CONTRACT

CONSENT IN A TRIAL & CARE ENVIRONMENT

SEVENTH FRAMEWORK PROGRAMME

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Project Overview

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Abstract

The CONTRACT consortium held the first stakeholder workshop in Hannover, Germany on 15 September 2011. CONTRACT analyzes the impact of the European Data Protection Directive and the Clinical Trials Directive on translational research by focusing on informed consent as a fundamental precondition for the legal processing of personal data and for conducting legally admissible trials. The main aims of CONTRACT are to document how ongoing and upcoming European and national translational projects deal with consent issues, define good practices, provide policy recommendations, and to offer a helpdesk on consent issues for partner projects.

The workshop aimed to discuss the results from the survey in WP2 (Problem Analysis) and get feedback on the draft guidelines for informed consent for use in European

research projects produced by Task 3.4 (Good practice cases for dissemination). This deliverable reports on the outcomes of this workshop and will become a basis for the development of the guide of good practices.

Table of Contents

Executive summary

The first CONTRACT stakeholder workshop took place in Hannover, Germany, on the 15th of September 2011.

Informed consent is a precondition for the success of translational research and acts as a legal and ethical requirement, enabling the active participation of patients in translational research. However, due to the fact that at least three different types of IC are relevant for translational research which are not consistent with each other, and there is no common understanding of informed consent in the literature difficulties in obtaining and handling informed consent frequently arise. The EU legislation has direct influence on issues of informed consent through the Clinical Trials Directive and Data Protection Directive.

The project aims to support European decision makers in identifying inconsistencies in the legal concepts behind the different rules for informed consent and in producing proper and consistent standards for informed consent, as well as to support stakeholders in day-to-day handling of informed consent issues.

This objective shall be reached by creating a wide picture of informed consent which will connect legal, IT and clinical expertise, be stakeholder-oriented, and by combining partner project's input considering the legislation analysis.

The workshop aimed to discuss the results of the survey from WP2 (Problem Analysis) and get feedback on the draft guidelines for informed consent for use in European research projects produced by Task 3.4 (Good practice cases for dissemination). This deliverable reports on the outcomes of this workshop and will become a basis for the development of the guide of good practices.

Experts from the academic community (legal, clinical and technical), as well as major organizations and EU project representatives from eight European countries gathered to exchange knowledge and experience on issues related to the impact of the Clinical Trials Directive and Data Protection Directive on translational research and clinical trials. A list of participants is included in the Annex to this deliverable.

The workshop programme comprised seven (7) guest presentations and two (2) CONTRACT project presentations, each followed by a short discussion, in addition to discussion session.

Initially, the design and the results of the CONTRACT questionnaire were presented, followed by a guest presentation sharing experience/ knowledge on informed consent through related projects of the UK National Healthcare Service and Electronic Health Record. Subsequently, the activities of the Telematikplattform für Medizinische Forschungsnetze in relation to informed consent were reported, followed by a description of the European Clinical Research Infrastructures Network and its relation to informed consent for European research, as well as a presentation of the European Organisation for Research and Treatment of Cancer perspective on patient information

and consent documents. Additionally the European Network for Cancer Research in Children and Adolescents goals and actions, as well as the aims of the recently formed European Clinical Research Council and critical issues to be addressed in connection to clinical trials and informed consent were shown. Furthermore a two-step procedure for gaining informed consent was proposed.

The general discussion session focused on questions considering: the procedure of signing informed consent forms in stressful situations; the problem of the Clinical Trials Directive mainly offering protection to the researcher rather than to the patient; the dependency of the patient on the provided information and on the doctor in taking a decision; the difference between standard treatment vs. clinical trial; the importance of gaining trust between the patient and physician; the general impact of the Clinical Trials Directive in declining trial numbers, rising costs and decreasing survival rates – a clear indication that the regulations must be changed; the need for a better model that serves the patient and enables patient to enroll in clinical trials; timing of informed consent; past and future benefits in participating in clinical trials; a possible regulatory strategy for split disciplines.

Following the discussion, the planned CONTRACT helpdesk was described, followed by a presentation of the Biobanking and Biomolecular Resources Research Infrastructure project and its waiver mechanisms. Finally, a thorough analysis of the concept of consent in relation to data protection and clinical trials, as it is defined by the Data Protection Directive and Clinical Trials Directive, was given. The workshop closed with final remarks from the CONTRACT external advisory board.

Acronyms

BBMRI	Biobanking and Biomolecular Resources Research Infrastructure
CT	Clinical trial
CTD	Clinical Trials Directive
CTMS	Clinical trial management system
DPD	Data Protection Directive
EC	Ethics committee
ECRC	European Clinical Research Council
ECRIN	European Clinical Research Infrastructures Network
EHR	Electronic Health Record
ENCCA	European Network for Cancer Research In Children and Adolescents
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FAQ	Frequently asked questions
IC	Informed consent
IRB	Institutional review board
IRI	Institute for Legal Informatics
IT	Information technology
LUH	Leibniz Universität Hannover
NHS	National Healthcare Service
PIS	Patient information sheet
SIOP	International Society of Paediatric Oncology
SOP	Standard operating procedures
TMF	Telematikplattform für Medizinische Forschungsnetze
UK	United Kingdom

Terms of reference

The first CONTRACT workshop had two major objectives: the first was to inform stakeholders about the ongoing processes and current status of the project, the second and main objective was to collect feedback from the stakeholders (institutions, EU projects, clinicians) during the development stage of CONTRACT's outcomes. The current report compiles the collected stakeholder and consortium member views.

Acknowledgements

The CONTRACT consortium wishes to thank all participants for their contributions and the valuable discussions, especially Dag Wiese Schartum and Cecilia Magnusson Sjöberg, from the external advisory board of the CONTRACT project, for their extraordinary engagement.

Disclaimer

This report summarizes stakeholders' views collected during the first CONTRACT workshop and does not necessarily reflect the opinion of the authors. The collected comments and recommendations will be considered during the future work of the CONTRACT project. The authors are not responsible for any errors, misinterpretations or omissions.

1 Introduction

In the introductory remarks and the project documentation the following information was distributed among the participants:

CONTRACT seeks to establish methods to understand the way the *European Data Protection Directive*[1] (DPD) and the *Clinical Trials Directive*[2] (CTD) have had and continue to have an impact on the success of translational research. The project will focus on **informed consent** (IC) as a fundamental precondition for the legal processing of personal data and for conducting legally admissible trials. The main aims of CONTRACT are to document how ongoing and upcoming European and national translational projects deal with consent issues, define good practices, provide policy recommendations, and to offer a helpdesk on consent issues for partner projects.

Translational research entails the communication and exchange of information. This also involves personal data being shared and transferred between care and research contexts, between different clinical disciplines and between different research groups, sometimes even in different countries.

Data protection regulations require that the data are collected only for specified, explicit and legitimate purposes and require in many cases the patient's IC for processing the data. However, requirements for adequate and valid IC can differ widely between the contexts of care and research and between different countries. Further differences exist in their legal bases, in their doctrine and in the consequences a breach of consent might have. Within translational research projects, at least three different forms of IC are relevant: consent to treatment, consent to research and consent for processing personal data, each separately defined.

Differences, as those mentioned above, produce a complex web of legal and ethical considerations which become even more problematic in trials conducted across national borders. In addition, IT-systems set up for care and for trials are frequently seen as different worlds and lack the interfaces needed to make the data transferable.

This results in legal uncertainty among researchers and clinicians and poses a serious challenge for the implementation of clinical trials (CTs), resulting in growing costs, delays in starting trials and, consequently, in a significant drop in the number of academic trials conducted.

[1] Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data ("*Data Protection Directive*").

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32002L0058:en:HTML

[2] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws,regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use" ("*Clinical Trials Directive*").

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32001L0020:EN:HTML

CONTRACT supports translational research projects – both ongoing and upcoming by:

- Analyzing different approaches to IC both in European projects and in European member states.
- Analyzing the IT-related representation of different understandings of IC and the outcome of these differences in the daily clinical and/or research routine.
- Advising translational research projects in all issues of IC.
- Delivering concrete policy recommendations as to how the European Union (EU) can both protect patient's rights and support translational research via a better structured approach towards consent issues.

The project focusses on issues of IC in vulnerable patient groups, where requirements for IC are at their most complexity. Furthermore, it will produce the following main outcomes for European translational research projects:

- A knowledge base of the problems and different approaches in matters of IC, in particular for vulnerable patient groups.
- An analysis of the legal and ethical reasons for these different approaches and the role played by EU-legislation.
- Identification of good practices in data protection related issues of IC and the transferability for translational research projects in general
- A policy-oriented study and set of recommendations for EU policy makers to optimize the handling of IC.
- A helpdesk offering concrete advice, FAQs and guidelines on IC issues while protecting patient rights and supporting more efficient execution of contemporary translational research.

As keystones of the dissemination and exploitation activities of CONTRACT, a midterm and an endterm workshop with relevant policy stakeholders and cooperating projects are planned. These workshops serve to elaborate and discuss lessons learned, good practice guidelines and future steps.

The first workshop was organized in month 12 by the University of Hannover and took place on the 15th September 2011. The main aim of this workshop was to discuss the results of the WP2 (Problem Analysis) survey and get feedback on the draft guidelines for IC for use in European research projects produced by Task 3.4 (Good practice cases for dissemination).

2 Welcome address, Nikolaus Forgó

Prof. Dr. Nikolaus Forgó, the head of the project management office at the Institute for Legal Informatics (IRI), Leibniz Universität Hannover (LUH) welcomed the participants and expressed his gratitude to them for their attendance at the workshop. He held an

introductory presentation, describing the background, the objectives and the organization of CONTRACT.

2.1 Summary

The background of the project is based on the point that the patient's cooperation, which has to be based on IC, is a precondition for the success of translational research. IC acts as a legal and ethical requirement, enabling the active participation of patients to translational research. However, due to the fact that three different forms of IC are relevant for translational research (consent to treatment, consent to research, consent for processing personal data), that these forms are not consistent with each other, and that there is no common understanding of IC in the literature, difficulties in obtaining and handling IC arise. This is also reflected in the poor availability of electronic tools (e-consent), which can only evolve upon clear legal frameworks. IC is even more critical when the person in question is not fully capable of taking an autonomous decision. This makes representation, assent and decisions taken in best interest of the patient questionable.

The EU legislation has direct influence on the IC through the CTD 2001/20/EC/Art. 2 (j), for consent for research, and the DPD 95/46/EC/Art. 2 (h), for consent for processing personal data, while the consent to treatment is only defined under national legislation.

Therefore CONTRACT aims to analyze and understand whether and how legal requirements of IC hinder translational research and how patients' legal and ethical rights are, or are not, protected in the best possible way. It further seeks to find out how far impediments are caused by either legislation on IC, lack of technical solutions, caused by legal boundaries as a result of not matching consent procedures, or clinical day to day handling issues of consent.

Furthermore the project aims to support European decision makers in identifying inconsistencies in the legal concepts behind the different rules for IC and in producing proper and consistent standards for IC, as well as to support stakeholders in day to day handling of IC issues.

This objective shall be reached by creating a wide picture of IC, which will connect legal, IT and clinical expertise, be stakeholder-oriented, and by combining partner project's input considering the legislation analysis.

Prof. Forgó finished his presentation by anticipating an interactive knowledge exchange procedure between the CONTRACT consortium and the guests/ stakeholders during the workshop.

3 CONTRACT presentation 1: Overview of the CONTRACT questionnaire and its results, Norbert Graf

Prof. Dr. Norbert Graf, head of the Department for Pediatric Oncology/ Hematology, University Hospital Homburg, presented an overview and the preliminary outcomes of the CONTRACT questionnaire.

3.1 Summary

Initially, a reference to current literature on issues regarding the participation of patients to CTs was given, showing that patients require adequate information about the trial logic, its voluntary nature, their rights to withdraw, as well as decision making power and awareness of their available choices before participating. Further, the literature shows that IC documents make a participation decision more difficult, while an emotion focused approach to consultation of doctors is necessary. Regarding an online consent 93% of patients usually consent in less than the minimum predicted reading time[3]. Concluding the literature review, current IC documents may not serve the intended purpose of protecting human participants, while at the same time becoming too long and complex without providing a sound basis for informed decision-making. Therefore the consent process, which is crucial to clinical research, should be strengthened by improving the readability of the consent forms.

Continuing, the design of the CONTRACT questionnaire was presented, the aim of which is to analyze the current situation concerning the legal, ethical, technical and clinical handling of consent in European projects dealing with vulnerable patient groups. The questionnaire and its analysis were conducted in three stages:

- Stage I, identification of target projects and relevant stakeholders.
- Stage II, drafting and dissemination of the questionnaire.
- Stage III, the analysis report.

The structure of the questionnaire is divided into six sections. The questions of the first three sections (*general questions, clinical care and research*) deal with:

- Different understandings of IC and its meaning by different stakeholders
- Different practices of IC between care and research environments
- National differences within European projects arising from differing implementation of EU legislation
- Barriers for translational research as a consequence of unclear or not existing IC
- Gaps between existing practice and legal and ethical regulations

The main questions of section four (*IT related*) deal with:

- In-depth analysis of the electronic mechanisms that support individuals' rights to control the disclosure of their health information for treatment (eConsent)
- The corresponding procedures and ICT technologies that guarantee the secure processing of personal data

[3] *Desch K, Li J, Kim S, Laventhal N, Metzger K, Siemieniak D, Ginsburg D: Analysis of informed consent document utilization in a minimal-risk genetic study. Ann Intern Med 155:316-322, 2011*

The main questions of section five (*legal/ ethical*) deal with:

- Legal and ethical issues of consent
- Data protection policies
- Procedures of control (audit) over the collection
- Negotiation of consent

The main questions of the sixth section (*handling)* deal with:

- The handling of consent forms, paper based and electronic

Participation statistics showed that 58 participants fully completed the questionnaire so far, while 145 completed only a part of it, resulting in a total of 203 participants. Answers came from 24 countries in the following order: Germany >> Greece > Belgium > Bulgaria > Switzerland > others. In general, a high experience in consent issues was noticed.

The results from the questionnaire analysis are summarized below. It must be noted that each question was analyzed independently of whether or not the participant fully completed the questionnaire. The percentage rates are generated on the basis of the respondents per question.

a) Section 1, general questions:

38% of the participants have signed an IC before, but only 42% of those received a copy of the IC. There is a high satisfaction rate among respondents with IC while medical and legal information needs to be more detailed. Different ICs exist in clinical care and research while the ability to re-consent is considered important. According to respondents, the physician plays an important role in the IC-giving process and an information sheet is of high relevance. Respondents answered that not more than 3 ICs are currently given at a time with not more than 5 pages, while they consider that less than 45% of the patients understand all items on ICs with barriers, seen with respect to research.

b) Section 2, clinical care related questions:

Half of chairpersons/ coordinators compile their ICs by themselves (69% use templates and 69% would pay for templates). 60% had to change the IC after ethical review and 91% believe that they have addressed all legal and ethical items. An information sheet is provided by 74% of the chairpersons/ coordinators. Respondents considered that a median of 24-48 hours needs to be given between diagnosis and signing the IC and finally the five most important topics to be included in IC for CTs are: Purpose of the trial > voluntary participation > foreseeable risks > data protection > benefit for patients.

c) Section 3, research related questions:

51% of researchers have experienced considerable barriers in their research projects, mainly due to the lack of IC. The questionnaire showed that scientists usually do not have an IC, possibly because they were not at the start of the trial.

d) Section 4, IT related questions:

Only 2 out of 10 have a Hospital Information System coming from a single vendor and 3 out of 8 store paper based IC electronically. One participant has e-consent in clinical care while 8 out of 19 manage consent related documents for CTs electronically. Clinical trial management systems (CTMS) of 37% can record electronically that the patient has signed the IC. Only in 2 cases (12%) a consent management system is provided by the CTMS. Only in 4 cases (24%) the patient can obtain an overview of the consent he/ she has given.

e) Section 5, legal/ ethical related questions:

53% of participants have to deal with different legal sources while most of them (74%) are aware of EU regulations but 11% do not fulfill them. This causes difficulties with an impact in 34% of projects. 72% have specific data protection policies and 58% have their own data protection officer. 36% want to have negotiable IC procedures while an accreditation is needed by 34% of the participants. In 55% institutions patients can access their data after signing an IC. 55% share non-personal data within the same country, 51% within EU and 38% outside the EU. In 88% of the cases the patient is informed about data sharing, but none of the institutes have specific legal support.

f) Section 6, consent handling related questions:

Nearly half of the patients are considered to be able to sign an IC electronically. An alternative between paper based and electronic IC is required by 47% of participants to be always available. An electronic form should be based on modules (78% requests). Possible modules are for care, trial, research, biobanking, data storage and data transfer. Patients should be able to withdraw IC by any way they wish as mentioned by the majority of participants.

3.2 Discussion

A technical question considering the access to answers of non-fully submitted questionnaires was answered by explaining that the submission of the questionnaire was possible in several phases, permitting access to the answers of each phase. Further comments on the questionnaire included the low participation rate, which could be explained due to the high prerequisites of experience and knowledge (e.g. requiring medical competence from a lawyer or IT specialist) of the participants, meaning that many questions could not be answered by average participants. Another problem occurred due to the uncertainty whether one should answer the questions as an individual or member of an organization, which, in combination with the overall experience on the questionnaire, resulted to a proposal for the future of having three different questionnaires instead of one with different parts. The results of the questionnaire can nonetheless be considered to be stable, because there was no significant change in the outcome within the last weeks (mid-term and end).

It is also noticeable that it is not possible to compare between different countries because of relatively low respondent rate, meaning that the results are based on

experience of individual countries. From that, a lesson learned is not to overstress a questionnaire's design, although it is not a direct limitation of the questionnaire.

Further comments on the questionnaire included that users felt uncomfortable with some of the questions due to a lack of knowledge. The mixture of addressing individuals/ organizations/ clinicians/ lawyers/ IT specialists may limit the power of analysis, so the roles of respondents should be selected more clearly (in the beginning).

A remark here states that the patient's opinion was not to be analyzed.

Other comments addressed the issue of not making a distinction between national law and EU law. The European law must be implemented and in the case of conflicts prevails over national law, so there should be a need to distinguish, probably in the case of analyzing multi-national vs. national trials.

E-consent related questions were further discussed, pointing out that the electronic signature is the most important characteristic of e-consent, having to assure that the patient is really the one who should sign, although the electronic signature may inhibit the e-consent process. It is also legally relevant that a "qualified" signature must be truly qualified. Generally, management of the e-consent raises security and legally relevant issues. To overcome the digital signature problem an IC could be signed traditionally and then be managed electronically. On the e-consent matter, the questionnaire showed that 40% think e-consent is possible, a number which seems to be unusually high.

4 Guest presentation 1: Cambridge Health Informatics, Peter Singleton

Peter Singleton, Director at Cambridge Health Informatics Limited and principal research fellow at University College London, presented his experience/ knowledge on IC through related projects of the UK NHS and Electronic Health Record (EHR).

4.1 Summary

After a short introduction to a number of related projects such as the Clinical eScience Framework (CLEF) – developing principles for a cancer-based research database (UK), DebugIT – a database for anti-microbial research (EU), DemReg – a research registry for dementia patients (UK), EHR4CR – EHRs for Clinical Research (EU) and VPH-Share – Virtual Physiological Human: Sharing for Healthcare - A Research Environment (EU), focus was given on IC related issues. There exist many types of IC (consent to treatment, consent to CT, consent to screening, consent to blood/organ donation after death, "consent to consent" (agree to be contacted for research), consent to data use for epidemiology/research, consent for non-medical uses – e.g. marketing), which all are trying to avoid various risks such as:

- Consent to treatment/surgery – dispute after the event; side-effects; risks in treatment – "I didn't know that ..." – treatment on un-informed

- Consent to CT – risk of "unknown"; possibly worse treatment – originally, coerced experiments
- Consent to data use – possible breach of confidentiality/privacy – plenty of examples of PIs checking medical records, but not of research breaches (or simply not be detected?)
- Consent for other uses: misuse, e.g. junk mail

In practice though, IC is usually used just to protect the doctor/ provider and not to help the patient. It makes the patient bear the risks (of any error or mistreatment as well) and is usually formulaic. Moreover it is a one-way process – patient told, patient gets "consented" – not a dialogue and rarely does it support a patient's "choice".

Concerning the legal aspect of IC, it is being regulated by the CTD and the OECD Principles/EU DP Directive, which raise a number of questions in terms of mental capacity of the one signing, the usage of consent as an evidence that an action was sanctioned/ agreed, as well as its usage to help the lawyer and not the patient.

Further on the definitions of privacy, confidentiality, security, consent, express consent and implied consent were given according to the NHS "Gaining Patient Consent to Disclosure report 2001" and focus on the consent developing process was set, where the most important thing is to help the patient make a choice in a difficult framework of many levels of consent (incl. dissent, passive/ active consent, implicit consent, express consent, express written consent) and timing issues such as ab initio/ once-off for life, remote, per episode, at point of care, at each point of confidence, patient-driven and change of consent.

There are also some operational aspects of consent such as recording what has been consented to by whom, using consent given in practice (enacting), maintaining consent, managing change of consent/ dissent, training consent recorders (& clinicians), cultural barriers (internal & external) and resourcing implications in combination with the varying medium of consent including general acceptance (e.g. nod or shrug), formal verbal acceptance (yes – I do), signed form, witnessed signed form, electronic consent (how to identify?), dissent only – written (to accept consequences).

Finally, current issues in connection with Mr. Singleton's work and experience from ongoing projects were presented:

a) General:

- What use of data is implicit/ tacit in consent to treatment? Is data-processing consent wholly separate from consent to treatment? What options must healthcare providers support?
- What level of "de-identification" is sufficient to remove need for "consent"?
- How "broad" a "consent to research use" is possible?
- Is research use of data like blood/ organ donation (only less painful/ risky)?

b) Project VPH-Share:

- How to define “consent” in semantic terms so one can deduce whether a particular study can access a particular data-set in line with individuals’ expressed wishes?

c) Project EHR4CR:

- Do we need “consent to consent”? Viz. to be approached for consent?

d) Project DemReg:

- Can the registry itself be used for research?

4.2 Discussion

The discussion was opened by the question of which type of consent (express consent vs. implied consent, dissent, future consent) is most suitable in encouraging participation at CTs and research in the context of giving people a choice – helping the patients – instead of defining a legal process. Creating awareness on this subject is important and implies fully informing the involved persons, which is a quite difficult task. Maybe it would be enough for people to know that the information exists and that it can be read later.

The possibility of future/ further use of data is also an important issue. A patient may re-consent once, but not every time the data is being used for another purpose. Therefore the perspective of the patient is important in a continuous learning process. If one benefits from the past, then help for future, probably non understandable research acts, is necessary. An idea would be for a patient to give a general consent to any research while keeping the option to opt-out any participation/ data usage in the future (i.e. “deselecting projects”). In Norway e.g. there exists a broad consent to biological human material where the patient receives regular information about projects and has an opt-out possibility.

A final comment stated that IC is just done for the protection of the physician, not the patient. The patient must be included and the IC must be done in such a way that helps patients. It is a different perspective.

5 Guest presentation 2: Telematikplattform für Medizinische Forschungsnetze (TMF), Anette Pollex-Krüger

Dr. Anette Pollex-Krüger from the TMF Office held a presentation on the activities of TMF in relation to IC. TMF is an umbrella organization for networked medical research, creating universal solutions for the optimization of essential working processes. In doing so, independently of the disciplines involved, it draws together research on a cross-disease basis, from clinics to general practitioners and from basic research to clinical research.

5.1 Summary

TMF was presented at start. It is an organization supporting medical research networks in Germany and has 89 Member organizations, which are:

- Disease-oriented Competence Networks in Medicine
- Coordinating Centers for CTs
- Networks for Rare Diseases
- German CT Register
- German National Genome Research Network (NGFN)
- Fraunhofer Institute for Toxicology and Experimental Medicine
- Patient Organizations
- German National Cohort

One of its aims is to clarify the legal and ethical framework for conducting medical research. TMF provides work materials, expert & legal opinions, the TMF book series, IT infrastructure & software tools, eServices and consultation.

The presentation further on focused on the legal and ethical framework conditions for medical research. The legal conditions restrict the collection, processing and use of data (and material) in CTs and research projects, or for their long-term storage through:

- Data and privacy protection laws and regulations (i.e. EU DPD, German Data Protection Act)
- Medical professional laws and regulations (if the sources of data or sample are within a treatment context)
- Ownership and utilization rights (i.e. for data and samples in biobanks: donors are free to transfer their property rights as owner of a biomaterial sample, i.e. to a biobank)
- Individuals' rights on parts of their body (while property may be given up, personality rights cannot)

The use of data and material for research purposes presupposes an IC by the patients. For consent to be operative, the data and/ or material must be collected, processed and stored only for a defined purpose, for a restricted time frame and for explicitly listed users. All these conditions must be mentioned in the patients' information section. Extending these restrictions is possible in certain circumstances, but only by applying additional safeguards and conditions in a rigid organizational framework, where the risk of re-identification is strictly observed. The TMF approach overcomes the barriers for keeping data indefinitely by using additional safeguards. This is possible because research is privileged by the constitution. The additional safeguards are:

- Establishing i.e. the medical research network as a legal instance with clear accountability

- Offering state-of-the-art information and communication security, including Public Key Infrastructure (PKI) techniques and access control
- Dividing informational powers by designating information and procedures to several independent parties; in particular, the establishment of Trusted Third Parties (TTPs) and separate storage of data, medical images, biomaterial, and corresponding analysis results
- Using pseudonymization

For data security, generic data security concepts are published in the TMF book series, vol. 1. Available software tools include pseudonymization software, PID-generator and a pseudonymization service (work in progress). For IC issues, there is a TMF checklist and guidelines which enable users to develop patient information and declarations of IC on the basis of relevant, documented and commented sources that meet regulatory requirements including comments and recommendations especially for clinical research using biospecimens (published in the TMF book series, vol. 3), as well as an online wizard for the web-based design of IC forms (www.tmf-ev.de/pew). The software assistant for web-based use of the TMF checklist for creation of patient information and IC guides the user through the compilation of the documents, proposes model/ generic texts and provides all required information (legal principles, opinions of ethics committees (EC) etc.).

Further developments cover elaboration of rules for patients not capable of giving consent, i.e. poly-traumatic patients, unconscious or demented patients and children, rules for revision of existing consents (re-consent) and an institutional patient consent for clinical research.

Considering research with patients without the capacity to consent there are general principles which must be met such as:

- The research project cannot be performed with other competent persons/ patients.
- Individual benefit for the included patients or at least essential information about the recognition, understanding of causes, prevention, or treatment of the disease leading to the incapacity is expected.
    - If direct benefit for the included patients is expected, then the research is possible.
    - If no direct benefit is expected, but other persons who are affected by the same disease or the participating patients in the future might benefit (indirect benefit), then the research might be possible if minimal risk and minimal burden for the patient is guaranteed.
    - If neither direct nor indirect benefit is expected, then research is ethically not acceptable.
- Only risks that are justifiable in relation to the expected benefit are expected.

- The legal guardian has given a valid consent on the condition that he has sufficient assumptions from his knowledge of the represented person of his/her readiness to participate in the study.
- No disapproving behavior of the person.
- Approval by a competent EC.

Remaining problems and open questions:

- If the legal guardian cannot be asked (e.g. acute incapacity to consent as in stroke research):
    - Best practices in Germany are based on timely involvement of a guardianship court (Heidelberger Modell) or an independent second physician (Gießener Modell).
- Randomized placebo-controlled studies:
    - Different opinions regarding possible direct benefit exist and direct benefit is necessary according to the German pharmaceutical law.
- Many different laws with different regulations and limitations for research exist, especially for studies where only indirect benefit is expected:
    - Standardization is needed, e.g. in accordance with the Oviedo Convention of the Council of Europe

5.2 Discussion

The discussion started with a question on re-consenting, asking if it would be possible to have an EC deciding for re-consent and if could some judgment be made that it is compatible (…). The problem is that if a patient did not consent to get contacted again, then a re-consent is not possible.

The discussion then focused on the handling of personal data within large repositories, where the purpose of usage of this data must be given in advance (purpose specification), a problem which produces a gap between the data protection and the research community needs. The question is, how specific must the purpose specification be? (Is this problem being dealt with at BBMRI?). Actually the DPD is very broad, but the interpretation seems to be a problem.

It is also open how specific the consent must be. More and more ECs prohibit a broad consent. Collected tissues are put in timeframe and need to be destroyed after that (15 years). Implementation of DPD and ECs are actually hindering the research.

The patient should have a choice to what he/ she consents – future research or only one future study.

Considering the evaluation of the tools provided by TMF, there is a feedback loop for the users, but concrete data was not available.

6 Guest presentation 3: European Clinical Research Infrastructure Network (ECRIN), Wolfgang Kuchinke

The presentation was held by Dr. Wolfgang Kuchinke from the Universitätsklinikum Düsseldorf, describing ECRIN and its relation to IC for European research.

6.1 Summary

ECRIN is based on the connection of coordinating centers for national networks of clinical research centers and CT units. ECRIN is a pan-European, distributed infrastructure providing integrated services to multinational clinical research in the EU.

Among the objectives of ECRIN lies the integration of the EU clinical research capacity by supporting investigators and sponsors in multinational studies through unlocking the latent potential on scientific and patient level, as well as the integration of public funding by avoiding duplication of studies & money, the harmonization of tools, training and practice for improved quality, credibility, transparency, and the harmonization of legislative systems with suggestions for a new EU directive.

ECRIN services include information provision on regulatory and ethical requirements, CT sites, CT units, insurance, cost evaluation, funding opportunities, contracting, and information on an adaptation of protocol for IC plus an IC form to local context, as well as consultancy on protocol design and methodologies and on systematic reviews, meta-analysis, and trial sequential analysis.

National ECRIN partners provide the following services during the conduct of a clinical research project (after acceptance of the project by ECRIN):

Submission to and interaction with competent authorities and ECs; Support with insurance contracting; Recruitment and evaluation of trial sites; Training of study personnel; Investigational medicinal product management; Development of central documents and trial master file; Project management; Data management; Adverse event reporting; Monitoring; Blood and tissue samples management.

Further on, the results of the ECRIN survey on national differences in legislative and regulatory frameworks for clinical research were presented, showing that there is a significant number of requirements for vulnerable populations to consider. Most countries have regulations for children, pregnant women, unconscious persons, people with psychiatric disorder and dementia but nearly no regulations (only one country with regulations) exist for healthy volunteers and the elderly.

Considering the existence of a waiver of IC under emergency conditions or critically ill patients, the survey showed that there is a mixed result with the possibility of a waiver of IC under emergency conditions (four out of seven countries offer this possibility). Furthermore, none of the countries asked an obligation to inform patients about the outcome of the trial exist. Nonetheless, two countries exhibit a “right to know” for the patient.

Following the analysis on national differences, ECRIN submitted the assessment of the Concept paper for public consultation – "Revision of the Clinical Trials Directive 2001/20/EC (2011)."

The proposals include:

- The EU legislation should promote harmonization of the activity of ECs through either guidance or a change to the Directive ensuring appropriate training and quality assurance, based on EU-wide specification.
- A European coordination of ECs should promote harmonized training, tools, and practice, including a common template for the IC requirements in the EU.
- The possibility of a waiver of consent in incapacitated patients should be mentioned in the new legislation with clear definition and procedure, and also with a clear procedure for the withdrawal of consent (full withdrawal from future experimental intervention and full withdrawal of all data; withdrawal from future experimental intervention, but collected data can be used) when the temporarily incapacitated patient recovers its ability to consent.
- Similarly, there should be clear procedures for the withdrawal of consent by proxies (full withdrawal from future experimental intervention and full withdrawal of all data)
    - Withdrawal from future experimental intervention, but collected data can be used.
    - Withdrawal from future experimental intervention, but collected and future data can be used) when the temporarily incapacitated patient never recovers.

ECRIN also prepared a set of standard operating procedures (SOP) on ethics (Deliverable 18), showing how to prepare an information and IC form for a multinational trial on medicinal products, including ECRIN SOP 005: "Informed consent in vulnerable populations and incapacitated patients."

For participants able to give IC, the SOPs are defined within a scope in which participants entering into a trial with a medicinal product must have given IC prior to participating in any procedure. The minimal requirements for patient information are given through a set of common elements plus country-specific elements. These elements are adopted for vulnerable populations and incapacitated patients.

General conditions and principles must prevail but each country must follow its own national legislation in relation to data protection in CT.

ECRIN deliverables are public.

6.2 Discussion

The role of ECs, which are intended to be independent, meaning that standard regulations/ harmonization cannot apply, was discussed. ECs should focus on expressing opinion only on the consent. The ECs are a problem on itself. Even

members of ECs are not harmonized (e.g. 1 clinician, 1 engineer, 1 lawyer). The question is if the ECs have to be chosen by rules, do they have to have a specific background etc.? In Europe there is no harmonization on who shall and who shall not be in an EC. As an example, within Germany there is a high number of ECs (40), and today one leading EC that has to clarify all issues with all the others within a specific timeframe in which they have to give their opinion/ report should be established.

Harmonization is probably only a formal measure, which will not help if issues of good practice and questions of trust cannot be solved through it. To some people it may make a difference if processing of medical data is carried out in a certain country and not in another, as they are not equally trustworthy.

So there is still a need to clarify different tasks and authorities of ECs on the national level. Ethical committees should only think about safety of the patient, while authorities should be responsible for the quality of medical products and the protocol.

7 Guest presentation 4: European Organisation for Research and Treatment of Cancer (EORTC), Anastassia Negrouk

Anastassia Negrouk, Head of International Regulatory and Intergroup Unit and EORTC Institutional Review Board (IRB) Chair, presented the EORTC perspective on patient information and consent documents.

7.1 Summary

EORTC is a private and not for profit organization created in 1962 with the main mission to promote and conduct research to improve cancer care. Its core activity encompasses the conduction of CTs (international, multidisciplinary, development of new treatments, definition of new standards of care and large academic trials). Today, EORTC spans a network of more than 300 institutions from 29 different countries (mainly EU), with ~2,000 collaborators (clinicians, pathologists, researchers etc.). More than 6,000 patients enter into EORTC trials each year (the EORTC database consists of more than 150,000 patients) with 50,000 patients being followed-up and 36 trials being open to patient entry.

Considering the patient information sheet/ IC, EORTC follows the following process.

- A general template in English, approved by the EORTC Institutional Review Board (IRB)
    - IRB is responsible for safeguarding the rights and welfare of subjects participating in EORTC CTs by:
        - protecting the privacy and confidentiality of the individuals' data
        - validating of the document templates for IC and patient information sheets
        - reviewing potential conflicts of interest reported to the EORTC

    - overseeing the CTs performed with the US cooperative groups & national cancer institutes under the Federal Wide Assurance (FWA)
- Study specific template, reviewed by the protocol review committee
- Translations are done by a professional company
- National coordinators make national adaptations
- Reviewed by patient organizations (not 100% of cases yet)
- Approved by ECs

The main issues in the whole process are connected with:

- The existence of multiple laws (CTs, data protection etc…)
- Divergence of national requirements (content & structure)
- Divergent terminology used for the same concept (i.e. data protection: anonymized vs. pseudo-anonymized vs. key codes vs. linked anonymized)
- Divergence of local (intra-national) requirements
- Trial complexity – multiple PIS/ICs & long documents
- Administrative & legal information overweight the science - > length of PIS/IC
    - Final documents miss the goal (protecting the sponsor & not informing the patient)
- Unclear rules for continuous information
    - Information vs. re-consent
    - Patients overwhelmed by irrelevant information
- Withdrawal of consent – no clear communication pathway
    - Withdrawal from treatment & future collection of data
    - Withdrawal from trial & use of already collected data & tissue
- Communication of trial results
    - Pertinence
    - Accessibility to information

This is shown in the increase of the average number of patient information & consent documents presented to patients within EORTC CTs from 1 in 1996-2000 to 1.5 2006-2010, while the median number of pages of each document has tripled in the same period reaching a maximum of 20 pages per document.

Considering the question whether modern technology is of any help in the patient information/ consent process, EORTC experience shows that from a total of 9 countries

and 113 institutions, which introduced DVDs in an EORTC trial, only 18% of doctors found the DVD useful, while 75% did not used it at all. In 2% of cases the EC did not approved the DVD (5% other reasons).

The latest EORTC Institutional Review Board recommendations are the following:

- One document should be used for the mandatory part & one document for all optional/ correlative projects.
- The mandatory part document should not have more than 8 pages.
- The document should start with the executive summary of 1-2 pages for trial specific easy to understand essential information.

EORTC concludes on the following current needs:

- To consider patient first
- To carefully choose the information pertinent to the patient before developing any PIS/IC
- To make a short comprehensive summary available (possibility for two level reading)
- To involve patient's representatives in the review of documents prior to their approval & use

7.2 Discussion

Within the context of the preceding presentation, the role of patient organizations resulted to be very important to help the patients make a choice on IC. The decision is a personal matter and the patient is making it on his/ her own, but somebody with experience would help a lot because in reality, individuals are not quite capable to make the choice. On the other hand, the future may be pointing towards a collective consent that doesn't leave people take decisions alone.

Another point is the withdrawal of consent, which is a very important feature, making a consent at all binding as long as one can withdraw from it. It may mean that the patient doesn't need much information as long as he/ she may change his/ her mind. Moreover a withdrawal could be initiated by the patient's organization, although it is questionable whether the patient organizations have sufficient qualities. In general, protection of the patient is very theoretic and cannot be confirmed in practice.

There seems to be a need for a flexible way of informing patients according to the "need to know" principle, which could benefit from ICT technologies: dynamic shaping of information and making the patient information procedure a whole process which keeps initial awareness brief and subsequently adds more and more information.

8 Guest presentation 5: European Society for Pediatric Oncology (SIOPE), European Network for Cancer Research In Children and Adolescents (ENCCA) Project Coordinator, Ruth Ladenstein

Prof. Ruth Ladenstein, president of the SIOPE board and coordinator of the ENCCA project, presented the ENCCA goals and actions, aims of the recently formed European Clinical Research Council (ECRC) and critical issues to be addressed in connection to CTs and IC. Furthermore a 2-step procedure for gaining IC was proposed.

8.1 Summary

ENCCA aims to establish a durable, European virtual institute for clinical and translational research in childhood and adolescent cancer that will define and implement an integrated research strategy and will facilitate the necessary investigator-driven CTs to introduce the new generation of biologically targeted drugs into standard of care for children and adolescents with cancer. The planned actions for the period 2011 – 2014 are:

- Policy activities to implement a European strategy for pediatric and adolescent oncology research.
- Integration, harmonization and optimization (CTs/ European CT templates & contracts/ IC, trials methodology, tumor banking, biology).
- Run a limited number of clinical and translational studies as examples.
- Facilitate sharing and partnerships in the chain of all stakeholders (academia, parents and patients organizations, charities, pharmaceutical companies, regulatory bodies, governmental bodies).
- Training and education.
- Harmonize ethical definitions and solutions.

To ensure that the needs of European CT groups and European national societies are met on the European level, the ENCCA project aims to create with SIOPE a number of council platforms to establish a common European voice for the respective stakeholders in Europe. Therefore in February 2011 SIOPE invited the heads of the European CTs to create the ECRC as a new common European platform. The ECRC will have the capacity to address the many common issues that cannot be solved by each group working in isolation. The ECRC may supply coordinated responses through SIOPE such as the currently ongoing CTD revisions with emphasis on risk-adopted approaches & risk categorization of CTs, a harmonized understanding of investigational medicinal products, insurance needs and rates. The close interaction of the ECRC with the Industrial Club of Interest, Intellectual Rights Committee and the Scientific Advisory Committee will allow for more formalized collaborations of CT groups with industry. The ECRC will serve as a forum to facilitate specific CT related issues including for example improved IC procedures (collaboration with CONTRACT).

The SIOPE – ECRC Clinical Trial Support Desk aims at offering close interaction of European CT Groups (develop a common European voice on the European level to facilitate trials in academia), a European Trial WEB Platform for SIOPE (information on active Haemato-Oncology trials in Europe for pediatric and adolescent patients) and providing trial related, harmonized documents to facilitate the current burden to start and run a CT in Europe.

The CT <u>needs</u> are the following:

- Clinical Trial Application (CTA) process template
- Clinical Trial Templates for phase I,II,III
    - Trial Master files
- Informed concerned templates CT participations – key items
    - Ages 6-10, 10-14, 14-18, > 18, parents (guardian)
- IC for access to tissues for research
    - National level for tissue storage and use in research
    - Consent to share tissues outside of countries and the EU
    - Generic consent for future research
    - Permission to share potential commercial benefits with pharmaceutical industry
- IC for future contact on long term follow up
- Define role and structure of Data Monitoring Committees
- Pan European Clinical Trial Sponsorship and harmonization of understanding on sponsor duties in academic trials
- Contract templates for the coordinating sponsor and national sponsors

The critical <u>issues</u> that need to be addressed considering CTs are:

- Risk based requirements for insurance in CT
    - Harmonize understanding of risks
    - Identify European Insurance companies as well as best rates on the market for which type of trial
- Declaration of investigational medical products (IMPD)
    - Common definition needed
- Pharmacovigilance and safety
    - Trans-European harmonization on expedited reporting of SAE – SAR – SUSAR
- Review key ethical differences for pediatric trials across Europe

  - Age of competency
  - Need for parental consent
  - Attitude towards phase I trials
  - Guidance towards harmonization for the composition and working procedures of administrative authorities
- Ethical review standards and procedures in European trials
- Influence EC Regulations: Balance of CTs versus best practice
- Decrease off label use through increased registration of pediatric drugs
- Central platform developed for harmonized European advice and counseling on CT
- Reinforce political lobbying on the European level with share and stakeholders

The critical <u>issues</u> with respect to <u>IC</u> are:

- The majority of pediatric oncology CTs
  - Represent multiple drug bets practice treatment concepts
  - Aim to improve established standards (i.e. comparison of standard approaches, add – on principles of one licensed, but off label drug etc.)
  - Off label use in pediatric cancer treatments is common (up to 80%)
  - Don’t have the primary aim of drug license
  - Are not pharmacy sponsored
- Inability to consent (patient and family) when diagnosis of a life threatening acute disease (cancer) is given
  - Similar to emergency trials: inability to listen, to fully understand, to judge what is best etc.
  - Unethical to pressure patient and family to full consent to meet regulatory requirements
  - Consent signatures within the 24 – 48 hour period are still often a matter of trust for the treating physician but do not reflect full understanding of presented disease threats, trial related questions and potential treatment threats
- Excessive increase of volume of IC
  - Unacceptable – unethical?
  - Bothersome for patients and families in acute situation
  - Increase from average up to 5 to a total of rather 30 pages

A proposed solution to IC is the following 2-step procedure:

Step 1: Conditional Consent (Acute Dx- life threatening cancer)

- Verbal consent with testimonies present (care team)
- Short written information on proposed trial and signatures/ date
    - A short 2 page maximum information and signature procedure
    - Explain benefits and risks (major drug related side effects)
    - Explain randomization eventually if necessary for trial entry
    - Highlight possibility to withdraw consent within 2 to 4 weeks and not to sign and to consent to step 2
    - Explain data protection (i.e. pseudonymization, etc.) and use of data

Step 2 : Final Consent electively after 2 to 4 weeks (max): (full consent procedure according to optimized current practice)

- Sign all trial related documents (consent to the trial, consent to data transfer, consent to use biological /human /tumor materials /tissue banking) according to suggested research of proposed trial)
- Aim for reasonable volume of information materials for signature
- Age standards in IC material are well established now

8.2 Discussion

Concerns on the proposed 2-step procedure were expressed. This procedure works in leukemia cases but could not work in radical surgery because the first step could not be undone. The first step could alternatively be limited to an informational discussion with the patients and the second would be legally valid.

A benefit from the 2-step procedure is the possibility to gain feedback from the patient in the second step.

9 CONTRACT general discussion – Problems of informed consent and Good Practices Cases – Norbert Graf, Griet Verhenneman, Magdalena Góralczyk

9.1 Summary

The general discussion began with a question to the participants asking to pick one concern each one has with regard to IC.

The first mentioned concern was related to whether one can legally rely on a signed consent that was given under an emotional stressed situation[4]. This concern is covered under the general procedure of signing, where the signature indicates an important decision, which is coupled with risks and consequences. The signature has an

[4] Randomized treatment is chosen at the beginning by 90% of parents. This percentage falls by 50% after 5 weeks. This is an indication for some kind of pressure during signing. It is not only a change in the perspective.

evidential function and is a requirement of the CTD. This again raises the question of it mainly offering a protection to the researcher rather than to the patient.

If a patient would not sign the participation to the CT, would he/ she get the standard treatment? Would it be better or worse? Is the participation really a free decision? The patient is actually dependent on the physician's suggestion/ guidance.

The decision is difficult and depends on the available information, and it requires time to process that information, which is a problem in critical urgent life threatening situations.

Legally, the regulation of clinician's duties in concern of the implications of a randomized trial vs. a standard treatment and the patient's ability to make a choice varies in the different national systems. It might be necessary to legally treat each case separately, although this is unacceptable for clinicians and would make their work impossible.

The definition of standard treatment is also quite unclear. On which basis is it standard? Who defines this? Everybody considers it to be standard, but can anybody define it?

Considering the question whether a new trial treatment is better than the standard treatment, it should be noted that a trial has guidance, quality control, advice, networks, an overall gain of quality and safety, indicating that the advantages of the trial are in a way also its side effects.

Resulting from all the above, the most important issue is gaining trust between a patient and the physician. Patients can't judge whether a treatment is good or bad for them. That means it is much more important how they are informed than what is included in the information, incl. consent forms.

The general impact of the CTD is that trial numbers have decreased, costs have increased and the survival rate has also fallen. This is a clear indication that the regulations must be changed. Moreover, the regulation doesn't say what "informed" means and it doesn't give outline of consent (consent on what?). The problem is not so much about the contents of the Directive, but about ECs judging what IC means in practice. There lies a major barrier. It could be that IC does not always need to be a huge document addressing all possible items.

There is a need to find a model that better serves the patient and does not need the long IC documents and still complies with the legal framework. This might solve the procedural problems but in case of litigation (when something goes wrong) problems still exist.

Even insurance companies give the weight on the disease itself, which is the primary risk of death especially in the field of oncology. Oncology cases are similar to emergency trials, could similar rules be applied? There is a need for exceptions according to disease type. A good practice approach would be very helpful in gaining insurance company cooperativity.

Considering timing of IC there is sometimes the need to get an IC on the first day, e.g. to store Leukemia cells. Is there a chance to store it first and ask for consent later when wanting to do research on it?

Right now an IC is necessary before the start of any treatment. This results in people declining completely on the one hand or unconditionally consenting on the other.

Research of the past has shown that easily one third of the patients does not need chemical therapy, knowledge that would be unknown without taking biomaterial and having bio-profiles. Past research has also shown that it is possible to tell in advance if a child needs chemotherapy, as a result of analyzing the molecular structure. Therefore a common understanding must be created that patients today are profiting from the research of the past.

Trying to solve those questions on a too general level will produce a regulatory problem. E.g. doing it for all trials on EU level implies a vagueness and uncertainty. The only solution is to split disciplines up, e.g. cancer research on children, with much more straight forward rules.

That would be a possible regulatory strategy but how many categories will be necessary is unknown (probably too many). Must they be defined with strict rules or rather within a framework? Distinguishing between industrial trials and investigator initiated trials would be helpful as there are no economic reasons for clinical/academic trials. There is a need to make it much easier to enroll patients into academic trials. The directive was initially developed in order to protect patients, which is not currently happening and this original purpose should be kept in mind.

10 CONTRACT presentation 2: the Helpdesk infrastructure, Manolis Tsiknakis

Prof. Manolis Tsiknakis, leader of WP6 and contributor to WP5 presented on behalf of Brecht Claerhout (leader of WP5) the proposed infrastructure of the CONTRACT helpdesk, one of the main outcomes of CONTRACT in order to support ongoing and upcoming translational research projects.

10.1 Summary

WP5 will provide day-to-day help for the projects participating in the questionnaire. The helpdesk will offer a data-protection-framework ready to run and hosted by the Center for Data Protection (CDP, www.privacypeople.org, a Belgian non-profit organisation founded by representatives of LUH and Custodix) and will provide a help forum for legal, ethical, IT-related and clinical questions related to IC and data protection in translational research. The service will initially be available for cooperating projects as a pilot phase – at the end of the project the helpdesk can serve as a project exploitation tool and offer its services for the general public.

The content and services of the helpdesk which would ideally be required must be based on evidence. Actual & expressed needs have to be correlated to the target user groups and filtered based on available resources/ capacity, as well as prioritized based

on urgency of needs. The target audience includes EU partner projects, organizers of multicenter/ international trials inside Europe and general public with a probably need to address lawyers & IT-specialists separately.

For producing useful advice it is important to identify the content differentiators regarding IC, which also allows for automation of the "knowledge provision" process.

The identified IC differentiators are the following:

- Nature of project: CT/ epidemiological project
- Type of trial:
    - Treatment trials: Drug development / therapy
    - Prevention trials
    - Diagnostic trials
    - Screening trials
    - Quality of Life trials
- Trial Phase: I-IV
- New data collection?: Prospective / retrospective
- Invasiveness:
    - Influences diagnosis or treatment of patients OR not
    - Involves obtaining body material
- Patients Included (vulnerable):
    - Adults
    - Adults under guardianship
    - Minors (age groups)
- Geographical Scope:
    - Country in which the study is originated
    - Multicenter OR not
        - Single center
        - Multicenter National
        - Multicenter International (inside Europe)
        - Multicenter International (outside Europe)
    - Sponsorship: Industry-sponsored / investigator-sponsored
- Randomized or not

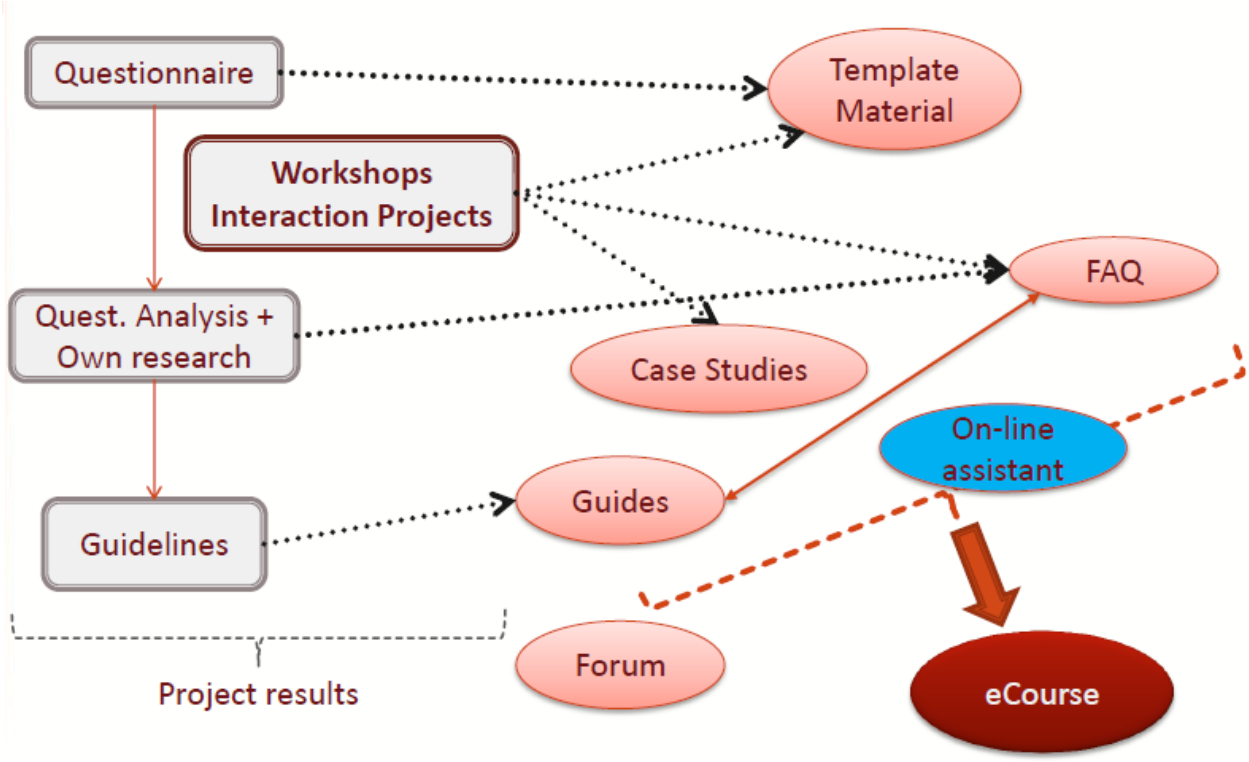
The helpdesk content will/ can include (ideas):

- Guides
- Frequently asked questions (FAQ)
- Case studies
- eCourse
- Template material: Consent forms, contracts etc.
- Forum

Important points:

- Focus on a well-defined target audience and well defined topics
- Prioritize depending on available results from the project, the available effort and needs expressed by stakeholders

The helpdesk services and dependencies are depicted below:



Further considerations in the development of the helpdesk include the preparation of relevant project deliverables (M3.1, D3.1, M3.2, M4.1, D4.2) with the helpdesk publishing in mind (delimited sections for each of the differentiators). The FAQ section can be populated either with answers from the questionnaire, discussions in the workshop or through a forum. Considering the case studies, to be valuable, they should refer to the guides & templates, which are difficult to build (could be fictional or by working out a case for an existing project/trial). A first case is to be worked out with Prof. Norbert Graf based e.g. on SIOP. The development of template material depends on the responses of the questionnaire in related questions (e.g. did you use a template to

write the consent forms for your project?) and existing templates from other sources. The main problem in using templates for IC is the suitability for each country especially in the context of the many aspects of the IC differentiators.

The establishment of a forum may give the helpdesk the possibility to provide consultancy on IC issues to projects but requires commitment to continuous administration in order to be kept up to date. Finally, an eCourse might be a nice feature of the helpdesk, although a lot of effort is required to produce the course material. Nevertheless it would open the door for a sustainable outcome of the project.

10.2 Discussion

The discussion first indicated the need for each tool of the helpdesk to be based on national law. If a tool is not related to national legislation, uncertainty will arise. Maybe it is more crucial to create an environment for discussions on proposed IC forms – interactively exchange of information between researchers– instead of a “knowing it all best” approach. For the CONTRACT helpdesk development it is important to have concrete propositions, e.g. a step by step harmonization out of a library of various consent forms for each country or a portal rather than a helpdesk that will provide decision support based on international legislation. In any case the exchange of information is the most important feature. Also the exploration of e-consent is very interesting but challenging, considering security issues, electronic signatures, management etc.

The basic idea behind the helpdesk is to develop a growing knowledge pool as a place for information collaboration.

Finally, maybe the project should design the architecture for a helpdesk, as described above, and let further development/ population with information to be done by the users/ practitioners. This preparatory action would include identifying and assessing available tools e.g. for dynamic form creation and test them in a specific scenario such as ICT in decision support to channel legal and other information. In addition to that, support for structured documents could be added, including a validation whether certain template would have all the needed elements. Eventually a library of different kinds of templates could be built.

11 Guest presentation 6: Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), Johannes Starkbaum

Johannes Starkbaum from the Life Science Governance Research Platform, University of Vienna, presented BBMRI project.

11.1 Summary

BBMRI was one of the first European Research Infrastructure projects funded by the European Commission (EC). The EC-funded preparatory phase of BBMRI came to its end in January 2011. During the past 3 years BBMRI has grown into a 53-member consortium with over 280 associated organisations (largely biobanks) from over 30

countries, making it the largest research infrastructure project in Europe. During the preparatory phase the concept of a functional pan-European biobank was formulated and has now been presented to member states of the EU and for associated states for approval and funding. BBMRI is in the process of submitting its application to the European Commission for a legal status under the ERIC regulation, with an expected start date at the end of 2011.

Key components of BBMRI are comprehensive collections of biological samples from different (sub-) populations of Europe, which should be linked with continuously updated data on the health status, lifestyle and environmental exposure of the sample donors. This can only be achieved in a federated network of centres established in most, if not all, European member states. Therefore, the format of BBMRI should be a distributed hub structure in which the hubs coordinate activities, including collection, management, distribution and analysis of samples and data for the major domains.

Such an action brings to the foreground various questions/ challenges that address harmonizing standards for sample/ data collection, storage and analysis, technical and legal data protective instruments, debates on IC: broad, open, assumed, etc., all in “Close interaction with the European public(s)”.

The access is free/ open to non-sensitive data (expertise, documents, publications, etc.), whereas access to bio-samples and medical data is bundled with ethical and legal requirements (Oviedo Convention, Helsinki Declaration, OECD Guidelines for biobanks 2009, etc.) and if industry is involved, the analysis is performed by expert centers.

“Fair access” (Berlin declaration 2003) to bio-samples is given under the following requirements:

- Scientific and ethical peer review of the project
- According to the given IC (if available)

Focusing on IC, “access to samples and medical data can only be provided in the context of a specific research project in accordance with the terms of the consent given by the donor” (BBMRI Final Rep.: 7)

In cases where the IC cannot be obtained for practical or scientific reasons, a) the ethical review boards can provide a waiver or b) anonymization can also waive the requirement.

The technical model of this mechanism allows that samples can only be viewed by the selection based on IC and K-anonymity, or by comparable privacy security models.

Developing an infrastructure "properly embedded into European ethical, legal and societal frameworks" (ELSI) requires specific preparation on ELSI issues, both on operational questions that deal with the immediate feasibility of the endeavour and on more fundamental questions. This will help in understanding how these issues may impact on the organization of BBMRI, and the public(s) perception of BBMRI and the public(s) engagement. Both aspects were analysed in the preparatory phase in WP6.

The data sets of this analysis/ survey came from 60 focus groups in research sites including Austria, Finland, France, Germany, Greece, Netherlands and United Kingdom and from a representative sample (15000 participants) of EUROBAROMETER 2010 (32 EU countries).

Results show that people understand both well the possible benefits and threads of providing data to such an infrastructure, while northern Europe populations show high support in providing data, western show medium support and eastern rather low support.

While the report to the European Commission's Directorate-General for Research "Europeans and biotechnology in 2010 - Winds of change?" shows a wide rejection of broad consent across Europe with concerns about long-term developments and data security. A reason for that is the existing knowledge gap on biobanks. The report mentioned above shows that passive awareness increases participation by 15% and active engagement adds another 7%. Similar effects are applicable to broad consent. Therefore there is a demand for transparency based on the fact that suspiciousness is often based on the limited insight to what's being studied and what happens with the data and furthermore the unknown future of data usage. On the other side, the study has also shown positive responses considering the benefit of donation to a biobank infrastructure, such as the benefit for future generations and the contact to specialists who might produce knowledge a family doctor does not have.

Concluding, BBMRI demands for large sample-sets collected with broad (or open) consent in a heterogeneous European landscape (technical, ethical, social and legal) with a great diversity and critical publics among all Europe.

Broad consent is widely rejected among Europe due to knowledge, trust, long-term developments and benefit sharing.

There is a dependency on public and political support: especially for expanding biobanking efforts.

Comprehensive and integrated approach is necessary with respect to national sensitivities and individual donors.

11.2 Discussion

The first question addressed the issue of how do expert centers perform the data analysis when industry is involved, showing that direct industry involvement is generally permitted but only feasible in some countries. In such a case industry cannot access the data directly and will receive only results and not the data itself.

With regard to the waver of IC by the EC, it is possible only if IC was not given (e.g. very old unidentifiable samples)

12 Guest presentation 7: K.U.Leuven, Eleni Kosta,

Dr. Eleni Kosta from K.U. Leuven presented a thorough analysis on the concept of consent in data protection and CTs a result of the DPD (1995/46/EC) and CTD (2001/20/EC).

12.1 Summary

In the DPD ***consent*** *is defined as any freely given, specific and informed* ***indication of his wishes*** *by which the data subject signifies his agreement to personal data relating to him being processed*. As stated by MANSON & O'NEILL in "Rethinking informed consent in bioethics", IC requirements have been extended from medical treatment and research to the secondary use of information and tissues, by incorporating them into the regulation governing **data protection**, uses of human tissues and genetic technologies.

The first usage of the term "consent" in a legal framework was in the Nuremberg Code (1947): "The voluntary consent of the human subject as an absolutely necessary condition for medical experimentation on human beings", followed by the Declaration of Helsinki (1964/2008), using the term "informed consent": "Medical research: freely-given informed consent, preferably in writing; No competent individual may be enrolled in a research study unless (s)he fully agrees". Later on the UNESCO Declaration on Bioethics and Human Rights (2005) also used the term (Scientific research: Prior, free, express and informed consent) and finally the CTD as it is known today:

Informed consent *is a* ***decision****, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.*

It is noticeable, that the DPD defines consent as an indication of the wishes of the data subject, while the CTD defines IC as a decision, which must be written, dated and signed. It focuses on the actual form of consent and not on the expression of the agreement of the individual. This attempt to make IC more exacting resulted in lengthy IC forms that the participants in CTs all need to sign.

On the other hand, MANSON & O'NEILL in "Rethinking informed consent in bioethics" suggested the meaning of IC as a means to "waive prohibitions on action that would otherwise be intrusive". FADEN & BEAUCHAMP in "A history and theory of informed consent" stated that IC, "from a moral point of view," is closely linked to the **autonomous choices** of patients and subjects. In a rights-based approach, this relies on the **autonomy** of the individual as a justification for IC requirements, while a duty-based approach for rethinking IC in bioethics (MANSON & O'NEILL) suggests to "shift [...] focus to agency, and in particular to the communicative actions and transactions by which knowledge is obtained and communicated, and to the norms and obligations most relevant to communicative actions". This would enable research on placebos and

medical treatment for patients who cannot take part in epistemically adequate consent transactions. In the context of the processing of personal data, a duty-based approach can be established on the information obligation of confidentiality.

12.2 Discussion

The question of IC and its relation/dependency to/on technical tools e.g. cloud computing was posed, resulting to the problem that it is very hard to verify actions and decisions in a cloud computing environment making it very hard to get a valid consent, which in turn would mean no service delivery possible.

There is a sudden shift from the authoritarian approach to the individualistic approach, which started much too far on one side and ended much too far on the other side. A way in between with new elements is needed. A paternalistic approach without going all the way back to the beginning is a possible way and no longer can we presume the data subject's decisive capacity.

13 Views of the External Advisory Board - Cecilia Magnusson Sjöberg, Dag Wiese Schartum

13.1 Summary

During the workshop, fundamental issues were discussed, showing the importance of having a legal overview, always in consolidation with the clinicians. Considering the helpdesk it should be cleared how the resources/ time will be used, whether CONTRACT will provide a theoretical analysis or a helpdesk/ e-consent digital model in a framework of the support action. One of the most important issues is differences in the national legislation, which must be included. The helpdesk must be truly open, so it will continue to evolve. A suggestion is to make a system specification combined with a demonstrator, which is based on dynamic forms for integrating multiple consent types. The open structure would allow participants to add material, and not only good advice should be given but legislation has to be presented together with mechanisms that warn in case of amendments.

14 Conclusion

The first CONTRACT stakeholder workshop successfully took place in Hannover, having benefitted from the participation of representatives from major key organizations and European projects.

The CONTRACT questionnaire proved to be valuable in analyzing the current situation concerning the legal, ethical, technical and clinical handling of consent in European projects dealing with vulnerable patient groups, although some limitations on judging between different countries were addressed, as a result of low participation rate and an unclear distinction between national law and EU law. The reason for low participation was probably the high prerequisites in terms of experience and knowledge needed for participants to answer the questions in combination with an uncertainty considering the role under which a participant should answer.

The general impact of the CTD shows falling trial participation rates, increasing costs and a declining survival rate. This is a clear indication that the regulations must be changed. **“There is a need to make it much easier to enroll patients into academic trials”** was the general message behind each discussion in the workshop. Moreover, the regulation doesn’t specify what “informed” means and it doesn’t give outline of consent, although the problem seems not so much to exist due to the differing contents of the Directive, but ECs interpretation of what IC means in practice. It could be that IC might not need to be in all cases a long comprehensive document addressing all possible cases. ECs play therefore a major role in the way the IC is prepared. The problem is the harmonization (EU-wide) on the level of ECs is difficult because they are intended to be independent, though their responsibility and authority should be clarified and better defined even on the national level. ECs should focus on expressing opinion only on the consent and assure patient safety, while authorities should be responsible for the quality of medical products and the protocol of the trial.

Encouragement of participation at CTs and research falls in context of giving people a choice – helping the patients – instead of defining a legal process. Creating awareness on this subject is important and implies fully informing the involved persons, quite a difficult task, which might be facilitated if there would be an easy to access information desk so that participants know that the information exists, is valid, and that it can be read anytime.

Re-consenting is a problem because if a patient did not consent to be contacted again, then a re-consent is not possible, not even via an EC. The patient should have a choice to what he/ she consents with respect to future research or only one future study.

Resulting from all the above, the most important issue is gaining trust between the patient and the physician. Patients are generally not able to adequately judge whether a treatment is good or bad for them. That means it is much more important how they get informed than what is included in the information and the consent forms. Another problem is that it requires time to process the given information in order to make a decision, which is a problem in critical urgent life threatening situations.

The role of patient organizations resulted to be very important to help the patients make a choice on IC. The decision is a personal matter and the patient is making it on his/ her own, but guidance from somebody with experience would help a lot. Moreover, the future may be pointing towards a collective consent that will not allow people to take decisions alone.

On the other hand, withdrawal of consent is a very important feature. It may mean that the patient doesn’t need much information as long as he/ she may change his/ her mind.

Considering the CONTRACT helpdesk the need for each tool to be based on national legislation has been expressed, otherwise uncertainty may arise. It is more crucial to create an environment for discussions on proposed IC forms, which will support an **interactive exchange of information** between researchers. The basic idea behind the

helpdesk is to develop a growing knowledge pool as a place for information collaboration.

CONTRACT should design the architecture for a helpdesk, supporting the above, and let further development/ population with information to be done by the users/ practitioners. This preparatory action would include identifying and assessing available tools e.g. for dynamic form creation and test them in a specific scenario. In addition to that, support for structured documents could be added, including a validation whether certain template would have all the needed elements. Eventually a library of different kinds of templates could be built.

Finally, the e-consent is with no doubt one of the most anticipated technical solutions to managing IC documents and to gaining IC, as it can provide a more flexible, dynamic (multimedia) way of informing participants while enhancing the feeling of trust by providing a possible widely accepted confident environment. It could give the possibility to withdraw anytime, such that broad consent scenarios could be supported. One of the big challenges that come with e-consent is managing of the electronic signature.

The key message which the project consortium will take from this meeting is that there is a great will in the community to cooperate in creating a more consistent picture of informed consent and that streaming that energy should be one of the project outcomes.

Hence for the upcoming second year of the project, CONTRACT will try to integrate the input provided during the workshop, as well as to stay in touch with all the participating organizations. An important task will be to possibly widely integrate the efforts of the community in the field into the project's work.

At closing all workshop participants agreed on the problems that were elaborated during the workshop and expressed their willingness to cooperate in solving them.

Figure 2 - The workshop participants

Appendix

Workshop participants

CONTRACT project consortium:

University/ Organization:	Name:
Leibniz Universität Hannover	Nikolaus Forgó
Leibniz Universität Hannover	Magdalena Góralczyk
K.U.Leuven	Griet Verhenneman
TEI Crete	Manolis Tsiknakis
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External advisory board of CONTRACT project:

University/ Organization:	Name:
Universitetet i Oslo	Dag Wiese Schartum
Stockholm University	Cecilia Magnusson Sjöberg

Guests:

University/ Organization:	Name:
K. U. Leuven	Eleni Kosta
European Clinical Research Infrastructure Network	Wolfgang Kuchinke
European Organisation for Research and Treatment of Cancer	Anastassia Negrouk
Cambridge Health Informatics	Peter Singleton
Biobanking and Biomolecular Resources Research Infrastructure	Johannes Starkbaum
European Society for Pediatric Oncology European Network for Cancer Research in Children and Adolescents	Ruth Ladenstein
Telematikplattform für Medizinische Forschungsnetze	Annette Pollex-Krüger
Leibniz Universität Hannover	Marc Stauch
Leibniz Universität Hannover	Wolfgang Kilian