ **Bisogno G**, Ferrari A, Prete A, Messina C, Basso E, Cecchetto G, Indolfi P, Scarzello G, D'Angelo P, De Sio L, Di Cataldo A, Carli M. Sequential high-dose chemotherapy for children with metastatic rhabdomyosarcoma. **Eur J Cancer**. 2009 Nov;45(17):3035-41. ▪ Pastore G, De Salvo GL, **Bisogno G**, Dama E, Inserra A, Cecchetto G, Ferrari A; TREP Group; CSD of Epidemiology Biostatistics, AIEOP. Evaluating access to paediatric cancer care centers of children and adolescents with rare tumours in Italy: the TREP project. **Pediatr Blood Cancer**. 2009 Aug;53(2):152-5. ▪ Ferrari A, **Bisogno G**, De Salvo GL, Indolfi P, Perilongo G, Cecchetto G. Italian Study on Rare Tumours in Paediatric Age (TREP); Associazione Italiana Ematologia Oncologia Paediatrica (AIEOP). The challenge of very rare tumours in childhood: the Italian TREP project. **Eur J Cancer**. 2007 Mar;43(4):654-9. ▪ **Basso G**, Veltroni M, Valsecchi MG, Dworzak MN, Ratei R, Silvestri D, Benetello A, Buldini B, Maglia O, Masera G, Conter V, Arico M, Biondi A, Gaipa G. Risk of relapse of childhood acute lymphoblastic leukemia is predicted by flow cytometric measurement of residual disease on day 15 bone marrow. **J Clin Oncol**. 2009;27:5168-74. ▪ Haferlach T, Kohlmann A, Wieczorek L, **Basso G**, te Kronnie G, Bene M Ch et al. The clinical utility of microarray-based gene expression profiling in the diagnosis and subclassification of leukemia: report on 3334 cases from the international MILE study group. **J Clin Oncol**. 2009 (in press) ▪ Bresolin S, Zecca M, Flotho Ch, Trentin L, Zandrando A, Sainati L, Stary J, de Moerloose B, Hasle H, Niemeyer Ch, te Kronnie G, Locatelli F, Basso G. Gene expression based classification as an independent predictor of clinical ourcome in juvenile myelomonocytic leukemia. J Clin Oncol. 2009 (in press)
LUMC	▪ Schrage YM, Briaire-de Bruijn IH, de Miranda NF, van Oosterwijk J, Taminiau AHM, van Wezel T, **Hogendoorn PCW**, Bovee JVMG. Kinome profiling of chondrosarcoma reveals SRC-pathway activity and dasatinib as option for treatment. **Cancer Res**. 2009;69:6216-6222 ▪ **Cleton-Jansen AM**, Anninga JK, Briaire-de Bruijn IH, Romeo S, Oosting J, Egeler RM, Gelderblom H, Taminiau AHM, **Hogendoorn PCW**. Profiling of high-grade central osteosarcoma and its putative progenitor cells identifies tumourigenic pathways. **British J Bcancer**. 2009 ▪ Szuhai K, Ijszenga M, de Jong D, Karseladze A, Tanke HJ, **Hogendoorn PCW.** The NFATc2 gene is involved in a novel cloned translocation in a ewing sarcoma variant that couples its function in immunology to oncology. **Clin Cancer Res**. 2009;15:2259-2268
KAROLINSKA	▪ Gleissman et al. "Docosahexaenoic acid metabolome in neural tumours: Identification of cytotoxic intermediates". **FASEB J,** 2009, Nov 12. [Epub ahead of print]. ▪ Hanaka et al. "Microsomal prostaglandin E synthase 1 determines tumour growth in vivo of prostate and lung cancer cells". **Proc Natl Acad Sci USA**. 2009, 106:18757-62. ▪ Baryawno et al. "Small molecule inhibitors of PI3K/Akt signaling inhibit Wnt/beta-catenin pathway crosstalk and suppress medulloblastoma growth". **Cancer Research.** 2009, in press.
UGent	▪ Vermeulen J, De Preter K, Naranjo A, Vercruysse L, Van Roy N, Hellemans J, Swerts K, Bravo S, Scaruffi P, Tonini GP, De Bernardi B, Noguera R, Piqueras M, Cañete A, Castel V, Janoueix-Lerosey I, Delattre O, Schleiermacher G, Michon J, Combaret V, Fischer M, Oberthuer A, Ambros PF, Beiske K, Bénard J, Marques B, Rubie H, Kohler J, Pötschger U, Ladenstein R, Hogarty MD, McGrady P, London WB, Laureys G, **Speleman F**, Vandesompele J. Predicting outcome for children with neuroblastoma using a multi-gene expression signature: a retrospective SIOPEN/COG/GPOH study. **Lancet Oncol.** 2009 Jul;10(7):663-71. Epub 2009 Jun8. ▪ Ambros PF, Ambros IM, Brodeur GM, Haber M, Khan J, Nakagawara A, Schleiermacher G, **Speleman F**, Spitz R, London WB, Cohn SL, Pearson AD, Maris JM. International consensus for neuroblastoma molecular diagnostics:report from the international neuroblastoma risk group (INRG) biology committee. **Br J Cancer**.

	2009 May 5;100(9):1471-82. ▪ Vandesompele J, Baudis M, De Preter K, **Van Roy N**, Ambros P, Bown N, Brinkschmidt C, Christiansen H, Combaret V, Lastowska M, Nicholson J, O'Meara A, Plantaz D, Stallings R, Brichard B, Van den Broecke C, De Bie S, De Paepe A, Laureys G, **Speleman F**.-Unequivocal delineation of clinicogenetic subgroups and development of a new model for improved outcome prediction in neuroblastoma.**J Clin Oncol**. 2005 Apr 1;23(10):2280-99. ▪ **Patent:** "Identification of neuroblastoma tumour suppressor genes" (ep.00870219.3-PCT/EP01/11199). Published patent application WO 02/26815. Inventors: F. Van Roy, K. Staes, K. Vandepoele, N. Van Roy, F. Speleman.
CHARITE	▪ Roy A, Cargill A, Love S, Moorman AV, Stoneham S, Lim A, Darbyshire PJ, Lancaster D, Hann I, Eden T, **Saha V**. Outcome after first relapse in childhood acute lymphoblastic leukaemia - lessons from the United Kingdom R2 trial. **Br J Haematol.** 2005;130:67-75. ▪ Hagedorn N, Acquaviva C, Fronkova E, **von Stackelberg A**, Barth A, zur Stadt U, Schrauder A, Trka J, Gaspar N, Seeger K, Henze G, Cave H, Eckert C. Submicroscopic bone marrow involvement in isolated extramedullary relapses in childhood acute lymphoblastic leukemia: a more precise definition of "isolated" and its possible clinical implications, a collaborative study of the Resistant Disease Committee of the International BFM study group. **Blood.** 2007;110:4022-4029. ▪ Bader P, Kreyenberg H, Henze GH, Eckert C, Reising M, Willasch A, Barth A, Borkhardt A, Peters C, Handgretinger R, Sykora KW, Holter W, Kabisch H, Klingebiel T, **von Stackelberg A.** Prognostic value of minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the ALL-REZ BFM Study Group. **J Clin Oncol.** 2009;27:377-384.
OLGA	▪ **Bielack S**, Carrle D, Casali PG; ESMO Guidelines Working Group. Osteosarcoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. **Ann Oncol.** 2009; 20 Suppl 4:137-9. ▪ Carrle D, Dantonello T, **Bielack S**. Pan-European Sarcoma Trials: Moving Forward in a Climate of Increasing Economic and Regulatory Pressure. **Sarcoma.** vol. 2007, Article ID 76405, 7 pages, 2007. ▪ **Bielack S**, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. **J Clin Oncol.** 2002; 20:776-90
SOUTHAMPTON	▪ Baggott C, Dodd M, *Kennedy C*, Marina N, Matthay KK, Cooper B, Miaskowski C. Changes in Children's Reports of Symptom Occurrence and Severity During a Course of Myelosuppressive Chemotherapy. ;J Pediatr Oncol Nurs. 2010 Aug 25. ▪ ***Kennedy C***. Developing pre-school surveillance tools for adaptive functioning: lessons for neuro-oncology. Eur J Paediatr Neurol. 2010 Sep;14(5):367. Epub 2010 May 6.

ANNEX 2
Glossary

A	AC	Activity Coordinator
	ALL	Acute Lymphoblastic Leukaemia
	AML	Acute Myelogenous Leukaemia
	AYA	Adolescent and Young Adults
C	CAg	Consortium Agreement
	CCLTS	Childhood Cancer Long-Term Survivors
	CESP	Confederation of European Specialists in Paediatrics
	CNS	Central Nervous System
	Council	European Clinical Research Council for Paediatric and Adolescent Oncology
	CTA	Clinical Trial Authorisation
D	DiBi	Digital Biobank
	DICOM	Digital Imaging and Communications in Medicine
	DNA	Desoxyribo Nucleic Acid
E	EAG	Ethics Advisory Group
	EBP	European Board of Paediatrics
	EC	European Commission / Executive Committee
	ECRC	European Clinical Research Council in Paediatric and Adolescent Oncology
	EDC	Electronic Data Capture
	EEIC	European Economic Interest Group
	EMEA	European Medicines Agency
	ENCR	European network of Cancer Registries
	ERA	European Research Area
	E-RDE	
	ETC	Educational Training Committee
	EU CTD	European Clinical Trial Directive
F	FDG-PET	2-Fluoro-2-Déoxy-D-Glucose Positron Emission Tomography
	FISH	Fluorescent In Situ Hybridisation
G	GA	General Assembly
	GIST	Gastro Intestinal Stromal Tumour
H	HSCT	Hematopoietic Stem Cell Transplantation
I	ICT	Information and Communication Technology
	IDCT	Investigator-Driven Clinical Trials
	IHE	Integrating the Healthcare Enterprise
	IMP	Investigational Medicinal Product
	INPC	International Neuroblastoma Pathology Classification
	IPRC	Intellectual Property Rights Committee
	IT	Information Technology
	ITCC	Innovative Therapies for Children with Cancer
J	JMML	Juvenile Myeolomonocytic Leukaemia
L	LINES	Low and Intermediate risk Neuroblastoma SIOPEN study
M	MDS	Myelodisplastic Syndrome
	MIBG	Méta-iodobenzylguanidine
	MLPA	Multiplex Ligation-dependent Probe Amplification
	MRD	Minimal Residual Disease
	MRI	Magnetic Resonance Imaging
N	NC	Network Coordinator
	NGO	Non-Governmental Organisation
	NHL	Non-Hodgkin Lymphoma
P	PDCA	Plan-Do-Check-Act
	PDCO	Paediatric committee
	PIP	Paediatric Investigation Plan
	PMT	Project Management Team
Q	QoS	Quality of Survivorship
R	RNA	Ribo Nucleic Acid
S	SAB	Scientific Advisory Board

	SAE	Statistical approaches for the Analysis of recurrent Events
	SOP	Standard Operating Procedure
	SUSARS	Suspected Unexpected Serious Adverse Reactions
T	TITE-CRM	Time-to-Event methods for the Continual Reassessment Method
	TKI	Tyrosine Kinase
	TYA	Teenagers and Young Adults
V	VHRL	Very High-Risk ALL
W	WPL	Work-Package Leader