CONTRACT

CONSENT IN A TRIAL & CARE ENVIRONMENT

SEVENTH FRAMEWORK PROGRAMME

European Commission Seventh Framework Programme

Call: FP7-HEALTH-2010-single stage

Contract No: 261412

Final Guidelines for Informed Consent and Data Security

Deliverable 4.2

Version 1.0

Editor:	K.U.Leuven / Griet Verhenneman
Work Package:	WP4
Status :	Final
Date:	30 September 2012
Dissemination Level:	PU **PU** = Public, **PP** = Restricted to other programme participants **RE** = Restricted to a group specified by the consortium; **CO** = Confidential, only for members of the consortium (including the Commission Services).

Document History

Version	Date	Author/Editor	Description/Comments
0.1	14/08/2012	Griet Verhenneman	Initial document compiling input
0.2	21/09/2012	Griet Verhenneman, Yvonne Braun, Magdalena Góralczyk	Internal document for review by consortium
1	30/09/2012	Yvonne Braun, Brecht Claerhout, Nikolaus Fórgo, Norbert Graf, Magdalena Góralczyk, Matthaeus Pediadits, Cédric Vansuyt, Griet Verhenneman	Final document

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Abbreviations

CIOMS	Council for International Organisations of Medical Services
CRF	Case Report Form
CRM	Clinical trial management
CTD	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 implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
CTR	Proposal 2012/0192 for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
DPD	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
DPR	Proposal 2012/0011 for a regulation of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and the free movement of such data, also called the General Data Protection Regulation
eCTD	Electronic Common Technical Document
EHR	Electronic Health Record
HIC	Health Insurance Commission
IC	Informed consent
ICH Guidelines	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICT	Information Communication Technology
PI	Principal Investigator
QES	Qualified Electronic Signature

RBAC	Role Based Access Control
RCT	Randomised clinical trials

Introduction

The aim of this document is to process and analyse the data gathered during the questionnaire phase of the project and to create a holistic reference document on informed consent. In addition information gathered within this paper will be a basis for creation of the Helpdesk structure. The document shall also be one of the ways of dissemination of CONTRACT outcomes, by presenting good practice cases recognised during the questionnaire phase of the project.

1 Who is this document directed to

1.1 First stage

On the first level the document was directed towards the External Advisory Board and participants invited to the First CONTRACT Workshop, which took place in Hannover on 15 September 2011.

The participants of the Workshop received a draft version of this document for review prior to coming to Hannover and discussed it during the meeting.

Their comments and suggestions fed into the upgraded version of the document.

At the second CONTRACT Workshop, which took place in Hannover on 6 September 2012, the final version of this document was discussed and the use of the CONTRACT helpdesk was demonstrated based on 6 scenarios.

1.2 Second stage

After the review the document was directed towards specialists working within the clinical environment with informed consent documents. It is intended to be a useful guideline for them in the preparation of such documents, as well as a reference which will allow them to verify their current informed consent forms and procedures.

Distribution channels: the Guide will be available for download from the CONTRACT webpage. Once the document will be translated into the Helpdesk structure it will be available to the partner projects of CONTRACT and later on, after the project completion, it will be kept online and publicly available for all interested persons.

2 Usage within Consortium

In order to use the project resources to the maximum the guide was not only the basis of Workshop I, II and a paper based deliverable but in addition it has become a part of the Helpdesk.

The good practices cases were fed into the Helpdesk and are be used by the IT specialists for the creation of a structure providing online support for people creating informed consent documents for interventional trials, observational trials, the use of biomaterial, the re-use of personal data and for assent forms.

3 Basis of the document

The current document builds on and further refines Deliverable D3.1: Initial Report and Guidelines on Good Practice Cases.

Additionally the document makes use of the results of observations and interviews carried out at the Homburg University Hospital.

4 Document structure

The document has been divided into four parts, which respond to the three main thematic topics of interest of the project:

1. *handling of informed consent in clinical environment*
2. *legal and ethical requirements for informed consent documents*
3. *ICT technologies for support of informed consent procedures*
4. *Overview of the legal framework of informed consent of four chosen EU Member States*

4.1 Section I – handling of informed consent in clinical environment

The first section aims at providing recommendations for how informed consent is obtained and focuses on the role of the treating physician and the clinic in obtaining informed consent, which fulfils all the requirements of legal and ethical nature.

In this section recommendations on how the doctor can approach a patient, how children shall be treated in case of need of informed consent and assent and other decisive factors which fall into the so called “soft skill domain” will be described.

Examples:

- Time given before signing of the informed consent document
- Re-consent procedures that are not compulsory for legal reasons
- Role of the physician in obtaining informed consent.

4.2 Section II – legal and ethical requirements for informed consent documents

This section complements the CONTRACT Helpdesk and shall help researchers in developing an ethically and legally compliant informed consent document. It provides tips on legal requirements for an informed consent form and suggests where possible (another helpdesk feature) phrases and sequences, which shall be part of the form.

A checklist containing all the important parts of informed consent documents will be provided. Where appropriate a template text is suggested. In addition the document shall help to create an information sheet for the patient / trial participant / data subject including information on his / her rights, as well as on the contact persons which he / she can turn to.

4.3 Section III – ICT technologies for support of informed consent procedures

This section aims at providing the reader with information on the newest and most advanced technology developments, which improve and support informed consent procedures. Among others it provides information on electronic mechanisms that support individuals' rights to control the disclosure of their health information for treatment (e-consent), and the corresponding procedures and ICT technologies that guarantee the secure processing of personal data in such a way that access to or transfer of the data is restricted.

4.4 Overview of the legal framework of informed consent of chosen EU Member States

To create a full picture of informed consent the study of European Framework is accompanied by studies of national legislation on informed consent in four chosen Member States: Belgium, Germany, Poland and the UK.

5 The approach

Due to constrained resources of the project the Guide and Helpdesk feature cannot offer the full route through all the possible design options of an informed consent document. Therefore the Consortium decided to create a guide that would serve for a specific case and will serve as a proof of concept. For that aim a close cooperation with SIOP Europe has been started and the guide shall be effective in creating a consent form for the clinical trial done by SIOP-RTSG (Renal Tumour Study Group) as a model for other groups.

II Informed consent guides

1 Section I – Clinical practice

1.1 Introduction

As consent is not only a legal challenge but also a key issue of the ethical practice in translational research. Good practices cases are helpful to serve the scientific community with models for their own projects that are not only legally compliant but also ethically state of the art. Studies show that there is still work to be done.

In a population-based survey in Germany - done during the lifetime of ACGT[1] - parents of children with cancer were asked about their experience with consent[2]. In this survey parents were asked about their child's participation in the clinical trial. As many as 19,1% of parents could hardly remember whether their child was, or was not a trial participant. Despite that the parents who recalled their child's study participation correctly felt as well informed as parents who recalled it incorrectly. The memory of signing a consent form decreased with time. Even with a high rate of 80.9% correct remembering of study participation status given by parents the survey identified weak points in the parental consent in Paediatric Oncology in Germany. This underlines the need for defining 'Good Practices Cases' of consent.

In 2010 Jenkins et al.[3] analysed barriers to randomised clinical trials (RCT) recruitment. They found that most of the patients were receptive to RCT participation. If information about the trial logic, voluntary nature and rights to withdraw were provided together with further treatment details, 83% of patients would potentially participate in the trial. The paper shows the importance and need for a clear communication and information to patients.

In the study of cancer patients involved in the phase I trial in 1995 Daugherty et al. observed that as many as 93% of participants stated that they had understood the information provided by their doctors and in the informed consent forms (33% said they had understood all, while 60% said they understood most of the information) – nevertheless only 33% of all the participants were capable of stating the purpose of their trial.[4]

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[1] ACGT: Advancing Clinicogenomic Trials on Cancer. FP6 project funded by the EU; http://www.eu-acgt.eu

[2] D.10.6.2 - Status report of the international and national empirical survey on patients' and parents' perspectives and needs – Deliverable within the ACGT Project, available online: http://eu-acgt.org/uploads/media/D10_6_2_final_01.pdf .

[3] V. Jenkins et al.: The attitudes of 1066 patients with cancer towards participation in randomised clinical trials. British J Cancer 103:1801-1807, 2010.

[4] C. Daugherty et al., "Perceptions of cancer patients and their physicians involved in phase I trials [published erratum appears in J Clin Oncol 1995 Sep;13(9):2476]," *Journal of Clinical Oncology* 13, no. 5 (May 1, 1995): 1062 - 1072.

In another study patients undergoing chemotherapy were asked about the role of informed consent documents in making their decision to accept treatment. The result was that 69% of them said that those documents played no role at all, while 6% mentioned that it actually made the decision more difficult. Only a quarter of interviewed patients thought that the consent forms have helped to make their decision easier.[5]

Moody et al.[6] have undertaken a study to explore perceptions and attitudes of parents and future parents to an expanded new-born screening programme in the United Kingdom and the necessary information provision and consent processes. They concluded that parents want guaranteed information provision with clear decision-making powers and an awareness of the choices available to them.

The value of a collaborative approach between patient / trial participant and the investigator in decision making with regards to clinical trial participation is supported by a study done by Tolerton et al.[7] In addition they also found that tissue analysis requires a more emotion-focused approach. This highlights a new focus for trial communication and confirms the need for doctors to remain flexible in their consultation style.

Desch et al. analysed the utilization of an informed consent document in a minimal-risk genetic study. They found that in an online consent procedure provided 93% consented in less than the minimum predicted reading time and concluded that current informed consent documents may not serve the intended purpose of protecting human participants as they don't read the information provided.[8] Of utmost importance is the fact that consent documents must not only provide the necessary information, they must also provide the content in a way that can be understood by the patient as mentioned by Pandlya[9]. The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) formed an ad hoc review team to address concerns regarding the overall readability and length of ICFs used for BMT CTN trials[10].

Numbers show that a clearer and more adequate informed consent form accompanied by a talk

[5] DT Penman et al., "Informed consent for investigational chemotherapy: patients' and physicians' perceptions," *Journal of Clinical Oncology* 2, no. 7 (July 1, 1984): 849 -855.

[6] Moody L, Choudhry K: Parental views on informed consent for expanded newborn screening. Health Expect 2011 doi: 10.1111/j.1369-7625.2011.00710.x. [Epub ahead of print]

[7] Tolerton Sk, Shaw J, O'Reilly A, Dunn S, Boyle FM: Exploring consent to randomized placebo-controlled clinical trials in oncology. Asia Pac J Clin Oncol 7:300-306, 2011

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

[9] Pandlya A: Readability and comprehensibility of informed consent forms for clinical trials. Perspect Clin Res 1:98-100, 2010.

[10] Dezen EM, Burton Santibanez ME, Moore H, Foley A, Gerstein ID, Gurgoi C, Majhail NS, Spellecy R, Horowitz MM, Murphy EA: Easy-to Read Informed Consent Forms for HematopoieticHematopoetic Cell Transplant Clinical Trials. Biol Blood Marrow Transplant 2011 Jul 30. [Epub ahead of print]

with a treating physician can improve both the recruitment rate, as well as the level of understanding among the patients. To overcome misunderstandings Chou et al.[11] developed a screening instrument called Therapeutic Misunderstanding Scale (TMU) for clinicians to better assess informed consent for participation in clinical trials research for use in future studies. In the article 'Is informed Consent broken?', published by Henderson[12], the author writes: "For as long as the federal regulations governing human subjects research have existed, the practice of informed consent has been attacked as culturally biased, legalistic, ritualistic and unevenly enforced. Its focus on meeting the regulatory requirements is seen as undermining a truly ethical process that produces informed and voluntary participation in medical research. Recent changes in the clinical translational research enterprise, with large scale genomic and other data sharing made possible by advanced bioinformatic technologies, may further challenge this goal. Study participants are asked to consent to future studies with unspecified aims, broad data sharing policies and ongoing uncertainties regarding confidentiality protections and the potential benefit of incidental genomic research findings. Because more research is conducted under these new conditions, the very nature of the researcher-subject relationship is shifting and will require new governance mechanisms to promote the original goals of informed consent."

Evidence already given by existing literature that there are many areas in which the procedure of informing patients and of receiving their informed consent could be improved is also supported by CONTRACT's own findings. CONTRACT developed and delivered a questionnaire to identify what researchers have to be aware of when asking for consent from an ethical, legal, organisational and clinical point of view when conducting translational research.

1.2 Results of the questionnaire done in this project (D2.2)

As a result of the questionnaire done within this project the following conclusions were drawn[13]:

- Clinicians, coordinators or chairpersons of a project want to compile Informed Consent (IC) by themselves using templates or a service.
- Templates need to be standardized and modular based and should help to pass Ethical Committees and other Regulatory Bodies in the first run.

[11] Chou PHB, O'Rourke N: Development and initial validation of the therapeutic misunderstanding scale for use with clinical trials research participants. Aging & Mental Health2011, 1-9, iFirst

[12] Henderson GE: Is informed consent broken? Am J Med Sci 2011 Aug 3 [Epub ahead of print]

[13] D2.2: Collation and systematization of questionnaire responses

- Modules are needed at least for care, trial, research, biobanking, data storage and data transfer.
- An information sheet needs to be provided that is easily understandable and allows patients to get as much information as they want to get in accordance to their abilities and wishes.
- The number of pages written information should not exceed 5.
- The number of different IC forms given to one patient at a time should not be more than 3.
- Adequate time (a median of 24 hours) needs to be given to the patients between signing informed consent and starting of the foreseen intervention.
- Informed consents need to include topics of research and biomaterial in an understandable clear and explicit way.
- There should be the possibility to store signed informed consent forms in the Hospital information system (HIS)
- An electronic system to manage consent related documents for clinical trials should be made available.
- Even if patients should continue to sign ICs on paper in the future, the IC forms should be made available also electronically for administrative purposes.
- The patient should be able to decide how he / she will sign IC (electronically or on paper).
- Re-consent should be made available automatically according to rules that are trial dependent.
- The identity of legal guardians needs to be recorded.
- Patients have to be able to easily obtain an overview of the consents he / she has given and they have to be able to reject IC at any time by any way.
- Patients should be able to access their personal data after signing the IC form.
- IC forms should be able to handle different legal requirements from different European countries.
- Sharing of data and biomaterial should be made possible between different countries within Europe.

1.3 Stakeholders interviews

Following and in addition to the questionnaire, the CONTRACT project conducted a survey amongst stakeholders aimed at analysing the best practices in obtaining informed consent focusing on vulnerable patient groups, in particular the paediatric population. Clinical trial site staff of the department of paediatric haematology and oncology of the university hospital Homburg was interviewed (face – to face) to find out about the best informed consent practices on ward regarding clinical research in minors. The participants were requested to answer the following questions:

1. Could you please describe the informed consent procedure for clinical trials in your hospital.
   - Where does it take place?
   - Who is involved in the process?
   - Oral conversation?
   - Usage of information sheet or other tools?
   - How much time for decision is normally given?
   - Documentation of consent process?

2. In which way are the minors/ adolescents integrated in the informed consent process?
   - Who is involved in the process?
   - From what age onwards are minors involved?
   - Any measurements to judge minors capability to consent?

3. How do you make sure that the parents/ legal representative(s)/ patients have fully understood the content/ implications of the clinical trial and that the decision to participate has been taken fully knowingly and voluntarily?
   - How do you deal with patients (respective parents/ legal representative(s)) with lack of German language skills?)

4. What happens if a patient (or respective parents/ legal representative(s)) does not want to take part in a clinical trial or wants to withdraw from a clinical trial?

5. How do you document and report the results of the clinical trials and especially adverse events/ serious adverse events? ((e)health records, paper CRF/ eCRF)
   - Who is responsible for documentation/ reporting?

6. In your opinion, what do you think is the biggest problem in clinical research with children?

Altogether, 7 people with clinical trials experience from 3 to 30 years were interviewed. The roles and responsibilities as well as clinical trials experience of the site staff is listed in the table below:

Principle Investigator

- *In general: Overall responsibility for the trial (planning and conduct)*
- *In particular: Obtaining informed consent, medical treatment of patients*

Investigator

- *In general: Conducting the trial (including recording and reporting)*
- *In particular: Obtaining informed consent, medical treatment of patients*

Study nurse

- *Completion of CRFs, nursing care of (study) patients, performance of non-medical study specific interventions*

Documentalist

- *Preparation of informed consent documents, completion of CRFs, investigator site file management*

The findings are summarized below while the entire interviews are published in annex 3.

From the findings of the interviews we can conclude that the consent discussion is first of all always an oral (face – to- face) discussion which takes place mainly in the visitor's room on ward, in a quiet, trustworthy, undisturbed atmosphere, if possible consent discussion on bedside should be avoided.

Primarily, the respective investigator meets with the patient or the parents/ legal representative(s). If needed also psychosocial site staff and/ or other participating specialists will or should be present. But it is to prevent that too many medical site staff attend the IC discussion, to not put patient/ subject/ parents/ designated representatives under any unnecessary pressure.

In case patient/ parents/ legal representative(s) do not have sufficient language skills to be able to follow the consent discussion an interpreter or site staff or family member with respective adequate language skills will attend the IC procedure.

Secondly it is from the age of 16 mandatory for the patients to take part in the discussion. From the age of 16 or even earlier (depending on mental maturity), the patient also dates and signs the consent form.

In general, all minors are informed about the research project, its procedures and implications in a personal discussion with the investigator. The investigator informs about the trial to the extent compatible with the subject's understanding using age – specific language, pictures, tables and models as well as assent forms (if available). Each conversation is individually tailored to the patient's mental and psychosocial development. There are no specific measurements to judge the minor's capability to consent, it rather depends on the investigator's feeling and experience in working with children.

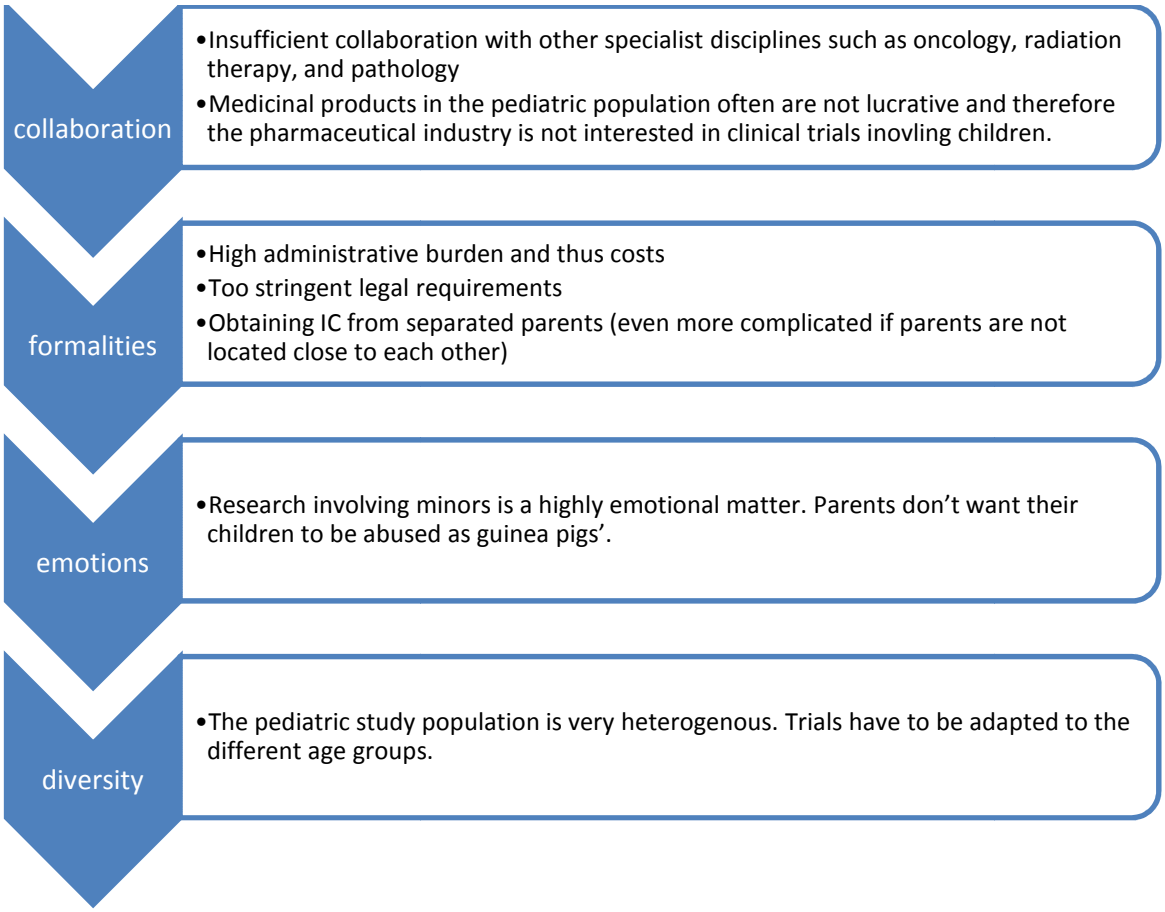
Thirdly, patients/ parents/ legal representative(s) are provided with a study specific patient information sheet and assent form (if available) at the beginning of the discussion. These informative leaflets are used as basis for the consent discussion. The trial and its implications are explained using clear and simple wording avoiding technical jargon. The talk is targeted at the patient's/ parents/ legal representative(s)' needs and wishes.

Fourthly, it was noticed that in general everybody is offered as much time as needed for consideration or second opinion, but on average decision time is 1 to 2 days. Due to the urgency of the treatment start and scope of the study, time for reflection might sometimes be limited.
Based on the patients/ subjects as well as parents'/ legal representatives' questions during and after the consent discussion the investigator gets an impression of the patient's/ parents'/ legal representative(s)' understanding of the core trial contents and main implications. Also sometimes the patient/ parents/ legal representative(s) are asked to summarize the main issues in their own words.

The trial participation is, fifthly, entirely voluntary. Patients/ parents/ legal representatives can refuse participation or withdraw from the trial at any time. Although this very rarely occurs, it is of course accepted and alternative treatment is offered.

Informed consent is finally recorded in the medical records. CRFs are mainly completed by the study nurse and the documentalist. SAE recording and reporting is exclusively investigators' task and is carried out according to the legal requirements.

According to the interviewees, the biggest/ most urgent problems in research involving minors are:



Research in minors in general and obtaining informed consent (from patents as well as minor patients) in particular are delicate matters. The informed consent procedure requires a high degree of tact and sensitivity, specific expertise, specific methodology and appropriately trained investigators. Although by implementing the regulation (EC) 1901/2006[14] on medicinal products for paediatric use the legislator encourages the development and accessibility of medicinal products for use in the paediatric population, the informed consent process has been unaffected. Also the recently released proposal for a regulation on clinical trials on medicinal products for human use[15] does not provide for any changes (simplifications) of the IC.

[14] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF
[15] http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf

1.4 Best practices

1.4.1 Informed consent process in clinical research: good practice guidelines

As will be further explained below[16], the EU Clinical Trials Directive provides in art. 3, 2d that a person can only enter a clinical trial after he/she has been informed of all aspects of the trial that are relevant to his/her decision to participate and after explicit written consent.

Informed consent definitions which apply to clinical research in Europe are given in the Clinical Trials Directive (CTD) and the ICH – Guidelines[17].

CTD (Article 2 j): "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;…."

ICH (E6 1.28): "A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form."

A detailed description of the IC procedure and the content of the consent discussion and the written informed consent form are given in the ICH GCP Guidelines E6 4.8.

Furthermore, the Council for International Organizations of Medical Sciences (CIOMS)[18] has drafted the International Ethical Guidelines for Biomedical Research Involving Human Subjects, which are internationally accepted and very widely utilized. Here informed consent is considered as "a decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation." This is followed by extensive descriptions and explanations on the subject of IC, the IC process and obtaining IC.

Regarding informed consent in research involving minors, the CTD (article 4) explicitly requires informed consent of the parents/ legal representative taking into account the presumed will of the minor and only after the minor has been informed about the trial, risks and benefits based on his/her age, maturity or psychological state. It is also a basic prerequisite that the investigator respects the minor's explicit wish to refuse or withdraw at any time.

According to the ICH – GCP Guidelines (4.8.12) "subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative" should also be informed about the trial in a way appropriate to their understanding, if capable these subjects should also date and sign the written informed consent.

[16] See section II2.3
[17] ICH http://www.ich.org/
[18] http://www.cioms.ch/

The CIOMS guidelines determine that research involving children may only be carried out after permission of parent or legal guardian and also after the agreement (assent) of each child to the extent of the child's capabilities have been obtained. Deliberate objection by a child to taking part in research or continue a research project should always be respected.

In general, informed consent should protect the individual's freedom of choice and respect the individual's autonomy. The IC process aims at gaining an independent, voluntary and truly informed subject's decision regarding the participation and continuation in a clinical research study. Furthermore, it should ensure utmost patient safety.

Gaining informed consent is an interactive process between the subject and the clinician (and, indirectly, with the whole study team).

The current best IC practices are outlined below:

STEP1: Preparation:

- Familiarize with study protocol, all patient specific procedures, all available patient information and consent form(s).
- Carefully select potentially eligible patients/ subjects
- Prepare checklist to ensure that all key points are covered during the patient/ subject's visit (e.g. patient information sheet and informed consent forms can serve as convenient checklist)

STEP2: Introduction

- Make an appointment with the patient/ subject and if applicable respective parents/ designated representatives and allocate sufficient time for the consent discussion
- Create an open atmosphere of trust (private, quiet place for counselling)
- Explain the consent process to patient/ subject/ parents/ designated representatives

STEP 3: Disclosure

- Provide all information patient/ subject needs to make an informed decision (nature, purpose of the treatment, significance, implications, risks, potential benefits, available alternatives, etc. see checklist included below)
- Keep all the information easy to understand and avoid medical and technical jargon
- Communicate with patience and sensitivity
- Consider patient's/ subject's general and health literacy, educational attainment as well as the primary language spoken
- Engage patient/ subject in consent discussion

Step 4: Understanding

- Check carefully patient's/ subject's understanding of the relevant facts and of the consequences of participation, e.g. asking open – ended questions, ask patient/ subject to repeat in own words the core issues of the study ("teach back")
- Repeat explanations, if necessary
- Provide patient/ subject with additional information/ fact sheets that can be taken home
- Encourage patient/ subject to ask questions

STEP 5: Consent

- Hand out consent form(s)
- Give patient/ subject sufficient time to read consent form and reconsider participation/ continuation, discuss with family, friends, GPs
- Provide patient/ subject with contact data (telephone number, e-Mail, etc.) for further questions
- Convince yourself that patient/ subject consent independently and voluntarily (free from coercion and from unfair persuasions, undue influence, inducements, intimidation)
- Obtain written, dated and signed consent

Specific considerations for IC for reserach involving children

- Include children/ adolescents in the IC process to the extent possible depending on their age and maturity
- Assess child's willingness to participate
- Information provided to the child should be adequate to his/ her individual level of understanding also considering individual psychological and intellectual maturity and social environment.
- Information might be supported by illustrated pictures and videos
- Staff involved in IC process should have experience in care and treatment of children in the respective age group
- Consent must be obtained from the parents, a legal guardian or other duly authorized representative representing the (presumed) will of the child
- Request verbal and/ or written assent depending on the child's age, mental and psychosocial development

Checklist IC discussion

- Diagnosis of the current medical condition
- Course of disease and prognosis with study treatment and with alternative treatments/ no treatment
- Purpose of the study
- Study treatments, including
  - Number and type of all therapies, procedures, tests (explaining also positive and possible side effects of the respective intervention; clarifying routine treatments and study procedures)
  - Duration of the subject's participation
  - Location, number, duration of (follow-Up) visits incl. visit interval
  - Description of investigational product (dosage, storage, intake)
- Study design (randomised, blinded, placebo controlled)
- Voluntariness of participation, withdrawal at any time
- Subject's responsibility (compliance)
  - follow all medical instructions from your investigator
  - attend all visits/ examinations
  - inform site staff about the course of the disease (side effects, discomforts)
- Expected benefits(also if there are no intended clinical benefits)
- Risks/ Discomforts/ Side effects
- Impacts on daily life (e.g. dietary requirements, fasting condition, other treatments to be avoided, driving ability, leisure activities)
- Alternative treatment methods
- Anticipated expenses
- Reimbursements
- Insurance (hand out of insurance documents)
- Confidentiality (Anonymisation/ pseudonymisation, data access, data protection)
- Address patient's/ subject's questions and concerns
- Convince yourself of patient's/ subject's understanding regarding relevant facts of the study and the consequences of participation
- Hand out of patient information and consent form(s)
- Contact details for further information
- Date for the next meeting (allowing patient/ subject for ample time to read information sheet(s) and content form(s), and discuss participation with family, friends, GP

1.4.2 Compiling consent forms in a research project

A web-based tool for creating informed consent templates will be made available on the CONTRACT webpage (www.contract-fp7.eu). It will allow researchers to compile their own consent templates (according to personal needs). In January 2012 a first version was made available for a limited audience, in September 2012 a second version was opened online. An informed consent creation tool should be modular, supporting modules for:

1. Consent for participation in a clinical trial
2. Consent for data sharing
3. Consent for research
4. Consent for bio-banking

Each of the modules should be written in a structured way taking the consent differentiators into consideration. These differentiators are described in "Trial characteristics & Informed Consent Working Document". Within the scope (resources) of CONTRACT, it is only possible to provide the legal information for the clinical trial consent module (with some constraints). Note however that clinical trial consent already spans a wide range of consents (for the trial itself, collection of biomaterial, reuse of data, …). The "mechanics" of the created generator will however be generic.

After compiling his template(s), a researcher should be capable of exporting in an editable format (e.g. MS Word) for further improvements, e.g. after ethical comment, for changing layout, etc. The template will also include placeholders where the researcher is expected to fill in details such as: the specific work plan, the objectives and pro and contra of their research (written in an understandable way for patients).

Although this is not possible within the scope of the CONTRACT project, it could be useful to further extend the informed consent generator with document management capabilities, so that researchers come back to the helpdesk to manage and further elaborate their informed consent documents.

The information sheet is an important part of the informed consent forms. The following topics need to be addressed in such an information sheet (still it should be concise and preferably not exceed 5 pages):

1. Name of the research project / trial / treatment
2. Description of the research project / trial / treatment including:
    a. Explaining the standard care of today including risks and outcome

b. Explaining other treatment options including risks and outcome
c. Explaining outcome with no treatment
d. Number of patients needed
e. Involved countries / centres
f. Explaining the following terms if needed:
    i. Randomization and blind study
    ii. Retrospective / prospective study
    iii. Observational / interventional study
    iv. Anonymisation / pseudonymisation
    v. Phase I / II / III / IV trial if needed

3. Description of the project / trial / treatment procedures
    a. Description of study drug (dosage, storage, intake), where applicable discontinuation of drugs
    b. Duration of the subject's participation
    c. Location, number, duration of (follow-Up) visits incl. visit interval
    d. Number and type of invasive and non – invasive interventions: ECG, laboratory examinations, blood tests, questionnaires etc.
    e. Blood tests: how often, amount of blood, what will be tested
    f. Subject’s responsibilities
4. Risks of the research project / trial / treatment
5. Advantages / benefits of the research project / trial / treatment
6. Voluntariness of the participation
7. Which data will be shared and to whom
    a. How long the data will be stored and where
    b. If personal data will be shared explain why and to whom
    c. In case of an opt-out solution describe what this means
8. If biomaterial is needed:
    a. Describe why and what will be the expected results

b. Describe who will get biomaterial

i. In case of an opt-out solution describe what this means

9. Issues regarding costs and compensation
10. Issues regarding insurance if needed
11. Issues regarding informed consent, re-consent, withdraw of informed consent
12. Name, address, telephone, fax, email of the principal investigator
13. Name, address, telephone, fax, email of the Sponsor of the research project / trial
14. Name of the project website for further information

a. In case of an opt-out solution the name of the website where to make choices

In case children are enrolled in a research project different information sheets for different age groups should be provided:

1. Children between 4 and 6 years → picture based
2. Children between 6 and 12 years
3. Children between 12 and 16 years
4. Teenagers between 16 and 18 years use the adult information sheet

In addition there needs to be an information sheet for parents, which will have the same content as the sheet for adults with the difference that it addresses parents and not a patient.

As a general note, it should be remarked that when a research project is finalized an end-report of the results should be provided by the researcher in addition to the scientific publications. This end-report should be written in a language understandable for patients. End-report and links to scientific publications of the research project should be made accessible through the above mentioned webpage.

Although implementing this is outside of the project scope, the informed consent generator could evolve into a full blown consent authoring system (including the document management) and be linked to an e-consent management system. When this is the case, finalised informed consent documents could be put immediately online on the e-consent system by the researcher. There, patients could then easily find the consent documents related to the trial/study/research project relevant for them online. The same system can be used by researchers to keep track of signed consents (recording patient consent electronically and by archiving scanned in signed documents), and by patients for validating what they consented to

in the past. Eventually (far future), it is imaginable that patients themselves would sign the consent forms electronically online in the e-consent system.

1.4.3 Giving consent by patients in a research project / trial / treatment

The treating physician or the principal investigator needs to be experienced in obtaining consent. Informed consent should be given in a comfortable surrounding and atmosphere without time constraints. The patient should be asked primarily who should be with him/her (family members, friends). In case of a foreigner a registered translator needs to be present.

The physician or principal investigator should introduce himself/herself and give background information about the research project / trial / treatment for which informed consent is needed. This should be done in a way encouraging the patient to ask questions at any time to help him understand.

In case of minors the child is primarily asked if he / she will attend the discussion with the physician / principal investigator. The child should always be stimulated to do so. There should never be discussions with parents alone without the knowledge of the child. The explanations during the discussion should always be in a way that the child will understand. [19] The child can decide at any time to leave the room and come back whenever he / she wants. In case of a teenager one should address him as the primary person to talk with. Every question should be answered honestly and truthfully and without neglecting hope by telling what can be done to cure. During the whole procedure of obtaining parents' permission all the actions should "show respect for the child's developing autonomy"[20] and be directed towards protecting the child or minors interests, but also their free will.

Depending on the consents to be given, each of them is explained (for treatment, for data processing, for research). It is explicitly said that the informed consent can be withdrawn at any time without giving a reason and without any negative influence for the patient.

If there are no questions left, the physician hands over the information sheet and the consent forms to take them for reading and perhaps to obtain a second opinion. The content of the information sheet and the consent forms are explained to the patient shortly. In case of a minor the respective information sheets will be given to the child and the parents. The information sheet and the consent forms need to be in the mother tongue of the patient. A new date at the

[19] Committee on Bioethics, "Informed Consent, Parental Permission, and Assent in Pediatric Practice," *Pediatrics* 95, no. 2 (February 1, 1995): 314 -317.

[20] Wilma C. Rossi, William Reynolds, "Child AssentAssen and Parental Permission in Pediatric Research", Theoretical Medicine 2003, no. 24: 131-148

earliest the next day will be fixed, where the patient can ask further questions and give informed consent.

After signatures are given the patient receives a copy of the informed consent form(s). In case of minors both parents will sign the informed consent and depending on the age of the child and the maturity (around 10 or above) he / she is asked to sign the informed consent as well. If re-consent is needed (e.g. in case of minors) it is explained that such a procedure will automatically start at due time. In case of an emergency situation, where consent needs to be given without a time interval between diagnosis and start of treatment, re-consent should be done as soon as the condition of the patient allows.

In case of the possibility of giving consent electronically (e-consent), the patient should be able to choose to give consent electronically or by paper forms. If paper consent forms are stored electronically the patient needs to be informed about the storage and how he can have or get access if possible.

If an opt-out solution for consent, in which a patient can, at any time, withdraw parts of his consent, is available, the patient needs to get information how he can change his consent. In this case a website should be provided where the patient can securely access his informed consents and where he can make choices about data sharing and research projects.

1.4.4 Giving re-consent by patients in a research project

The way of giving re-consent is in principal the same as for consent.

1.4.5 Storage of signed consent forms in a research project

All signed consent forms in a research project need to be stored. This can be done paper based and additionally electronically. In case of paper based storage the original consent form should be stored centrally at the location of the principal investigator (preferably in the investigator site file). It is advisable to file a copy in the patient chart. A further copy of the signed informed consent is always given to the patient/parents/ legal representative.

In case of e-consent a signed consent should be printed and given to the patient with the information, where the file is stored and how he can access the file.

1.4.6 Access to informed consents by patients in a research project

This paragraph applies only in case of e-consent.

For each study/trial/research projects a website will be available, where patients can get access to their own consents via a portal. This website will give them the possibility to electronically

sign consents related to the project and revoke them at any time. The information about the website is given to the patient by the treating physician during the first talk about consent issues. This information is also given as a written document to the patient. In this document it is explicitly written how the patient can create his secure account for accessing the website.

On the website instructions how to use the website and information about consent in general are provided. The patient is able to print out all information he needs.

If a patient electronically signs or revokes his consent via the website the PI and the treating physician need to be informed about this decision immediately. In the data management system of the trial/study/research project a table must be provided listing all possible consents a patient can give. This table needs to be automatically and immediately updated if the patient gives or revokes consent for one of the trials of the project. The information in this table provides the basis for the researcher, what research can be done with the data of this specific patient.

The website should also provide the information about the PI or the person he can contact in case of questions. An email request should be accessible on this website and should lead directly to the treating physician of the patient. The email account of the treating physician is provided by the data management system of the trial.

The website needs to be written in the mother tongue of the patient. All documents the patient can access are also provided in the mother tongue of the patient. The patient is also able to choose another language, if needed.

In case a legal representative has to give consent personal data of this person (name, birth date, address, identifier) needs to be given and stored in the system. In case of a minor the personal data of both parents are stored.

2 Section II – Developing a legally compliant informed consent document

2.1 Introduction

2.1.1 What is this document?

These guidelines aim to support researchers and clinical trials investigators who seek to create informed consent documents compliant with the European legislation that is consistent with the framework established by the clinical trials and data protection legislation on the level of European Union.

In preparation of those legal guidelines CONTRACT brought together representatives from across the health research spectrum. That included the project consortium – which consists of physicians, security and legal experts. Secondly it also included the insights of different stakeholders, who were brought together on September 15, 2011 in Hannover during the first CONTRACT workshop to discuss a first draft of these guidelines and on September 7, 2012 to discuss the final guidelines and the demonstrator of the helpdesk and informed consent guide. A full account of those discussions can be found on the project webpage[21]. The views of both workshops were, whenever possible, integrated into this document.

The idea of this document was to provide a comprehensive overview of what needs consideration whenever undertaking research in the European Union, which would outstretch trough more than one of the Member States. What was especially stressed within the guidelines was the use of personal data – whenever that is to be done this document should be helpful in doing so compliant with conditions of the European data protection framework.

Informed consent is a widely discussed theme. There were and are many attempts to explore and provide advice on that subject. Grasping the whole depth and complexity of these matters exceeds the outcomes of both CONTRACT Project, as well as of this document. Therefore there are a number of limitations as to what the legal part of guidelines encompasses.

a. Legislation taken into account

b. Scope of informed consent documents

c. Patient / research subject / data subject for whom the document is being drafted

a. Legislation taken into account

As mentioned already before, the focus of the guidelines lies on European legislation. Two major legal acts in that regard are in scope of this document:

[21] See: http://www.contract-fp7.eu/

- Directive 2001/20/EC of 4 April 2001, of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use – onwards „the Clinical Trials Directive“, or Directive 2001/20/EC;
- 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 – onwards „the Data Protection Directive“, or Directive 95/46/EC.

These guidelines provide detailed advice regarding compliance with the two mentioned directives.

It is recognised that due to its special status the European directives are not used within the Member States of European Union directly, but each of the Member States needs to transpose the directives into its own legal system. CONTRACT guidelines advice mainly on that European level. Reason for that is current practice within the clinical trial arena – more and more clinical trials are being done not in single centre, but multi centre environment and the centres in which the trials are done often encompass not only whole of Europe, but outstretch also outside of Europe borders. It is therefore not feasible to give a complete overview on the level of national regulations.

That is why the given document should be of support at the first step of informed consent documents development – drafting a document compliant with European legislation. At a second stage the clinical investigator or researcher needs to secure that the document is compliant with legislation on the national level. For that reason he or she will need to consult a specialist on national law of each of the participating countries.

In order to further facilitate creating informed consent documents the document offers limited support for the aforementioned second stage – for four countries also national guidelines are provided giving clarification into the specific requirements on the national level. In order to give insight into diversified legislation the following criteria for country choices were used:

- Legal system: common law legal system (UK) opposed to the civil law legal system (Germany, Belgium, Poland)
- European Union Membership: a new European Union Member State (Poland) opposed to the old Member States (Germany, Belgium, UK)
- Country size: small (Belgium) opposed to bigger (Germany, Poland, UK) area

b. Scope of informed consent documents

The process of signing informed consent form represents parts of the control which a person has over his / her own life. That means that such documents can be created for a variety of social contexts. In the medical practice they are used to acquire consent of a patient for different reasons. The first is informed consent for care – legally that consent is based within the national legislation, therefore it will not be presented in detail in this guide apart from an overview of the legal status of consent to treatment in the four chosen national legislations. Furthermore, informed consent is a precondition for clinical trials – consent for taking part in the clinical trial is part of this guide. Consecutively taking part in clinical trial requires data processing – for which the legal basis can in many cases be found in the consent of the person, whose data is being processed – therefore informed consent for data processing is also part of this guide. In addition consent for tissues or cells sampling etc. could be necessary[22] in some clinical trials, but that specific consent will not be analysed in this document.

[22] See the Directive 2004/23/Ec Of The European Parliament And Of The Council Of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, available online: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:en:PDF .

c. Patient / research subject for whom the document is being drafted

As explained in paragraphs above informed consent documents are changing depending on different factors – those factors can be the law, which compels certain elements of the document, or the scope for which the document has to be prepared, but another factor which will cause changes within the informed consent document is the person to whom this document is directed. Depending on whether he or she is or is not capable of giving consent the document will be directed to the patient / trial participant directly or to his / her legal guardian. Within the CONTRACT project the focal point is laid on vulnerable populations. That means that also those guides are directed to people developing informed consent forms for the vulnerable patients trial – whenever the text passages are proposed they are therefore not directed to the patient, but to the parents of a child, who is to participate in a trial.

2.2 An overview of informed consent

The concept of informed consent is one of the key elements of modern medical ethics[23]and stems from both moral and legal theory.[24] It is rooted within the principles of autonomy and self-determination[25], which are, as writes Berg the values most prized within western civilization.[26]

Donelly specifies that consent is the principal legal mechanism which delivers autonomy to the person in question[27] therefore giving practical worth to so highly valued right.

In brief, the rule of informed consent states that no medical intervention (be it of preventive, diagnostic, therapeutic or research nature) can be done without the patient's agreement.

Therefore, valid informed consent is an act of authorisation, which legalises the medical procedure.

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[23] For exhaustive account on the informed consent as a ground of medical ethics compare for example: :Kenyon Mason and Graeme Laurie, *Mason and McCall Smith's Law and Medical Ethics*, 8th ed. (OUP Oxford, 2010), 4; Tom L. Beauchamp and James F. Childress, *Principles of Biomedical Ethics (Principles of Biomedical Ethics*, 6th ed. (OUP USA, 2008), 57; Ruth R. Faden and Tom L. Beauchamp, *The History and Theory of Informed Consent* (New York ::: Oxford University Press, 1986), 3; Jessica W. Berg, Paul S. Appelbaum, and Lisa S. Parker, *Informed Consent: Legal Theory and Clinical Practice*, 2nd ed. (Oxford ;;; New York: OUP USA, 2001), 14.

[24] As writes for example Ezekiel J. Emanuel, *The Oxford textbook of clinical research ethics* (Oxford ;;; New York: Oxford University Press, 2008), 613. : "Legal rules embodied in judicial decisions and in statutes and regulations are at the heart of modern bioethics."

[25] Sheila McLean, *Autonomy, consent and the law* (Taylor & Francis, 2009), 40; Helena Leino-Kilpi, *Patient's autonomy, privacy, and informed consent* (Amsterdam ;;; Washington DC: IOS Press, 2000), 55.

[26] Berg, Paul S. Appelbaum, and Parker, *Informed Consent*, 14.

[27] Mary Donnelly, *Healthcare Decision-Making and the Law: Autonomy, Capacity and the Limits of Liberalism* (Leiden: Cambridge University Press, 2011), 52.

2.2.1 History

Despite its popularity and importance the doctrine of consent is in its current shape a relatively new concept.[28] Originally the patient accepted doctor's decisions without any questions.[29] It is only recently when patients gained the possibility to authorise doctor's actions.[30]

The first written ethical code mentioning consent was written in 1947 as an outcome of horrific atrocities of the German scientists and physicians in the concentration camp prisoners during the World Word II. After the trial on the Nazi Doctors the tribunal presented the first code of human experimentation ethics – the so-called Nuremberg Code[31], which is "generally seen as the first authoritative statement of consent requirements in biomedical ethics". The Court prefaced it with the following sentence: "All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts." The document consists of ten rules, of which the first states: "**The voluntary consent of the human subject is absolutely essential."**

Nuremberg Code nourished the development of many declarations and codes of conduct on medical care and research, of which the best known[32] is the Helsinki declaration[33]. The declaration has been amended multiple times, recently in year 2008.

Moral theory and ethics of medicine are the foundations in which the doctrine of informed consent finds justification. The medical ethics last on a set of moral principles – autonomy, beneficence and justice and it is the first of them that lays the ground for informed consent.

Respect for autonomy is, as write Faden and Beauchamp, part of "the liberal Western tradition of the importance of individual freedom and choice, both for political life and for personal development".[34] What gives people (and does not give animals) the possibility to act autonomously and make choices on their own life? As Brock states – it is the capability to form values, not just desires (…) to form and act on a conception of the good life." That autonomy

[28] Berg, Paul S. Appelbaum, and Parker, *Informed Consent*, 249; Leino-Kilpi, *Patient's autonomy, privacy, and informed consent*, 55. On the opposite some authors find the roots of informed consent in the Roman "Volenti non fit iniuria" rule – compare: Ansgar Ohly, *"Volenti non fit iniuria": die Einwilligung im Privatrecht* (Tübingen: Mohr Siebeck, 2002), 25.

[29] Dan W. Brock, *Life and death: philosophical essays in biomedical ethics* (Cambridge University Press, 1993), 23.

[30] O'Neill, Onora, and Neil Manson, *Rethinking informed consent in bioethics* (Cambridge; New York: Cambridge University Press, 2007), 4.

[31] The Nuremberg Code is available online: http://ohsr.od.nih.gov/guidelines/nuremberg.html .

[32] O'Neill, Onora, and Manson, *Rethinking informed consent in bioethics*, 2.

[33] Full title: World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects as revised in 2008, available online on the WMA webpage: http://www.wma.net/en/30publications/10policies/b3/index.html .
The declaration has been amended a number of times – the original one was adopted in 1964.

[34] Faden and Beauchamp, *The History and Theory of Informed Consent*, 7.

allows humans to take their lives in own hands and make decisions on their own account.[35] The "principal legal mechanism through which the right of autonomy has been delivered is informed consent"[36]

Autonomy is the first consideration when thinking of informed consent, but it is not the only one. Brock adds to that account: individuals best understanding (in principle) of their own interest and therefore their predestination to make choices on their life, the public support for ethical medical research, as long as it is conducted in the ethically compliant manner and finally rational participation in research, which requires making informed choices[37].

2.2.2 Preconditions for a valid informed consent

Having the background on philosophical justifications of consent it has to be noted that purely offering an informed consent form document to the patient or research subject is not sufficient for a successful informed consent process, neither is solely the patient's signature, which validates the consent. There are a number of elements, which have to be achieved so that one can speak about **valid** informed consent.

"Legal, philosophical, regulatory, medical and psychological literatures have generally discussed informed consent in the terms of its "elements."[38] The list of those elements differs but three are commonly agreed upon. In order for consent to be valid it must be – informed and voluntary, while the person giving it should be competent[39].

Those three elements are analysed in detail below[40].

[35] That autonomy, which is backing the doctrine of informed consent is as far reaching that it allows making choices against one owns interest (in the common understanding) and refusing treatment e.g. as Court wrote in the US case Malette v. Shulman (1990) 67 DLR (Rth) 321 (Ont CA) „For this freedom to be meaningful, people must have the right to make choices that accord with their own values, regardless of how unwise or foolish those choices may appear to others." In principle such understood autonomy is accepted, while at points controversial. The case is different when consent is being given by a legal guardian.

[36] Faden and Beauchamp, *The History and Theory of Informed Consent*.

[37] Emanuel, *The Oxford textbook of clinical research ethics*, 607.

[38] Faden and Beauchamp, *The History and Theory of Informed Consent*, 274.

[39] Compare: Faden and Beauchamp, *The History and Theory of Informed Consent*.Allan M. Tepper and Amiram Elwork, "Competence to Consent to Treatment As a Psycholegal Construct," *Law and Human Behavior* 8, no. 3/4 (December 1, 1984): 207.

[40] See II2.2.2.1 Informed, II2.2.2.2 voluntarism and II2.2.2.3 capability.

2.2.2.1 **Informed**

The term "informed" has been seen by some authors as such an imminent part of consent that it eventually became a part of the notion itself, others criticise addition of the descriptive term "informed" and argue that one can only speak about consent when it is informed.

Withstanding the debate – the requirement of consent to be informed requires that any potential patient or participant of the study has to be provided with "appropriate information". That information should enable him to achieve a sufficient understanding of the matter and take a deliberate decision.

That raises further questions – what is appropriate information? Appropriate information can be understood on multiple levels: on what topics exactly should the information be provided, to what depth should the provided information go and finally, how should the information be offered in order to fit to the needs of a specific patient or participant.

Beauchamp and Childress emphasise that information offered to the patient before commencing treatment should include "diagnoses, prognoses, the nature and purpose of the intervention, risks and benefits and recommendations"[41]. The Declaration of Helsinki determines that participants in research projects should be provided with information on "the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal".[42] Further accounts also specify the kinds of information that needs to be offered[43], but as Brock[44] notes the depth and detail to which the information should be provided is not specified.

There is a number of discussions when it comes to the information, which is provided to the patient – critics argue that patients and participants cannot really understand all the provided information[45], further that the complete information never actually can be provided. It is also

[41] Beauchamp and Childress, *Principles of Biomedical Ethics (Principles of Biomedical Ethics*, 158.

[42] Art 13 of the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, available online on the WMA webpage: http://www.wma.net/en/30publications/10policies/b3/index.html .

[43] Compare: Brock, *Life and death*, 49. Also compare with the requirements of the Clinical Trials Directive, which are explained in the Guide.

[44] Emanuel, *The Oxford textbook of clinical research ethics*, 608.

[45] Jay Katz, "Informed Consent - A Fairy Tale - Law's Vision," *University of Pittsburgh Law Review* 39 (1978 1977): 137; F. J. Ingelfinger, "Informed (but Uneducated) Consent," *New England Journal of Medicine* 287, no. 9 (1972): 465-466.

argued that the information provided should be provided as material information showing not an objective impact, but a subjective impact of the intervention on life of a particular patient[46].

The question of how much information is sufficient for consent to be informed is somewhat connected to another question: how should the information fit the specific participant – as mentioned earlier the information should be not only provided, but also provided in a way that the prospective patient or participant can understand – that is why the relevant information necessary for a valid consent will differ in each particular case. Therefore balance has to be created between allowing access to information and making information available for the patient (allowing asking questions and receiving detailed information) but not overwhelming patient or trial subject with the information he or she is neither willing to receive, nor is capable of understanding.

2.2.2.2 **Voluntarism**

For consent to authorise any health-care related procedures (both when it comes to care, as when it comes to research) it must be voluntary or in other words it has to be freely given. This implies "that the individual is free from external pressure to make a particular decision"[47]. Involuntary consent can include: consent made under coercion or duress, under pressure, or under manipulation or undue influence[48].

- Coercion – "a patient's decision is coerced when the patient is threatened, either explicitly or implicitly, with unwanted and avoidable consequences unless the patient makes the desired choice."[49]
- Manipulation – is probably a common phenomenon within the health-care setting – it is easy for a physician or researcher, due to disparities in knowledge and status and difficult situation of the patient to influence the process of decision-making (by i.e. withdrawing information)[50]. "It is a common criticism that "the informed consent process is meaningless because they (the physicians) can get the patient to agree to whatever they want.

2.2.2.3 **Competence / decision-making capacity**

Inherent in the doctrine of consent is the principle that only people of sound mind have the right to make their own decision about what shall be done with their bodies – therefore "that

[46] Steve Clarke and Justin Oakley, *Informed consent and clinician accountability: the ethics of report cards on surgeon performance* (Cambridge University Press, 2007), 135.
[47] Sheila McLean, *Autonomy, consent and the law* (Taylor & Francis, 2009), 51.
[48] Brock, *Life and death*, 43.
[49] Ibid., 44.
[50] Ibid., 46.

the patient must possess the capacity to receive, comprehend and utilize the information with which he or she has been provided".[51] Such understood competence is the patient's ability to participate in medical decision-making.

The decisional capacity is discussed in both law, as well as in ethics and in medicine, which makes the matters relatively complex. Two levels of discussion can be recognised: the theoretical legal framework and the practical assessment or capacity.

Authors, especially in medicine, use the term competence to talk about whether one can take health-care-related decisions. In law the term of competence has a defined role (cf infra[52]).

2.2.2.3.1 Legal framework

Western jurisdictions presume that healthy adults have full competence and are therefore capable of making decisions on their own account. Children gain full competence together with reaching the so called "age of majority" which is the moment in which minors are recognised by law as adults (exemptions apply when they meet special criteria). The competence allows them to take decisions concerning not only health issues, but also making other decisions in all spheres of life i.a. managing their own affairs, taking financial decisions, or marrying.

As previously mentioned the legal capacity is based on presumptions. The law determines *prima facie* who has legal capacity and who lacks legal capacity. Law puts limitations on certain classes of persons and specifies whether they have full, limited or no capacity. When it comes to adults the principle states that adults have a full capacity. The division among the classes differs among the jurisdiction, but traditionally children have limited legal capacity. The second class of individuals without full legal capacity are incapacitated adults – those are people with mental illnesses, alcoholic disease etc, who lost the legal capacity by a competent authority's decision in full or in part and hence have no or limited legal capacity to take decisions about their healthcare.

There is though a number of cases in which people who are adults and have prima facie full legal capacity may nevertheless not be competent to consent[53]. That is when the psychological assessment of decision-making capacity is needed.

Unfortunately, the legal framework with regard to legal capacity is not harmonised within the European Union. Robinson and Andrews (2010) identified this lack of harmonisation as one of the bottlenecks for informed consent in the EU[54]. They found that the majority of Western

[51] Tepper and Elwork, "Competence to Consent to Treatment As a Psycholegal Construct," 207.

[52] See II2.2.2.3.1 and II2.2.2.3.2.

[53] Such a situation is highly controversial as it touches primary questions of the human rights and autonomy, asking in how far those rights can be taken away from an individual.

[54] Robinson, K. and Andrews, P. (2010) "(More) trials and tribulations: the effect of the EU directive on clinical trials in intensive care and emergency medicine, five years after its implementation", J Med Ethics, 36: 322-325.

European countries (like Belgium, Denmark, Finland, France, Hungary, Ireland, The Netherlands, Norway, Spain and Sweden) provide some kind of hierarchical order for family members to act as legal representative when the person unable to consent did not appoint a legal representative in advance. Generally legislation in these countries always requires this person to have a close connection to the patient. In other European countries such as Austria, Germany, Italy, Switzerland and Poland preference is given to a legal representative appointed by a judge or a legal guardian or welfare attorney in the UK. Some European countries like Belgium, Denmark, Ireland and the UK allow healthcare professionals too to act as legal representative, but this is often limited to intensive care situations or considered to be a last resort only.

Within the CONTRACT project one example of such a scheme is provided in annex 2. For the following consent guide we presume that the most common case in paediatric trials will be the parent(s) consenting for the child.

2.2.2.3.2 Assessment of capacity

The capacity to consent covers a set of abilities that enable a person to take health related decisions independently. There is no fixed set of abilities[55], which prove decisional capacity or their lack, but scholars agree on a set of four[56] that need to be met. Those abilities compromise: understanding given information, appreciation of the situation, reasoning and finally making and communicating the decision taken. [57]

- Understanding given information – patient can receive given information and comprehend it – he can understand the physician's advice, the treatment and research options and alternatives.
- Appreciation of the situation – is the ability to judge with a set of important values, how a particular decision will help him in achieving what he believes is good for him.

[55] P.S. Appelbaum and T. Grisso, "Assessing patients' capacities to consent to treatment," *The New England Journal of Medicine* 319, no. 25 (December 22, 1988): 1635-1638.

[56] For a comparison of legally relevant criteria for in assessing decision- making capacity of patients see i.a.: Paul S. Appelbaum, "Assessment of Patients' Competence to Consent to Treatment," *New England Journal of Medicine* 357, no. 18 (2007): 1836.

[57] There is no common legal standard on assessment of legal capacity Paul S. Appelbaum, "Assessment of Patients' Competence to Consent to Treatment." Laura Weiss Roberts, "Informed Consent and the Capacity for Voluntarism," *Am J Psychiatry* 159, no. 5 (May 1, 2002): 705. Or Michael Church and Sarah Watts, "Assessment of mental capacity: a flow chart guide," *Psychiatric Bulletin* 31, no. 8 (2007): Fig. 1.

- Reasoning – patient is capable of deliberating and reasoning how the decision will affect him and his life, which means that patient or research subject must understand causal relations, probability and percentages, as well as logical reasoning.[58]
- Making and communicating the decision – is capability to finally taking the decision and communicating it (in an understandable way).

2.3 Introduction to Informed Consent in Clinical Trials

Currently there is no widely accepted definition of a 'clinical trial'. A clinical trial is a specific type of medical research. Often the term is restrictively used for research done in a clinic or a hospital, but it is more than that. Legal regulations too, like the European Clinical Trials Directive use the term in a restricted way. The European Clinical Trials Directive (Directive 2001/20/EC) only applies to drug research in interventional trials[59]. This is indicated in the title of the directive as well as in article 1 and in the definitions in article 2. But clinical trials are more than interventional trials involving drug research.

Generally a first distinction is made between interventional clinical trials and non-interventional or observational clinical trials. Doppelfeld (2010) describes the difference as follows: "Observational research excludes any intervention on the part of the researcher, who stays in an observing position.", "Interventional research may be performed with physical interventions penetrating the human integument, i.e. the skin. Interventional trials without a physical intervention include preventive medicine aimed at changing the behaviour of groups or whole populations". A typical example of observational research is medical epidemiology. Interventional research differs from simple blood sampling over research in surgery to the proposal to avoid certain types of food. A second distinction can be made between those trials involving (investigational) medicinal products and those not.

Additionally one could also distinct the scientific use of removed and stored biological material of human origin and its related data[60]. In some Member States this type of medical research is subject to the same legal regulations as other types of clinical trials, but in many others specific exemptions are foreseen. We therefore do not consider this type of medical research when describing how to develop informed consent forms for clinical trials.

Given the different impact of these different types of medical research on the person consenting to the trial or the legal representative and the different legal requirements which

[58] Raymond J. Devettere, *Practical decision making in health care ethics: cases and concepts* (Georgetown University Press, 2009), 73.

[59] Articles 1, 1.; 2 (a), (c) and (d) Clinical Trials Directive.

[60] E. Doppelfeld, "Appropriate Regulations for Different Types of Medical Research" in A. den Exter (ed.) 2010, Human Rights and Biomedicine, Maklu Antwerpen, 105-116.

may apply, this distinction will be a first important element in the informed consent form. As will be shown further on in the guide, this consequently also means that the first and probably largest part of the informed consent form for clinical trials will be all about explaining what type of trial is run and what the impact of this trial on the person consenting may be.

Next it is important to realize that the regulation of clinical trials involving persons unable to consent, like children, is stricter. Since the informed consent of the participant is regarded the uttermost condition for the involvement of any person in medical research, and this condition cannot be fulfilled as usual, specific protective provisions must be respected. First of all it will have to be justified why the involvement of children is necessary and explained why the results cannot be obtained through research involving persons who are able to consent for themselves. Because the informed consent is such a central condition to the conduction of a clinical trial and it cannot be fulfilled by a child, the Ethics Working Group of the Confederation of European Specialists in Paediatrics (2003) stresses that medical scientific research should never be carried out in a paediatric population if it can also be carried out in an adult population[61]. International good practice principles such as the Helsinki Declaration state that the consent of the legal representative should be complemented with the represented person's assent[62]. Secondly it will have to be checked which specific requirements or conditions national legislation foresees for the representation. Since this is regulated differently in the Member States, European regulations abstained from detailed provisions on this aspect. As indicated above, Robinson and Andrews marked the lack of a definition of legal representative in the Clinical Trials Directive as a bottleneck for international trials and those running trials in countries with a narrow interpretation of the concept legal representative[63]. Nevertheless, also the current Proposal for a Clinical Trials Regulation 2012/0192 does not address this issue. Moreover, consideration 22 explicitly states that "Regarding the rules concerning the determination of the legal representative of incapacitated persons or minors, those rules diverge in Member States. Is should therefore be left to Member States to determine the legal representative of incapacitated persons and minors". Accordingly, article 2 (16) defines a minor as "a subject who is, according to the laws of the Member State concerned, under the age of legal competence to give informed consent". Article 2 (17) defines an incapacitated subject likewise as "a subject who is, for other reasons than the age of legal competence to give informed consent, legally incapable of giving informed consent according to the laws of the Member State concerned. Article 2 (18) finally defines legal representative as "a natural or legal

[61] D. Gill on behalf of Ethics Working Group of the Confederation of European Specialists in Paediatrics 2003, "Guidelines for informed consent in biomedical research involving paediatric populations as research participants", Eur J Pediatr, 162:455-458.

[62] World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects, 1996, principle 28.

[63] Robinson, K. and Andrews, P. (2010) "(More) trials and tribulations: the effect of the EU directive on clinical trials in intensive care and emergency medicine, five years after its implementation", J Med Ethics, 36: 322-325.

person, authority or body, which according to the national law of the Member State concerned, gives informed consent for a subject who is incapacitated or a minor".

2.3.1 Legal framework for informed consent for clinical trials

On European level only one legal document deals with informed consent for clinical trials: the already mentioned European Directive 2001/20/EC of the European Parliament and 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, more commonly known as the Clinical Trials Directive.

The first objective of this directive was to simplify and harmonise the administrative provisions governing clinical trials by establishing a clear procedure to avoid delays and complication linked to the multinational character of many clinical trials[64]. The Directive created a legal framework for the International Conference on Harmonisation guidelines, which provided an internationally recognized set of good clinical practices and informed consent templates also for the paediatric population[65]. As described under the history of informed consent above, these ICH guidelines were in their turn based on the Nuremberg Code and the Declaration of Helsinki. Nevertheless, the practices, methods and standards for the approval of drugs and medical devices as well as the standard of conduct for clinical trials had been very divergent among Member States[66]. The rules and guidelines for the approval, conduct and management of clinical trials in Europe were however not only included to smooth clinical trial procedures, but also to protect the clinical trial participant in a standardised way. One of the most crucial elements in this protection is the requirement to obtain his consent before participation.

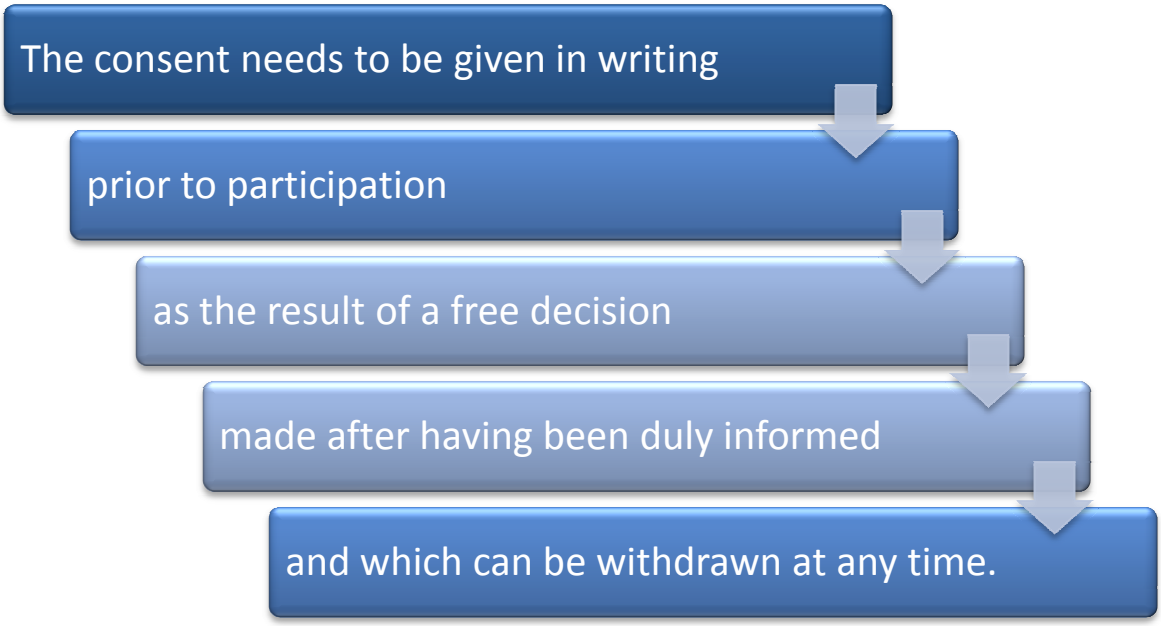
The Clinical Trial Directive defines informed consent in article 2 (j) as: "decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented […]". Clearly this definition contains some similar general principles as can be found in the Data Protection Directive[67] and several ethical guidelines such as the Helsinki Declaration[68] and the ICH guidelines[69]:

[64] Consideration 6 Clinical Trials Directive; C. Trouet, M. Gobert and M. Podoor (2007) Clinical Trials in Belgium, Oxford Antwerp.

[65] ICH E11 (2000) ICH Harmonised Tripartite Guideline. Clinical Investigation of medicinal products in the paediatricpeadiatric population E11.

[66] Shorthose, S. (ed.) (2010) Guide to EU Pharmaceutical Regulatory Law, Kluwer Law International.

[67] 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.



As Kosta describes in her recently defended PhD thesis: informed consent requirements in medical research and bioethics have a close link with the requirements for informed consent in data protection[70]. "As the consent of the data subject in the context of data protection was closely linked to the processing of information and tissues, the informed consent requirements that existed in medical research and bioethics have influenced the regulation governing data protection"[71]. Kosta however notices one important difference between the two concepts of consent in the Data Protection Directive and in the Clinical Trials Directive. In the Data Protection Directive consent is understood as a means for the data subject to indicate his wishes. In the Clinical Trials Directive, the consent of the trial participant is considered to be a decision. By for example requiring the informed consent to be given in writing, the informed consent forms used for clinical trials have been formalized. This led to the adoption of lengthy informed consent forms, as described in D4.1. under section 2.4.2. The Process of Consenting and informed consent form.

The definition of informed consent in the Clinical Trials Directive also contains some guidance on how to draft an informed consent form as it indicates that this form should contain information on the

[68] World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects, 1996, principles 22 and 24.

[69] ICH E 6(R1) (1996) ICH Harmonised Tripartite Guideline. Guideline for good clinical practice E6(R1).

[70] E. Kosta, "Unravelling consent in European data protection legislation, A prospective study on consent in electronic communications", 1 june 2011, Doctoral Thesis Faculty of Law K.U.Leuven.

[71] E. Kosta, "Unravelling consent in European data protection legislation, A prospective study on consent in electronic communications,", 1 june 2011, Doctoral Thesis Faculty of Law K.U.Leuven; N. Manson and O. O'Neill, Rethinking informed consent in bioethics, 2007, Cambridge University Press, Cambridge.

- nature,
- significance,
- implications,
- and risks

of taking part in the clinical trial which is presented. Text passages for each of these sections are suggested in the guidelines below[72].

Next to the Directive itself, the Commission also provides more detailed guidelines in relation to clinical trials in a list of separate documents, including "Detailed guidance for the request of the authorization of a clinical trial on medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial", "Guideline on the data fields from the European Clinical Trials Database (EudraCT)" and "Annex VI to Guidance for the conduct of good clinical practice inspections – Record keeping and archiving of documents". These guidelines were last updated on March 30th 2010 and they are available through the European Commission's website in Volume 10 of Eudralex[73]. A specific guideline on informed consent is however not available.

The Clinical Trials Directive of 2001 is currently however under review. In its Communication of 10 December 2008 the European Commission announced that an assessment would be made of the application of the Clinical Trials Directive. This assessment would consider, in particular, various options for improving the functioning of the Clinical Trials Directive with a view to making legislative proposals, if appropriate, while taking the global dimension of clinical trials into account. A Proposal for a Regulation of the European Parliament and of the Council on Clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC was launched on July, 17 2012. The new proposal does not alter the definition of consent to a large extend, but as indicated in D4.1. Recommendations to the Commission, Section 3.2.2.1. Informed consent in the Proposals for CTR, the biggest change is probably that consent is no longer defined as 'a decision', but 'a process'. The new article 29.2. now furthermore stipulates that "Written information given to the subject […] shall be kept concise, clear, relevant and understandable to a lay person"[74]. We refer to D4.1. Recommendations to the Commission Section 4., for a discussion on the consequences of both changes and commentary of the provisions when reading them together with the new Proposal for a General Data Protection Regulation 2012/0011.

[72] See: Consent for participation in a clinical trial.
[73] http://ec.europa.eu/health/documents/eudralex/vol-10/.
[74] Article 29, 2. Proposal for CTR

2.3.2 Approval of the informed consent forms

Before commencing any clinical trial, the sponsor must obtain the approval by the Ethics Committee within the Member States where the trial is to take place. One of the factors that will be considered in deciding on the permission is your informed consent form and procedure.

The Ethics Committee is an independent body which assesses the protection of the participant's rights, safety and well-being by reviewing and approving or disapproving the clinical trial protocol, the suitability of the investigator, the facilities and - most importantly to this project - the methods and documents to be used to inform trial subjects and obtain their informed consent[75]. The latter function of the Ethics Committee is explicitly mentioned in article 6, 3., g) of the Clinical Trials Directive: "In preparing its opinion, the Ethics Committee shall consider, in particular: (g) the adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent as regards the specific restrictions laid down in Article 3"

The Ethics Committee is composed of healthcare professionals and non-medical experts. When commencing a clinical trial in paediatrics it is important to realise that national legislation may explicitly require that experts in this field are also included in the Ethics Committee. This is for example the case in Belgium[76]. Trouet signals that "the legal status, composition, function, operations and regulatory requirements pertaining to the independent ethics committee may differ among countries"[77]. The same findings were recorded by the survey "Diversity of Ethics Committees in the European Union" carried out by the EMA[78]. Notwithstanding these different regulations, the ethics committee should always be able to act independently and in agreement with good clinical practices. This is also stressed in the Helsinki declaration. In principle 15 it is emphasised that the Ethics Committee should be independent of the researcher, the sponsor and any other undue influence[79]. The Clinical Trial Directive requires one single Ethics Committee opinion per Member State, regardless of the number of participating sites per State, this does for multi-centre trials still mean the informed consent form does have to be approved under national legislation by the Ethics Committees of all Member States the trial is run in[80].

An important change under the Proposal for a Clinical Trial Regulation is the new authorisation procedure. The proposed Regulation continues to stress the necessity of every clinical trial to

[75] Article 2, k) Clinical Trials Directive.

[76] Article 7, 6° Belgian Law of 7 May 2004 concerning experiments on the human person; C. Trouet, M. Gobert and M. Podoor, 2007, Clinical Trials in Belgium, Intersentia, Antwerp – Oxford, 135.

[77] C. Trouet, M. Gobert and M. Podoor, 2007, Clinical Trials in Belgium, Intersentia, Antwerp – Oxford, 135.

[78] Shorthose, S. (ed.) (2010) Guide to EU Pharmaceutical Regulatory Law, Kluwer Law International.

[79] World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, 1964, principle 15.

[80] Article 7 Clinical Trials Directive.

be assessed by a reasonable number of independent persons "who have collectively the necessary qualifications and experience in all relevant fields, including the view of lay persons"[81]. But different from the CTD, the Proposal for CTR now leaves it up to the Member States to establish which bodies should approve a clinical trial and how they should do so: "What matters is that Member States ensure an independent, high-quality assessment within the timelines as set out in the legislation" the explanatory memorandum specifies.

Two new articles regulate the authorisation procedure attributing a specific role to "the reporting Member State" (article 6) and "any Member State concerned" (article 7). The division of roles between a reporting Member State and Member States concerned reflect the Commissions' aim to establish a swift procedure allowing international cooperation while not neglecting Member State's national peculiarities.

- Article 6 explains the assessments which have to be made by the reporting Member State. This assessment concerns in particular the compliance with those elements where national legislation is less of a barrier: the risk-benefit balance, the manufacturing and importation of medicinal products, labelling requirements and the investigator's brochure.
- Article 7 details the assessments which have to be fulfilled by each Member State participating in the clinical trial. They concern matters which are often subject to national – diverging – legislation. Examples are: recruitment of subjects, the use and storage of biological samples, the suitability of trial subjects and sites, as well as all matters concerning informed consent and data protection.

This implies that the informed consent forms for both the participation in a clinical trial and for the processing of personal data will have to be assessed by each "Member State concerned" individually. As indicated in D4.1. this is a major concern to the CONTRACT project.

2.4 Introduction to data protection

In every aspect of life data related to individuals is being collected and processed – whenever an individual signs up to a library or register on a website he / she needs to provide his / her personal data. An extreme case of such collection comes in place in the health-care environment. Whenever an individual visits his / her physician, or goes to a clinic, as well as whenever his / her blood is tested a vast amount of data concerning him / her is being collected – that includes "personal data" – like name or phone number, but it also includes "sensitive personal data" - like information about health.

[81] Explanatory Memorandum Proposal for CTR, 5.

As the European Union is based on fundamental rights[82] it seeks to protect the fundamental rights of its citizens / of individuals. One of the rights EU expressly recognised is the right to the protection of personal data.[83]

In recent years the collection and processing of personal data is more and more frequent. Also the possibilities of analysing such data and using it for a variety of reasons are expanding. As the data traffic is more and more transborder, a holistic approach embracing the whole of European Union became indispensable.

2.4.1 History

The first pieces of legislation in the field were enacted in the early 70s and the first important international instruments were introduced in 80s by OECD[84] and CoE[85]. As the amount of data traffic became higher and the data flows increased, the sole guidelines which were not binding and therefore did not create homogeneous rules became insufficient.

The next step in the development of a common data protection framework was the adoption of the Data Protection Directive, which took place in 1995. It is "the most influential, comprehensive and complex international policy instrument."[86]

2.4.2 Data Protection Directive

The aforementioned directive is also what constitutes the most important part of the secondary legal framework of data protection. The Data Protection regime must be respected, whenever a processing of data which falls into the category of "personal data" occurs. The directive describes personal data in article 2(a) as:

> *'Personal data' shall mean any information relating to an identified or identifiable natural person ('data subject'); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an*

[82] See Preamble of the Charter of Fundamental Rights of the European Union, available online: http://www.europarl.europa.eu/charter/pdf/text_en.pdf .

[83] Ibid., see art. 8.

[84] Organisation for Economic Co-operation and Development Guidelines on the Protection of Privacy and Transborder Flows of Personal Data adopted on 23.09.1989, available online: http://www.oecd.org/document/18/0,3746,en_2649_34255_1815186_1_1_1_1,00&&en-USS_01DBC.html

[85] Council of Europe Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data adopted on 28.01.1981, available online: http://conventions.coe.int/Treaty/en/Treaties/Html/108.htm

Compare: Nikolaus Forgó et al., *Ethical and Legal Requirements for Transnational Genetic Research: Rechtsstand: Mai 2010*, 1st ed. (Munich: Beck Juristischer Verlag, 2010), 67.

[86] Ibid., 68.

> *identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity;*

The directive recognises also a specific category of personal data – that is „sensitive data", which lies under a special, stricter regime of data protection. The sensitive data is defined in art. 8§1 as:

> *„Personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, and the processing of data concerning health or sex life."*

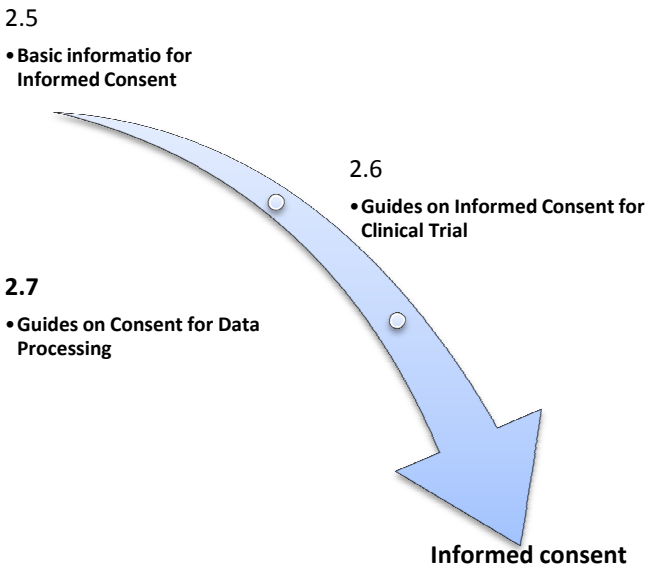
Whenever, in understanding of the Directive, collecting or processing of personal data takes place it requires a legal basis. The bases for processing are defined in art.7 and art. 8 of the Directive and include consent, as well as performance of tasks in public interest, legal interests, or protect the vital interests of the data subject. Processing of sensitive data is generally prohibited and only legal if one of the specific exception criteria applies. One of these exceptions for making the processing of personal sensitive data legal is informed consent.

Whenever processing of personal data comes in place it should be compliant with the data processing principles.[87]

[87] Compare the Art. 29 advice on the rules set out in the Directive; see online: http://ec.europa.eu/justice/data-protection/data-collection/obligations/index_en.htm .

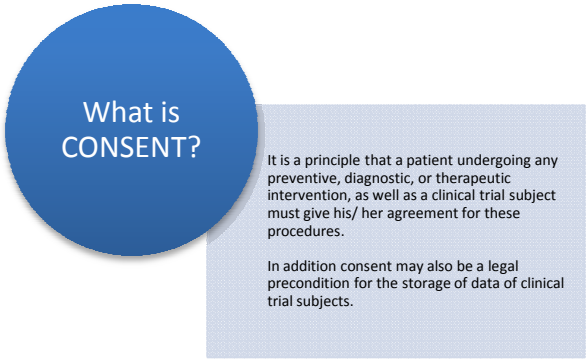
2.5 Introduction and basic information needed for the informed consent form

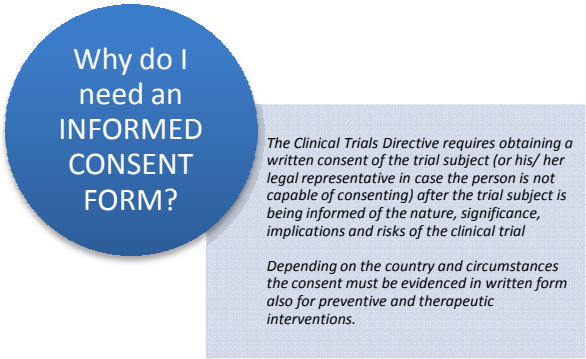
The following section provides support for researchers in developing consent forms. It is therefore directly targeted on the researcher:



Dear Researcher,

You are about to start developing your consent form. This guide can support you to create a legally and ethically compliant document, which shall help to provide the patient with sufficient information to consent to the procedure.





This document, however, cannot and is not intended to replace professional legal consultancy that you might consider receiving before starting with your research.

Please note that this Guide contains also text passages which will be / you should include(d) in the informed consent form

For whom are you developing an informed consent form for? – patient's legal capability to give consent

Patient's legal capability is essential, as it will determine whether the individual can sign the informed consent document on his/ her own, or whether he / she needs to be represented by a legal guardian / legally authorized representative. Hence, depending on the legal capability, the text of your informed consent document will be directed to different persons.

- Adult with full legal and mental capacities
  A mentally competent adult who has a right to give or refuse consent in his / her own name
- Adult with full legal capacities but mentally unable to consent (incapacitated adult)

  A person who is not capable of consenting or refusing consent for many reasons – he/ she may be unconscious or uncommunicative and his/ her condition may be caused by mental disabilities (both transitory, as well as chronic). In case of an incapacitated adult an authorised person has to make a decision on his/ her behalf.
- Adult without legal capacity
  Individual for whom a guardianship proceeding was initiated. The person has been determined by court as lacking the capacity to manage his / her own affairs and therefore is not capable of consenting – the consent has to be obtained from the legal guardian.
- Child / minor
  Children and minors who did not yet achieve the age of majority are not capable of giving a valid consent. Instead the legal guardian(s), which are in most cases parents of the child, need to be asked for informed consent. Their consent shall represent the presumed will of the minor.

For a more detailed insight on who should represent the patient in individual cases, please see our patient representation scheme in ANNEX 2, or compare the national law on capacity.

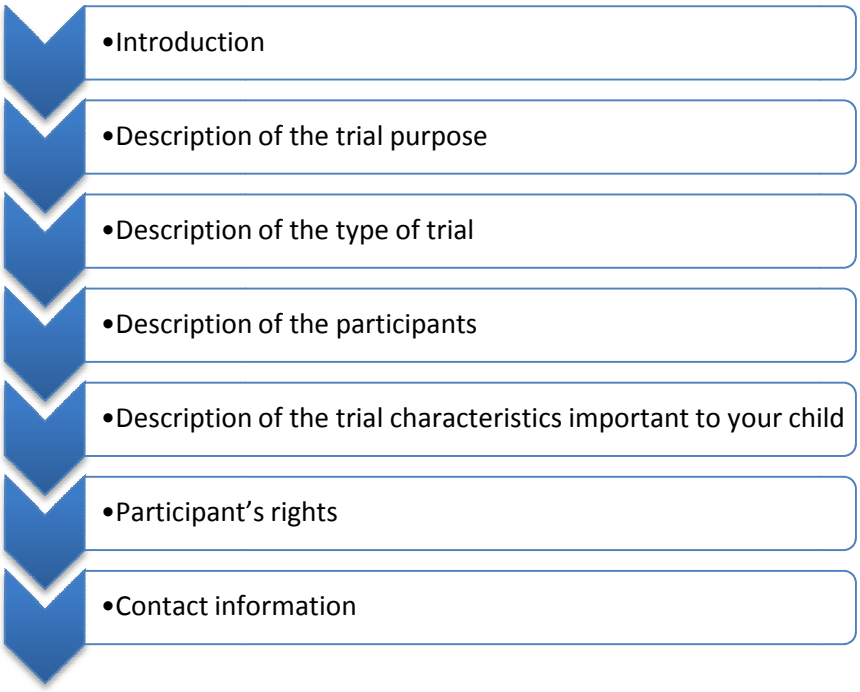
From this point on you will be guided through the process of creating your informed consent

form. You will be asked to make a choice between different options which influence the content and phrasing of the informed consent documents.

Please be aware that at current stage the text within the informed consent form's phrases is directed to the parent signing an informed consent for his / her child.

2.6 Informed consent for clinical trial

Under this part a guideline to help you develop an informed consent form for participation in a clinical trial is created. The guideline can be considered a step-by-step manual consisting of **7 sections:**



Each section is divided in the required subsections with suggested text passages. The choice of sections and subsections is based on analysis of the legal requirements as described above and on the good practice cases as identified through the CONTRACT questionnaire.

2.6.1 Introduction

Since an informed consent is only valuable when given after the future participant is being duly informed of what the participant will be consenting to, the informed consent form should always start with an explanation of the trial he / she is about to participate in. The information should be clear to both parents (or other representatives) and child. The legal representative receives the same information as persons who are consenting for themselves. The represented

child must be included in the authorization procedure to the extent of his or her maturity and understanding[88].

You should therefore first of all explain why consent is needed and what it serves for. We suggest to include the following text passage:

> *Your child is about to participate in the clinical trial, which was presented to you by [e.g. physician / counsellor], was developed by [investigator/sponsor] and coordinated by [physician / research centre / hospital]. In order to enrol your child, you need to sign this Informed Consent Form. By signing this Informed Consent Form you agree to the participation of your child in this trial and confirm that you understand the goal of the trial, how it will impact your child and what his / her and your rights are.*

2.6.2 Description of the trial purpose

In order to obtain a lawful informed consent, the consent should be purpose-specific. Although in modern medical research, specifically on biological material of human origin, this principle is under pressure, a specific consent remains the standard requirement for all research using physical interventions[89]. You should therefore in the second section include a clear description of the trial, clarifying the purpose of the trial and why the patient's participation is requested.

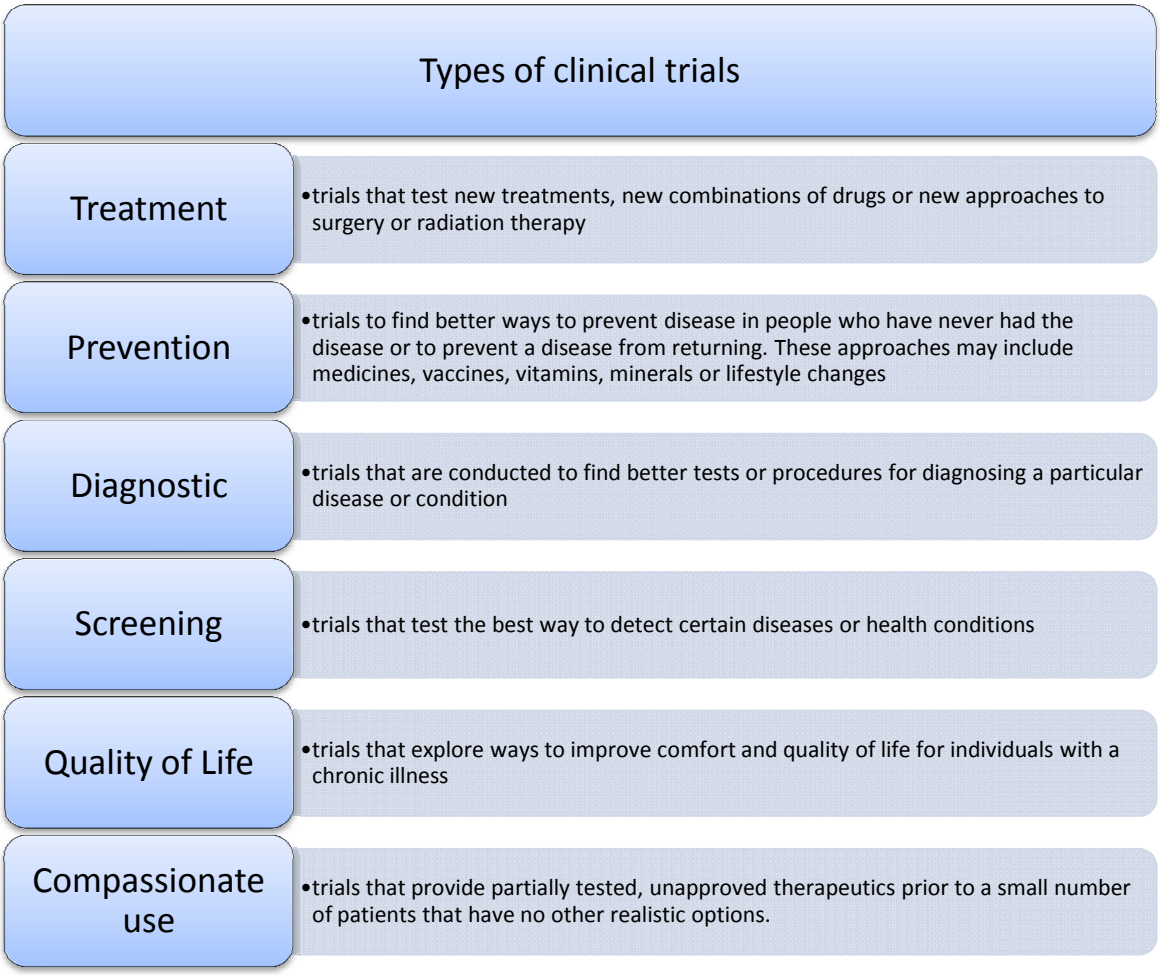
This description should be specific enough for the patient to understand the benefits and possible drawbacks of the participation in the trial. The following aspects should be explained:

- The trial classification (phase I, II, III) and what this means:
- Whether the trial or project concerns new treatments, new medicinal products or new indicators for old medicinal products
- Whether it foresees new approaches to known therapies: surgery, radiation,…
- Whether it envisages changes in approved clinical practices, clinical administration,…

This corresponds with the following categories:

[88] E. Doppelfeld, "Appropriate Regulations for Different Types of Medical Research" in A. den Exter (ed.) 2010, Human Rights and Biomedicine, Maklu Antwerpen, 105-116.

[89] E. Doppelfeld, "Appropriate Regulations for Different Types of Medical Research" in A. den Exter (ed.) 2010, Human Rights and Biomedicine, Maklu Antwerpen, 105-116.



We suggest to include a text passage starting with:

> *The purpose of this clinical trial is…*

2.6.3 Description of the type of trial

For the same reason as the description of the trial purpose, you should specify which type of trial you are running. This section will most likely be quite extensive as it must include several subsections characterising the trial:

A. Interventional or non-interventional nature of the trial;

B. Single or multi-centre trial;

C. Conformational or non-conformational trial;

D. Randomised and blinded;

E. Prospective or retrospective character of the trial.

Finally it is advisable to also include the F. **Information on the sponsor** in this section of the informed consent document because he is the one responsible for the trial's aims.

Please note that the information provided under these paragraphs should be understandable for the persons they are addressed to, i.e. patient/participant. Therefore it is advisable to only use commonly known medical terms or provide an explanation for the more uncommon terms. Both the oral and written information should be adapted to the capacity of the person consenting. When working with children this is no less of a requirement. The child should be able to understand the information and only then be assisted in arriving at an independently taken decision. Consequently the way information is provided in the consent may have to differ from the style used in the assent.

(based on Gill, D. and the members of the Ethics Working Group of CESP (2003) "Guidelines for informed consent in biomedical research involving paediatric population as research participants", Eur J Pediatr, 162:455-458.)

A. Interventional or non-interventional trial

When describing the nature of the trial, you should pay specific attention to its interventional or non-interventional character, sometimes also called therapeutic or non-therapeutic character. As described above, on European level only interventional trials are regulated. Furthermore, good clinical practices require the specification of the trial classification, which is related to the interventional or non-interventional character.

For interventional clinical trials the informed consent procedures need to comply with the Clinical Trials Directive. To non-interventional/observational trials, this Directive does not apply (art 1, 1. Clinical Trials Directive).

Non-interventional trials are defined by the Directive as: "a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of the collected data". Those trials are not regulated by the Directive.

However, the fact that the European Directive 2001/20/EC does not apply, does not imply that informed consent is not required for non-interventional trials. Informed consent for treatment is required at all times and good clinical practices equally need to be observed. It is furthermore important to check your national legislation in order to verify if specific regulations or requirements are foreseen for consent for non-interventional trials.

When you are running an interventional trial the following text passage can be suggested:

> *The clinical trial your child will participate in is an interventional trial. This means that it can influence his / her diagnosis and treatment.*
>
> *Interventional trials are regulated under Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. We assure you that the trial is fully compliant with this regulation.*

When you are running a non-interventional trial the following explanatory text passage could be included:

> *The clinical trial your child will participate in is a non-interventional trial. Non-interventional trials may also be called observational trials. This is because his / her diagnosis or treatment will not be influenced by participating in the trial. A therapy is not provided by this trial. The trial will only monitor your child [and his / her disease].*

B. Single or multi-centre trial?

Even though trial participants will most likely always be treated in one and the same facility, it may be important to them to know whether the trial is being run in just a single centre or in multiple centres as this may have an influence on the risk balance.

For a single centre trial the explanation to be included is fairly straight forward:

> *The trial is a single-centre trial. It is run only in…*

Article 2, b) Clinical Trials Directive defines a multi-centre trial as follows: “a clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States and/or in Member States and third countries”. We suggest including the following text passage in your informed consent form:

> *The trial is a multi-centre trial. This means that participants are not only engaged here, but also at other centres in other locations [to be specified]. Consequently also researchers from these centres will have access to your child's results and data .*

When this is the case, it is furthermore highly advisable to indicate that the trial results, as well as personal data of the trial participants are shared with other institutes, research centres at other trial locations, or with other researchers, whether by a central database or decentralised storage. Because this has however mainly consequences for data protection and will only in a lesser extent have consequences for consenting to the clinical trial as such, it is strictly speaking however also possible to only include this in the consent form for data protection.

C. Conformational or non-conformational?

The conformational or non-conformational character of the trial holds important information for the trial participant. Since this trial participant will moreover most likely not be familiar with the difference, it is important to extensively explain this in a way understandable to laymen.

When you are running a conformational trial we suggest the following text passage:

> *The trial is a conformational trial. This means that the study is based on preceding studies with the same trial question but this time [in a prospective way to confirm retrospective results] or [with a larger population] or [with children instead of adults]. A conformational trial is needed in order to [please explain why you opted for a conformational trial].*

When you are on the other hand running a non-conformational or exploratory trial you can provide the following straight forward text passage:

> *The trial is a non-conformational or exploratory study. This means that no other study with this purpose has been previously conducted.*

Additionally and in order to further clarify, you could explain the patient that some trials are opposed to the one he / she is participating in respectively non-conformational or conformational. This may however be done orally and does not have to be included in the informed consent form. This is also confirmed by the Ethics working group of the Confederation of European Specialists in Paediatrics. In their guidelines to informed consent they stress that "written information alone is not sufficient for assuring the informed assent/consent of either the child-participant or the parents/legal representatives". Time should be available to

"sufficiently discuss" the participation in the trial with the physician as well as amongst themselves and with other family members[90].

D. Randomised and blinded?

In order to attain the best possible results many trials opt to have a randomised and double-blinded study design. When applying these techniques, this has a consequence: additional personnel which is not directly involved in the trial is required for administrative tasks, packaging and labelling[91]. For this reason and because this study-design may have a direct or indirect impact on the treatment of the participant, this is regarded an important trial characteristic which should be included in the informed consent form.

For randomised studies we recommend to include:

> *The study is a randomised study. This means that participants are allocated at random to receive one of several clinical interventions. We do this because we seek to measure and compare the outcomes of participants who received standard practice, a placebo or no intervention at all. Consequently, it may be that your child is put on standard treatment (which is most common), a placebo or may not receive any intervention at all.*

When a trial is blinded we suggest to include:

For a single-blinded study:

> *The study is a single blinded study. This means that certain information on your child's treatment may be kept from you to avoid conscious or subconscious interference with the study results.*

For a double-blinded study:

> *The study is a double blinded study. This means that certain information on your child's treatment may be kept from you and from the researchers to avoid conscious or subconscious interference with the study results.*

When a trial is open label we suggest including:

[90] Gill, D. and the members of the Ethics Working Group of CESP (2003) "Guidelines for informed consent in biomedical research involving paediatric population as research participants", Eur J Pediatr, 162:455-458.

[91] Welzing, L., et al. (2007) "Consequences of Directive 2001/20/EC for investigator-initiated trials in the paediatric population – a field report", Eur J Pediatr, 166:1169-1176.

The trial is an open label study. This means that both you and the researchers will know which treatment is administered to your child.

E. Whether it concerns a prospective or retrospective trial.

A prospective trial implies that participants are selected and followed from the moment of selection on. In case of a retrospective trial information about the participants is not only collected from the moment they are selected on, but also 'look back' and collect data from the participant's history. Since you are required to describe the characteristics of the clinical trial in this informed consent form, you should also include whether it is prospective or retrospective. The consequences of this differentiation however mainly impact the collection of data. In case of a retrospective trial you will also collect data from the patient's history, in case of a prospective trial you will only collect new data. Reference has to be made to the consent form for data protection as the informed consent forms for clinical trial too need to expressly deal with data protection issues.

For a prospective, respectively a retrospective trial we suggest the following text passages:

The trial is a prospective trial. This implies that…

The trial is a retrospective trial. This implies that…

F. Trial sponsor.

Article 2, h) Clinical Trials Directive defines the sponsor as: "an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial". In many cases this will be too much of a responsibility for a single individual. A company or institution will be assigned the role, often representing the coordinator of the trial[92]. This company or institution then bares the overall responsibility for the trial, including checking the trial documents, assuring that all sponsor responsibilities are followed and all necessary registrations have been carried out.

We suggest including the following passage:

[92] Welzing, L., et al. (2007) "Consequences of Directive 2001/20/EC for investigator-initiated trials in the paediatric population – a field report", Eur J Pediatr, 166:1169-1176.

The trial is sponsored by… and was approved by the ethical committee of… The trial was officially registered at EMA. The EURDACT number given to this trial is…

2.6.4 Participants

After having introduced the trial, it is advisable to specify how you selected/are planning to select your participants/patients. In the case you work with minors an extra clause should be included in your informed consent form explaining why it is necessary to include them in the clinical trial. It is advisable to refer back to this paragraph when describing the risks and benefits.

For vulnerable patients (children, but also other persons legally incapable of consenting) you should explain why it is necessary to work with them. Additionally you should emphasize that their participation is only approved because their personal benefits outweigh the risks of the trials.

Only under exceptional circumstances the Clinical Trials Directive allows clinical trials where the personal benefits do not outweigh the risks. Such trials should always directly benefit the group of patients participating in the clinical trial and concern research essential to the validation of data obtained in clinical trials on persons able to give consent, not children, or to validate data obtained via other research methods than clinical trial. Additionally, it should always relate to either a clinical condition from which the minor suffers or be of such a nature that it can only be carried out on minors. In any case all precautions should be taken in order to afford the best possible protection of the child and the interests of the child should always prevail over those of science and society.

Consequently, when you are running a clinical trial including children and personal benefits do no outweigh the personal risks, but has significant expected benefits for a group of children who have for example the same disease, this trial should be a validation of earlier research results obtained through research on for example adults. An example of such a trial would be a phase I or II trial done to find the correct dosages for children of a new drug without knowing or not even testing for response when no other treatment is available.

Please do however check your national legislation as it may contain detailed requirements for the protection of children in clinical trials.

Following this requirement we suggest the following text passages to be included in the informed consent form:

- When the personal benefits for the child outweigh the risks of the trial:

> *The participants to this clinical trial were selected according to the following criteria: […] We work with children, not adults because […] We assure you that your child was only selected because his / her personal benefits outweigh the risks of the trial. A detailed description of the risks and benefits will be provided below.*

- Or when the benefits for the child may do not outweigh the risks of the trial, but significant scientific value is expected:

> *The participants to this clinical trial were selected according to the following criteria: […] We work with children, not adults, because […] The study is likely to have significant scientific and clinical value for children, but we cannot guarantee you that your child's personal benefits outweigh his / her personal risks. We do guarantee that all possible precautions have been taken in order to afford your child the best possible protection and that the interests of the child will always prevail over the interests of science or society.*

Additionally we advice to include the following clause in order to emphasize and ensure the informed consent was given freely:

> *By agreeing to your child's participation in this trial, you recognize that the participation is voluntary and was not forced on you or your child in any way.*

2.6.5 Trial Characteristics important to your child

After having informed the patient/participant on the general characteristics of the trial and why he / she was selected, it is of major importance to clearly point out what he / she may expect: the risks, potential side effects and discomforts and benefits, as well as the duration of the trial, and possible costs, reimbursements and compensation.

A. Risks and benefits

Every medical intervention is linked to the proportion of risk to benefit. In routine medical care the benefits and risks of methods used in diagnosis or therapy, as Doppelfeld (2010) explains, are calculated in statistical analysis of the results achieved from the application of these: "Usually before accepting a method for routine care or before admitting a drug to the market, valuable data on their benefit and risk, as gained through medical research, must be presented to a competent body or authority"[93]. But in clinical trials this is of course different as the risks

[93] E. Doppelfeld, "Appropriate Regulations for Different Types of Medical Research" in A. den Exter (ed.) 2010, Human Rights and Biomedicine, Maklu Antwerpen, 105-116.

and benefits will to a lesser or greater extend be unknown. The researcher may for example not be sure that the results of the trial will entail an actual benefit for the individual participant, but only be able to guarantee the participant a potential benefit. It is therefore important to inform the representative and the child on the expected results, both possible advantages and disadvantages, and on which indications these expectations are based (e.g., prior use in research projects or applications in clinical trials). In this description the benefits should not outshine the risks. Many research ethical committees also rely on the expression: "The lower the probability of benefit, the lower the acceptable risk".

When involving children, this balance will be guarded even better. As explained in the previous section, a legal representative should only authorize the participation of a child when there is a potential direct benefit for the child based on the due risk and benefit assessment. When no potential direct benefit for the child is expected, it the Convention of Oviedo and the Clinical Trials Directive stress that the risk and burden have to be minimal and this should remain exceptional.

When describing the risks and benefits this should be done in such a way that the patient can understand and assess them. The risks should for example clearly describe the degree to which the testing is invasive and might have consequences and to what extend this differs from the standard alternative treatment. Both the risk threshold and the degree of distress have to be defined specifically. It is advisable to refer to randomisation and blinding, as this may have consequences for the patient. The benefits should be honest and should not outshine possible alternative treatments.

We advise to include the following text passages in your informed consent form to describe the risks and benefits:

This clinical trial has been designed to minimise pain, discomfort, fear and other foreseeable risks in relation to the disease and developmental stage, but it is important to realize that by enrolling your child to this clinical trial, you do expose your child to possible risks, side effects and/or discomforts. The risks include: […]. Potential side effects and discomfort can consist of one or more of the following

elements: […]. We will constantly monitor your child for these risks, side effects and discomfort.

The benefits of the trial are expected to include: … [differentiate personal benefits from benefits to the scientific and clinical world]

The trial will run for [… days/months/years]. The results of your child [will/will not] be available to the researchers for further use during [… days/months/years]. We will however contact you for re-consent from you and your child at […age/time].

The drugs used in this trial are […] and expected risks and benefits include […]

The procedures required for this trial include […] Their specific risks and benefits are…

When describing and explaining the risks and benefits Pinxten, Nys and Dierickx (2010) signal that one should realise that children as well as their parents are mainly interested in why it would for them be worthwhile to participate in a trial, rather than "merely being informed about the trial, the risks and benefits according to the specificities as described in the study protocol"[94]. It should thus be noted that when you orally discuss these passages of the informed consent with the trial participant, you do so against the background of the patient's course of disease, medical history, current treatment and prognosis.

B. Costs and reimbursements

As described in the general introduction to the concept of informed consent, an informed consent can only be considered valid when freely given. The freedom of the consent also implies that no financial coercion of any kind may be used when entering participants in a trial. Unjustified financial payments or other awards may be considered as such undue influences. Moreover, when children are participating in an interventional clinical trial in the sense of the European Clinical Trials Directive, any financial inducements or other incentives to participate apart from normal compensation are forbidden.

[94] Pinxten, W., Nys, H. and Dierickxs, K. (2010) "Frontline ethical issues in pediatric clinical research: ethical and regulatory aspects of seven current bottlenecks in pediatric clinical research", Eur J Pediatr 169:1541-1548.

We therefore suggest to include the following two text passages:

> *The costs and reimbursements you may expect are […] Compensation for […] will be provided.*

> *Other incentives or financial inducements are not provided since in Europe they are forbidden generally under art. 4 (d) of Directive 2001/20/EC for all clinical trials involving children.*

2.6.6 Your child as a patient and his rights

You should point out that the patient has at all times the right

- to refuse participation,
- to withdraw his / her consent to participation.

These rights should at all times prevail over the interests of science and society[95].

The right to refuse participation is naturally another consequence of the free character of the informed consent. In order to allow the participant to make a free decision information should also be provided on possible alternative treatments and their risks and benefits.

In article 3 (2) e the Clinical Trials Directive specifies that an informed consent can furthermore be revoked and participation to the trial can be withdrawn at any time. Just like the opinion of the minor has to be taken into account before entering the clinical trial, the minor too has the right to ask for withdrawal. When the minor refuse to take further part in the clinical trial, this has to be respected[96]. The trial participant should be shown how to withdraw and should be made aware of the consequences of his / her withdrawal. However, these consequences should be with minimum burden for the patient and the patient must not be pressured to remain in the trial.

The established standard medical treatment and available alternative treatments must therefore be explained and described in this section. We suggest to include the following text passage:

[95] ICH E 6(R1) (1996) ICH Harmonised Tripartite Guideline. Guideline for good clinical practice E6(R1) and ICH E11 (2000) ICH Harmonised Tripartite Guideline. Clinical Investigation of medicinal products in the paediatricpeadiatric population E11.

[96] Shorthose, S. (ed.) (2010) Guide to EU Pharmaceutical Regulatory Law, Kluwer Law International.

> *You and your child may refuse participation as well as withdraw your participation at any times. You are free to make this choice without having to provide any justification for your decision.*
>
> *If you do not wish your child to participate in the trial, this does not mean he / she will not be treated. His / her medical team will in such a case rely on alternative treatments currently available and adhere to current standard clinical practice. These alternative treatment options include: […]*
>
> *When you decide to withdraw your child from participation during the trial, we will make sure the consequences of this decision will be as minor as possible and the transition to alternative treatment will be as smooth as possible in collaboration with your child's medical team. There will be no penalties or sanctions imposed on you.*

Under article 3, 2. f) European Clinical Trials Directive you are obliged to make provision for insurance. This insurance has to cover the liability of the investigator and the sponsor for indemnity or compensation in the event of injury or death attributable to the trial[97]. A similar obligation may exist in your national framework, so you should always check this before starting the clinical trial.

We suggest to include the following text passage in your informed consent form, but because the insurance terms and conditions may be quite lengthy we propose to clearly refer to separate documentation for the full details on the insurance taken.

> *We guarantee you that provision has been made for insurance or indemnity to cover possible liability of the investigator and sponsor. Details on this insurance can be found [please specify where or through which contact person]*

Last but not least, you should inform the participant in this section of the informed consent form about the privacy and confidentiality measures which will be undertaken. The respect for and promotion of the dignity, privacy and confidentiality of the child and his or her family as well as the dignity, privacy and confidentiality of the child *in* his or her family is considered one of the fundamental ethical principles to informed consent in paediatrics[98].

[97] Welzing, L., et al. (2007) "Consequences of Directive 2001/20/EC for investigator-initiated trials in the paediatric population – a field report", Eur J Pediatr, 166:1169-1176.

[98] Gill, D. and the members of the Ethics Working Group of CESP (2003) "Guidelines for informed consent in biomedical research involving paediatric population as research participants", Eur J Pediatr, 162:455-458.

In order to guarantee the privacy and the confidentiality of your child's participation in the clinical trial we are taking all possible precautions and had the trial approved by the ethical committee of […] More information on the measures taken can be found in the informed consent form for data protection.

2.6.7 Do you have further questions?

Finally you should provide who the patient can contact in case of further questions. As the name of the form you are creating holds and as was explained above when describing the general principles to informed consent: the patient has to right to be fully informed and should be able to address his / her questions to an appropriate contact point. Furthermore it is explicitly required in article 3, 4. Clinical Trials Directive that the participant is provided with a contact point where he can find more information. It may be that there are several contact points available for different questions because these questions require a different background or expertise. That is no problem, but if it is the case, it is advisable to make a clear distinction between the type of questions that have to be addressed to different people. This section of the informed consent form should be something the patient / participant can fall back on in case of doubt.

This could for example include:

- Person responsible for medical/clinical questions
- Person responsible for data protection aspects / publication of the study
- Person responsible for commercial aspects

Do you have further questions?

In case you or your child have further questions or doubt, please don't hesitate to contact one of the following persons:

[…]

We are there to help you.

It is furthermore advisable to include the details of the main contact persons in the trial such as

- The sponsor
- The principle Investigator

For your information we also include an overview of the persons responsible for this trial below:

** The Sponsor: this is the person, company, institution or organization which takes responsibility for [the initiation, management and/or financing of the trial]:*

** The Investigator [or principal investigator in the case of a team]: this is the doctor responsible for the conduct of the clinical trial on your trial site: […]*

2.7 Consent for Data Processing

If you have chosen to create an informed consent form for a clinical trial you and your institution are obliged to obtain additional informed consent for the reasons of data processing.

The reasons for this is two-folded – firstly what is required from any researcher starting a clinical trial under the Clinical Trials Directive regime is to protect privacy and data of the clinical trials subjects according to the rules established under the Data Protection Directive.

As the Clinical Trial Directive in art.3 pt.2 c. states:

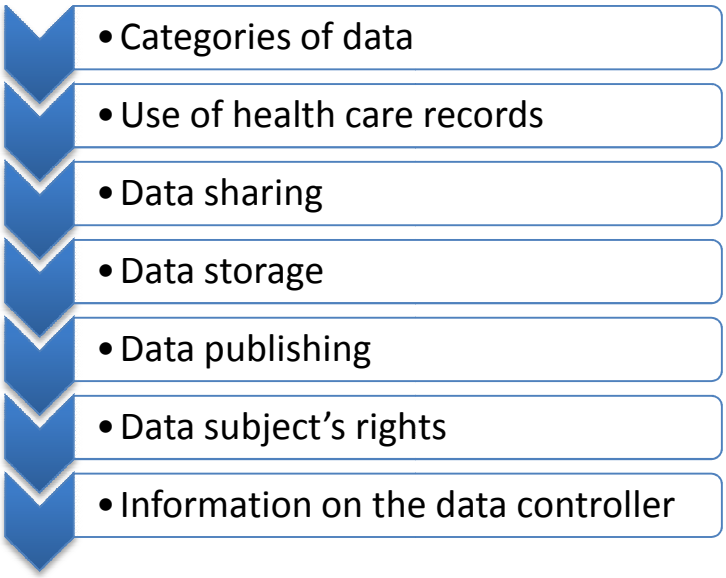
the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him in accordance with Directive 95/46/EC are safeguarded;

Therefore following the legal guidelines are simply your legal obligation.

Second reason, which is also the reason underpinning both Directives, are the rights of the person in question. Whether you see the person as a patient, as a clinical trials subject, or as a data subject in every given case every effort should be made to ensure that this person is aware of his / her situation and has control over it.

Therefore the person should be made aware what will happen to his / her data and what could happen to it, just as he or she is being aware of their treatment or the trial they are going to take part in. The data subject should be given a chance to choose whether they agree with such a use of their data, or would they rather refuse to consent. For this aim you should establish an information sheet where you explain the clinical trial subject, who for the reasons of data processing is called data subject, what data you will exactly collect, who will access these data and for how long. After giving these data you should seek data subject's consent for data processing.

Below you will establish what kind of information is relevant for your consent procedure.



2.7.1 Categories of data

What kind of data will you collect and why does it make a difference?

Data Protection Directive diversifies between two categories of data – sensitive and non-sensitive data. The difference is crucial as the regime for processing of sensitive data is stricter. In most of cases you will need sensitive data of your patients!

What kind of data will you need?

- Non- sensitive personal data
  What is personal data?
  Personal data is a term defined in the Data Protection Directive; it means "any information relating to an identified or identifiable natural person ('data subject'); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity" (Art.2 of the Directive)

For the purpose of our clinical trial we will collect and record personal data about your child. This data will include information such as name and date of birth.

We will treat the data of your child with highest level of care. It will be processed (stored, transferred, edited and deleted) in accordance with data protection regulations

- Sensitive data concerning health
  - Health information
  - Genetic data
- Additional sensitive data
  - Ethnic origin

  What is sensitive personal data?
  According to the Data Protection Directive sensitive personal data is "personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, and the processing of data concerning health or sex life." (Art. 8 of the Directive)

For the purpose of our research study we will collect and record personal and sensitive personal data about your child. This data will include information such as

name and date of birth, information about your child's health, his genetic information.

We will treat the data of your child with highest level of care. It will be processed (stored, transferred, edited and deleted) in accordance with data protection regulations

2.7.2 Use of health care records

By asking the data subject for his consent you and your organisation will be allowed to process patient data from the moment of the consent. In many cases to conduct your research successfully you will not only need this new data, but will also need to access the valuable medical data of the data subject, which were collected before for the medical purposes. Maybe they were collected by you and your organisation and you already have access to them, maybe you will need to obtain it from other sources. But in case you will use these data you need to inform the patient whether you will access his health care records and for what purpose and seek his / her consent for this aim.

- Retrospective data

For our research we will use the personal data of your child, which was gathered in the course of previous treatment. We will use the data from (explain from which source the data will be taken –from your own database, or any other).

- Prospective data

For our research we will use only the personal data of your child which is collected during the trial

- Both

For our research we will use both the personal data of your child collected previously in the course of treatment as well as additional information to be collected during the trial.

Please consider that depending on your national legislation you may be required to notify the data collection to your national data protection authority. You may also be required to undertake a preliminary control from that authority

2.7.3 Data sharing

The European legislation requires that the data subject will not only be informed about the information which will be processed but also about the identity of the person(s) who are in possession / capable of accessing the information, therefore it is important to name whether and if yes with whom will you share the information with.

If you would like to share personal data of patient, he / she will need to consent to this. The patient needs to be informed about organisations which will have access his / her data.

Will you share the collected data?

- No
- Yes
    - Within my organisation

During our research study we will share the data of your child with different personnel members within different units of our organization.

    - With other organisations
        - With organisations in European Union, or outside of European Union, based in countries with adequacy of data protection proven by EC*
        - With organisations outside of European Union without adequacy of data protection proven by EC

*List: currently EU recognises the following countries as having the same level of protection: *Andorra, Argentina, Australia, Canada, Switzerland, Faeroe Islands, Guernsey, State of Israel, Isle of Man, Jersey, United States - check whether the organisation your cooperating have joined the "safe harbour"*

In case you would like to share personal data with any organisation that is not based in one of the countries from the list above please consider that special procedures on data transfer to third countries will apply. The organisation will have to guarantee that the data will receive an equivalent protection, as the one offered within European Union and might have to undertake a certification by data protection authority.

> ✎ *During our research study we will share the data of your child with partner institutions. Their names and addresses you can find at the end of this information sheet.*

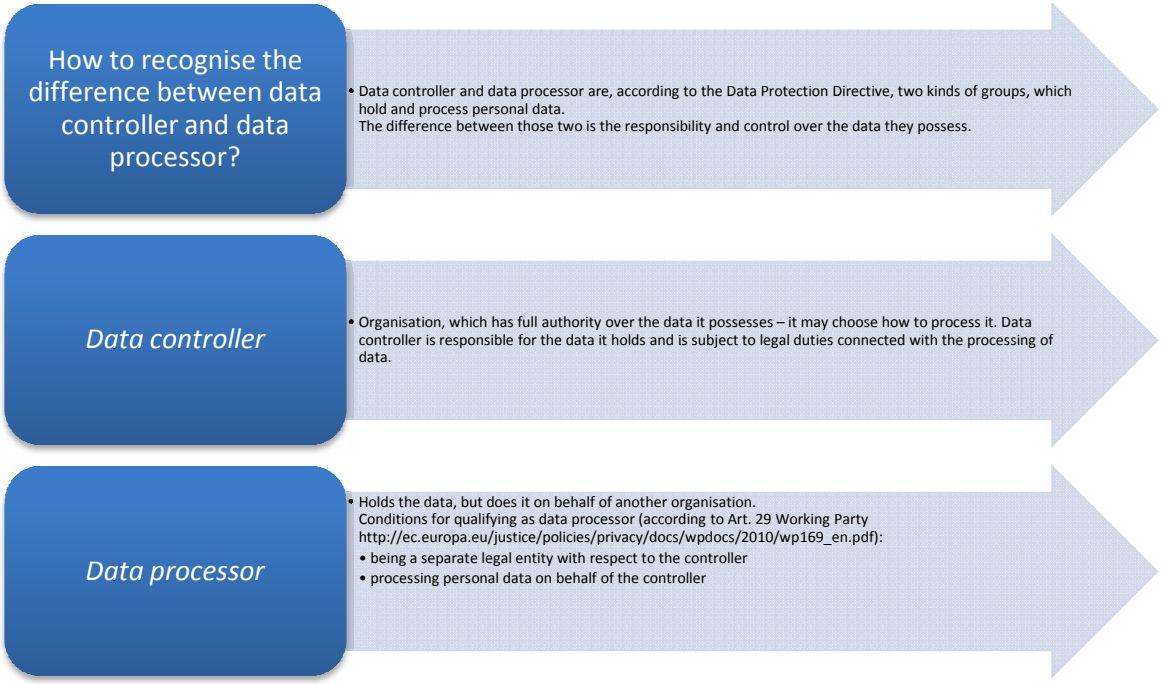
2.7.4 Data storage

Why is that important? The reason is similar as by the question of sharing data with other institutions – the data subject should be aware of who has access to his / her information. If the data which you will accumulate will not be stored by your own institution, but at another entity you should make sure in what role (controller or processor) this institution stands.

Will you store the data of your trial subjects within your own institution?

- Yes
- No, but I am nevertheless the only data controller
- No and the organisation where the data is stored is also data controller and not only data processor

In case the organization within which the data is stored is also a data controller it should be added to the list of organizations, which have access to the trial subject data within the information sheet.



2.7.5 Data Publishing

If you publish the results of the study this will be done with anonymised data. In some cases, e.g. rare diseases anonymisation may not be possible. In any case you should consider acquiring consent for publishing of the study results.

Would you like to ask for consent to publish the study result?

- Yes

> *The encoded and when possible anonymised data of your child may be included in the publication of study results*

- No

2.7.6 Data subject's rights

Besides informing the data subject about what will happen to the data concerning him / her you should also explain what rights he / she has.

> *Data subject's rights*
>
> *Most importantly you have a right to withdraw your consent to data processing.*
>
> *At any time of the trial you will also have the right to access data. You may turn to the person named at this information sheet and receive information on whether the*

data concerning your child is being processed, for what purposes and who does process your child's data. Furthermore you may at any time see what kind of data are being processed.
You may also at any time have the right of rectification – this means that you may turn to the data controller named in this information sheet in order to change any false information.

2.7.7 Information on the data controller

It is advisable to include the details of the main contact persons responsible for the data

Remember to include all the institutions, which will have access to the data.

- Controller

For your information we also include an overview of the institutions who will access the data of your child and persons responsible for them:

The Data Controller(s):

the person responsible:

3 *Section III. IT and security systems for informed consent handling*

The role of information and communication technologies in the area of health care is continuously increasing, since coordination of health care relies more and more on electronic transmission of confidential patient information, between several health care community services.[99] As a fact, the paper-based medical record progressively becomes electronic and the concept of confidential information to be exchanged requires patient's consent, referred as e-consent. Patients should be able to delegate, give or withhold their e-consent to people that they want to access their private electronic health information. The importance of sufficient security standards in e-consent mechanisms can be further understood by considering that distributing sensitive data over the network, without the sufficient security measures, might lead to substantial breaches of personal privacy.

The issues to be raised when dealing with e-consent vary and are closely aligned with information privacy, legislation, patient rights and national culture issues. The key challenge is to make the e-consent mechanism simple enough for the end user in such a way that it retains its expressiveness, usability and security without loss of information. According to a research[100], that was conducted with general practices and health consumers, the following issues have been identified:

- Limitation of health professionals' access to records;
- The ability of individuals to limit access to their records and to indicate the circumstances with which access would be permitted;
- The degree of the health professional's awareness of restricted or total access to a patient's record;
- Audit trails through which an individual can track the path of a record; and
- the individual's nomination of an agent authorization to control access to their record;

This section aims to review the newest and most advance technology development methods that can improve the informed consent procedures. Among others it provides information on electronic mechanisms that support individuals' rights to control the disclosure of their health information for treatment (e-consent), and the corresponding procedures and ICT technologies that guarantee the secure processing of personal data in such a way that access to or transfer of data is restricted. In specific the following three topics are reviewed:

- Improvement of Informing the patient

[99] C. Ruan, V. Varadharajan, "An Authorization Model for E-consent Requirement in a Health Care Application", 2003, pages 191-205, volume 2846.

[100] G. Heather, "e-Consent design and implementation issues for health information managers", 2004, Australia : Health Information Management, Health Information Management Journal, 33(3): 84-88.

- Improvement of procedure for creating the IC forms & documentation package (e-consent)
- Improvement of administrative flow during trial execution

3.1 Improvement of informing the patient

Informed consent is a critical component of clinical research and finding the proper method for presenting information to potential participants of clinical trials may improve the informed consent process. Audio-visual interventions (presented for example on the Internet, DVD, or video cassette) are one such method.

A relative statistical review that was conducted, aimed to assess the effects of providing audio-visual information alone, or in conjunction with standard forms of information provision, to participants in the informed consent of potential clinical trial, in terms of their satisfaction, understanding and recall of information about the study, level of anxiety and their decision whether or not to participate[101]. The authors searched the Cochrane Consumers and Communication Review Group Specialised Register (searched 20 June 2006); the Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Library, issue 2, 2006; MEDLINE (Ovid) (1966 to June week 1 2006); EMBASE (Ovid) (1988 to 2006 week 24); along with other databases, including reference lists of included studies and relevant review articles.

The selection criteria of the review were:

- Randomised and quasi-randomised controlled trials comparing audio-visual information alone, or in conjunction with standard forms of information provision, with standard forms of information provision alone, in the informed consent process for clinical trials; and
- Trials involved individuals or their guardians asked to participate in a real (not hypothetical) clinical study;

According to the review's conclusion, the value of audio-visual interventions for people considering participating in clinical trials remains unclear. Evidence is mixed as to whether audio-visual interventions enhance people's knowledge of the trial. One of the studies showed improved retention of knowledge amongst intervention recipients. The intervention may also have small positive effects on the quality of information disclosed, and may increase willingness to participate in the short-term; however this evidence is weak. There were no data for several

[101] Ryan RE, Prictor MJ, McLaughlin KJ, Hill SJ, Audio-visual presentation of information for informed consent for participation in clinical trials, Cochrane Database Syst Rev. 2008 Jan 23;(1):CD003717.

primary outcomes, including harms. In the absence of clear results, trial lists should continue to explore innovative methods of providing information to potential trial participants. Further research should take the form of high-quality randomised controlled trials, with clear reporting of methods. Studies should conduct content assessment of audio-visual and other innovative interventions for people of differing levels of understanding and education; also for different age and cultural groups. Researchers should assess systematically the effects of different intervention components and delivery characteristics, and should involve consumers in intervention development. Studies should assess additional outcomes relevant to individuals' decisional capacity, using validated tools, including satisfaction; anxiety; and adherence to the subsequent trial protocol.

Several efforts have been reported, aiming to assess the potential effect of a computer-based system on accrual to clinical trials. In the context of a study that was contacted in USA, was developed methodology to identify retrospectively and prospectively patients who are eligible or potentially eligible for protocols[102]. Using a computer-based eligibility screening system, for each clinic visit and hospitalization, patients were categorized as eligible, potentially eligible, or ineligible for each of the 17 protocols active during the 7-month study period.

The results of the study showed that none of the patients was enrolled on a clinical trial during the 7-month period. Thirteen patients were identified as eligible for protocol; three patients were eligible for two different protocols; and one patient was eligible for the same protocol during two different time intervals. Fifty-four patients were identified as potentially eligible for a total of 165 accrual opportunities, but important information, such as the result of a required laboratory test, was missing, so that eligibility could not be determined unequivocally. Ineligibility for protocol was determined in 414 (35%) potential opportunities based only on conditions that were amenable to modification, such as the use of concurrent medications; 194 (17%) failed only laboratory tests or subjective determinations not routinely performed; and 346 (29%) failed only routine laboratory tests.

As a conclusion, the study claims that there are substantial numbers of eligible and potentially eligible patients who are not enrolled or evaluated for enrolment in prospective clinical trials. Computer-based eligibility screening when coupled with a computer-based medical record offers the potential to identify patients eligible or potentially eligible for clinical trial, to assist in the selection of protocol eligibility criteria, and to make accrual estimates.

[102] J. Kamal, K. Pasuparthi, P. Rogers, J. Buskirk, and H. Mekhjian, Using an information warehouse to screen patients for clinical trials: A prototype**,** AMIA Annu Symp Proc. 2005; 2005: 1004.

3.2 Improvement of procedure for creating and managing the IC forms (e-consent)

3.2.1 Level of consent

One of the most common challenges to be addressed, when dealing with consent management in health care, is how to enforce patient's desire to control access, usage and update the information stored within a health information system. So far, common practice has recognized four distinct levels of consent[103], regulating current and future information requests:

- ***Level 1: general consent*** – According to this level, a patient is assumed to give blank consent to any information request. That implies that no further agreement is required neither for a new episode of care nor for the release of data for other purposes.
- ***Level 2: general consent with specific exclusions*** – This level asks the patient to accept a general consent, however it allows him/her to exclude certain categories of information (e.g. gynaecological or sexual disease information), identified parties (e.g. insurance companies), or disclosure for a particular purpose (e.g. for employment).
- ***Level 3: general denial with specific consents*** – In this level, the patient denies all access to his / her health data with the exception of certain categories of information (e.g. demographic details related to a specified medical condition), identified parties (e.g. general practitioner), or disclosure for a particular purpose (e.g. for a prostate cancer survey).
- ***Level 4: general denial*** – According to this level, the patient expressly denies consent for information to be used in future circumstances. As a result, each new episode of care or request to use personal health information requires explicit consent.

3.2.2 Characteristics, benefits and limitations of e-consent systems

General consent is the simplest model of consent to implement, in terms of administration, however it has a high risk of abusing patient trust. That can lead patients to withhold information that is necessary for the effective treatment, due to fear that the information will not be used carefully. In addition, this model does not provide the potential of easily changing circumstances[104]. On the other hand the general denial model provides maximum security for privacy and confidentiality but is extremely complex in terms of administration since healthcare providers must ask patients permission through consent procedures at every decision point. This is both time consuming for the professional and complicated for the patient due to the fact

[103] Coeira E, Clarke R., "E-consent: the design and implementation of consumer consent mechanisms in an electronic environment", Journal of the American Medical Informatics Association 7 December 2003; paper M1480; doi 10.1197.

[104] D'Arcy G G., "Getting the HIPAA consent and notice mix right – for patient and provider", Health Management Technology 2002; 23 (7); 10.

that he / she will have to come in contact with several different providers over a course of treatment and each care person has to be aware of the applicable disclosure rules.

In case of level 2, 3 and 4, an e-consent system is capable of ensuring that all the required checks have been made before gaining consent and can simplify the acquisition and storage of the consent outcome, ensuring its currency and availability to all the people that are involved in the care process. The same system can also test the eligibility of the patient for treatment and authenticate the identity of the caregivers. In addition, the e-consent system can adopt procedures for informing patients about the consequences of their decision and empower them to give permission for treatment, decide about the use of information, or the implications of their refusal to do so. This is a significant benefit as the software can prevent granting of consent until the patients have acknowledged to have read and understood the consequences of their decision. That gives both patients and professionals the security of a legal, documented choice made under controlled, auditable and reproducible conditions[105]. Finally, such systems can include a mechanism through which patients can decide about the information that they want to be disclosed.

The common characteristics of an e-consent system are:

- privacy protection
- patient education
- capture consent
- release information

These characteristics are significant drivers for the development of e-consent systems in modern computer-mediated healthcare. They can be used to approve or deny consent in different circumstances in advance of any treatment or release of any kind of information, by reducing or eliminating subsequent requests for patient's consent. This is also useful in cases of situations when the patient is unconscious or unable/unreachable to provide any consent and in cases when the informed consent has to be obtained from a patient's family or other approved person.

Nowadays, it is not possible to define the limitations of an e-consent system, since no such system has been fully implemented yet in any nation's public health sector. The main concern, regarding the development of such a system, is the cost. However the reduction of risk and medical error, and the potential increase in quality of care, should outweigh this concern in the medium or long term. Furthermore, it is not known yet whether patients will accept such a system and whether that might raise new issues as well.

[105] Coeira E, Clarke R., "E-consent: the design and implementation of consumer consent mechanisms in an electronic environment", Journal of the American Medical Informatics Association 7 December 2003; paper M1480; doi 10.1197.

3.2.3 Access Control

Any secure information system needs to adopt access control mechanisms that regulate information data sharing among multiple users[106]. Two common methodologies that have been widely used in the implementation of such systems are the Discretionary Access Control model and the logic based approaches. The discretionary Access Control model has been widely accepted and used in real world security systems. It governs the access of subjects to the objects on the basis of the subject's identity and of authorizations that specify the access rights. Objects constitute the patients' files, records, fields in records and subjects are the active users that access the objects (physician, nurse etc.) Each request for access to objects is checked against specified authorization. On the other hand, logic based approaches have the advantage of separating policies from the implementation mechanisms, giving policies precise semantics and providing a unified framework, capable of supporting multiple policies. The fact that logic based approaches have strong expressive and reasoning power is ideal for supporting a complex set of e-consent instructions, along with the necessary inclusions and exclusions when accessing health related data.

Another example of access control is the Role Based Access Control (RBAC), which is an approach the attention of which has been increased today, as it reduces the complexity and cost of security administration. This approach is based on decoupling users from privileges by the inter-positioning of roles. Roles are assigned to users and authorize access to certain objects with given privileges[107]. Usually, roles reflect the responsibilities of users that have a certain position in the context of an organization (nurse, physician, etc.).

3.2.4 Best Practices - International Developments in e-consent

As mentioned above, there have not been developed any commercial technologies for explicit e-consent systems so far. However, public health sectors have initiated projects for the development of such a mechanism in several countries. These countries usually have ongoing e-health initiatives that form strategies for the advance of integrated electronic health systems or electronic health records (EHR).

A study aiming to examine the consent mechanisms that are currently used or proposed by the countries of Canada, England and Netherlands[108], was conducted in order to determine whether they could be utilized in implementing the respective existing consent requirements

[106] C. Ruan, V. Varadharajan, "An Authorization Model for E-consent Requirement in a Health Care Application", 2003, pages 191-205, volume 2846.

[107] J. Reid, I. Cheong, M. Henricksen, and J. Smith, "A Novel Use of RBAC to Protect Privacy in Distributed Health Care Information Systems", 2003, In Safavi-Naini, Rei & Seberry, Jennifer (Eds.) 8th Australasian Conference on Information Security and Privacy (ACISP 2003), July 9-11, 2003, Wollongong.

[108] J. Pritts, K. Conno, "The Implementation of E-consent Mechanisms in Three Countries: Canada, England, and the Netherlands (The ability to mask or limit access to health data)", 2007.

for sensitive health information in the United States. The three countries were planning on incorporating electronic mechanisms, supporting individuals' rights to control the disclosure of their health information for treatment, in their nationwide electronic health information infrastructure. General speaking, these mechanisms are based on coding data such that access to or transfer of data is restricted. This is often referred as "masking", "sealing" or "sealing and locking" and is usually applied at the data source. Masking functionality can be applied at different levels of data granularity or by specific user or category of users. The study claims that this process can include access permissions such as "read only" and "may not re-disclose" and adds that the period during which the permission is granted can be stipulated. This operation is currently available in electronic health information systems in all three countries, to various degrees. In some cases, the individuals can give providers a keyword, allowing them to override masking.

In Australia, the Commonwealth Department of Health and Ageing has funded an electronic consent research project in order to develop consumer consent in Electronic Health Data Exchange. Several universities and organizations were involved in this project. The used e-consent mechanisms utilized digital signatures, public key infrastructure, Kerebos technology[109] (a network authentication protocol) and different consent models were trialled in different Australian states. Patients have the choice not to give permission to certain individuals or to limit access to certain individuals only. In addition, the "Better Medication Management System" (MediConnect) was developed by the Australian Government Department of Health and Ageing and the Health Insurance Commission (HIC), in consultation with health care professionals and consumer groups[110]. By contrast to other models, the MediConnect trial provided more choices, since consumers were able to choose restricted access to particular parts of the record[111].

In the context of the New Zealand PAS project, a survey that was contacted elucidated a number of issues and principles related to the design and implementation of an e-consent framework. These issues and principles can be summarized in a set of recommendations as shown below[112]:

- Central strategic health organizations must engage in confidence building measures with consumers;

[109] "Kerberos: The Network Authentication Protocol", URL: http://web.mit.edu/ kerberos/, accessed on 26-07-2011.

[110] NSW Ministerial Advisory Committee on Privacy and Health Information. Panacea or Placebo? Linked Electronic Health Records and Improvements in Health Outcomes, 2000.

[111] Aitken, J., and Gilhotra, H., "HealthConnect: making consent and privacy a priority", Health Inf. Manage. J. 33(1):18–20, 2004.

[112] P.A.B.Galpottage and A.C. Norris, Patient consent principles and guidelines for e-consent: a New Zealand perspective, Health Informatics Journal vol.11 (1), 2005, pp. 5–18.

- Future e-health systems must be built with provisions for future interaction with an e-consent system;
- An e-consent system should be non-intrusive and utilize existing resources and practices;
- Any e-consent system must be fully scalable;
- Communication between healthcare provider and consumer must indicate that personal information will not be misused;
- Prevailing regulations and legislation must be fully complied with and their impact communicated to the consumer;
- Consumers should be able to know who has seen what of his / her personal information using audit trails;
- Consumers should be informed of any pathways to opt out of information disclosure and the resulting consequences;
- Systems should maintain an audit log of consumer and provider access to information;
- Funding, support services, personnel training and user education aspects with regards to e-consent must be considered;
- Integration into legacy systems and interoperation between future e-health portals must also be considered;
- The impact of digital signatures and certificates on e-consent systems needs to be analyzed from a policy perspective;
- The proposed framework should take into account some policies for sharing personal health information for medical follow-up studies, genetic research and emergencies;
- Clear identification of third parties in all e-health transactions is needed to inform the patient;
- Decide the granularity of control of individual information within electronic information systems;
- E-consent systems should record whether the consumer was adequately informed of all choices and consequences;
- E-consent systems should verify that the patient has sufficient capacity to give consent and retained relevant information;
- A consumer should be able to grant a longitudinal consent with regard to his / her personal information;
- Consumers should be made responsible for the privacy and security of their own health information;
- A patient should be able to do so using common Internet/web browser technology to improve acceptability;

3.2.5 Improvement of administrative flow during trial execution

3.2.5.1 Improving Clinical Trial Efficiency with Optimized Processes

Costs for conducting clinical trials are rapidly increasing due to the growing number and complexity of clinical trials, accompanied by longer trial duration. Clinical organizations can no longer manage trials using uncoordinated, manual, and paper-intensive methods of the past. They need a better approach – one that streamlines trial management, reduces trial length, and lowers expenditure.

One of the major gaps in current clinical trial management approaches is suboptimal relationship management. Clinical organizations must do a better job in managing relationships with trial participants, especially investigators and subjects.

Several state-of-the-art Clinical Trial Management System are built upon a CRM paradigm. CRM strategies offer a new, innovative approach to managing clinical trials. The approach focuses on strengthening relationships with trial participants, especially investigators and subjects, by using CRM software solutions. CRM solutions enable robust processes that enhance collaboration and information sharing across the many different teams involved in clinical trials. The result is closer, more productive participant relationships. CRM solutions also gather and maintain a wealth of valuable data that can be leveraged for a variety of other purposes, such as marketing, sales, and pharmacovigilance.

3.2.5.2 Robust Global Trial Management

Clinical trials are increasingly global in nature, conducted concurrently across multiple geographies. Making trial information accessible to the right people at the right time with the right level of detail becomes ever more critical. Some Clinical Trial Management System enable global clinical organizations to maintain a centralized trial management database while providing users with the most relevant and appropriate information based on their specific roles and responsibilities. Thus, real-time trial information is available not only to clinical research associates managing individual sites, but also to regional managers responsible for geographic areas, to global trial managers managing global trials but also enable a more efficient communication and interaction with patients.

3.2.5.3 Improve Investigator Relationships and Site Performance

Finding eligible subjects with the right health profile for a trial is often time-consuming and daunting, and failure to line up enough patients in time often accounts for days lost during clinical trials. In addition, the quality of data collected on each trial subject can vary significantly from site to site.

Identifying the investigators with the right subject demographics is a critical first step. Investigators with outstanding track records on meeting enrolment and performance targets bring tremendous value to clinical organizations. Competition to secure the service and loyalty

of these prized investigators has intensified in the past few years. Leading clinical organizations have started applying the CRM paradigm to manage interactions with their investigators. Using Siebel Clinical Trial Management System as a centralized repository for all investigators, organizations can collect and track all relevant information about their investigators, from personal profiles to disease specialties, and from past trial experiences to current trial performance.

By analyzing comprehensive investigator data, clinical organizations are able to identify the investigators most suitable for a trial. Furthermore, Siebel Clinical Trial Management System can be used to provide personalized services to investigators by facilitating communications to the study team and by providing investigators with timely and accurate payments. The results are improved investigator relationships, faster enrolment, better trial quality, and lower trial costs.

3.2.5.4 **CTD Software and Tools**

The Electronic Common Technical Document (eCTD) was developed by the International Conference on Harmonisation (ICH) as a standard format for the submission of regulatory documents in the US, Canada, Europe, and Japan. The eCTD, based on the CTD, electronically organizes submission content into specific modules, sections, and documents via the use of an XML (extensible markup language) backbone. Essentially, this backbone structures the eCTD submission so that each document (or "leaf") resides in a ‘subfolder’ of a specified section, and each section in a ‘folder’ of its specified module.

eCTD is nowadays the only acceptable format for the electronic submission of regulatory documents to the FDA (for both CDER and CBER). In the past few years, the FDA has begun to actively encourage sponsors that submit paper applications to begin the process of transitioning to eCTD submissions. For most drug companies, this means that many significant changes need to be made and many new business processes need to be developed.

Depending on the provider, a software package could include any combination of the following applications and tools for FDA eCTD submissions:

- Authoring Templates and Style Guides
- Regulatory Document (MS Word or PDF) Editor Tools
- Standardized Data Preparation Tools (SAAS, CDISC)
- Product Label Creation Tool (SPL/PLR)
- eSubmission Assembling, XML publishing, and Validation Tools
- eCTD Viewer

3.2.6 Every-day scenarios for e-consent

By describing six possible every-day-situations we want to demonstrate how e-consent could aid the informed consent process in day-to-day practice. For each of the six scenarios the technical means which could be of use in obtaining and managing consent have been analysed together with the legal requirements to these means.

In deliverable D4.1. Policy Recommendations to the Commission an analysis was included of e-consent solutions already existing today. Based on this analysis examples are provided of how the existing systems deal with the technical requirements of the six scenarios. Are these cutting edge solutions capable of fulfilling the expectations of the practitioners?

The legal analysis of the six scenarios assesses the feasibility under the current European legal framework and highlights points of particular attention.

It is important to mention that the commercial solutions of electronic consent provide little information regarding the supported policies. Consequently it was not always clear whether certain aspects of the described scenarios are satisfied.

3.2.6.1 Short summary of the technical solutions analysed[113]

***SecureConsent*[114]**

ConsentSolutions provides innovative approaches to improving the consent process through the use of electronic media. Its main purpose is focused on supporting trial staff and developing interactive, user-friendly software and web sites that help candidates and patients understand and make an informed decision about clinical trial participation. The system provides a medical terminology library and integrates a participant-comprehension tracking approach which minimizes the costly expense of ineffective pre-procedure consent. Trial candidates are assisted in acquiring the necessary information in order to make an informed decision about the research they are considering.

***iMedConsent*[115]**

The iMedConsent application enhances the education, discussion and documentation associated with the informed consent process for physicians, ambulatory surgery centres and hospitals. The commercial solution is integral to healthcare organizations' efforts to streamline

[113] For a full description of the solutions: D4.1. Policy recommendations for the Commission, section 3.1.3.

[114] SecureConsent, http://www.consentsolutions.com

[115] iMedConsent, http://www.dialogmedical.com

internal practices, standardize communication across the enterprise and better document informed consent encounters.

Basic Patient Privacy Consents (BPPC)[116]

BPPC is an IHE profile[117] that provides a mechanism to record the patient privacy consent(s), and a method for Content Consumers to enforce the privacy consent appropriate to the use. This profile was identified as "Basic", since there is a lack in standards, meeting the complex need of including patient's wishes regarding the access and control of "their" data.

Consentir

Consentir[118] is a policy (rule) based patient consent management system that utilizes patient consent information along with operational policies as input. The system aims to protect patient information in a real time manner by applying policy based consent management.

3.2.6.2 Analysis of six every-day-situations

Scenario 1: Control

Dr. Hartman is recruiting prospects at a high pace. Dr. Cuddy as trial chairman would like to check if all trial participants have signed consent.

A trial consent management system would allow Dr. Cuddy to check if a specific patient has signed consent for a specific purpose (in this case Dr. Cuddy's trial).

Such a system would also allow Dr. Cuddy to download the scanned signed consent form.

a) Technical requirements:

- **Security to view consent**

The control scenario will be supported by all the existing solutions, taking into account that the system will be secured through a Role Based Access Control (RBAC) mechanism.

[116] "Basic Patient Privacy Consents", http://wiki.ihe.net/index.php?title=Basic_Patient_Privacy_Consents, last updated on 13-10-2010, accessed on 20-08-2012.

[117] Integrating the Healthcare Enterprise (IHE) is an initiative aiming at the integration of information systems of modern healthcare institutions. Within this initiative, the Infrastructure Technical Framework specifies the interactions of a subset of functional components (IHE Actors) of the healthcare enterprise, in terms of a set of coordinated, standards-based transactions.

[118] Atif Khan, Sarah Nadi, David R., "Consentir: An Electronic Patient Consent Management System", Cheriton School of Computer Science University of Waterloo Ontario, Canada.

The EnCoRe architecture accepts requests to retrieve data coming from an employee/ administrator, an application/service, or an external workflow manager that connects to an EnCoRe system of an external organization. In all cases, authorization is obtained from the privacy-aware access control policy enforcement component.

b) Legal requirements:

- **Questions of access to patient's personal information**

Technically the systems proposed can offer a good overview of informed consent forms for any person having interest in the access to patient files. What has to be considered from the legal point of view that those access rights have to be limited to persons having a legal ground for accessing personal data of the patients (which is no different to the typical paper based environment, however the facility with which such access can be granted in the e-consent solutions makes this an even more important issue). Three different situations of access to personal data are relevant and of different legal consequences.

I) Access is granted to the entity who is mentioned in the consent for data processing as having access to patient files. A possible situation: clinical trials sponsor has a yearly audit performed by an external auditing company in all of its clinical trial sites, therefore all the informed consent forms have a clause allowing that specific auditors access to the patient files, including informed consent forms – in such a case the auditor can be allowed to access informed consent forms.

II) Access is granted to a public authority which by law is authorised to audit the conduct of clinical trial and therefore to processing of personal clinical trial subject's data. The public authority has to be granted access to the personal files of data subjects and data subject does not have to give an informed consent for that reason.

III) Access is granted to a third party, where consent for data processing by that entity has not been obtained. In such a case no legal ground for processing on the side of third party exist and as such access to personal data should be refused.

- **Electronic signatures**

As it was explained above a hand-written signature can only be replaced by a qualified electronic signature - QES (as defined in the E-Signatures Directive). However, the use of electronic signatures is not prevalent in Europe and the above-mentioned qualified electronic

signatures are complex in its application operation, therefore are not widely used on a daily basis.

Therefore introducing an e-consent system which could replace paper-based forms stands before a legal challenge. All of the patients/trial subjects would need to use a qualified electronic signature in order to sign their consent forms, currently those are hardly used on every day basis. Practical consequences of such an approach would make it impossible to use such an approach.

Scenario 2: Reminder

At a party Peter hears about abuse of data by an insurance company. Peter starts to worry about his previous participation in a clinical trial. He remembers signing consent, but cannot recall what the content was.

a) Technical requirements:

- **Universally Unique Identifier (UUID) patient (e.g. social security number)**
- **Where is consent stored (e.g. central national register)?**

Secure-consent provides each candidate with a secure, trial specific user ID, which is used for logging in the system.

COMS envisions a strong patient involvement to take patients' rights into account giving patients full control of the management of the access rights. All users (patients) are assigned with a global identification code (MPI-ID).

The EnCoRe architecture accepts data access requests from an existing data subject's web browser, using the requestor's identification.

b) Legal requirements:

- **Patient empowerment and improved informed participation**
- **Security issues**
- **Identity management issues**

Seemingly all of the services described dispose with functionality allowing patients to access their data stored within them. Two issues have to be kept in mind in this respect – in how far those systems offer a sufficient level of security to the data stored and in how far they are capable of sufficient authorisation and identity management of users.

Offering data access is in accordance with right of access of the data subject (Article 12 of the Data Protection Directive) and furthermore also goes in line with the patient empowerment trend. However in any such system a special attention has to be paid to the security and authentication questions, which have to be examined on case by case basis, keeping in mind Article 17 of the Data Protection Directive and the requirement posed within. This requires that: "appropriate technical and organizational measures to protect personal data against accidental or unlawful destruction or accidental loss, alteration, unauthorized disclosure or access, in particular where the processing involves the transmission of data over a network, and against all other unlawful forms of processing" have to be introduced by the data controller.

Scenario 3: Re-consent scenario

Peter and Lois gave their consent for their 17-yo son Chris to participate in a trial that will run for the next 5 years. The trial management system alerts the trial investigator/chairman that one of its subjects will need to sign a new consent.

a) Technical requirements:

- **Alerting system**

All non-commercial solutions support re-consent, however an alerting mechanism is explicitly described in the EnCoRe architecture, which incorporates a notification mechanism. Its external workflow manager component is in charge of communicating notifications of updates/changes (about personal data and privacy preferences). Additionally, the BPPC profile supports notification of patients (through sending email) and new consent to be captured.

b) Legal issues:

- **Consent and assent (questions of legal age of maturity), legal representation**
- **Re-consent (Clinical Trials Directive, Data Protection Directive)**

Whenever considering obtaining informed consent it has to be taken into account who is the person obliged to give it. For that reason the health professional has to observe the legal age of maturity and the questions of legal representation – it is also currently the case. However, the process can be facilitated by introducing consent management system – in often complex cases of multiple consent and assents (i.a. minors and their parents) those solutions can support the physician in obtaining all of required consents and when needed monitor the need of re-consent, as required in case the subject gets legally adult.

Scenario 4: Consent for screening scenario

A hospital is participating in an innovative project to automate trial recruitment. Peter allows access to his data, if it's for recruitment purposes.

Data will only be viewed by local hospital people. This is a form of a broad consent.

a) Technical comments

Consentir supports four different types of actors: doctors, nurses, hospitals and patients. All hospitals have a "members only" policy where only members of the hospital are authorized to access patient information. However, the system is a simple prototype that demonstrates the applicability of using ideas from the semantic web to the problem of reasoning with patient consent. The condition allowing access to data only for recruitment purposes is not mentioned.

Heidelberg University Hospital's approach (COMS) represents a universally deployable architecture which benefits from its flexibility and can hence be used in any setting where the management of patients' consents is required. It is capable of managing advanced or non-advanced patient privacy consents for both opt-in and opt-out based RHIN. Patient can select which organization or which provider is allowed to review documents inside the PEHR and which system is granted to publish new documents to the record. However, it is not clear whether the COMS architecture support any specific policies for trial recruitment.

Within the EnCoRe architecture, the data subject (user) has the possibility to define and even change his/ her consent/ privacy preferences. These include access control policies that not only describe security constraints (who can access what) but also privacy constraints based on data subjects' preferences such as approved/ banned purposes (e.g. research) for using data, black/white lists of entities that can handle data, etc.

The IHE-BPPC basic profile allows specific patients' documents to be used for specific research projects.

b) Legal issues:

- **Consent for recruitment and contacting again**
- **Re-consent (Clinical Trials Directive, Data Protection Directive)**

In that scenario individual consents on secondary use of his health data which was collected in the clinic before (in course of treatment, or trial). The scope of such a consent is sharply described – the data subject allows scanning his/ her data for the purpose of taking part in a possible future trial to which he or she may be suitable. In case such a trial will be found hospital team member will re-contact the data subject (of which he/she is informed). The

individual will be approached by physician and can eventually be enrolled in the new trial – for that reason a usually procedure of obtaining informed consent for trial participation will be carried out.

Scenario 5: Conditional consent scenario.

Peter consents to participating in a longitudinal study. One can access his data on one condition: the data must be anonymised.

a) Technical requirements

- **Audit trail to verify anonymisation**

Conditional consent scenarios are supported by Consentir, where patients allow access to all their information except for documents that are classified as sensitive, or for certain people. EnCoRe supports obligation policies, enforcing constraints and duties that have been defined both by organisational policies and data subjects' preferences, which among other are dealing with transformation and minimisation of personal data. Likewise, the BPPC profile supports similar policies. However, none of the solutions mention anything specific about anonymisation.

b) Legal issues:

- **Negotiability of consent**

This scenario exemplifies possibilities of negotiable consent. Patient is asked whether his/her data can be used for a secondary purpose. If patient is in favour patient and physician can discuss details of the use. In this particular case patient allows only use of anonymised data.

- **Consent for anonymisation**

As anonymisation of the data is also data processing the patient will be asked to consent for anonymising of his/her information. The outcome of that process will be data which is no longer personal (and no consent for their processing will be needed).

Scenario 6: Opt out vs. opt in solution

- ✓ *Dr. Hartman has the possibility to analyse pseudonymous EHRs to detect patients that may help to answer his research question with their data. Peter is identified as such a patient, and he will automatically be notified that Dr. Hartman wants to use his data for a specific research. Peter then can disagree at any time to participate with his data in this research*

project. If Peter doesn't respond, the general consent applies and Dr. Hartman can use Peter's data for that specific research.

- ✓ *Dr. Hartman has the possibility to analyse anonymously EHRs to detect patients that may help to answer his research question with their data. Peter is identified as such a patient, and he will automatically be notified that Dr. Hartman wants to use his data for a specific research. Peter then can agree at any time to participate with his data in this research project. If Peter doesn't respond, the general denial of consent applies and Dr. Hartman cannot use Peter's data.*

a) Technical Comments

Heidelberg University Hospital's approach also supports opt-out scenarios, is very flexible and can be adapted to other settings in other regions. Opt-out is supported by EnCoRe by disclosing personal data along with consent/ privacy preferences. The BPPC profile supports opt-out of sharing outside of local event use, with- or without emergency override.

b) Legal issues:

- **Opt-in vs. opt-out consent (Data Protection Directive);**

Opt-out solution gives data subject the possibility to withdraw his / her consent, after he / she was informed about the processing taking place. However in the light of Data Protection Directive such consent does not fulfil the requirement of explicitness, posed by Article 7 towards consent for processing of medical data.

Therefore the legally acceptable solution is an opt- in scenario where active data subject's consent is sought.

- **Broad consent (Data Protection Directive)**

Also broad consent is seen as not fulfilling the requirements of Data Protection Directive (for more elaborative account see above)[119].

Therefore, each time the patient is informed that his / her data shall be used the doctor has to wait for an explicit consent on patient's side and only then can start the data processing.

As such this scenario will be similar to the Scenario 4 – Consent for screening. Patient gives a consent for screening of his / her data but when the data should be used for a particular research a new consent has to be obtained.

[119] See **Fehler! Verweisquelle konnte nicht gefunden werden.**

3.2.7 Conclusion

Privacy, confidentiality and access are important factors in the successful implementation of EHR systems. Therefore, incorporating consent mechanisms is essential and their development is a step that can inspire patient trust as their medical records increasingly becomes computerized and electronically exchanged among healthcare professionals. Such mechanisms need to maintain privacy without impeding the healthcare process and thus to achieve the best health outcomes for consumers.

Through the discussion above, it has emerged that a variety of different consent behaviours are possible and that their operation depends on the health sector and individual patient preference. From a technical point of view, most consent models require methods for capturing specific inclusion and exclusion criteria, defining patients' explicit consent intentions. As a conclusion, there cannot exist any obvious single set of design criteria that can be uniformly adopted. The specific implementations of an e-consent system will always trade-off issues such as a patient's desire to protect confidentiality, the impact of consent systems on clinical work, and the cost of designing and maintaining a potentially highly complex system. A general approach to e-consent is required, which will be customizable according to the local needs of differing health sectors and will accommodate a variety of patient wishes.

III Study of the legal framework for informed consent within the national legislation of Belgium.

1. Legal age of majority and capacity to consent

In principle, only adult patients with full legal capacity can lawfully consent to treatment, participation in a clinical trial or data processing. The patient needs full awareness and adequate reflection capacities to process the information presented to him, at the time it is presented[120]. When a patient does not meet the requirement of full legal capacity, the Belgian legal framework foresees representation arrangements[121]. This is also the case for children. Children are considered to not have full legal capacity. Nevertheless and in contrast to legally incapable patients of age, children do need to be involved in the decision making process when it concerns their health.

1.1 General remarks on age of majority and capacity for acts in law

Under Belgian civil law a person is since 1990 considered a minor when under 18 years of age[122]. When the child is a patient, these representation arrangements are foreseen by the Belgian Patient Rights Act[123] appointing the parents or legal guardian as person(s) to consent[124]. The consent of one of the parents is enough when representing their child. If the parents cannot reach an agreement on an important decision concerning the health of the child or if their decision isn't in the interest of the child, a judge can charge the parental authority to one of the parents[125].

The minor patient needs to be involved as much as possible taking into account his age and maturity. The minor can decide himself on the proposed intervention if he is capable of reasonably assessing his interests and if the health care provider considers him mature enough[126]. The maturity of a child and his capacity to decide needs to be assessed case by case. This assessment will take into account personal capabilities, character, life experience, type,

[120] Cfr. J.L. FAGNART, "Information du patient et responsabilité du médecin", Brussel, Bruylant, 2006, 81.
[121] Art. 12 – 15 Wet van 22 augustus 2002 betreffende de rechten van de patient, *B.S.* 26 september 2002, (in English translated "Law on Patient Rights" or "LPR").
[122] artikel 488, Belgian Civil Code.
[123] Art. 12 LPR
[124] Art. 12 §1 LPR.
[125] Art. 374 §1, second paragraph Belgian Civil Code.
[126] Art. 12 §2 LPR.

consequences and risks of the intervention, as well as emotional, social and psychological development[127].

1.2 Consent for care

As indicated above, the Belgian Patient Rights Act indicates that the child's parent(s) or legal guardian have to give informed consent for his or her treatment. Doctrine and jurisprudence however indicate that the child too has to consent when he "has a view to reason"[128]. In case this child has not consented, the healthcare professional violates the child's right to physical integrity, just like this would be the case when dealing with an adult[129]. In case of conflicting opinions of the child and the parent(s) the decisive opinion will depend on the above described maturity and capacity to decide of the child. This decision needs to be taken before court.

Before consenting, the child has the same rights to information as an adult. He has to be informed about his health condition, diagnosis and prognosis, as well as the treatment and expected procedures. This information has to be given in a for the child understandable and comprehensible manner without underestimating the child's abilities. A decision not to inform the child is possible, but this should never be based on the interests of the parents nor the healthcare professional, only on the best interest of the child. The child may of course also decide himself not to be informed.

1.3 Consent for clinical trial participation

The Belgian Law concerning Experiments on the Human person (hereinafter LEH) regulates the participation of minors to clinical trials, or "experiments" which is the term used by this law.

An experiment involving minors is only allowed when informed consent is obtained from the minor's parents exercising the legal authority of the minor or in absence of parents, his legal representative. This consent has to at all times reflect the minor's assumed will. The minor does have to be involved in the execution of the right to informed consent by the parents or representative, taking into account his age and maturity. For this reason the minor has to be provided with information on the experiment adjusted to his age and level of understanding.

[127] T. VANSWEEVELT, "De persoonlijkheidsrechten van minderjarigen en grenzen van het oudelijk gezag: toestemming van de minderjarige in een medische handeling", in *Juridische aspecten van de geneeskunde,* A. HEYVAERT e.a., Antwerpen, Kluwer Rechtswetenschappen 1989, 272-276; see for more information also: www.hospichild.be, the website for administrative, economic, social and professional aspects of the hospitalisation of children under 16.

[128] "oordeel des onderscheids" in Dutch; B. Brouwers, "Jeugdsanctierecht in Europa: is uithandengeving een evidentie?", Jura Falconis, jg 44, 2007-2008, vol 1, 3-38.

[129] Article 5 LPR.

The information needs to be provided by pedagogically trained staff prior to the informed consent of the parents.

In principle both parents need to consent, but when circumstances are such that this is difficult to achieve, the Civil code allows the assumption of the consent of the other parent[130]. When parents disagree the treating physician should – in consultation with the minor – decide in the best interest of the minor[131].

When the minor expresses his explicit wish not to participate or to withdraw from participation, this wish needs to be examined and respected by the researchers to the extent that the minor is ought to be able to judge and evaluate his situation. The parents or representative of the patient too can decide to withdraw the minor from further participation, this may however never have negative repercussions for the minor[132]. In paediatric oncology this rule has remarkable consequences since standard care leads almost always to a worst prognosis. One could therefore question if there really is a choice for the parents: can they refuse their consent? Can they withdraw the minor from the trial? In practice this decision will be made in deliberation between the parents, the minor and the physicians. If no agreement can be reached a judicial procedure is open, however to the best of our knowledge there are no precedents of such cases.

This approach reflects the approach of the Law on Patient Rights only partially. Whereas, as indicated above, the Law on Patient Rights allows the minor who can be considered to evaluate his interests reasonably to exercise his rights independently, this is not the case for the LEH. The LEH only states that the opinion of the minor should be respected when he explicitly requests to not or no longer participate[133].

1.4 Consent for data processing

In Belgium the protection of personal data is regulated by the Data Protection Act[134]. The Data Protection Act does not foresee a differentiation between minors and adults. In article 1 §8 DPA consent is described as the expression of one's or his representative's will.

[130] J. Ter Heerdt, Het experiment beproefd. Een juridische analyse van medische experimenten met mensen, Antwerpen, Maklu, 2000, 143.

[131] R.D'Haese, "Medische contracten in het licht van de eerbied voor de fysieke integriteit. Informed consent – vereiste als raakpunt.", 2010, Tijdschrift Voor Belgisch Burgerlijk Recht, 435.

[132] Art 7 LEH.

[133] C. Trouet, 2007, Clinical Trials in Belgium, Intersentia, Antwerp – Oxorfd, 135.

[134] Wet van 8 december 1992 tot bescherming van de persoonlijke levenssfeer ten opzichte van de verwerking van persoonsgegevens, BS 18 maart 1993, in English Data Protection Act or "DPA".

Consequently, the legal age of majority and the capacity to consent is regulated by general principles in Belgian civil and criminal law for non health related situations and the Belgian Law on Patient Rights for health related issues.

2. Consent for care

The informed consent principle entails that the health professional is only allowed to intervene after the patient has given his informed and free consent with the medical treatment[135]. In other words the informed consent is a prerequisite and has to be given before the treatment is started. This implies not only that the healthcare professional can act only upon consent, it also implies that he has to provide the patient with adequate information[136].

The requirement of an informed consent for care is an application of the right of self determination of the patient and his right to physical integrity. This principle is part of the medical deontology[137] and as shown above several international legal and ethical sources[138]. It also has been accepted in Belgian jurisprudence and literature for a very long time[139]. In Belgium the informed consent principle has, more concrete, been adopted in the Patient Rights Act. This act specifies the content of the information that has to be given to a patient as well as the conditions which apply when the information is given[140]. The PRA also regulates the right of the patient to deny or retrieve his consent[141] and contains an exception for emergencies[142].

2.1. Definition of consent

The Belgian Law on Patient Rights does not provide an explicit definition of informed consent. However, in article 8 §1 it does state that: [translation] "*The patient has the right to informed, preceding and freely consent to every intervention of the healthcare professional. This consent is given explicitly, except when the healthcare professional may reasonably deduct the consent*

[135] Art. 9 LPR.

[136] T. VANSWEEVELT, "Le débiteur de l'information, le lien de causalité et le consentement éclairé", *T.Gez./Rev.dr.Santé* 1999-2000, 281.

[137] Art. 29 and 33 of the Medical Code. This code only applies to physicians, not pharmacists. Pharmacists do fall under the scope of the Belgian law on patient rights.

[138] The principle has been adopted in the European Manual for medical ethics, the European Charter of the Rights of the patient, in the Declaration of Amsterdam concerning the promotion of the rights of the patient and the Treaty of human rights and biomedicine.

[139] Cass. 14 december 2001, *J.L.M.B.* 2002, 532; *R.G.A.R.* nr. 13.494; *T.Gez./Rev.dr.Santé* 2001-2002, 239.

[140] Art. 8 §3 LPR.

[141] Art. 8 § 4 LPR.

[142] Art. 8 § 5 LPR.

from the patient's way of acting after having informed him. At the request of the patient or the healthcare professional the consent is put in writing and added to the patient's medical history."

2.2. Informed consent as an act in law

According to art. 2 of the Belgian Law on Patient Rights all (healthcare) practitioners as defined in the Royal Decree nr. 78 of 10 November 1967[143] and the Law of 29 April 1999[144] have to comply with the requirement to consent. In practice it concerns physicians, dentists, pharmacists, physiotherapists, nurses, certain paramedics and practitioners of legally defined non-conventional disciplines.

2.3. Form of informed consent

Explicit

In principle, the patient has to consent explicitly with a specific intervention, unless the health care professional can deduce the patient's consent from his conduct or what he says[145]. Indications such as the patient's spontaneous exposure of his upper-arm for the collection of blood, or the fact that a patient puts himself voluntarily under a scanner can be considered as such conduct.[146]. The implicit patient consent is however only valid under condition that the patient's conduct is unambiguous and that he acted with full knowledge[147].

Oral

In principle the consent for treatment does in Belgium not depend on a written statement. Article 8 §1 of the Belgian Law on Patient Rights states that in principle informed consent can be given orally. An oral consent is thus sufficient for a healthcare provider to perform a specific intervention, however, except when the patient can requests for confirmation in writing[148]. A written copy of the given information allows the patient to read it trough all over in a quiet setting. The healthcare professional is – of course - also allowed to attend his patients with a written copy without a specific request but as part of his standard procedure, for example by

[143] Royal Decree nr. 78 of 10 November 1967 concerning the performance of health care professions, *B.S.* 14 november 1967.
[144] Wet van 29 april 1999 inzake de geneeskunde, de artsenijbereidkunde, de kinesitherapie, de verpleegkunde en de paramedische beroepen, *B.S.* 24 juni 1999.
[145] Art. 8 §1 LPR.
[146] S. TACK en T. BALTHAZAR, "Patiëntenrechten – Informed consent in de zorgsector: recente evoluties", *C.A.B.G.,* 2007, 5/6, 26.
[147] Proposal of law concerning the rights of the patient, M.v.T., *Parl.St.* Kamer 2001-2002, 1642/001, 25.
[148] Art. 8 §3 *juncto* 7, §2, second paragraph LPR.

means of an information brochure. Please note that such an information brochure or any other written copy, may however never replace the oral discussion[149].

2.4. Information to be addressed in the informed consent form

The duty to inform encloses the obligation to present the patient with all kinds of information elements which are necessary to consent with complete knowledge to a certain treatment or intervention.

Article 8 §2 of the Belgian Law on Patient Rights states that information needs to be given on at least *"the goal, the nature, the degree of urgency, the duration, the frequency, the contra indications relevant for the patient, side effects and risks related to the intervention, the follow-up, the possible alternatives, the financial consequences, the possible consequences in case of a denial or retreat of the consent, and all other clarifications relevant for the patient or the practitioner, including the legal regulations related to an intervention"* have to be explained to the patient.

- Provide the patient with a clear oversight of the intervention: the painful and/or invasive nature of the intervention, its possible urgent nature[150], the duration of the treatment, the number of interventions that will be necessary and the frequency by which they will be effectuated. For instance, a cancer patient who has to undergo chemotherapy has to be able to assess precisely or at least approximately the number of treatments he will need as well as the period in which they will be given[151];
- Communicate all contra indications, side effects and risks known or which should be known and relevant for a normal patient who finds himself in the same situation[152];
- Judgement of risk relevance according to the risk frequency, the gravity of the risk and the physical, mental and socio-economic disposition of the patient[153];
- If several treatments are available, the practitioner is obliged to inform the patient[154] but not to discuss every alternative in detail[155]. If certain alternatives are equal and can have the same result, the practitioner has to inform his patient about this and has to

[149] Proposal of law concerning the rights of the patient, M.v.T., *Parl.St.* Kamer 2001-2002, 1642/001, 20.

[150] H. NYS, "Gneeeskunde, Recht en Medisch handelen", *Algemene Praktische Rechtsverzameling*, Mechelen, Kluwer 2005, 155-156.

[151] S. TACK en T. BALTHAZAR, "Patientenrechten – Informed consent in de zorgsector: recente evoluties", *C.A.B.G.,* 2007, 5/6, 5.

[152] Rb. Antwerpen 12 mei 2004, *T.Gez./Rev.dr.Santé* 2005-2006, 221.

[153] Y. LELEU en G. GENICOT, Le droit médical : aspects juridiques de la relation médecin-patient, Brussel, De Boeck & Larcier, 2001, 67.

[154] Rb. Leuven 10 februari 1998, T.B.B.R. 1998, 163.

[155] Antwerpen 16 september 2002, T.Gez./Rev.dr.Santé 2003-2004, 26.

explain the pros and cons of these treatments. This entails for example the difference in price, duration of the rehabilitation, health risks etc[156];

- Information on the total price of the treatment as well as on the fees, the non-refundable part of the medical expenses and the supplements he will have to pay[157];
- All other possibly important elements of information (for example the presence waiting lists for a specific treatment) hereby balancing what that patient would like to know or what would be useful to him in his specific situation[158].

2.5. Rights of the patient

A patient has the right to refuse or withdraw his consent for a specific intervention[159]. This right is first of all based on the physical integrity of the patient. Secondly, it is also a result of the agreement on medical treatment between the patient and the health care provider. As discussed in the previous paragraph, such an agreement demands the patient to consent prior to the intervention. *E contrario*, the patient also has the right to refuse or withdraw his consent to a specific treatment. This too has to be respected by the health care provider, even when it applies to a treatment of vital importance.

3. Consent for clinical trials participation

3.1. Legal framework

In Belgium, clinical trials are regulated by the Law of 7 May 2004[160] concerning experiments on the human person (LEH), transposing the European Clinical Trials Directive. The Law was however modified several times since, transposing the Commission Directive 2005/28/EC as well as answering to challenges brought before court.

The LEH is complemented by several Royal Decrees:

- The Royal Decree of 30 June 2004 as modified by the royal decree of 18 May 2006 implementing the LEH for clinical trials involving medication for human use.

[156] J.L. FAGNART, "Information du patient et responsabilité du médecin", Brussel, Bruylant, 2006, 50-72.
[157] Proposal of law concerning the rights of the patient, M.v.T., Parl.St. Kamer 2001-2002, 1642/001, 26.
[158] J.L. FAGNART, "Information du patient et responsabilité du médecin", Brussel, Bruylant, 2006, 73; W. DIJKHOFZ, "Het recht op informatie en geïnformeerde toestemming", T.Gez./Rev.dr.Santé 2003-2004, 104.
[159] Art. 8 §4, first paragraph LPR.
[160] Belgian Law of 7 May 2004 concerning experiments on the human person, B.S. 18 mei 2004 (hereinafter LEH).

- The Royal Decree of 6 June 1960 as modified by the royal decree of 30 June 2004 and almost completely abolished by the Royal Decree of 18 May 2006 on the production and distribution of medication.
- The Royal Decree of 15 July 2004 determining the retributions to be paid in the context of an application for a clinical trial or an experiment.
- The Royal Decree of 27 April 2007 providing the fees to be paid in the context of Article 30§6 LEH (inspections).

Next to the Royal Decrees the LEH has also been clarified by several Circulars[161].

The Law concerning Experiments on the Human person

In contrast to the European Clinical Trials Directive, the Belgian LEH is applicable to more than just interventional clinical trials involving medicinal products. The LEH covers all types of experiments on the human person, interventional clinical trials as well as non-interventional clinical trials[162]. The Belgian legislator considered a comprehensive legal framework for experiments on the human in Belgium to be necessary for the transposition of the Clinical Trials Directive and the Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. This comprehensive approach should moreover preserve the competitive position which Belgium has had for a long time at the international level[163].

- The LEH defines “experiment” in article 2, 11° as “any trial, study or investigation carried out on the human person with the aim of developing knowledge particular to the exercising of health care professions as referred to in Royal Decree No. 78 of 10 November 1967 concerning the health care professions”[164]. Naturally this is a very broad definition. The category of “experiments” is therefore in second instance split into experiments involving medicinal products and those not involving medicinal products. Experiments not involving medicinal products are for example experiments with medical devices and experiments with surgery techniques. Experiments involving medicinal products are also called clinical trials.

[161] A full list of these circulars can be found in C. Trouet, 2007, Clinical Trials in Belgium, Intersentia, Antwerp – Oxford, 135.
[162] Art 3 LEH
[163] R. Demotte Minister of Social Affairs and Public Health in 2007, Preface in C. Trouet, 2007, Clinical Trials in Belgium, Intersentia, Antwerp – Oxorfd, 135.
[164] Under this Royal Decree health care professions include medicine, dentistry, pharmaceutical sciences,…

- A clinical trial is in article 2, 7° LEH defined as "every investigation on a human person intending to find or confirm clinical, pharmaceutical or other pharmaco-dynamic effects of one or more medicinal products for research, as well as to find or confirm side effects, study the resorption, distribution, metabolism and excretion of one or more medicinal products to determine the safety and effectiveness of these products". This includes Phase I to Phase IV trials.

The definition of "experiment" was challenged twice before the Constitutional court due to discussions on the division of competences between the federal and regional governments[165]. We will not discuss the reasoning made before court because they are of minor importance to this project, but for the sake of completeness it can be added that the LEH is not applicable on studies or investigations which fall under the competence of the regions. These competences include preventive healthcare, medically justified exercising and the protection of the environment. However, when studies, also on these competences, are executed by a healthcare professional as defined in the Royal Decree No. 78 of 10 November 1967 concerning the health care professions, the competence of the federal government can never be contested and the LEH will always be applicable.

Types of research which are not covered by the LEH are:

- Research on embryos in vitro
- Research on corpses
- Research on human biological material which is already separated from the body (bio-banks)
- Retrospective non-interventional research.

With regard to the exception for human biological material which has been separated from the body, or bio-banks, it should be noted that this is regulated separately in Belgium. More precisely, this is regulated by the law of 19 December 2008 on the use of human material for medical use or scientific research[166].

With regard to the last exception it should be noted that the exclusion by the LEH does not influence the applicability of the Data Protection Regulations. Informed consent for data processing will thus still have to be obtained (cf. infra[167]).

[165] Arbitragehof, 16 november 2005, nr. 164/2005; Arbitragehof, 21 maart 2007, nr. 48/2007.

[166] Wet van 19 december 2008 inzake het verkrijgen en het gebruik van menselijk lichaamsmateriaal met het oog op de geneeskundige toepassing op de mens of het wetenschappelijk onderzoek, *BS* 30 december 2008.

[167] See section 4.5

3.2. Definition and requirements of consent

The Belgian LEH does not contain an explicit definition of “consent”.

In article 5 LEH the law enumerates the conditions under which an experiment can be initiated or continued. Condition number 7 indicates that the participant or his representative needs to have consented to his participation and that a contact point has to be available where the participant can turn to for more information.

The conditions to this consent are further specified in article 6 LEH:

- the consent has to be free;
- given in writing. When the participant cannot write consent may be given orally in the presence of at least one adult witness independent from the sponsor and researcher;
- after having been informed on at least:
    - the type
    - the significance
    - the objectives
    - the implications
    - the expected risks and benefits and
    - the circumstances under which the experiment will take place
    - the identification of the ethical committee responsible for the approval of the trial and its advice given on the trial
    - the right to withdraw consent at all times and without any risk to detriment

The information has to be provided in a written document, needs to be clearly formulated in way understandable to the individual participant and this participant needs to be told that he has to opportunity to further discuss the informed consent form with a member of the research team.

3.3. Informed consent as an act in law

Three remarks can be added to the informed consent as an act in law:

- A minor cannot consent, but his opinion needs to be taken into account. For this we refer to the discussion on the capacity to consent above[168].
- Exceptions to the requirement of written informed consent are foreseen by the LEH.
- Even though the law explicitly states that the withdrawal of informed consent may not have negative repercussions, this does not imply the trial cannot be continued.

Exceptions to the requirement of written informed consent

The Belgian LEH foreseen in article 3 §3 that a written informed consent does not need to be obtained from the participant for non-interventional experiments conducted by the federal government or an institution for public advancement when the aim of the experiment is to investigate the "quality of the activities performed by healthcare professionals". In this case the consent of the participant is assumed. Only when he or she explicitly refuses participation, he or she will not be involved in the experiment. The participant has in other words a right to opt-out. Hospitals and healthcare professionals are obliged to inform their patients about this right to opt-out and refer them to a contact point when they request additional information.

A second exception is foreseen for emergency situations. "When the experiment is directly linked to the live or die situation of the patient or to his clinical state which may lead to serious and permanent injuries, informed consent cannot be obtained due to this emergency situation and participation is essential to confirm results of experiments on persons who are able to consent or experiments using different research methods" the patient may be included in the experiment without his prior consent[169]. This is stricter than what is the case for informed consent for treatment. Treatment may be administered to the patient without his consent when the action is necessary for the health of the patient. In case of treatment this exception is linked to the professional obligation to provide help from the physician[170].The Ethical Committee moreover has to approve of the exemption from informed consent when deliberating on the study protocol. And informed consent has to be obtained from the patient as soon as he or she is able to provide it[171]. This is similar to the exception foreseen in the new Proposal for Clinical Trials Regulation. Under the new Regulation patients may also be enrolled in a previously approved clinical trial when due to due to the unconsciousness of the patient and the absence of an immediately available representative it is not possible to obtain consent

[168] See section: III1.3

[169] Art 9, 1° LEH.

[170] R.D'Haese, "Medische contracten in het licht van de eerbied voor de fysieke integriteit. Informed consent – vereiste als raakpunt.", 2010, Tijdschrift Voor Belgisch Burgerlijk Recht, 435; W. Dijkhoffz, "Het recht op informatie en geïnformeerde toestemming", *T.Gez.,* 2003-04, 120.

[171] Art 9, 6° LEH.

prior to the intervention[172]. Under the Belgian law this is not explicitly specified, but under the Proposal for Clinical Trials Regulation, this exception is also open to minors. Article 32, 2. a) states that regarding minors "the informed consent shall be obtained as soon as possible from the legal representative".

Consequences of withdrawal

Even though the withdrawal of informed consent to participation in an experiment may not have a repercussion, this does not in principle imply that the participant can request the destruction of the research data already collected at the time of his withdrawal[173]. "The data collected up to the time of withdrawal can be used in the context of the experiment and as described in the initial informed consent" Trouet explains. "The legislator balanced several interests: the privacy of the individual research subject and the interest of the investigator and that of the other research subjects participating in the same experiment".

There is however one exception to this: when the consent could initially not be obtained due to the emergency of the situation, the participant must have at time of withdrawal the right to request full destruction of all research data collected from him[174].

3.4. Consent and the type of clinical trial

Interventional versus non-interventional

The LEH first of all distinguishes interventional from non-interventional trials.

- Non-interventional trials are defined as: "Research in which medication is prescribed as usual, in accordance with the requirements as established under the licence for the introduction of the medicinal products on the market. Patient selection to a therapeutic strategy is not in advance determined by a research protocol, but depends on standard medical practice. The decision to prescribe a medication is taken independently from the decision to engage the patient in the experiment. The patient does not have to undergo extra diagnostic or control procedures. For the analysis of the results epidemiological methods are used"[175].
- All other trials are assumed to be interventional.

[172] Proposal for a Clinical Trials Regulation, 2012/0192, consideration 23 and article 32.
[173] C. Trouet, 2007, Clinical Trials in Belgium, Intersentia, Antwerp – Oxford, 135.
[174] Amendment No. 73 of Y. Avontroodt c.s., *Parl. St.* Kamer, 9 March 2004, 0798/004.
[175] Art 2, 8° LEH

For interventional trials, the LEH foresees certain specific requirements, but this does not affect the informed consent form in any other way than a difference in description of the type of trial. The most important difference is that for interventional trials an additional permission needs to be obtained from the minister[176].

Single centre versus multi-centre trials

A single centre trial is defined as: "an experiment conducted following one protocol and on a single location"[177]. A multi-centre trial on the other hand is: "an experiment conducted on the basis of one protocol, but at different locations en consequently by multiple researchers. It may concern locations in one Member State or in different Member States or countries"[178]. The difference is particularly important for the choice of ethical committee.

3.5. Rights of the clinical trials subject

The protection of the clinical trial subject is the essence of the LEH. Article 4 of the law refers explicitly to the Good Clinical Practices and article 5 enumerates nine basic principles to which each experiment has to adhere. These nine principles are very similar to those mentioned in the Clinical Trials Directive and include, as already mentioned,

- the right to consent
- the right to get more information at a contact point
- the right to further discuss the trial with the investigator or a member of the research team
- the right to withdraw his consent at all times without negative detriment.

3.6. Authorisation of the informed consent forms by ethic committees and competent authorities

In Belgium two authorities have a role to play in the approval of clinical trials: the ethic committee and the ministry of public health.

Ethics Committee

[176] Chapter IX LEH.
[177] Art 2, 13° LEH
[178] Art 2, 14° LEH

Ethics Committees can under Belgian law be established by a hospital, a medical faculty or research fund or the Scientific Association of General Practitioners. No matter to which institution the Committee is linked, it does however have to be an independent body. Additionally, the Ethics Committee has to prove it assesses a minimal amount of protocols per year:

- 5 new protocols of multi-centre experiments as single Ethics Committee;
- or 20 new protocols of multi-centre experiments as single or non-single Ethics Committee.

The Minister for Public Health recognizes Ethics Committees for 3 years[179].

The most important task of the Ethics Committee is to advise the investigators and sponsor prior to the start of their experiment. Part of this advice focuses on the informed consent procedure and form. Next thereto the Committee will also check the adequacy and completeness of the information provided to the participants.

Minister for Public Health

When the trial concern an interventional trial involving medicinal products, an authorization from the minister for public health is required prior to the start of the trial[180]. In practice and following the Royal Decree of 30 June 2004 as modified by the royal decree of 18 May 2006 implementing the LEH for clinical trials involving medication for human use, this task is executed by the Research & Development department of the Directorate-General Medicinal products. The informed consent form needs to be submitted for approval as part of this procedure[181].

Last but not least it has to be noted that the fact that some types of Clinical trials may not be subject to the LEH, this does not automatically imply that these trials are not subject to control. Either the sponsor can choose to ask for approval by an Ethics Committee or they can be submitted for approval based upon the Code of Conduct of the pharmaceutical industry[182].

[179] Art 2, 4° LEH

[180] Art 10, 2° and 3° and art 12 LEH.

[181] A. Vijverman, "Medische experimenten op mensen. De wet van 4 mei 2007 en haar toepassing in de praktijk: De krachtlijnen en het toepassingsgebied van de wet", T.Gez. 2005-2006, 1-21.

[182] C. Trouet, 2007, Clinical Trials in Belgium, Intersentia, Antwerp – Oxorfd, 135p

4. Consent for data processing

4.1. Data protection framework in Belgium

Data Protection Act

The Data Protection Act of December, 8th 1992[183] (hereinafter DPA) transposes the European Data Protection Directive into Belgian law. The intended purpose of the DPA is to protect personal data when automatically processed. This protection is a part of the right to privacy as safeguarded in article 22 of the Belgian Constitution.

Law on Patient Rights

The second important Belgian law protecting patient data is the already mentioned Law on Patient Rights[184]. The Law on Patient Rights protects the patient in his relation with health practitioners by granting a number of rights. Examples of such rights are the right to free choice of practitioner, the right to good care and the right to information, the right to a carefully maintained and securely stored patient file, as well as the right to privacy. For the latter the Law on Patient Rights refers to the Data Protection Act[185].

4.2. Data subject

The data subject is the identified or identifiable person whose data have been processed[186].

Article 1 §1 DPA includes the definition of data subject in the definition of personal data as follows: " *for the application of this law, 'personal data' is every information concerning an identified or identifiable natural person, hereinafter called 'the data subject'; a person is considered identifiable when he or she can directly or indirectly be identified, more specifically by using an identification number or one or more specific elements characterizing for his or her physical, physiological, mental, economical, cultural or social identity.*"This definition is a more or less literal translation of the definition as provided in article 2 (a) Data Protection Directive.

In order to determine whether or not a person is identifiable, one should take into account all the means which reasonably might be used to identify the data subject. For instance, the data subject is no longer considered identifiable if identification would require an unreasonable amount of time and effort. Factors that may be taken into consideration when evaluating whether or not the data subject is identifiable are for instance the type of information, the

[183] Wet van 8 december 1992 tot bescherming van de persoonlijke levenssfeer ten opzichte van de verwerking van persoonsgegevens, *BS* 18 maart 1993.
[184] Wet van 22 augustus 2002 betreffende de rechten van de patiënt, *BS* 20 december 2002.
[185] Art 10 LPR.
[186] Art 2, a) DPD and art 1 §1 DPA.

knowledge which one has already, the structure of the data set, the available techniques, the nature of the data and the number of characteristics that are processed. Again, this shows the Belgian interpretation does not differ greatly from the European interpretation.

4.3. Personal data and sensitive personal data

"Personal data" is defined by the DPA as "any information relating to an identified or identifiable natural person"[187] and is considered to be very broad. Any type of information that pertains to an individual is considered personal data. For example, not only text, but also photos and even sound qualify as personal data.

The Belgian Data Protection Act has instituted several separate restrictions and requirements for the processing of what are called "*special categories of data*". Special categories of data include personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership and the processing of data concerning health or sex life. The processing of such data is, as a rule, prohibited[188]. Different from the European Data Protection Directive, however, the Belgian Data Protection Act provides two separate articles for the processing of health data on the one hand (article 7) and for the processing of other sensitive data on the other hand (article 6).

The exemptions foreseen for the processing of health data are included in article 7 of the Act. The general prohibition to process health data does not apply in case of one of the following exemptions:

a) the data subject has given his **written consent** to the processing of those data; provided that the data subject may withdraw his consent at all times […];

b) the processing is necessary for the purposes of carrying out the obligations and specific rights of the controller in the field of **employment law**;

c) the processing is necessary to accomplish a goal established by or by virtue of a statute designed for the administration of the **social security**;

d) the processing is necessary for the **promotion and protection of the public health**, which includes medical examination of the population;

e) the processing is rendered **mandatory by a law**, regional decree or ordinance, or edict for reasons of considerable public interest;

[187] Art 1 §1 DPA.
[188] Art. 6, 7 and 8 DPA.

f) the processing is necessary to **protect the vital interests** of the data subject or of another person where the data subject is physically or legally incapable of giving his consent;

g) the processing is necessary **to prevent a real danger** or to suppress a particular criminal violation;

h) the processing relates to data which are **manifestly made public** by the data subject;

i) the processing is necessary for the establishment, exercise or defence of a **legal claim**;

j) processing of the data is required for the purposes of **preventive medicine, medical diagnosis, the provision of care or treatment to the data subject or a relative, or the management of health-care services**, and where those data are processed under the supervision of a health professional;

k) the processing is necessary for **scientific research** pursuant to the conditions set forth by Royal Decree […].

4.4. Consent

The Belgian Data Protection Act defines the concept of 'consent' as "every freely given, specific and informed indication of the data subject's wishes, with which the data subject or his legal representative accepts that personal data concerning the data subject will be processed"[189]. In other words, the DPA requires the fulfilment of three cumulative conditions: free, specific and informed. Next thereto and different from the European Directive, the Belgian DPA requires the consent for the processing of health data to be in writing. The legality of this provision could be challenged in the light of the Directive and the freedom to transpose given to the Member States, but this has not been the case up until now[190].

Consent must be given freely

'*Free*' consent means a voluntary decision, by an individual in possession of all of his faculties, taken in the absence of coercion of any kind, be it social, financial, psychological or other[191]. Any consent given under the threat of non-treatment or lower quality treatment in a medical situation cannot be considered as 'free'. Consent given by a data subject who has not had the

[189] Art. 1 § 8 DPA.

[190] See for example: C-468/10 - ASNEF et FECEMD, available online at: http://curia.europa.eu/juris/celex.jsf?celex=62010CJ0468&lang1=fr&lang2=DE&type=NOT&ancre=

[191] H. Nys en I. Vinck, Nieuwe wetgeving inzake patiëntenrechten, 2003, Kluwer Mechelen.

opportunity to make a genuine choice or has been presented with a *fait accompli* cannot be considered to be valid either[192].

Consent must be specific

'*Specific*' consent must relate to a well-defined, concrete situation in which the processing of medical data is envisaged. Therefore a 'general agreement' of the data subject e.g. to the collection of his medical data for an EHR and to subsequent transfers of these medical data of the past and of the future to health professionals involved in treatment would not constitute consent in the terms of article 1 DPA.

Consent must be informed

To give an '*informed*' consent entails the consent is given only after being provided with the necessary information to counterbalance the advantages and risks arising from the agreement to process personal (medical) data. In other words, the data subject has to be able to fully appreciate and understand the facts and implications of an action. Moreover, the data subject also has to be aware of the consequences of not consenting[193]. Therefore transparent and accurate information has to be provided in a clear and understandable manner on for example the nature of the data processed, purposes of the processing, the recipients of possible transfers, and the rights of the data subject. This includes also an awareness of the consequences of not consenting to the processing in question. Vague or general phrasing is thus not sufficient, as it will not enable the data subject to make such an analysis. Consequently the information will have to be provided at the latest before the data processing starts.

Article 9 of the DPA states that if the personal data is obtained with the subject data himself, the controller has to provide him with [at least] the following information elements:

- name and address of the controller and, if such is the case, of his representative;
- the specific purposes of the processing;
- the existence of a right to object on request and free of charges against the intended processing when personal data are obtained for purposes of direct marketing; in that case, the data subject has to be informed before the personal data are for the first time disclosed to a third party or used for purposes of direct marketing on behalf of third parties.

[192] Article 29 Working Party "Opinion 323/2007 on the processing of health data in electronic health records (EHR)" (WP 131).

[193] T. LEONARD and Y. POULLET, "La protection des données à caractère personnel en pleine (r)evolution. La loi du 11 décembre 1998 transposant la directive 95/46/CE du 24 octobre 1995 », *J.T.* 1999, 380.

Because of the importance of the transparency principle in the DPA, it is furthermore advisable to also provide the next information elements:

- the recipients or categories of recipients of the data;
- whether or not obliged answer and the possible consequences; and
- the existence of the right of access to and the right to rectify his personal data.

Finally, a few additional information elements have to be included in the informed consent when dealing with medical data:

- the reason why you want to process the selected data (art. 26 Royal decree);
- the list of authorized users or categories of authorized users who have access to the data (art. 26 Royal decree);
- the legal basis on which is relied for this data processing to the data subject or the Belgian privacy commission) (art. 25, 4° Royal decree).

Consent must be in writing

Although the European Data Protection Directive only requests an explicit consent when processing health data, the Belgian legislator chose to explicitly demand a '*written*' consent. Article 7 DPA states clearly that the consent of the data subject has to be in writing when processing health data. No explicit reason for this choice is mentioned in the preparatory works.

This implies that in order for e-consent to be valid under Belgian law the use of qualified electronic signatures is obligatory. A procedure using the Belgian electronic identity card is the most obvious method to apply. Not only is the eID obligatory for each civilian, also the eHealth platform (Belgium's public institution charged with the organisation of electronic services and information exchange in health care) relies on the eID for authentication and authorisation procedures[194].

4.5. Consent for the use of retrospective data

Belgian Data Protection law provides several possibilities to use personal health data for scientific research. A distinction has to be made between the use of retrospective data in a way compatible with the original purpose of the processing and the re-use of retrospective data.

[194] For more information see www.ehealth.fgov.be. Information available in Dutch and French only.

When the collection of retrospective data is the original purpose of the data processing or is compatible with the original purpose and within the reasonable expectations of the data subject, normal data protection rules apply. Informed consent will thus have to be obtained from the data subject as described above. Additionally the law emphasizes that "appropriate safeguards should be foreseen", but does not specify what they are[195].

When retrospective data are in second instance *re*-used for clinical trials or other scientific research, not only "appropriate safeguards" have to be taken, but specific provisions are foreseen. These specific provisions can be found in Chapter II (concerning the secondary use of personal data for historical, statistic or scientific purposes) of the Royal Decree in implementation of the Law of 8 December 1992 on Privacy Protection in relation to the Processing of Personal Data of 13 February 2001. This Royal Decree provides a gradual system from (1) anonymous to (2) encoded to (3) non-encoded personal data. The conditions applying to each of the steps increase in strictness[196].

- When only using anonymous data for the retrospective research the Data Protection Act does no longer apply and a new informed consent is thus not required.
- When using encoded (pseudonymised) data only, the Royal Decree does not require an informed consent either, but does impose an obligation to inform the data subject.
- When non-encoded data are retrospectively used, informed consent or re-consent does need to be obtained from the data subject.

It should be noted that retrospective non-interventional clinical trials are excluded from the above discussed Law concerning Experiments on the Human Person. Nevertheless, these trials too are subject to data protection regulations.

4.6. Rights of the data subject

The data subject has first of all the right to access the informed consent document at all times and receive all the information concerning the data in the consent. In contrast with the consent for care this duty to provide information does not entail an active duty for the controller. The information only needs to be provided when the data subject addresses an explicit request to the controller.

Apart from the right to access, the data subject is also granted the right to withdraw his consent at all times[197]. Although the data subject can never demand the controller to assign a

[195] Art 4 DPA.
[196] D. DE BOT, *Verwerking van Persoonsgegevens*, Antwerpen, Kluwer, 2001, 101.
[197] Article 5, a) DPA and article 7, §2, a) DPA

retroactive effect to his withdrawal, it does entail that the informed consent is no longer a valid legal basis and no more data can be processed. It entails also that all the previously processed sensitive data have to be deleted[198].

4.7. Supervisor Authorities and their role

The informed consent form for data processing is in Belgium not subjected to prior authorization from supervising authorities. It may however happen that an Ethics Committee retrieves the form when assessing a clinical trial.

Data Protection Authorities, in Belgium the Commission for the Protection of Privacy[199], do in general not request the informed consent form for prior authorization. Such a request may be formulated when explicit authorization is required by one of the Sector Committees, but in all other cases a notification of the data processing to the Commission is sufficient. Within healthcare this general rule implies that the informed consent forms will always be subject to the evaluation of the Sector Committee for Health since the processing of health data always needs to subjected to approval of that Sector Committee. However, in the limited number of cases where the Sector Committee was actually consulted, it happened that they approved the data processing without approving the informed consent form because they only judge the data processing aspects, not the clinical aspects[200].

[198] See D. DE BOT, Verwerking van persoonsgegevens, Antwerpen, Kluwer, 130 and 144

[199] www.privacycommission.be

[200] See for example Beraadslaging nr 11/067 van 20 september 2011 met betrekking tot de latere verwerking van persoonsgegevens die de gezondheid betreffende door de onafhankelijke ziekenfondsen met het oog op het informatief aanschrijven van leden die in aanmerking komen voor deelname aan een gezondheidsgericht begeleidingsprogramma, 8.

IV Study of the legal framework for informed consent within the national legislation of Germany

1. Legal majority age and capacity to consent

The question of capacity to consent to any intervention in one's own fundamental rights, thus the right to dispose over these fundamental rights, is one of the essential dogmatic questions of German constitutional law. While a general existence of such capacity can be deduced from art. 2 I of the German Constitution[201], granting the fundamental right to free development of one's personality and, thus, the freedom of choice, the academic legal controversy focuses on the limits of such freedom. Consequently, it basically comprises two very closely related sub-questions:

a) How far does each fundamental right hold an indefeasible core which cannot be affected under any circumstances and hence cannot be subject to any disposition by the right holder;
and

b) How far - beyond that - will lack of age and of maturity limit the individual, who is the subject of those fundamental rights in disposing over them.

The latter question, particularly, has been subject to continuous legal controversy since the very early days of German Constitution back in the 1950s[202], as the constitution does not provide any such provisions. More than six decades later, hence, approaches and conclusions are manifold. The debate has let emerge the term "Grundrechtsmündigkeit"[203] as a generic name for this dogmatic field, which expresses the maturity to deal with one's fundamental rights.

Additionally, legal capacity as well as legal responsibility of minors in the light of both age and maturity rise fundamental dogmatic questions not only in context of constitutional law, but in many different fields as well, such as penal law and civil law. Nevertheless, these differ

[201] Grundgesetz für die Bundesrepublik Deutschland in der im Bundesgesetzblatt Teil III, Gliederungsnummer 100-1, veröffentlichten bereinigten Fassung, das zuletzt durch Artikel 1 des Gesetzes vom 21. Juli 2010 (BGBl. I S. 944) geändert worden ist, hereafter GG. Available online in English: http://www.gesetze-im-internet.de/englisch_gg/index.html

[202] As an example might serve, Krüger, Grundrechtsausübung durch Jugendliche (Grundrechtsmündigkeit) und elterliche Gewalt, (ExerciseExcersise of Fundamental Rights by AdolescentsAdolescentes and Parental Authority), FamRZ 1956, 329 ff.

[203] Nadja Michael, *Forschung an Minderjährigen : verfassungsrechtliche Grenzen* (Berlin: Springer, 2004), 90.*Forschung an Minderjährigen*, 90.

significantly and cannot be taken directly to draw any conclusions regarding fundamental rights.

German Civil Code[204] itself may serve as a good example for the fact that beyond age and maturity of the subject, the context of any particular provisions and their particular purposes shall be taken into account when considering capacity of disposition. Thus, provisions of contract law establishing limitations for minors to conclude contracts serve different antagonistic interests of the parties addressed. Firstly, minors shall be protected against economic disadvantages following decisions and legal statements, the consequences of which he or she might not yet be able to foresee. Secondly, the very same minors shall not be limited more than necessary in their legal and economic freedom, which is also particularly to enable learning to deal with the particular and typical threads involved. Thirdly, adults potentially dealing with minors shall be protected to the extent that there shall be transparent and clear rules defining cases in which contracts allegedly concluded with minors shall be in fact void or at least temporarily non-effective.

For this purpose, the legislator introduces a subtly balanced system of scales and age limits to encounter the aforementioned set of issues. However, as it comes to tort law (hence still civil law), scales of maturity and responsibility of minors already differ significantly. The reason for that is, obviously, that understanding risks and consequences of own actions as well as the need of protection has to be judged differently in case of damages caused by a minor than in case of conclusion of contracts.

This being said, it becomes evident, that general rules on majority and capacity by civil law (or any other field of law) cannot simply be taken as scales for creating such rules in context of constitutional law, more precisely fundamental rights. However, they may serve as a first point of orientation which afterwards has to be looked at critically and possibly be adjusted.

§ 2 BGB defines that legal majority arises from the completion of the eighteenth year of life, thus a minor becomes of legal age on his or her eighteenth birthday. The age of legal majority as provided for by § 2 BGB not only shows relevance in civil law, but also beyond, e.g. constitution defines in Art. 38 II GG that eligibility follows legal majority, thus implicitly referring to § 2 BGB.

Consequently, any person of legal age does not face any limitations regarding legal actions, as long as no particular circumstances such as learning disabilities require particular protection of such individual. Beyond the age of eighteen one more age limit is of legal relevance, referring to

[204] Bürgerliches Gesetzbuch in der Fassung der Bekanntmachung vom 2. Januar 2002 (BGBl. I S. 42, 2909; 2003 I S. 738), das zuletzt durch Artikel 1 des Gesetzes vom 27. Juli 2011 (BGBl. I S. 1600) geändert worden ist, hereafter BGB or German Civil Code, available online in English: http://www.gesetze-im-internet.de/englisch_bgb/index.html

the age of 21. This, however, concerns few particular cases, such as criminal procedure law (under which adults between 18 and 21 can be treated similar to minors under certain circumstance) or isolated provisions of criminal code, such as § 182 III StGB[205], which applies only on individuals of twenty-one years of age and older.

As a result, any adult having reached the age of eighteen years is capable to consent, including disposing over protection given by fundamental rights (as far as this disposition as such can be legal, see above[206]). A first conclusion therefore is, that any adult of eighteen years and older who does not suffer from any dysfunction affecting his or her freedom of choice is capable to consent to any medical treatment as well as to participation in any clinic trial. In addition and as a consequence of Art. 2 I GG, he or she shall not face any limitation in giving such consent, as far as no rights of thirds are affected. Therefore, any individual of legal age is not only capable of consenting autonomously but in addition any statement of third party cannot override the individual's autonomous choice. The capacity of an adult to consent to medical treatment and participation in clinical trials therefore is absolute.

Below the age of eighteen many different rules on responsibility and capacity apply in context of different legal fields. Constitution itself only refers in Art. 38 II GG to the age of eighteen as age limit for the right to vote (and to legal age as such, being nowadays the age of eighteen, too, as age limit for eligibility; see above).

Under the rule of civil law minors have a limited legal capacity to contract (§ 106 BGB), which is further specified in §§ 107 – 113 BGB and do not provide for any further particular age limits. Legal responsibility under the rule of civil tort law (§§ 823ff. BGB) begins with the age of seven (§ 828 I BGB) respectively ten years (unintended accidents in traffic, § 828 II BGB) under the precondition that the minor is capable and mature enough to recognize his or her responsibility (§ 828 III BGB). Under the rule of criminal law any individual of fourteen years and older is responsible (§ 19 StGB), while sentences will not be the same for minors as for adults, depending on the particular rules of the criminal procedure code.

As can be seen, provisions on age limits below legal age differ significantly depending on systematic context and purpose of the respective provisions.

In context of fundamental rights this leads back to the controversy originally referred to and in which three major streams can be identified[207].

[205] Strafgesetzbuch in der Fassung der Bekanntmachung vom 13. November 1998 (BGBl. I S. 3322), das zuletzt durch Artikel 1 des Gesetzes vom 6. Dezember 2011 (BGBl. I S. 2557) geändert worden ist, hereafter StGB, available online in English: http://www.gesetze-im-internet.de/englisch_stgb/index.html

[206] Limitations might, for example, occur, when the disposition has an effect on the human dignity of the acting individual.

[207] A good overview can be found at: *Jickeli* / *Stieper*, in: Staudinger, BGB, vor § 104, Rn. 102.

From the lack of provisions on age limits in context of fundamental rights within the constitution itself, it has been concluded that any minor being factually capable to exercise his or her fundamental rights is legally capable to do so, too[208].

In opposition to this approach some have seen legal age as it is provided by the civil code as a general age limit for legal statements which *e contrario* rule out any disposition over fundamental rights by minors[209].

A third stream differentiates between different fundamental rights and provides manifold approaches to identifying legal capacity in context of particular fundamental rights[210].

Against the second approach it can be argued that such approach neither recognizes the particular relation between state and citizen nor does exercising fundamental rights typically involve such contractual actions as referred to primarily by the civil code[211]. Beyond that, scope and purpose of protection as provided by civil law are of fundamentally different nature. The question whether the parents as legal representatives of a 17 year old should be entitled to conclude contracts for the minor is likely to have to be measured by differently than the question whether the same parents shall consent to a particular medical treatment or participation in clinical trials, possibly opposing the will of their child.

Likewise, assumption of legal capacity to exercise fundamental rights with the moment of factual capacity to do so – thus, e.g., granting the minor the right to take part in a demonstration from the age, at which the minor is physically capable to do so, regardless of any consent of his or her legal representatives – faces certain objections. In certain cases, particularly in context of medical treatment and of clinical trials, exercising fundamental rights involves facing particular risks, the consequences of which a child or an adolescent might not yet be capable to foresee and judge. Growing up as a process of learning and development involves gaining capacity to freely decide. Neither is such capacity given by the moment of birth nor will it be lacking entirely until the very moment of reaching legal age. As a result, capacity to consent has to follow the development of each adolescent and may differ regarding different fundamental rights and different particular cases. In this regard, the third of the streams

[208] Jarass, Hans, and Bodo Pieroth. *Grundgesetz für die Bundesrepublik Deutschland*. 11. Aufl., [Rechtsstand: 1.4.2010] ed. München: Beck, 2011, Art.19; Hohm, Karl-Heinz. "Grundrechtsträgerschaft und Grundrechtsmündigkeit Minderjähriger am Beispiel öffentlicher Heimerziehung" NJW (1986), 3107; Robbers, Günther. "Partielle Handlungsfähigkeit Minderjähriger im öffentlichen Recht" DVBI (1987), 709.

[209] Rüfner, in: HdbStR V § 116 Rn 23, Bleckmann, Staatsrecht II – Die Grundrechte4 § 17 Rn 12.

[210] Joachim Martens, Grundrechtsausübung als Spiel ohne Grenzen?, NJW (1987), 2561; Starck, in: Starck, Christian, Mangoldt, Hermann von, Klein, Friedrich, Kommentar zum Grundgesetz, 6. Auflage München 2010, Art. 1. Abs. 3, Rn. 186; Schwerdnet, Eberhardt, Kindeswohl oder Elternrecht? Zum Problem des Verhältnisses von Grundrechtsmündigkeit und Elternrecht, AcP 173 (1973), 227, 241 ff.

[211] Jickeli / Stieper, in: Staudinger, BGB, vor § 104, Rn. 103.

mentioned above provides the approaches which appear to be most adequate for building up fair criteria in context of capacity to dispose over fundamental rights.

However, fundamental rights as laid down in the German constitution have been widely recognized as rights which are only governing the relation between the subject and the state and its authorities. A direct effect of fundamental rights between individuals ("unmittelbare Drittwirkung") has been denied by the wide majority of authors participating in the legal controversy and has not been recognized by the Constitutional Court (Bundesverfassungsgericht). For this reason, fundamental rights can neither govern the relation between a minor patient and his or her parents nor between such patient and the responsible for a particular clinical trial.

They do, however, oblige the legislator to shape both legal relations in a way which corresponds with the fundamental rights of the individuals involved. In context of clinical trials this is achieved by § 40 IV AMG[212]. The provision thus not only transposes art. 4 of the Clinical Trial Directive, but also establishes the legal balance of both the fundamental rights of parents and the child deriving from art. 2 I of the German Constitution in combination with its art. I 1 (for the minor) and art. 6 II (for the parents) as well as balancing freedom of choice respectively self-determination of the minor and protection of the very same, which is necessary to assure attainment of the fundamental right's purpose.

Consequently, § 40 IV AMG primarily entitles legal representatives of the minor to consent for him or her after having been informed, while following the minor's presumed will. The minor has to be informed adequately corresponding to his or her age and intellectual maturity. If the minor expresses his or her will not to participate in the trial this decision has to be respected. If the minor has the capacity to recognize nature and consequences of the particular clinical trial his or her informed consent are required as well.

This approach taking into account intellectual maturity and capacity to self-determination of the minor forms a concrete transposition of the constitutional principles described above. It corresponds with the transition from a young child being in need of complete protection and not yet capable of deciding for itself to a mature and experienced adult fully capable of forming an autonomous will and thus no more in need of protection. It additionally considers individual level of development, thus not following any inflexible age limits apart from legal age at eighteenth birthday.

[212] Medicinal Products Act - Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. I S. 3394), das zuletzt durch Artikel 1 der Verordnung vom 19. Juli 2011 (BGBl. I S. 1398) geändert worden ist, hereafter Arzneimittelgesetz – AMG;

The approach, however, does not allow a particularly mature and grown up adolescent to fully consent autonomously. Though such minor can prevent his or her participation in clinical trials against the will of his or her legal representatives, he or she cannot, oppositely, participate, if the parents do *not* consent. As a result, protection of the minor always prevails, be it on initiative of the parents or on initiative of the minor himself. Consequently, the minor becomes only fully autonomous in exercising this particular fundamental law when of legal age. Taking into account the particular risks of clinical trials, this decision of the legislator should, nevertheless, not face any constitutional concerns.

2. Consent for care

Consent is of crucial importance in understanding of both medicine and law. In medicine it constitutes the core of the physician-patient relation. In law, it is what makes the difference between an illegal assault and an acceptable medical intervention. Understanding of consent as eliminating the illegality of intervention into the physical integrity dates as far back as year 1894 where the Reichsgericht (German high court at the time) found[213] that an operation was an aggravated battery in understanding of German Penal Code, as patient's consent was missing.

Today the principle of consent is deeply rooted through the entire German legal system. Based in German Constitution, of which art. 2 states that „Every person shall have the right to life and physical integrity" the protection continues through the Civil Code (Sec. 823) and Penal Code (Sec.223) which both offer protection to the body, health and freedom of a person. Civil Code explicitly puts the above-mentioned rights in the disposition of the right owner[214] and allows him to make a decision over intrusion into his private sphere. That is the purpose of consent, upon which, in year 1989, BGH elucidated:

> *"Consent to a medical intervention implies that the patient waives the right to absolute protection against having a physical injury committed upon himself or herself, within the scope of the proposed intervention. Furthermore, the patient assumes the risk of the side effects and possible complications of treatment. If valid consent is lacking, the medical intervention is an unlawful violation of the patient's bodily integrity."*[215]

[213] RG, 31.95.1894, 1406/94

[214] Erwin Deutsch, *Medizinrecht : Arztrecht, Arzneimittelrecht, Medizinprodukterecht und Transfusionsrecht* (Berlin : Springer, 2008), 132.

[215] BGH VersR 1989, 851. The English wording of the decision is taken from :A576–86

The physician should therefore together with the patient establish whether, and if yes to which extent, the eventual treatment or diagnostic procedure should take place – consent is an outcome of this agreement and constitutes a legal and ethical basis of any actions of the doctor.

Generally consent has three distinctive layers[216]:

- Consent for intervention: whenever the physical integrity of the individual is being violated by an operation, a collection of blood sample, or other, patient's consent waives the protection of his physical integrity[217];
- Consent for the risk: by consenting the patient agrees not only to the intervention, but also accepts the risk, which is an inevitable part of any such intervention (though not including potential mistakes) [218];
- Consent for the exhaustive investigation: consent for the collection and inquiry of the patients data[219]

A sine qua non condition for an effective consent is the information, which will allow the patient to make use of his right to self-determination and autonomy. To make use of those rights the patient has to be conscious about his / her choices and their consequences. Information which is given to him / her should be fit to his / her wishes, needs, capabilities and knowledge he possesses. The patient should receive sufficient information to weight, after giving due consideration, reasons for and against the doctor's proposal for treatment or diagnostic.

3. Consent for clinical trials participation

3.1. Legal framework of clinical trials in Germany

Germany does not have one comprehensive regulation on research on human subjects[220], neither has it one comprehensive regulation on patient's and trial subject's rights[221].

[216] Erwin Deutsch, *Medizinrecht*, 134.

[217] Erwin Deutsch, *Medizinrecht: Arztrecht, Arzneimittelrecht, Medizinprodukterecht und Transfusionsrecht* (Berlin : Springer, 2008), 138.

[218] Ohly, *Volenti non fit iniuria*, 244.

[219] Erwin Deutsch, *Medizinrecht*, 134.

[220] Erwin Deutsch, *Forschungsfreiheit und Forschungskontrolle in der Medizin: zur geplanten Revision der Deklaration von Helsinki = Freedom and control of biomedical research* (Berlin; Heidelberg [u.a.]: Springer, 2000), 65.

Furthermore, it should be noted that the Germany is a Federal state, which results in legislative power being divided between the German Federation and the German Lands.[222] This division is also to be seen in the area of clinical trials where the federation is responsible for the medical research in general, while the Lands have in their competence legislation concerned medical professions (as well as all the other professions).

On the federal level regulations on research on human subjects are introduced in different acts[223]:

Medicinal Products Act - Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. I S. 3394), das zuletzt durch Artikel 1 der Verordnung vom 19. Juli 2011 (BGBl. I S. 1398) geändert worden ist, hereafter Arzneimittelgesetz – AMG;

Medical Device Act - Medizinproduktegesetz in der Fassung der Bekanntmachung vom 7. August 2002 (BGBl. I S. 3146), das zuletzt durch Artikel 13 des Gesetzes vom 8. November 2011 (BGBl. I S. 2178) geändert worden ist, hereafter MPG;

Transfusion Act - Transfusionsgesetz in der Fassung der Bekanntmachung vom 28. August 2007 (BGBl. I S. 2169), das durch Artikel 12 des Gesetzes vom 17. Juli 2009 (BGBl. I S. 1990) geändert worden ist, hereafter TFG.

The regulations in the scope of this document are placed in the Medicinal Products Act (AMG), as the 12th amendment of this act from 9 July 2004 introduced to the German law the regulations of the European Clinical Trials Directive. The law covers only clinical trials of medicinal products on human beings and chapter 6 focuses on the control over the clinical trial before its commencement.[224]The amendment brought thorough changes in Chapter 6 – Protection of human subjects in clinical trials. Most importantly it laid upon the investigator, the sponsor and other persons involved in the trial the obligation to comply with the good clinical practices introduced by art. 1 (3) of the Directive. The AMG delegates in sec. 12 Sub-sec. 3 Nr. 2 to the Federal Ministry the power to issue an ordinance ensuring the proper conduct of the clinical trial and the obtention of documents which correspond to the state of clinical knowledge. The mentioned ordinance is the Ordinance on Good Clinical Practice (GCP-V) which is responsible for bringing into the German legal system the Clinical Trials Directive (2001/20/EC), as well as the Directive 2003/94/EC (principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational

[221] Jochen Tauplitz, "Landesbericht Deutschland," in *Die klinische Prüfung in der Medizin Europäische Regelungswerke auf dem Prüfstand = Clinical trials in medicine : European rules on trial*, by E Deutsch (Berlin: Springer, 2005), 139.

[222] Ibid.

[223] Ibid., 140.

[224] Erwin Deutsch, *Kommentar zum Arzneimittelgesetz (AMG)* (Berlin, Heidelberg : Springer-Verlag Berlin Heidelberg, 2010), 419.

medicinal products for human use) and Directive 2001/18/EC (on the deliberate release into the environment of genetically modified organisms).

3.2. Definition of Consent

Chapter 6, sec. 40 of the AMG introduces a set of requirements which are indispensable for clinical trials conduct. As states the official explanatory statement of the AMG,[225] the price of medical development in disease treatment is high risk on the side of research subjects during the testing of medicine products. That requires that all individuals involved in clinical trials as trial subjects need legal protection, the purpose of which shall be balancing risks and achievements.

Chapter 6 is focused on bringing safety and the aforementioned balance into the conduct of clinical trials, by stating the rules according to which the trial may take place. One of the basic instruments aiming to protect the trial subject is the obligation to obtain subject's informed consent.

Despite that the AMG refers to consent, the act itself fails to provide any definition of the term. Thee, German legislator introduces in Sec 3 (2b) of GCP-V, the definition there proposed is identical as a German translation (and so the official version) of the Clinical Trials Directive:

"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 after receiving appropriate documentation[226], 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."

Notwithstanding that the AMG does not define what consent itself is it does oblige the sponsor and the investigator to fulfil a number of requirements needed for obtaining a valid informed consent, defining of those requirements follows in the Sec. 40 Sub- sec. 1.

Those can be divided into a couple of areas: who and when should provide the information, how outstretching the information should be, what kind of additional information the subject has to be made aware of and finally in what form should the consent be given.

The German legislator stresses out the importance of the manner in which the information is provided to the future trial subject (sec. 40 sub-sec 2 of AMG). It requires that the person

[225] Bundestagsdrucksache (BT-DRS)

[226] The English version of the Directive defines consent as „appropriately documented", whereas the German version defines „after receiving appropriate documentation" („nach Erhalt einer entsprechenden Dokumentation").

presenting information has to be the investigator himself (therefore has to be directly involved in the clinical trial) and also his professional background has to be appropriate – only a physician, or in the case of a dental trial, a dentist is allowed to present the information to the participant. After receiving the information (about the scope of information provided see below) the participant should also have an opportunity to have a counselling session with an investigator about any other conditions surrounding the conduct of the clinical trial. Finally besides the face- to face explanations the future participant should also receive information in writing.

Only after having received this information the clinical trial subject can be asked for consent. As a rule the consent should be provided in writing, but the legislator does provide an exception for persons who cannot give informed consent in writing – in such a case oral consent is sufficient, but consent has to be obtained in presence of one witness.

Information provided to the trial subject

The scope of information, the trial subject should be provided with, is specified by sec. 40 sub-sec. 2. It is the nature, the significance, the risks and the implications of the clinical trial which shall be made transparent to the future trial subject. While explaining the nature of the trial the investigator shall take specific care to ensure patient's understanding of the experimental nature of the treatment[227] that he or she will undergo. Furthermore, beyond the objective consequences of the trial, true for any possible participant, also the subjective ones, which particularly concern this specific patient, shall be explained and discussed with the patient.[228] By doing so, the discussion should not be limited to medical consequences, but should also clarify any indirect influences on the day-to-day life of the trial subject.

The law is very brief in clarifying the scope of information which should be provided to the participants, therefore as a complementary regulation the document "Basic principles of clinical trials of medicine products on humans" shall be analysed. The paper, which does not have any binding power, was published by the German Ministry for Youth, Family, Women and Health on 19 December 1987. It provides a comprehensive list of topics which should be part of the interview between the investigator and a the trial subject (while the fact that the document is not binding has to be kept in mind):

- Goal and course of the trial,
- Kinds of treatment and allocation of the patients in the treatment groups (for example randomisation)

[227] Erwin Deutsch, *Kommentar zum Arzneimittelgesetz (AMG)*, 428.

[228] Axel Sander, *Arzneimittelrecht: Kommentare*, Loseblatt-Ausgabe. (Stuttgart: Kohlhammer Verlag, 2010), Erl. § 40 AMG 30.

- Possible impacts and risks by pregnancy and for unborn
- Expected outcomes / effects
- Other treatment possibilities
- Possibility of further meetings and clarifications
- Explanation that the informed consent can be revoked at any time.

Moreover, besides providing ample information about the trial the investigator shall also take care to explain the participant his / her right to withdraw from the clinical trial at any time by revoking his declaration of consent. Such a withdrawal can be done before the investigator orally or in writing.

In addition the person has to consent, after being duly informed about the purpose and scope of the recording and use of personal data, especially medical data (further information in Pt. 4.1).

3.3. Rights of the clinical trial subject

Legislator seeks to balance the uneven relation between the trial subject and the investigator by awarding the trial subject with rights which give him / her sufficient control over his / her participation in the trial.

The strongest and therefore most important of those rights is the right to decide whether he or she wishes to take part in the trial at all – the right to consent. The value of this right is put high also by the legislator, as the trial may only be commenced, as writes the Sec. 40 of AMG, when consent, as one of 3 conditions, is fulfilled.

The control of the trial subject over his / her participation continues trough in the course of the trial. At any moment of the trial AMG gives trial subject the right to revoke his / her consent and therefore stop participation. To make consent revocation a realistic option legislator prescribes that a withdrawal from trial should not avail with negative consequences for the participant.

Connected to the right to consent is the right to information. This right is very vast. The law awards the trial participant with two level of rights to information. Firstly, the trial participant should obligatorily be informed on the core information regarding the trial, consent, data processing. Secondly, the participant is also awarded with a right to receive additional information, which the particular participant may find useful – he or she therefore has a right to have not only first obligatory meeting with an investigator, but can also, if that is his / her wish, subsequently meet the investigator one more time to further discuss his / her trial participation

and receive auxiliary information. Also during the trial course the contact person should be available, to whom participants can turn to.

Finally, an important precondition assuring participant's capability of taking advantage of his / her aforementioned rights, is the right to be informed about the fact that he or she possesses these rights as a trial participant.

3.4. Authorisation of the informed consent forms (by ethic committees and competent authorities)

The clinical trials on humans are dependent on fulfilment of very complex legislative requirements – those requirements are than double verified by competent authorities.[229] On the guard of compliance of those requirements stand the ethics committees and federal authorities. As the law states (sec. 40 § 1.) the trial can only begin after a favourable opinion by an Ethics Committee, secondly after an approval of the competent higher federal authority.

Ethics committee

The ethic committees have to be created accordingly to the federal state law(s)[230]. Their main responsibility is to protect interests of the clinical trial subjects and therefore they can, among others evaluate also the informed consent forms.

Sec. 7 of the GCP-V lists of all the requirements of an application which the sponsor has to submit before the commencement of the trial. Among other the list includes a list of all documents which has to be attached to the application for both – the federal authority and the competent ethics committee and additionally lists documents which have to be presented to the ethics committee. Sec. 7 sub-sec. 3. is concerned with the latter and in the point 9 it requires all the information and documentation which the trial subjects are going to receive (in German), as well as an account on the procedure of obtaining informed consent .

Higher federal authority

Sec. 40 does not determine which entity is the competent higher federal authority for authorising clinical trials. That is to be established according to the sec. 77 sub-sec. 2 of the AMG. The section exhaustively names the tasks of the Paul Ehrlich Institute (the Federal Agency for Sera and Vaccines)[231] and the competence for all other medicinal products falls into the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und

[229] Erwin Deutsch, *Kommentar zum Arzneimittelgesetz (AMG)*, 419.
[230] Erwin Deutsch, *Kommentar zum Arzneimittelgesetz (AMG)*, 431.
[231] More information on Paul Ehrlich Institute on the webpage: http://www.pei.de

Medizinprodukte - (BfArM))[232]. Sponsor should therefore request authorisation of the clinical trial from one of the two mentioned entities, accordingly to their competence: The Paul Ehrlich Institute or the Federal Institute for Drugs and Medical Devices

According to the sec. 77 sub-sec. 2 the Paul Ehrlich Institute (PEI) is the competent authority for sera, vaccines, blood preparations, bone marrow products, tissue preparations, test allergens, test sera, test antigens, gene transfer medicinal products, somatic cell therapy medicinal products, xenogenic cell therapy medicinal products and genetically engineered blood components.

Both institutions jointly produced guidelines on application for the authorisation of the clinical trials[233] which present all the important aspects of applying for authorisation. The guidelines, just as the GCP-V do not require from the sponsor to submit the informed consent forms, which should be only presented to the competent ethics committee.

4. Consent for data processing

4.1. Legal framework of data protection in Germany

The German framework on data protection reflects the system of German legislation, with its division between laws legislated on the competence of the Federal Republic and those legislated by the German lands. According to this division there are some areas of law which fall under exclusive legislative power of the Federal Republic, or of the lands, but there are also areas where laws can be enacted on both levels that is, under the so called concurrent competence to legislate (konkurrierende Gesetzgebung).

Also in case of the data protection Federal Republic and German lands share competence. The federal law defines a legal framework for handling of the personal data by the public bodies on the state level and in certain cases on the level of the land, and in case of private bodies.[234] In most of the cases of the controller being a public body of the land it is the data protection act of respective land which will be applicable. The 16 land regulations (similar in many aspects but different in details) will not be analysed in this document, which is only concerned with the federal legislation.

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[232] More information on Bundesinstitut für Arzneimittel und Medizinprodukte on the webpage http://www.bfarm.de/

[233] The guidelines can be found online in both German: http://www2.bfarm.de/bekanntmachungen/3bk_kp.pdf and English: http://www.pei.de/cln_236/SharedDocs/Downloads/EN/pu/klin-pruef/3rd-announcement-en,templateId=raw,property=publicationFile.pdf/3rd-announcement-en.pdf

[234] Marie-Theres Tinnefeld, Eugene Ehmann, and Rainer W. Gerling, *Einführung in das Datenschutzrecht*, Neuaufl. (München: Oldenbourg, 2004), 250.

The main German legal act concerned with data protection is the Bundesdatenschutzgesetz – the Federal Data Protection Act[235].

The first BDSG was introduced in the year 1977 and was a subject of a novelisation in year 1990 which followed the so called Volkszählungsurteil (population census decision) from 1983, further novel was brought by the transposition of the Data Protection Directive on 11 May 2001, of which changes came into force on 23 May 2001.[236] Since then BDSG underwent a number of further novelizations.

The second legal act important for the processing in the clinical trials is the Medicinal Product Act – AMG, which among provisions concerned with the consent for clinical trial demands from the investigator obtaining also the consent for data processing and provides for additional specific rules. The provisions of AMG can be seen as *lex specialis* to the more general norms of the BDSG.

4.2. Data subject

The German law provides a definition of data subject within the section 3, where the "personal data" is defined. The data subject is an individual, whose data is processed and therefore the one about protecting whom the law is concerned.[237] German definition is shorter and more concise than the one provided by Data Protection Directive and does not provide any explanation of what is understood as identifiable.

Sec. 3 sub-sec. 1 states: "Personal data" shall mean any information concerning the personal or material circumstances of an identified or identifiable natural person ("data subject").

The German law, just as the Directive, introduces a division between identifiable and identified natural persons; and understanding of these terms in Germany are similar – as data relating to the data subject should be understood as all that data which has a direct link to the data subject, or through which the link to the data subject can be established.[238]

4.3. Personal data and sensitive personal data

German data protection law follows the Directive's distinction between personal data in general and sensitive personal data in particular.

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[235] Bundesdatenschutzgesetz in der Fassung der Bekanntmachung vom 14. Januar 2003 (BGBl. I S. 66), das zuletzt durch Artikel 1 des Gesetzes vom 14. August 2009 (BGBl. I S. 2814) geändert worden ist, hereafter BDSG. Available online: http://www.gesetze-im-internet.de/bdsg_1990/BJNR029550990.html

[236] Tinnefeld, Ehmann, and Gerling, *Einführung in das Datenschutzrecht*, 249.

[237] Peter Gola and Rudolf Schomerus, *Bundesdatenschutzgesetz BDSG Kommentar*, 9th ed. (München: Beck, 2007), 113.

[238] Ibid., 106.

The definition of personal data in general was quoted above. Within the general category of personal data, sec. 3 sub-sec. 9 introduces additionally '*special categories of personal data'* as a subcategory. Unlike the Directive, the German law formally provides a separate definition for sensitive data, while following substantially the explanations provided in art. 8 of the Directive. Therefore a special protection is offered to *„information on racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, health or sex life.*"

German law introduces also a division in the categories of personal data dividing it on the one concerning personal and other concerning material circumstances of a natural person, the data concerning the person himself / herself is the one which is directly connected to the person itself, their identity and character (such as name, address, date of birth); [239] while the data concerning material circumstances is the data connected to circumstances connected to one (as ownership of land, rapports to other people, or having a telephone conversations).[240] Despite the existence of this division in the German law the borders between those two categories of data are fluent and in the data protection law play no major law, as the law is applicable in the same manner to both of the categories.[241]

4.4. Consent

Section 4a provides the following provisions on consent:

> *"(1) Consent shall be effective only when based on the data subject's free decision. Data subjects shall be informed of the purpose of collection, processing or use and, as necessary in the individual case or on request, of the consequences of withholding consent. Consent shall be given in writing unless special circumstances warrant any other form. If consent is to be given together with other written declarations, it shall be made distinguishable in its appearance.*
>
> *(2) In the field of scientific research, a special circumstance as referred to in subsection 1 third sentence shall be deemed to exist if the defined purpose of research would be seriously affected if consent were obtained in writing. In this case, the information referred to in subsection 1 second sentence and the reasons the defined purpose of research would be seriously affected shall be recorded in writing.*

[239] Ibid., 109.
[240] Ibid.
[241] Tinnefeld, Ehmann, and Gerling, *Einführung in das Datenschutzrecht*, 279.

(3) Where special categories of personal data (Section 3 (9)) are collected, processed or used, the consent must also refer specifically to these data."

As can be seen from the quoted provisions the BDSG provides for formal requirements, but not a definition of consent. Nevertheless consent in data protection is regarded as corresponding to the nomenclature of the German Civil Code (BGB) and should be understood as in the sec. 183, as a prior declaration of agreement[242].

The consent is a manifestation of the constitutional right of informational self-determination[243] and is therefore a fundamental condition of data processing[244] and only specific statutory provisions can enable data collection without it.

4.4.1. Requirements with regard to consent:

Freely given

Consent, according to the German legislator, has to be based on the free decision of the data subject. In that point the German law follows the Directive in expecting not only that the consent has been given, but also requiring that the consent is an actual decision of the data subject. For that reason in judging the validity of consent also the context should be taken into account, only in that case one can speak about consent without coercion (German wording of BDSG "Ohne Zwang").[245]

Nevertheless it is widely seen[246] that, despite the legislative efforts, data subject consent cannot be really freely given whenever the data subject has little choice due to the stronger position of the data controller, or where consent for processing is part of another agreement.

Informed

In order for the consent to be valid it has to be based on information which shall be provided to the data subject – in general the data subject has to be aware to what does he or she consent. Sec. 4 provides a general outline of information which have to be communicated to the data subject – those are the purposes for which the data will be collected, processed and used and, depending on the necessity, or upon request, the consequences of withholding the consent.

In addition Sec. 4 sub-sec. 3 of the BDSG underlines the obligation to explicitly inform the data subject, whenever sensitive data will be collected and explicitly relate to these data. BDSG

[242] Gola and Schomerus, *Bundesdatenschutzgesetz BDSG Kommentar*, 169.
[243] Spiros Simitis, *Bundesdatenschutzgesetz*, 6th ed. (Baden-Baden: Nomos, 2006), 365.
[244] Ibid.
[245] Ibid., 383.
[246] Gola and Schomerus, *Bundesdatenschutzgesetz BDSG Kommentar*, 178; Simitis, *Bundesdatenschutzgesetz*, 383.

follows here the Directive, which requires a special handling of such data[247] – the data subject should be therefore made aware not only that he consents for processing of his data, but that the consent is given for sensitive data.

4.4.2. Formal requirements

Timing

The consent must be given before the initiation of data processing as it is the ground legalising the processing itself.

It should be also noted that belated declarations do not change the illegality of data processing[248] therefore no matter whether the consent was obtained later, or was not obtained at all – for a given period of time the processing has been illegal (as long as no other ground for data processing existed) – any kind of declaration given after the start of data processing cannot change this illegality, it can only have influence on eventual claims[249]

In writing

The Data Protection Directive requests from the controllers obtaining "explicit consent" – in that formal requirement the German legislator is much stricter as in every case of consent for data processing the controller should obtain consent in writing.

In case the consent for data processing is obtained together with other written declarations the legislator requires that it is "distinguishable" from the other parts of the declaration. That shall secure, that data subject fully understands that the consent is a separate declaration of will. Furthermore, as writes Simits,[250] due to this fact, consent should not be incorporated to any kind of general explanatory documents.

As a general rule BDSG requires fulfilling high formal requirements by obtaining consent for each data processing in writing, but provides also an exception where special circumstances justify other form. The legislator does not specify those circumstances and therefore allows for using this clause in abstract cases.

The only case which was specified in BDSG is scientific research. The law allows consent not in writing whenever a "defined purpose of research would be seriously affected" by requesting consent in writing. However loosening from this formal requirement at the same time obliges the researchers to, in writing, document reasons why the purpose of research would be affected by obtaining written consent. Together with that also the purpose of collection,

[247] Simitis, *Bundesdatenschutzgesetz*, 389.
[248] Ibid., 373.
[249] Ibid.
[250] Ibid.

processing or use of data and the consequences of withholding consent should be documented in writing.

4.4.3. Consent for Processing of Retrospective Data

As mentioned in the chapter before consent has to be given before the beginning of the processing – any later given consent does not legalise the processing which has started before. The consent for processing of retrospective data therefore needs to be based on an assumption that a collection exists which was legally collected for a single purpose. One of the main rules of data protection law is that the data collected for a specified and lawful purpose shall not be processed for other purposes – in Germany this rule is known as "Zweckbindungsgrundsatz" – the principle of dedicated use.[251] that rule binds the data collected to the original purpose of collection and defines that any use which would not be done accordingly to the original collection purpose is illegal.[252]

However German law enables use of already existing data for a new purpose (notwithstanding whether they were collected or saved) in a number of cases. The always applicable ground for using or processing data for a new purpose is consent. Additionally in connection with medical research one can consider provisions with regard to public bodies (Sec. 14) and private bodies (Sec. 28).

Sec. 14 and 28 accordingly allow, among others, to change the purpose of recording, alteration or use of data when it is necessary for scientific research, whenever in addition the scientific interest in carrying out the research project significantly outweighs the data subject's interest in ruling out the possibility of collection and the purpose of the research cannot be achieved in any other way or would require a disproportionate effort (sec. 14 sub- section 2, point 9).

4.4.4. Specific provision for processing by research institutions

German law provides a section which is focused only on processing and use of personal data by research institution. It provides rules on the conduct of research.

Firstly it constrains the possibility of use or processing of the data which originally were collected for research – it is strictly forbidden to use it or process it for any other purpose than scientific research. Therefore it is an exemption from the general rules (in sec. 14 and sec. 28) which allow (after fulfilling specific conditions) for alteration of purpose of the data processing. Sec. 40, which is concerned with specific norms for processing and use by research institutions, requires them in addition to render all the personal data anonymous as soon as the research

[251] Jürgen Kühling, Anastasios Sivridis, and Christian Seidel, *Datenschutzrecht* (Hüthig Jehle Rehm, 2011), 237.

[252] Hans-Jörg Bullinger and Michael ten Hompel, *Internet der Dinge: Www.internet-der-dinge.de* (Dortmund: Springer, 2007), 374.

purpose allows it. Until then the means allowing identification should be kept separately from the original body of data to secure the information collected. The information should be combined only for the research purpose.

Finally the personal data of data subjects can only be published once the consent of the data subject has been obtained, or in case of research on events of contemporary history – to present their outcomes, when the personal information is essential to them.

4.4.5. Consent according to AMG

Whenever a clinical trial is commenced AMG – German law specified on the conduct of clinical trials on medicine products[253] requires and regulates not only consent for participation in clinical trials but also obtaining consent for the reasons of collection and processing of data. Therefore for clinical trials provisions of sec. 40 of AMG have to be considered *lex specialis* for the general provisions of BDSG.

The AMG does not explain the rules of data protection for clinical trials, but focuses only on the consent and its prerequisite.

Art. 40 states, among others, that the clinical trial can only be conducted where consent referring specifically to the collection and processing of health- related data has been given.

Prior to obtaining consent for the aforementioned reasons data subject needs to be provided with information about purpose and scope of the recording and use of the data, especially the medical data (which is very much in accordance with the information duty, which is introduced in BDSG). In addition the person should be informed about the eventuality that also other bodies may have access to the data during the conduct of inspections of the trial conduct, and in its pseudonymised form during scientific evaluation, obtaining marketing authorisation and that in case of undesirable events these pseudonymised data will be submitted to an European database. Furthermore the person should be made aware about irrevocability of consent for data processing and consequences of revoking of the consent for participation in clinical trial for the personal data collected[254].

4.5. Rights of the data subject

The Data Protection Directive awards data subjects with a number of rights and German legislator follows that approach and therefore the data subjects have also in Germany similar rights as the ones offered by the Directive. The general framework of data subject's rights is

[253] See 3.1 Legal framework for clinical trials in Germany
[254] 4.5 Rights of the data subject.

defined in sec. 6 of BDSG where the rights of access and rights to rectification, erasure and blocking are named. Those rights are what guarantees data subject's factual control over the data and assures the informational self-determination.[255]

Right of access allows the data subject to confirm whether and what kind of information are kept about him by the data controller, this as a consequence, allows the data subject to control whether processing of the data takes place legally.[256] Upon a request data subject shall receive information on recorded data and their source, the recipients of this data and purpose of the data[257].

Right of access enables making use of the other rights given in art. 6 – rectification (if the data is inaccurate), erasure (if unlawfully recorded, or no longer needed), and blocking (if erasure is not possible due to legal or practical reasons).

Furthermore sec. 6 safeguards the data subject rights by excluding the possibility to diminish the aforementioned rights by contracts of any kind.

Right to revoke consent

BDSG does not explicitly grant data subject the possibility to revoke consent, neither it does remark the revocation at any other way. However it is argued[258] that withdrawal has the same function as the consent itself and, just as the consent, aims at awarding the data subject with the right to control the flow of his / her data. Therefore the data subject may at any moment revoke consent, which should be done in the same manner in which the consent was given.

Specific provisions from the AMG will apply when consent for the purpose of clinical trials has being given. Sec. 40 sub- section 2a pt. 2 states that consent for processing of data for clinical trial purposes is irrevocable.

However revocation of the consent given according to AMG for participation in the clinical trial will also have effect on the handling of data subject's data within the trial. The data will be in that case no longer collected (as the person is no longer trial participant). Nevertheless the data which already was collected may be still used. The usage of this data is however limited to very specific actions:

- to determine effects of the investigational medicinal products,
- to ensure that those interests of the person concerned which are worthy of special protection are not prejudiced

[255] Simitis, *Bundesdatenschutzgesetz*, 559.
[256] Simitis, *Bundesdatenschutzgesetz*, 559.
[257] Art. 19 and art. 34 of BDSG
[258] Simitis, *Bundesdatenschutzgesetz*, 391; Gola and Schomerus, *Bundesdatenschutzgesetz BDSG Kommentar*, 183.

– to satisfy the obligation to provide complete marketing authorisation documents.

In case of revocation it will be determined directly whether the data may be needed for any of above mentioned reasons and the data no longer needed will be deleted directly, all the other personal data shall be deleted when no longer needed as long as no duty exists and no statutory retention periods apply.

AMG requires also, that the person giving consent for collection and usage of his personal data should be informed about the irrevocability of consent for data processing, as well as consequences for the data of revoking of the clinical trial participation consent.

4.6. Supervisor Authorities and their role

Data Protection Directive puts the member states under an obligation to establish supervisory authorities. Art. 28 requires that one or more public authorities should be created which should be held responsible for monitoring the application of the Directive provisions.

Germany fulfilled the obligations laid upon it by art. 28 by creating a complex network of supervisory authorities on both land and federal level. As the lands were responsible to establish the authorities there is no unified system of data protection bodies, but rather a mixture of Supervisory Authorities being part of the State Ministries of Internal Affairs and independent Authorities with full powers[259]

The role and obligations of those authorities are explained in sec. 38 of BDSG. The Authorities have the right exercise control over the data collections and therefore are given a wide range of means to obtain needed information (among others requesting all necessary information from data controllers, but also entering the premises of the controller).

The most important and most relevant for consent issues is the power to order measures to remedy violations of data protection law. In case of serious violations, especially those which constitute a serious threat to privacy, the data protection authorities may go as far as to prohibiting the collection, processing or use of the data.

Those remedies may be used, among others, where a legal ground for processing of the data is missing – whenever therefore, despite the general obligation, informed consent has not been obtained the Supervisory Authorities may enforce countermeasures.

[259] D. Beyleveld et al., *The Data Protection Directive And Medical Research Across Europe (Data Protection and Medical Research in Europe: Privireal)* (Aldershot: Ashgate Pub Ltd, 2005), 136.

V Study of the legal framework for informed consent within the national legislation of Poland

1. Legal majority age and capacity to consent

Polish legislation on the capacity to consent is somewhat complex. It is the case as during recent years there was a number of changes as it comes to the medical law and each of new acts has in addition introduced a chapter on capacity to consent to treatment or for clinical trial.

Therefore the legislation on this account is scattered and when assessing whether an individual can consent the following Polish legal acts have to be taken into account:

- Polish Civil Code[260], which includes general information on the age of majority;
- Act of 6 November 2008 on Patients' Rights and the Commissioner for Patients' Rights; [261]
- Act on doctor's and dentist's profession of 5 December 1996; [262]
- Act on the Pharmaceutical Law of 6 September 2001. [263]

1.1 General remarks on age of majority and capacity for acts in law:

According to the civil code, attainment of capacity for acts in law in Poland takes place at persons 18th birthday. From that moment on a person is considered an adult and therefore has a right to take single-handed decisions on her life[264]. However before that age Polish law differentiates between children under 13 years old, which possess no capacity for acts in law and minors above that age, which have limited capacity for acts in law.

Hence the general rule for legal competency is that every adult has a right to consent to any procedure in medical context.

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[260] Dz.U. 1964 nr 16 poz. 93, available online in Polish on the webpage of Polish Parliament: http://isap.sejm.gov.pl/DetailsServlet?id=WDU19640160093. Retrieved on 20.09.2012

[261] Dz.U. 2009 nr 52 poz. 417 , available online in Polish on the webpage of Polish Parliament: http://isap.sejm.gov.pl/DetailsServlet?id=WDU20090520417. Retrieved on 20.09.2012.

[262] Dz.U. 1997 nr 28 poz. 152, Available online (in Polish) on the webpage of Polish Parliament: http://isap.sejm.gov.pl/DetailsServlet?id=WDU19970280152, Retrieved on 20.09.2012.

[263] Dz.U. 2001 nr 126 poz. 1381 Available online (in Polish) on the webpage of Polish Parliament: http://isap.sejm.gov.pl/DetailsServlet?id=WDU20011261381+2009%2407%2420&min=1. Retrieved on 20.09.2012.

[264] However according to Polish law also a person who entered into marriage automatically becomes an adult and does not lose that status in case of divorce

Besides the distinction between adults and minors Polish Civil Codes, just as most of the European Acts recognise two limitations of capacity for acts in law. First is the full legal incapacitation; second is the partial legal incapacitation.

A person may be completely incapacitated if he is not capable of controlling his behaviour due to mental illness, mental retardation or mental disturbances of any other kind, in particular alcoholism or drug addiction. If the above-mentioned person is in a state, which does not justify full legal incapacitation, but the person requires assistance to manage his affairs he may be partially legally incapacitated.

The decision on full or partial incapacitation is taken by the guardianship court, which in case of full legal incapacitation establishes a guardianship and in case of partial legal incapacitation a curatorship.

Therefore in the context of health related decisions health care providers may have to obtain consent for an adult, a minor, a fully incapacitated adult and a partially incapacitated adult. The legal differentiation between the minors above and under 13 years is not acknowledged within the acts concerned with the decision making in the medical context, instead the legislator introduces the border of 16 years, after which consent has to be obtained also from the minor (see below).

1.2 Consent for care:

As states art. 17 of the Act on Patients' Rights along with adult patients, also minors who have attained age of 16 have a right to consent. Art. 17 awards also the statutory representative of a minor, of a completely incapacitated, or of incapable of conscious consent a right to give consent to treatment on their behalf. In case of lack of the statutory agent a factual representative may consent for examination (and so not treatment) of the individual under his representation.

The law awards the minor, incapacitated, mentally ill or handicapped patient also the right to raise an objection to medical treatment for which consent has been given by his statutory agent or factual representative. Patient may object to medical treatment whenever he possesses sufficient level of understanding. The right to object in case of minors is limited to patients above 16 years old and eventual rights of younger minors, even those which posses sufficient level of understanding, are not mentioned in the Act. In case of raising such an objection it is the Guardian Court, which has to take the decision. In taking this decision the Guardian Court should follow the best interest of the minor[265]. Before taking any decision the court should, as states art. 576 of Family and Guardianship Code hear out the child, whenever state of child's health and level of child's development will allow it. Furthermore the Court should, whenever

[265] Compare art. 109 of Polish Family and Guardianship Code of 25.02.1964 - Dz.U. 1964 nr 9 poz. 59; available online (in Polish) http://isap.sejm.gov.pl/DetailsServlet?id=WDU19640090059. Retrieved on 20.09.2012

possible, follow sound wishes of the child. On the other hand Court should also hear out child's legal guardian, as well as individuals, which are close to the child.

As explained above Polish law states that minors who have attained the age of 16 may give a valid consent and contrary all of minors who have not attained that age border are not in position to consent for treatment. However providing such a sharp age border is controversial. Obviously the age of 16 is only a convention where no special change within the individual takes place, which would allow him more capacity. Due to that fact it can easily be that persons of less than 16 years may well be factually capable of consenting, however due to Polish law are devoid of that right.[266]

The problem has been recognised not only by scholars, but also by the Children's Ombudsperson who, making use of his statutory right, has filed a complaint to the Polish Constitutional Court.[267] In the inquiry the Ombudsperson has asked whether the legal acts establishing this age border are in accordance with Constitution, especially with Art. 41 on bodily inviolability.

Polish Constitutional Court has decided to take a pragmatic approach to the case at hand and rather than relating to the questions of minor's autonomy and inviolability has focused on the practical obstacles of control over factual capacity to consent. Due to that the Court has decided that the laws establishing the border of 16 years are is in accordance with Polish Constitution. Firstly the Court has disregarded the fact that in Polish Civil Law the border of 13 years is introduced for a limited legal capacity, reasoning that there is no obligation to introduce such a border in other branches of law. Secondly it has stated that making the capacity to consent dependent on the minors development would require institutional control of that development for every individual case. That would cause a need for a professional institution for this task in every health establishment and would delay health care.

For that reason the general rule was kept at 16 years with exceptional cases like bone marrow transplant where the border of 13 years is introduced.

1.3 Consent for clinical trial participation:

In legislating minors' consent for taking part in clinical trial Polish legislator followed the general rules established for capacity to consent for treatment. Hence minors may take part in a clinical

[266] Similar debate had taken place in United Kingdom where the so called Gillick competence was developed (Gillick v West Norfolk and Wisbech AHA [1986] 1 AC 112 – compare; Stauch et al., *Text, cases and materials on medical law and ethics.*, 159.)

[267] K 16/10 from 2011.10.11. Available online: http://www.trybunal.gov.pl/OTK/otk_odp.asp?droga=(otk_odp)&sygnatura=K%2016/10 (in Polish). Retrieved on 20.09.2012.

trial (or another medical experiment) if consent of their statutory guardian has been obtained. In addition the same age border as in treatment is introduced and therefore, accordingly to art. 25 of the Act on doctor's profession all minors above the age of 16 have to be asked for consent. This however does not revoke the need to obtain guardian's consent – in case of minors above the age of 16 a consent of both the minor and his/her legal guardian is required.[268] Additionally law requires asking for consent those minors, who did not attain the age of 16 but are capable of forming their opinion and recognising the meaning of consent.

Therefore the law differentiates here between two different cases in which seeking for minors consent is necessary. First – if the minor attained the age of 16. Second – when the minor is capable of recognising his / her position and meaning of his / her consent. In both of those cases a written consent of the minor is a necessity (in addition to the consent of minor's legal guardian). In order to obtain such consent the researcher, or another person experienced with children should give the minor comprehensible information about the clinical trial, its risks and gains. Furthermore Polish law requires that the minor is clearly informed about the importance of his/ her wishes during and at any moment of the trial.

Clear rules are also provided for clinical trials with fully incapacitated. In their case it is their statutory guardian, who shall give consent. However if the fully incapacitated, just as the minor, can with discernment give his/her opinion about trial participation also his/her written consent is necessary. The researcher should provide the person with the same information, as in case of minors.

In case of an individual with full capacity for acts in law which is not capable of expressing her consent it is the guardianship court which should make the decision on participation. However the court should follow individuals wishes, if any of those are known – therefore if the person, while being capable of expressing consent and having full capacity for legal acts, refused to participate in the particular clinical trial his / her wishes shall be followed.

2. Consent for care

Since 2008 Poland has a law which sole focus are patient – physician relation – it is the Act from 6 November 2008 on Patients' Rights and the Commissioner for Patients' Rights. The act, besides determining patient rights is also concerned with connected obligations of doctors and any other health care professionals.

Paragraphs relevant for consent can be found in the Chapter 5 – "Patient's right to consent to medical procedures", as well as in Chapter 3 – "Patient's right to information"

[268] Taking into account that as a rule minors are represented by both their parents it will be three persons consenting for clinical trial participation

Art. 16, from the aforementioned Chapter 5, states:

> *Patient has a right to give consent to specific health benefits, or to refuse consent, after receiving information according to art. 9.*

The article clearly awards patients with right to give or refuse consent after being duly informed. At the same time art. 16 imposes upon the health care provider the duty to obtain patient's consent, or accepting patient refusal to give consent. The consent is what eliminates the illegality of the activities of the health care provider[269] and excludes criminal responsibility of the physician.

Art. 17 further specifies that such consent should also be obtained from a patient before every medical examination. It also defines the form in which consent should be given: the consent or refusal should be either in speaking, or by any behaviour, which, without a doubt shows the will, or lack of thee, to undergo procedures proposed by the doctor.

Specific form is required in case of surgery, or any treatment or diagnostic procedures with increased likelihood of risks for the patient. In that case the consent should be provided in a written form.

Polish law anticipates also cases in which physician can carry out medical examinations and treatment without patients consent, as well as with his/ her objection. Such cases are described in the Act on doctor's profession of 5 December 1996 r. Art. 33 of the aforementioned act states that whenever patient needs an immediate medical help physician can act without patient's consent if due to patient's health condition or age patient cannot give consent and furthermore it is not possible to contact his statutory agent, or factual guardian. In that case, whenever possible doctor should consult with another doctor.

The aforementioned case of surgery, or any treatment or diagnostic procedures with increased likelihood of risks for the patient also requires specific conduct if patient is unable to consent – in that case consent of the statutory agent is needed, and in case patient has no statutory agent, or contacting the agent is not possible – the consent of the guardianship court. If the statutory agent had refused to consent the physician can proceed only after receiving the consent of guardianship court.

Also in case of surgery or risky diagnostic or treatment the doctor can proceed without consent, if delay caused by seeking consent could impend the patient with danger of loss of life, serious injury, or serious health disorder. Before proceeding the physician is required, whenever possible, to consult another doctor possibly of the same speciality. The persons or institutions responsible for the patient should be informed about actions taken without delay; also the

[269] Bettina Heiderhoff and Grzegorz Żmij, *Tort law in Poland, Germany and Europe* (Munich: Sellier European Law Publishers, 2009), 68.

patient should be informed. Information about the treatment should, as well as annotation on lack of consent and reasons for it should be included in the medical records.

Clearly art. 33 is concerned with emergency cases, in which physician would have to choose between following the Hippocrates Oat and facing eventual criminal liability, or abandoning treatment due to impossibility of obtaining consent. For that reason the lawmaker has included a possibility to in exceptional cases accept treatment without a valid consent**.**

The next aspect which was casuistically explained in Polish law is the change of course of treatment. if the doctor must, due to circumstances that occur during treatment or diagnostic, change the scope or methods used, he/she may do so even without obtaining consent, if it is not possible to immediately obtain it from the patient or his/her representative.

Independently of the requirement of consent Polish law awards every patient with a right to information. Patient has a right to obtain this information prior to giving his consent. The way this information should be provided, as well as its kind has been described in Chapter 3 of the Act on Patient's right – Patient's right to information.

Art. 9 defines that patient has a right to receive information about state of his health, however the same article allows the patient not only to receive information, but also to decide that he/she does not wish to receive any information on his health. Generally the chapter is concerned not only with the patient's right to receive information, but also to control it – therefore next to the decision whether patient wants to be informed himself/herself also the decision who else should be informed about his/her medical condition is left to the patient.

Paragraph 2 specifies the scope of information, which should be given to the patient (or in some cases to his statutory agent) and the way this information should be given. The information given should be accessible for the patient and it should encompass his health state, possible and proposed diagnostics and treatment methods, as well as foreseeable consequences of the treatment or lack of thereof. Finally the doctor should inform the patient about the outcomes of treatment and the prognosis.

The person, who should give patient this information is mainly the physician, but similar information can be requested from a nurse or midwife, whenever they are responsible for providing any health care related services.

Art. 31 of the Act on the doctor and dentist's profession provides an exception from the general obligation of informing the patient. Namely in exceptional situation, when the prognosis is disadvantageous for the patient, the doctor may limit the information given to the patient, if, according to his/her opinion, it is in the interest of the patient – in those cases the doctor should inform patient's representative. Even in that case patient preserves his/her right to request information – in such a case, notwithstanding the his/her own opinion whether the information will benefit the patient physician has to disclose the information to the patient.

In addition to the law all of Polish physicians have to follow a self regulatory code of conduct prepared by National Chamber of Physicians and Dentists: "Code of Medical Ethics"[270] from year 2003. For breach of those rules physician can be held liable and face disciplinary punishment from the Chamber. The Code regulates, among others, the relation between physician and patient. Those in general once more reinforce the need to keep patients informed and to obtain patient's agreement to care and treatment.

Polish law on information and consent for health care is complex and scattered through many legal acts. Despite that the rules are widely casuistic the main of the Polish consent for care framework is relatively simple and similar to the European standard. Patient has a right to information about his/her state of health, furthermore he/she is in control on whether, to what extent and to whom (including himself) this information will be provided. On the second step patient has a right to consent to treatment *after* receiving the information on his condition and available options.

Nevertheless the relatively simple framework faces practical obstacles when conditions of consent have to be defined, or the scope of information has to be considered. An important role of specifying and defining right to information and right to consent has been taken by Polish Supreme Court. Thee together with Polish Courts of Appeal has in couple of landmark decisions précised the general legal norms.

Case law clearly states that any treatment, even the one given accordingly to the state of art and successfully concluded is illegal if carried out without valid consent.[271] In cases where the treatment has been given despite lack of consent the liability of physician is not grounded in medical error, but is an outcome of his/her omission to obtain consent. Furthermore courts adopt an opinion that consent can only be valid if the patient was aware and deliberate about his/her decision. The requirement of being aware and deliberate with regard to consent is fulfilled by sufficiently informing the patient. As indicated by the Polish Supreme Court: "It can be claimed that patient has given his consent for surgery only then if this consent has proceeded after receiving an accessible information, hence lack of such information condemns the consent to be invalid."[272]

The Courts have in their rulings established also the standards of information disclosure by defining what exactly information should be provided to the patient before consent can be obtained. The scope of sufficient information has been defined by the Supreme Court as such information which enables the patient to take a decision while being aware of what he is

[270] Available online on the webpage of National Chamber of Physicians and Dentists: http://www.nil.org.pl/dokumenty/kodeks-etyki-lekarskiej (in Polish). Retrieved on 20.09.2012.

[271] Judgement of tofthe Court of Appeal of Warsaw of 31.03.2006 – I Aca 973/05

[272] Judgement of the Polish Supreme Court of 17.12. 2004 : II CK 303/04, available online: http://pub.sn.pl/orzeczenia.nsf (in Polish).

deciding on and what consequences may this decision bare. Therefore the doctor should provide patient with information about kind of treatment, its aims, and *all of usual* consequences.[273] The information provided should encompass both the main effects of the treatment, as well as the side effects. Finally also adverse events, if probable, should be explained to the patient. However the scale in which this explanations will be given depends strongly on the urgency and necessity of the procedure which patient shall undertake, as well as on the probability that this adverse events may occur.[274]

3. Consent for clinical trials participation

3.1. Legal framework of clinical trials in Poland

Poland became a member of the EU on 1st May 2004 – the accession has caused a duty of implementation of the EU law and so extensive changes in the Polish legal system. Among other legislation, also the national pharmaceutical legislation had to be amended and made compliant with the European framework.

The country started implementing the EU Clinical Trials Directive in April 2004 and the law came into force on the date of Polish accession to EU. Later on - in 2007 – Polish authorities have introduced a major amendment of the Pharmaceutical Law to further improve the compliance with the EU legislation. In 2011 a so-called "small amendment" was introduced to further improve the compliance with the EU framework.

Current regulation of clinical trials is dispersed among many legal acts, most important of them are:

- The Constitution of The Republic of Poland of 2 April 1997, which in Chapter II – The Freedoms, Rights and Obligations of Persons and Citizens in art. 39 regulates the consent to medical experimentation;[275]
- Act on doctor's and dentist's profession of 5 December 1996, regulations of the 4th Capital about medical experiment;
- Act on the Pharmaceutical Law of 6 September 2001, regulations of the 2nd Capital about clinical trials of the healing products.

Those acts are specified by a number of Health Minister Orders on clinical trials:

[273] Those has been precised in the Supreme Court Judgement of 20.11.1979 – IV CR 389/79, similarly also on 28.09.1999 – II CKN 511/96. Available online: http://pub.sn.pl/orzeczenia.nsf (in Polish).

[274] Judgment oft he Supreme Court of 28.09.1998 – II CKN 511/96. Available online: http://pub.sn.pl/orzeczenia.nsf (in Polish).

[275] Dz. Ust. 1997 Nr. 79 poz. 483. Available online: http://www.sejm.gov.pl/prawo/konst/angielski/kon1.htm . Retrieved 20.09.2012.

- Health Minister Order in matter of the Central Records of Clinical Trials of 29 November 2002;
- Health Minister Order in matter of specific requirements of Good Clinical Practice of 11 March 2005;
- Health Minister Order in matter of way and range of inspection of clinical trials in range of accordance these trial with requirements of Good Clinical Practice of 10 December 2002;
- Health Minister Order in matter of determination of detailed requirements of Good Clinical Practice of 10 December 2002;
- Health Minister Order in matter of detailed principles of appointing and financing a bioethical commission of 11 May 1999;
- Health Minister Order in matter of way of conduct clinical trials with part of minors of 30 April 2004.

Currently in the Ministry of Health a new project of law on clinical trials is being discussed.[276] The new law shall separate all the relevant provisions in one act and bring more specific provisions on the rights and duties of trial subjects, number of clinical trials in one clinical site, as well as precise some of the informed consent requirements.[277]

3.1.1. Historical development of informed consent notion

The development of informed consent in Poland can in fact be seen as a development of two autonomous concepts – the consent of patient and the duty to inform the patient about state of his/her health and about the physicians actions has taken in Poland a similar development as in other countries – the Medical Code of Ethics from 1884 called for sparing from the patient as much information as possible[278] – it is only with time, and also, as an effect of the Nuremberg Code, that the duty to duly inform the patient has been introduced in practice. In 1946 Polish Supreme Court gave a ruling on an experimental treatment with mustard gas – the Court stated that the doctor should give detailed information on the experimental treatment and in case he has not done that the full civil responsibility for the results of the experimental treatment is justified. However the first legal act to explicitly mention both duty to inform and obtain

[276] Draft of the regulation can be found online on the webpage of Polish Ministry of Health: http://www.mz.gov.pl/wwwmz/index?mr=m491&ms=0&ml=pl&mi=56&mx=0&mt=&my=131&ma=017621 (in Polish). Accessed: 01.11.2011

[277] As discussed in Gazeta Prawna: http://praca.gazetaprawna.pl/artykuly/439449,mz_nowa_ustawa_wyeliminuje_nieprawidlowosci_w_badaniach_klinicznych.html (in Polish). Accessed: 20.12.2011

[278] Piotr Zaborowski and Adam Górski, "Informed consent and the use of placebo in Poland: Ethical and legal aspects," *Science and Engineering Ethics* 10 (March 2004): 168.

consent has been enacted in 1950 – it is the Act on the physicians profession[279] which stated that operation requires patient's consent. Therefore the duty of obtaining consent was limited to operations only and the Medical Code of Ethics from 1967 left informing the patient in other cases to the judgment of the treating physician, who shall take into account patients good.

3.1.2. Current law

The first act concerned with consent is Polish Constitution. Thee states in article 39:

> *No one shall be subjected to scientific experimentation, including medical experimentation, without his voluntary consent.*

Furthermore there are two main legal acts to be taken into account in the questions of clinical trials, and so also in the questions of informed consent in them.

The first and older one is the Act on doctor's profession of 5 December 1996[280]. This act can be seen as a *lex generalis*, while the Pharmaceutical Law from 6 September 2001 is the *lex specialis* for clinical trials.

The ADP introduces the category of medical experiment and in the question of informed consent it follows the approach of dividing obligation of the doctor to inform the patient (and so patient's right to receive information) and the duty / right to obtain consent. Consent issues are regulated in the Act on the doctor's profession in article 24 and following articles.

According to ADP the medical experiments can be divided into exploratory and therapeutic experiments, where exploratory experiments aim at widening medical knowledge and medical discoveries. Main scope of therapeutic experiments on the other hand is to directly benefit the patient.

The Pharmaceutical Law focuses on just one category of medical experiments – that is clinical trials with medicinal products, which are, according to this act, defined as medical experiments on people with the use of medicinal products. While for the medical experiment definition the Pharmaceutical Law refers to the aforementioned Act on doctor's profession.

These scattered regulations create a difficult taxonomy of medical experiment, according to Krekora at all.[281] clinical trials should be located within the group of medical experiments, dependent on their type will be seen as medical exploratory experiments or medical therapeutic experiments.

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[279] Dz.U. z 1950 r., nr 50, poz. 458,

[280] Dz.U. 1997 nr 28 poz. 152, Available online (in Polish) on the webpage of Polish Parliament: http://isap.sejm.gov.pl/DetailsServlet?id=WDU19970280152 (Access 01.11.2011)

[281] Krekora, Świerczyński, and Traple, *Prawo Farmaceutyczne*, 37a.4.

3.2. Definition of consent

The definition of informed consent is included in art 37f. §1 and states:

> *"An expression of informed consent is understood as a written, dated and signed statement of will of taking part in a clinical trial, which is given voluntarily by a person capable of giving such a statement, and in case o a person incapable of giving such a statement – by her statutory guardian; this statement shall mention that it has been given after receiving appropriate information with regard to nature, significance, implications and risks of the clinical trial".*

3.2.1. Informed consent as an act in law

The Polish definition from this article differs from the definition provided by the Directive – whilst the Directive describes "informed consent" as a decision to take part in a clinical trial Polish law describes "expression of informed consent" as a statement of will. [282]

The new regulation of clinical trials had brought clarity to understanding of consent as a legal act. Before the changes in 2004 a debate on the legal character of informed consent among judicature has taken place[283] – there are at least two trends in understanding consent – one as a statement of will, and second underlining the difference between consent and statement of will in the classical understanding. Safjan[284] explains: difference stating that the essence of consent is not to create legal effect but aims at disposing, in an autonomous way, personal rights. Hence whilst the Polish law has been clear about understanding of consent the judicature disputes the same topics as the German one.

That the legislator, while bringing this new definition of consent explicitly qualified the "expression of informed consent" as statement of will has made it possible to use the Civil Code regulation on that regard (art. 60 of the Civil Code).

Such understanding of informed consent even more underlines the controversy that this term raises among Polish commentators of the notion. The term is often named as "imprecise and false"[285]. As a declaration of will, consent should, they argue, also fulfil the requirements of

[282] Ibid.

[283] Malgorzata Świderska . Forma zgody na zabieg medyczny**.** Prawo i Medycyna 2007;9(27).

[284] Marek Safjan „Prawo i medycyna. Ochrona praw jednostki a dylematy współczesnej medycyny", Oficyna Wydawnicza, Warszawa 1998. s. 35

[285] Mariusz Kondrat et al., *Prawo farmaceutyczne Komentarz* (Warszawa: Wolters Kluwer Polska, 2009), 37b.9.

giving such a declaration – therefore it is discussed whether consenting without being duly informed can be valid, as it does not fulfil the requirements placed by art. 82 of the Polish Civil Code, which states that declaration of intent, shall be "conscious". Following such argumentation the addition of adjective "informed" to consent is not only useless, but also false as every consent by its own nature has to be informed.

3.2.2. Form of informed consent

For a valid expression of informed consent the law entails a specific form and distinguishes between three valid forms of consent: the direct consent, the substitute consent and the parallel consent.[286]

The direct consent is the prevailing form given in most cases- it has to be given in writing, dated and requires a hand-written-signature. Furthermore consent has to include an explicit clause that it has been given after being duly informed on all the required information (the scope of information has been further elaborated on in "Information to be addressed in the informed consent form"). Equivalent to that consent is the substitute consent given by the statutory agent or guardianship court (compare pt. 1. "Legal capacity"). The third form of consent - the parallel consent is a combination of both – it includes the consent of the statutory agent and the person represented (compare also pt 1.)

On a side note it should be mentioned that Pharmaceutical Act allows, just as does the Directive, in exceptional cases where the consent cannot be given in writing, expressing the consent verbally. Verbal consent requires attendance of two witnesses and should be evidenced in the medical file of the potential research subject. The Act does not precise neither who may be a witness, nor in how far should the verbal consent be documented, therefore the general civil regulations shall be used in this regard.

The verbal expression of consent, which is enabled by the article 37f. pt.1 stands in opposition to the requirements of the consent for processing of sensitive data, which, by the force of art. 27 of Act on Protection of Data is required to be in writing.

3.3. Information to be addressed in the informed consent form

Art. 37f. only generally emphasises the need of informing eventual trial subjects. Specific requirements as to what information should be addressed in the informed consent form are included in the Health Minister Order in matter of specific requirements of Good Clinical Practice of 11 March 2005, which is based on the authorization contained in art. 37g.

[286] Ibid., 37f.4.

§7 of the order contains the formal obligations required by Polish law for a valid consent of the future trial subject. Those requirements can be grouped with regards to the form of information given: which should be both written and oral, its quality that should be adjusted to the comprehension of the trial participant, and finally the timing of informed consent – the information should be offered to the participant prior to participant's consent. Finally there is a general order to the researcher that he/she should withdraw himself from exerting any influence over the subject.

The ordinance includes also an exhausting list of information, which has to be given to participant about:

1) The character of clinical trial and its purpose;

2) The trial treatment(s) and the probability for random assignment to each treatment;

3) The trial procedures and examinations to be followed, especially information about any individual examinations;

4) The subject's responsibilities;

5) Those aspects of the trial that are experimental. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, foetus, or nursing infant;

6) The reasonably expected benefits;

7) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks;

8) The compensation and/or treatment available to the subject in the event of trial-related injury;

9) The anticipated prorated payment, if any, to the subject for participating in the trial;

10) The anticipated expenses, if any, to the subject for participating in the trial;

11) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled;

12) That the monitor(s), the auditor(s), the controller(s) will be granted direct access to the subject's original medical records for verification of clinical trial procedures;

13) That records identifying the subject will be kept confidential and if the results of the trial are published, the subject's identity will remain confidential;

14) That the subject or the subject's statutory agent will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial;

15) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury;

16) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated;

17) The expected duration of the trial;

18) The approximate number of subjects involved in the trial.

3.4. Consent and the type of clinical trial

The regulations included in art. 37a and following have the same scope as the Directive 2001/20/EC – therefore they are concerned only with clinical trials on medicinal products for human use (the law provides also regulation on clinical veterinary trials). Also the informed consent described is provided solely for this category of trials. Polish law provides also more general regulation on the medical experiment, which includes other types of trials – all medical experiments are described in the Act on doctor and dentist's profession. This act does not contain a definition of medical experiment[287], but according to Kondrat the medical experiment in Polish law can be understood as a deliberately planned research activity, which is conducted accordingly to generally accepted rules of scientific inquiry, especially in definite, recurrent and controlled conditions.[288]

Medical experiments are further divided into research medical experiments and curative medical experiments.

[287] Ibid., 37a.4.
[288] Ibid., 37a.4.

Research medical experiments are defined as those which main aim is developing the state of medical knowledge, and from the clinical trials on medicinal products the non-therapeutic trials and in a wide extent also therapeutic trials of cognitive type should be considered as research experiments.[289]

Curative experiments are those in which introducing new methods in therapy, diagnostics or prophylaxis aims at direct benefiting of the patient. Into the category of curative experiments the confirmative therapeutic trials and therapeutic trials in the clinical praxis should are usually included.[290]

3.5. Rights of the clinical trials subject

In order to balance the weaker position of trial subjects the legislator, following Good Clinical Practice requirements, as well as conventions and legal acts has equipped trial subjects with rights in order to equalise their position

The strongest of all rights given to the patient is the right to consent for taking part in the trial and to withdraw from the trial at any time, without any resulting detriment.

The researcher is obliged to respect the will of patient and without delay withdraw his/her participation. That does not *per se* mean that this withdrawal has to be immediate – the researcher should secure that there are no negative results of discontinuing the trial with regard to the patient.[291] If however clinical subject refuses any examinations or treatment which are part of the trial researcher should respect his/her will and cease to provide thee, even at risk of patient's harm.

Furthermore the research subject has a right to a wide range of information – starting with information on the right to withdrawal, trough the right to receive additional notice about any change of the closing date of clinical trial.

Finally any research subject has a right to receive proper medical care, especially at all cases of adverse events after the use of the medicine products.

In the course of clinical trial also the general right to respect for physical and mental integrity, as well as right to privacy and data protection should be observed[292]. Those rights are under Polish law interpreted consistently with the rights as introduced by international charters and conventions on patient's and human rights.

[289] Ibid., 37a.4.
[290] Ibid.
[291] Ibid., 37d.1.
[292] Ibid., 37d.4.

On the side note it should be added that Polish commentators argue[293] for treating trial subjects as patients and therefore applying also patient rights when it comes to the interest of the trial subjects. The reasoning under this opinion is that the trial is, as a rule, conducted within a health care centre and therefore even healthy volunteers can be seen as patients. Consecutively next to the Pharmaceutical Law also the Act on Patients' Rights and the Commissioner for Patients' Rights has to be applied as well.

3.6. Authorisation of the informed consent forms (by ethic committees and competent authorities)

Commencing clinical trials is conditioned with obtaining authorisation of competent authorities. In Poland in charge of this authorisation are the President of Office for Registration of Medicinal Products, Medical Devices and Biocidal Products and competent Ethic Committee.

Both authorisations can be obtained separately in two proceedings which can be conducted at the same time. The requirements for the authorisation by the President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products are described in art 37m – 37p of the Pharmaceutical law and requirements for receiving the opinion of ethics committee are included in art 37r – 37u.

For both procedures the sponsor is required to submit the informed consent forms and the information brochures, which should be provided to the patient.

President of the Office for Registration of Medicinal Products (…) inspects the applications and attached documents on compliance with the Pharmaceutical Law. Further also non-accordance of the planned trial to the Good Clinical Practice requirements is a ground to refuse authorisation. Furthermore Polish law contains a provision that President should also judge whether the application is in accordance with the principles of community life and will not threat public order. Especially by mentioning the principles of community life the legislator reinforces one more time patients' rights and gives the possibility to evaluate informed consent forms. The, somewhat special, notion of community life originates from Polish Civil Code and aims at introducing moral rights into law. By including it in the Pharmaceutical law Polish legislator opens the President a possibility to refuse authorisation to applications which are considered unethical. This clause is criticised as being too wide and judgemental[294], or as awarding the President the same scope of evaluation as the ethical committee.[295]

The ethics committee while pronouncing its opinion on the clinical trials should, just as the President, take into account informed consent forms. They role as guardians of research subject's rights and well-being of trial participants gives the ethic committee a wide scope of

[293] Ibid.

[294] Krekora, Świerczyński, and Traple, *Prawo Farmaceutyczne*.

[295] Kondrat et al., *Prawo farmaceutyczne Komentarz*, 37o.5.

competence in the process of review of all aspects of informed consent. The committee should take into account not only the sole informed consent, but should also judge the whole of procedure of obtaining informed consent. In case of a trial with participants which are unable to consent the committee should also judge the underlying motives of those person's participation.

For commencement of any trial sponsor must secure a positive opinion of the ethics committee as well as an administrative decision authorising the trial. That should, as a rule, secure that not only is the trial ethically and procedurally compliant, but so are the informed consent forms and informed consent procedures for this trial.

4. Consent for data processing

4.1. Data protection framework in Poland

Polish data protection regulations are relatively new, as they were only introduced in 1997. In general 1997 was an important milestone for development of the Polish data protection framework – in that year the new Constitution of Poland was adopted; secondly the Act on Data Protection was passed on.

Polish Constitution is in so far important to the data protection framework as it includes two provisions granting protection to private life and privacy. Furthermore article 51 of Constitution obliges the state authorities to specify the principles and procedures of collection and access to information by statue – the promised statue is the Act of 29 August 1997 on the Protection of Personal Data.

This statue was a first Polish law concerned exclusively with protection of data. Any prior protection had been given by the civil law regulations[296], although by sectorial regulations concerned only with certain areas of life[297].

Bases for regulating the area of data protection were: from one side building of the state of law standards, from the other the international obligations of Poland. Those obligations were mainly connected with aspiring to the membership in European Union and therefore the need for adapting Polish legislation to EU legislation, as well as membership in Council of Europe. The first obliged Polish government to comply with the 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, while the second caused Poland to sign (in 1999) and ratify (in 2002) the Convention

[296] Articles 23 and 24 of Polish Civil Code are concerned with personal rights

[297] Partial regulations were and are still to be found in many acts in different areas of legislation, such as education, foreigners, labour, insurance or banking.

number 108 for the Protection of Individuals with regard to Automatic Processing of Personal Data from 1981.

The directive and its transpositions in Member States of EU had a deep impact on the bill of 1997 and in 2001 and 2004 further activities were taken in order to amend Polish act on the Protection of Personal Data, to secure full implementation of the directive. The amended Act entered into force at the day of Polish accession to European Union.[298]

The Act on the Protection of Personal Data is a complex legislation, which establishes a framework not only for itself, but also for other legal acts which have data protection provisions included. It gives the basic level of protection of individuals, while allowing any other legal act to higher the level of protection. That was especially important to all the acts existing prior to thee, as it automatically secures the increase level of protection for all of them and therefore creates the minimum level of protection for the data subject.

Additional general provisions on data processing had been also placed in the Pharmaceutical Law.

The legislator tried to follow the European approach and balance the rights of the data subject, against the freedom of information and interest of third parties in access and usage of information, hence rights of the data subject are opposed to the commercial rights.

4.2. Data subject

Major definitions of the act are explained similarly as they are in the Directive. Who is the data subject can be defined upon jointly reading art. 2 and art. 6 of the law. Art. 2 indicates what is the subject matter of the act and limits this matter only to processing of the data in regard to private persons. Art. 6 defines that personal data has to be information concerning private person – therefore two points are widely discussed among the commentators – firstly whether and how should the protection take place in case of legal persons and secondly whether the law should apply to deceased or yet unborn.

Polish law does not give a straight answer whether the data of deceased persons should be considered as personal data and given legal protection under the Act on the Protection of Personal Data, but in general understanding[299] as well as in opinion of Inspector General for the Protection of Personal Data February[300] only living persons are entitled to data protection. As to

[298] „Seventh report on the situation regarding he protection of individuals with regard to the processing of personal data and privacy in the European Union and n third countries", p. 100 available online: http://ec.europa.eu/justice_home/fsj/privacy/workinggroup/annual_reports_en.htm

[299] Janusz Barta, Paweł Fajgielski, and Ryszard Markiewicz, *Ochrona danych osobowych : komentarz*, 4. wyd., stan prawny na 1 listopada 2006 r. ed. (Kraków: Wolters Kluwer Polska, 2007), Art. 6 pkt. 10.

[300] Opinion from 12. 02. 2001 - GI-DP-024/145/01/427 and Online Guide of GIODO: http://www.giodo.gov.pl/319/id_art/974/j/pl/ (in Polish)

conceived but unborn commentators argue that protection should be offered to them in the same way it is offered to persons already born.[301]

4.3. Personal data and sensitive personal data

The personal data is defined as any information relating to identified or identifiable private person. The definition of personal data is therefore a transposition into the Polish legal system of the definition from the Directive.

The difference between the Data Protection Directive and Polish law appears in the definition of sensitive data – Polish legislator was here much more concrete and to the catalogue provided by the Directive added membership in political parties and religions, genetic code data and information about addictions. Yet it is discussable whether this additions are needed, or whether above mentioned are included in the more general catalogue provided by the Directive and can though be derived from more general political and religious beliefs and health information.

4.4. Consent

Consent is defined in art. 7 of the Act:

> *„The data subject's consent - shall mean a declaration of will by which the data subject signifies his / her agreement to personal data relating to him / her being processed; the consent cannot be alleged or presumed on the basis of the declaration of will of other content; the consent may be revoked at any moment."*

This definition differs from the definition provided by the Directive: in understanding of Polish law consent is not an indication of wishes (as defined by the directive's art 2 (h)) but it is a declaration of will. That opens the possibility of using the Polish Civil Code for interpretation of the declaration – as the act misses provisions on the capability to consent, or on conditions which make consent null and void.

Forbidding of alleged or presumed consent is significantly more strict than in the Directive and is yet another ground for a specific consent for data processing in case of clinical trials – as notes Barta[302] whenever consent for data processing is asked for the request has to be formulated explicitly and has to stand out among other information coming from that person, at any case the consent should refer the data subject to other documents.

[301] Barta, Fajgielski, and Markiewicz, *Ochrona danych osobowych*, Art. 6 Pkt.10.
[302] Barta, Fajgielski, and Markiewicz, *Ochrona Danych Osobowych*, 7. Pkt 31.

Polish legislator's approach to secure a higher level of protection for the data subject is also visible in the form required by the law. There is no requirement of form for the processing of normal categories of data, but art. 27 §2 requires consent for processing of sensitive data to be written (excluding the erasure of the data which, according to art. 27 of the Act on Protection of Personal Data does not require consent of the data subject). That is a deviation in comparison to the Directive, which requires "explicit consent" only.

In 2010 the Act was amended and to the definition of consent a new requirement added - now art. 7 states that data protection consent may be revoked at any time.

4.5. Consent for the use of retrospective data

Obtaining consent for processing of retrospective data is different than obtaining consent for processing of a prospective data. While giving his/her consent for data processing the data subject authorises the use of his data from the moment of consent onwards. That the consent has to be given prior to the data processing is not explicitly mentioned in Polish law, but results from its general idea – as data processing needs a legal basis, once the only basis for processing is consent, the processing cannot start until the consent has been given.

Usage of retrospective data signifies that the data controller will have access to data collected prior to obtaining consent. That is usually the case in clinical trial as a former patient, whose health data was collected, now will appear in a double role – he/she may continue to be a patient, but will also become a trial subject.

As a rule processing of sensitive data is forbidden, but art. 27 introduces exemptions from this general rule.

The former collection of data was done upon one of the exemptions by the Act on the Protection of Personal Data, which is included in art 27§2 pt.7) – processing for purposes of preventive medicine, the provision of care or treatment. But once the patient becomes a trial subject the processing will have a second purpose – it will be processed for conducting a clinical trial.

That constitutes two difficulties: the collection will have a different purpose and the new purpose of the collection would need new authorisation.

By principle the data which is collected can only be used for the purpose it was collected. Therefore a health record has a use limited to diagnosis and treatment of patient.

Such an exemption is not included in the art. 27, or in any other Polish legal act. Therefore processing of this data needs another legal ground – such a ground is consent of the trial subject.

The data subject should therefore be therefore asked for additional distinctive authorisations: to access and use the his medical records which were collected before.

4.6. Rights of the data subject

Act on the Protection of Personal Data includes a chapter, which focuses on Rights of the Data Subject. Chapter 4 responds to the obligations of controller and develops rights which stem from them.

Art. 24 – 26 awards the rights to data subjects by obliging controllers on procedures which they should follow while collecting the data. In such a case, notwithstanding whether the data is collected from the data subject (as described in art. 24) or from other source (art. 25) the data subject should be informed about crucial elements of this collection.

Such an information in case of collecting the data from a data subject should include:

- information identifying the controller and information on his seat;
- the purpose of data collection, and, in particular, about the data recipients or categories of recipients, if known at the date of collecting;
- about the subject's right of access and rectification;
- whether submitting the data in question is obligatory or voluntary, and in case of existence of the obligation about its legal basis.

In case of obtaining the data from another entity data subject needs to be informed about all of above mentioned, except the last (as the data does not need to be submitted). Additionally the controller should inform the subject about the source from which the data is. Art. 25 obliges the controller to inform the subject about the cases in which it is possible to object to data processing.

Art. 32, which is the main one introducing in Chapter 4 the rights of data subject focuses on control, which the subject has over his data. The major difference between this article and the aforementioned articles is that the information mentioned in them has to be directly provided to the data subject. The art. 32 on the other side provides general rights of the data subject which the data subject has at his disposal. Furthermore the catalogue of rights introduced in art. 32 is wider.

Art. 32 distinguishes three categories of rights[303]: the rights to information, the right to rectification and the right to oppose to data processing.

[303] Ibid., Art. 32 Pt. 1.

§1 Pt. 1 – 5a include so called right of access and it very much repeats obligation described in the art. 24 and 25. The information provided to the data subject in some cases has to be more extensive and additionally the data subject may request the information since when the data is being processed and may request the content of the data, which should be given to him in an intelligible form.

§1 Pt. 6 includes the rights from the category of rectification. Referring to this paragraph the data subject can "demand the data to be completed, updated, rectified, temporally or permanently suspended or erased." In order to use that rights the data subject must prove that the data „are not complete, are out-dated, untrue or collected with the violation of the act, or that they are no longer required for the purpose for which they have been collected

Finally §1 introduces the right to forbid or oppose to the data processing and defines the requirements of such requests.

The data subject may lodge a request to the controller in order to be informed about all his rights regarding his personal data and the controller is obliged to give this information within 30 days, upon request this information should be given in writing.

4.7. Supervisor Authorities and their role

The statutory authority for the data protection purposes is the Inspector General for Personal Data Protection (GIODO)[304], which was established on basis of the Act on the Protection of Personal Data.

The tasks of Inspector do not include any general requirement of control over obtaining informed consent, but art. 12 makes the Inspector responsible over general supervision over ensuring compliance with the data protection regulations. In case of violation of the data protection rules in Poland Inspector General may take legal action and non compliant obtaining of informed consent can definitely be seen as such a breach.

The Statutory task of the Inspector is keeping a national register of personal data filling systems. That task responds to the obligation of the controller to notify a data filling system, whenever this filling system falls under the art. 7 pt.1 – is therefore "a structured set of personal data which are accessible pursuant to specific criteria, whether centralized, decentralized or dispersed on a functional basis"

It should also be noted that the regulation on clinical trials also requires the trial sponsor to act compliantly with the data protection rules and respect the privacy of trial participants, therefore indirectly also the Ethics Committee and President of the Office for Registration of Medicinal Products are responsible for safeguarding trial participants' rights in the area of data

[304] See Inspector General official webpage: http://www.giodo.gov.pl/. Among others the webpage allows filing a claim online.

protection and the data subject may notify GIODO about any alleged breach of his/her rights concerning data protection (or any other alleged breach of data protection law in general).

VI Study of the legal framework for informed consent within the national legislation of the UK

1 Legal age of majority and capacity to consent

Consent is in the UK only considered a valid consent when the subject has the capacity to make the decision to consent. For those who lack the capacity to consent a mix of common law and regulation determines the legality of the treatment, participation in clinical trials and data processing.

A distinction is made between the patient competent to consent and a patient with the capacity to consent. As described by Pattinson[305]:

- A patient can be regarded **competent** when his cognitive faculties are such that he is able to make a decision with respect to the given situation. When he lacks such cognitive faculties he is considered incompetent.
- A patient is considered to have the **capacity** to consent when he is as an individual legally recognized to have decision-making authority.

1.1.1 General remarks on age of majority and capacity for acts in law

UK legislation is characterized by a difference in approach to the assessment of the legal age of majority for clinical trials and for other healthcare issues. While in implementation of the European Clinical Trials Directive 2001/20/EC UK law foresees a set of rules on the capacity to consent in the Medicines for Human Use (Clinical Trials) Regulations 2004 for clinical trials, common law foresees a different approach for consent for medical treatment and data protection.

In UK law for most purposes a child or minor is someone below the age of 18. This reflects the fact that they have yet to attain the age of majority. For children lacking the legal capacity to consent the notion of "proxy consent", both parental and court, is commonly used[306]. Parental responsibility is defined by s.3(1) of the Children Act 1989 as: "all the rights, duties, powers, responsibilities and authority which by law a parent has in relation to the child and his property". Parental responsibility is under s.2(5) in principle always gained by the mother at birth. For fathers it depends on the marital status. When the parents of the child are married, the father too will in principle automatically gain parental responsibility. If they are not married, the father can claim parental responsibility through jointly with the mother registering

[305] S.D. Pattinson, Medical law and ethics, 2006, Thomson Sweet & Maxwell.
[306] S.D. Pattinson, Medical law and ethics, 2006, Thomson Sweet & Maxwell.

the child at birth, or by making a so called "parental responsibility agreement" or through court order[307]. Next to the mother and the father, parent responsibility can also be given to a legal guardian or to a professional representative (natural person or local authority) as appointed by the court[308]. In principle this may be the doctor responsible for treatment or a person nominated by the relevant healthcare provider. Only with regards to clinical trials, it is specifically mentioned in the law that this person may not be connected to the trial. This means there may be no financial, professional or personal interest in the progress of the research. This includes junior staff members whose career may be influenced by senior researchers, but is it on the other hand not necessary to exclude all people working in the same hospital or local authority[309].

1.2 Consent for treatment

Based on the Family Law Reform Act 1969 and common law principles, Pattinson[310] summarises the consent for treatment of a child in three scenarios. Consent can be given by

- A child who is 16 or 17 years old[311]
- A child under 16 who has sufficient understanding and intelligence[312]
- A proxy

Children 16 or over can consent to medical treatment under s.8(1) of the Family Law Reform Act 1969: "The consent of a minor who has attained the age of 16 years to any surgical, medical or dental treatment which, in the absence of consent, would constitute a trespass to his person, shall be as effective as it would be if they were of dull age; and where a minor has by virtue of this section given an effective consent to any treatment it shall not be necessary to obtain any consent for it from his parent or guardian". The child of 16 and over is, in other words, presumed to possess the capacity to consent for treatment. The child's competence to consent can however be refused when he fails to satisfy the common law based so called *Re C* test[313]. The Re C test is a three-stage test to judge one's competence to consent. Originally it was applied to adults, but case law also applies the test to children. The test accepts that decisions on treatment are taken in three stages: "fist comprehending and retaining treatment

[307] S.4(1) Children Act 1989.
[308] S.5(6), s.12(2), s.33(3)(b) and s.44(4)(c)
[309] K. Robinson and P. Andrews (2011) "'(More) trials and tribulations': the effect of the EU directive on clinical trials in intensive care and emergency medicine, five years after its implementation", JME, 36, 6, 322-325.
[310] S.D. Pattinson, Medical law and ethics, 2006, Thomson Sweet & Maxwell.
[311] Family Law Reform Act 1969, s.8(1).
[312] Gillick v West Norfolk and Wisbech AHA, 1986, A.C. 112.
[313] Re C (Detention: Medical Treatment) 1997, 2 F.L.R. 180, 195-196.

information, second, believing it, and third, weighing it in the balance to arrive at choice"[314]. The Re C test therefore asks three questions:

- Can the patient understand and retain treatment information?
- Can he believe it?
- Can he weigh it sufficiently to make a choice?

The *Re MB* case confirmed this approach and further determined that a patient will only be regarded incapable if "some impairment or disturbance of mental functioning renders the person unable to make a decision"[315]. The purpose of the three stage test is to determine whether there is such an inability[316].

Even when a child is considered capable and competent to consent, he or she may however always agree to parental inclusion in the decision making process[317].

Since 2007 these common law rules have been codified in the Mental Capacity Act[318]. The Mental Capacity Act applies only in England and Wales. In Scotland the Adults with Incapacity (Scotland) Act 2000 and the Age of Legal Capacity (Scotland) Act 2001 provide an equivalent. For Northern Ireland no equivalent statute is foreseen but similar common law principles apply[319].

To **children under 16** the Mental Capacity Act does not apply[320]. The Family Law Reform Act states in s.8(3) that "nothing in this section shall be construed as making ineffective any consent which would have been effective if this section had not been enacted". Consequently, one must rely on common law principles to clarify the legal situation. "In the landmark ruling of Gillick v West Norfolk and Wisbech Area Health Authority the house of Lords empowered a minor to consent to medical treatment when she reaches an age and maturity to judge what the treatment entails and assess its benefits and disadvantages", Cave describes[321]. This ruling has been so fundamental to UK law that the consent for treatment of a child under 16 is now referred to as "a Gillick competent child". For such children the competence to consent to treatment is judged on a case by case basis. Whereas the child of 16 and over was presumed to possess the capacity to consent to treatment but can be regarded incompetent after failing the

[314] Re C, 1994, 1 All E.R. 819, 823.
[315] Re MB, 1992, 2 F.L.R. 426, 437.
[316] S.D. Pattinson, Medical law and ethics, 2006, Thomson Sweet & Maxwell.
[317] S. Andrew Spencer (2004) "Research governance regulations and paediatric research", Current Paediatrics, 14, 532-539.
[318] Mental Capacity Act 2005
[319] Royal College of Nursing Research Society (2011) "Informed consent in health and social care research", available online www.rcn.org.uk.
[320] Mental Capacity Act 2005, s.2(5).
[321] E. Cave (2011) "Seen but not heard? Children in clinical trials", *Medical Law Review,* 1-27.

Re C test, the child under 16 is presumed to lack this capacity but can be found competent after passing the Gillick test[322]. Traditionally the Gillick test takes into account only the child's age and the outcome of the decision. Nevertheless it is argued in doctrine that the judgement of Gillick competence should not be merely status- and outcome-based, but account should also be taken of their ability to comprehend and assimilate the information[323].

The difference in approach to children of 16 years and over or these under the age of 16 is also reflected in their capacity to **refuse treatment**. A child with the capacity to validly consent does not automatically have the capacity to validly refuse treatment[324]. Under the age of 18 children cannot validly refuse treatment when one of their proxies does consent to the treatment. "The court or anyone with parental responsibility can consent even in the face of a refusal from a competent child", Pattinson states. A Gillick competent child can thus give consent to treatment, but cannot always withhold it if it is deemed to be in its best interest to receive treatment, provided someone consents on the child's behalf[325]. The child's rights to autonomy are not omnipotent Cave stresses: "they must be balanced with her welfare rights or her developmental interests"[326]. Parents, a legal guardian or the court too must therefore always act in the best interest of the child. When disagreement exists on what is the best interest of the child, court ruling should be sought[327].

Where more than one person, for example the mother and the father, have parental responsibility the consent of one is usually sufficient[328]. When agreement cannot be attained amongst those with parental responsibility, court ruling should again be sought. This has been the case for a number of very specific issues, usually quite fundamental, drastic cases or cases with far-reaching consequences. Examples cases brought before court are immunisation, male circumcision and organ and tissue transplantation. In these rulings non-medical factors potentially play a much larger role. But this again depends on the case. A different approach was taken for example taken in the Re C case on immunisation compared to the Re J case on circumcision[329].

[322] S.D. Pattinson, Medical law and ethics, 2006, Thomson Sweet & Maxwell.

[323] J. Fortin (2006) "Accomodating Children's Rights in a Post Human Rights Act Era", Medcial law review, 299; as cited by E. Cave (2011) "Seen but not heard? Children in clinical trials", *Medical Law Review,* 1-27.

[324] Re R, 1991, 4 All E.R. 177 and Re W, 1993, Fam. 64.

[325] E. Cave (2009) "Adolescent Consent and Confidentiality in the UK", European Journal of Health Law, 16, 309.

[326] E. Cave (2011) "Seen but not heard? Children in clinical trials", *Medical Law Review,* 1-27.

[327] As a consequence of the Gillick case.

[328] S.2(7) Children Act 1989.

[329] Re C, 2003, EWCA Civ 1148 versus Re J, 1992, 2 F.L.R. 678.

1.3 Consent for clinical trial participation

Consent for participation in research is partly regulated by the same principles as outlined above and partly by the Medicines for Human Use (Clinical Trials) Regulation 2004[330]. This is because the latter only applies to clinical trials as defined and regulated in the EU Clinical Trials Directive: clinical trials involving investigational medicinal products.

Research other than a clinical trial involving investigational medicinal products

The participation of children to research other than a clinical trial in the sense of the EU Directive is in fact not regulated in the UK. Not by law, nor by common law. But, professional bodies do turn to common law for guidance. The UK Medical Research Council advises that, due to the inherent risks involved in research combined with treatment, Gillick will probably apply, but dual consent should be encouraged[331]. Cave consequently concludes that, even though it still has to be tested in court "it is possible that a researcher who secures the consent of the Gillick competent child, but not her parent or guardian, may commit a battery, provided his research involves physical contact with the young person"[332]. Even though a Gillick competent child would be able to consent to treatment him or herself, he or she would thus have to bring the matter before court if he or she wishes to participate in research without his or her parent's consent, arguing that the research would be in his or her best interests. Inverse the General Medical Council also recommends that "children and young people should not usually be involved in research if they object or appear to object in either words or actions, even if their parents consent"[333]. When however taking into account the common law principles for consent to treatment as described above it could be questioned whether Gillick competent children could not be forced to continue with the research when this is in the best interest of their health or welfare.

The question whether or not common law principles in general and Gillick competence more specifically should be used to judge the participation of children to research other than clinical trials involving investigational medicinal products, is however a in doctrine contested question. Hunter and Pierscionek argued that Gillick competence should only apply when the research is of minimal risk and has direct benefit to the child, or when it is of minimal risk and of great societal benefit[334].

[330] Medicines for Human Use (Clinical Trials) Regulation 2004.

[331] Medical Research Council, Medical Research Involving Children (2004) 5.3.1.a.

[332] E. Cave (2011) "Seen but not heard? Children in clinical trials", *Medical Law Review,* 1-27.

[333] GMC (2007) 0-18 years: Guidance to All Doctors, 38.

[334] D. Hunter and B. Pierscionek (2007) "Children, Gillick CompetencyCompentency and Consent for Involvement in Research", Journal of Medical Ethics, 33, 659.

In any case, it should be stressed again that the Gillick competence should be assessed by someone independent to the research project because the investigator's personal interests may affect his ability to judge.

Clinical trials involving investigational medicinal products

To clinical trials involving investigational medicinal products as regulated by the European Clinical Trials Directive the principles described above do not apply as the Family Law Reform Act and the Mental Capacity Act 2005 are for these situations replaced by the Medicines for Human Use (Clinical Trials) Regulations 2004.

The Medicines for Human Use (Clinical Trials) Regulations 2004 does nevertheless make the same distinction between children under and above 16 years of age. Children under 16 are called 'minors'. Children of 16 and above are protected in their autonomy similarly as under the Family Law Reform Act.

Trials involving minors require the written consent of the person with legal responsibility before participation: "Informed consent given by a person with parental responsibility or a legal representative to a minor taking part in a clinical trial shall represent the minor's presumed will"[335]. "However capable or mature, a minor is unable to give sole consent until the occasion of his or her 16th birthday" Cave concludes[336]. The Medicines for Human Use (Clinical Trials) Regulations 2004 does impose a duty to inform the minor according to his or her capacity of understanding, but there does not seem to be any legal obligation to obtain his assent either. The Medicines for Human Use (Clinical Trials) Regulations 2004 only states in Schedule 1, Part 4, Paragraph 7 that "the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in the previous paragraph to refuse participation in, or to be withdrawn from, the clinical trial at any time is considered by the investigator". The Regulations thus takes a fully status-based approach. This is remarkable because in this rule, a parallel with the Gillick competence and the Family Reform Act is missing. Moreover, it could in conflict with article 8 ECHR.

1.4 Consent for data protection

Personal data are in the UK protected by the **Data Protection Act 1998**. This Act does not state that it is applicable to adults only, so it should be interpreted as being applicable to any competent patient.

Next to the right to Data Protection, UK common law also entails an **obligation of confidence**. In the Gillick case the House of Lords recognised that children too could in certain circumstances request their doctor not to share health information with their parents. In this

[335] Schedule 1, Part 4, Para 13 Medicines for Human Use (Clinical Trials) Regulations 2004.
[336] E. Cave (2011) "Seen but not heard? Children in clinical trials", *Medical Law Review,* 1-27.

case the statement primarily concerned contraceptive treatment[337]. Nevertheless, discussion arose in doctrine and case law on the exact implications of the Gillick case. Kennedy and Grubb argued that it is analytically preferable to found the duty of confidentiality on the child's ability to form a confidential relationship or an expectation that the information will be kept secret[338]. "Both the capacity to consent and capacity to request confidentiality would turn on the child's ability to understand what is entitled by the activity in question" Pattinson summarises this approach[339]. The logical this approach may be, it is however difficult to reconcile with UK case law. In the Re C case for example it was decided that "children, like adults, are entitled to confidentiality in respect of certain areas of information"[340]. The latter is also supported by the Campbell case in which the House of Lords linked the action for breach of confidentiality to article 8 right to privacy. Where the child is competent, he or she could demand non-disclosure as a result of patient autonomy being a key component of his or her private life[341].

2 Consent for care

In the UK too, consent is an essential requirement to lawful medical treatment. Treatment without a valid consent can amount to both a tort and a crime. It can more specifically give rise to an action for battery, negligence or assault. The requirement of consent for treatment is largely common law based.

2.1 Informed consent as an act in law

The law of consent in the UK is tied up closely with the tort of trespass to the person, which comprises assault, battery and false imprisonment. In Collins v Willcock these three torts were described: "an assault is an act which causes another person to apprehend the infliction of immediate, unlawful, force on his person", "a battery is the actual infliction of unlawful force on another person" and "false imprisonment is the unlawful imposition of constraint on another's freedom of movement from a particular place"[342]. The law of consent is thus largely common law based.

In medical practice the tort of battery implies that a patient may sue where a doctor performs an operation without consent, even if the operation is medically required and improves the patient's health. One condition thereto is however that the act to perform medical treatment

[337] Gillick v Wes Norfolk and Wisbeck AHA, 1986 A.C. 112.

[338] I. Kennedy and A. Grubb (2000) Medical Law, Butterwords London.

[339] S.D. Pattinson, Medical law and ethics, 2006, Thomson Sweet & Maxwell.

[340] Re C, 1990, Fam. 39, 48.

[341] Cambell v MGN, 2004, UKHL 22 and before Pretty v UK, 2002, 35 EHRR 1.

[342] Collins v Wilcock, 1984, 3 All E.R. 374, 377-378; See also: S.D. Pattinson, Medical law and ethics, 2006, Thomson Sweet & Maxwell.

without consent was intentional. On the other hand, the tort of battery is actionable per se, so no suffered harm needs to be proven[343].

Under criminal law not obtaining consent may amount into assault. A doctor who acts contrary to public policy will risk prosecution for assault when it occasions in actual or grievous bodily harm or murder. This consistency with public policy is however only a requirement under criminal law, not under civil law. An otherwise valid consent will be rendered ineffective when it contravenes public policy and occasions in bodily harm[344].

2.2 Definition of consent

A definition of informed consent for medical treatment is not available in the UK. In the Sideway v Bethlem Royal Hospital case it was clarified that consent is in essence an "internal state of mind". Consent to what would otherwise be a battery is, in the words of Lord Diplock, "a state of mind personal to the victim of the battery" Pattinson clarifies. Pattinson subsequently states that "consent is a process that might not be complete even where the patient has signed a form, so a completed "consent form" can be no more than evidence of consent" [345].

Through common law, it became clear that for consent to be legally valid, it must satisfy three requirements:

- It must be given voluntarily.
- The patient must have the capacity to consent.
- The patient must be able to understand the nature of the treatment in question.

2.3 Form of informed consent

The law of consent does not require a written or an explicit verbal agreement. Implicit consent is accepted when it is based on the patient's conduct.

However, this does not mean that every apparent consent always amounts into a valid consent. When one of the three conditions to the validity of consent is not respected, implicit consent cannot be accepted.

[343] S.D. Pattinson, Medical law and ethics, 2006, Thomson Sweet & Maxwell.
[344] S.D. Pattinson, Medical law and ethics, 2006, Thomson Sweet & Maxwell.
[345] S.D. Pattinson, Medical law and ethics, 2006, Thomson Sweet & Maxwell.

2.4 Information to be addressed in the informed consent form

The information to be addressed in the informed consent form for care is again connected to the two torts which may arise from not providing enough information: the action for battery and the action for negligence. The information requirement for the criminal law of assault is the same as that for battery[346].

- No **battery** will be committed where the patient understands the **broad nature of the treatment**. The patient has in other words to be broadly aware of the nature of the treatment. For the action in battery the information threshold is quite low. An action in battery is only available if the doctor treats the patient against the patient's will, if he would administer another type of treatment or when he obtains the patient's consent by fraud. Two examples of actions accepted by courts as situations in which not enough or not the right information was provided are firstly the case in which a doctor conducted unnecessary treatment: the administration of unnecessary treatment was said to have a different nature than the administration of necessary treatment[347]. A second case concerned a boy whose foreskin was removed instead of his tonsils due to an administrative error. In this case too it was (naturally) judged that no valid consent had been available[348].
- An action of **negligence** can be brought when not enough information was provided on the **risks of the treatment**. What information a doctor must disclose to avoid liability in negligence used to be judged through what became widely known as the Bolam test: the doctor needs to disclose all information which should be disclosed by a reasonable body of medical opinion[349]. Since the end of the '80s however, attempts have been made to interpret the Bolam test in a less "doctor knows best" manner. In the Bolitho v City and Hackney HA case the House of Lords made it clear that the Bolam test should refer to a responsible rather than a received body of opinion[350]. A reasonable doctor should disclose the information that a "reasonable patient" would want to make an informed decision[351].

Inspired by on the one hand moves to informing the patient on European level, for example by article 8 (1) of the European Convention on Human Rights and Biomedicine: the right to private life and on the other hand the guidance provided by the medical profession itself taking a more patient centred approach, UK common law is now confronted with a change in the direction of

[346] The description in this section is based on the findings of S.D. Pattinson, Medical law and ethics, 2006, Thomson Sweet & Maxwell.

[347] Appleton v Garret, 1996, P.I.Q.R. P1

[348] Chatterron v Gerson, 1981, 1 Q.B. 432, 443.

[349] Bolam test as applied in Sideway v Bethlem Royal Hospital, 1985, A.C. 871.

[350] Bolitho v City and Hackney HA, 1998, A.C. 232.

[351] Pearce v. United Bristol Healthcare NHS Trust, 1999, P.I.Q.R. 53.

law. The General Medical Council for example states that doctors providing information must do their "best to find out about patient's individual need and priorities" and to "provide patients with appropriate information, which should include an explanation of any risks to which they may attach particular significance"[352].

3 Consent for clinical trials participation

3.1 Legal framework

As already indicated in the description on the legal age of maturity and capacity to consent above, UK regulation on the consent for participation in clinical trials makes a distinction in the participation to clinical trials that fall under the European Clinical Trials Directive and those outside of the scope of the directive. This differentiation is caused by the limited scope of the Medicines for Human Use (Clinical Trials) Regulations 2004 implementing the European Clinical Trials Directive and as amended in 2006 by amendments No. 1928 and 2984 implementing EU Directive 2005/28/EC. The UK opted to create a new set of rules that apply only to clinical trials involving investigational medicinal products and not to create a new set of rules that regulate all research[353]. Other research is regulated through other statutes such as the Mental Capacity Act 2005 and common laws.

The following sections focus on the informed consent for clinical trials involving investigational medicinal products[354].

3.2 Definition of consent

The Medicines for Human Use (Clinical Trials) Regulations 2004 do not contain a definition of consent, but in section 3, Part I, Schedule 1, the Regulations state that a person gives informed consent only if his decision is:

(a) given freely after that person is informed of the nature, significance, implications and risks of the trial;

(b) either

i. is evidenced in writing, dated and signed, or otherwise marked, by that person so as to indicate his consent, or

ii. if the person is unable to sign or to mark a document so as to indicate his consent is given orally in the presence of at least one witness and recorded in writing.

[352] GMC 1998, para 6.

[353] E. Cave (2011) "Seen but not heard? Children in clinical trials", *Medical Law Review,* 1-27.

[354] The regulation of informed consent in other types of research will be added to this country report in a later version.

In part II, 9. the Regulations stress again that consent should be a freely given and informed consent: "freely given informed consent shall be obtained from every subject prior to clinical trial participation".

3.3 Informed consent as an act in law

In the UK a lot of emphasis is put on the fact that informed consent in **an ongoing process**. This emphasis originates from the common law principles as described above[355]. The Royal College of Nursing Research Group for example stresses that researchers must ensure that participants continue to understand what the research is about and what their participation involves. Therefore participants should be provided with any new information which might influence their decision to continue participation in the research. Subsequently they also stress that informed consent should not only be revisited informally, but also formally through the provision of a new information sheet. This is for example advisable in longitudinal research and after a significant change in the research project.

3.4 Form of informed consent

In contrast to the common law principles regulating informed consent for care, the Medicines for Human Use (Clinical Trials) Regulations 2004 do require the informed consent to be given in **writing**[356].

In order to confirm that he actually does consent to participation, it has furthermore become standard practice to require the participant to **sign** the informed consent form. By signing the informed consent form evidence is provided that a discussion on the form has taken place. Participants should thus not be requested to sign the form until they have been given adequate information about the study and only after they have had the time to consider their decision. Nevertheless, the fact that the informed consent form is signed does not yet prove that the consent is truly informed. Therefore it is not a guarantee to full legal validity[357].

Exceptions to the written informed consent can be made in emergency situations and in case of anonymised research.

- In **emergency situations** a delayed consent is accepted when obtaining informed consent from both the participant and his legal representative is impossible[358]. An

[355] See: VI1.1.1

[356] Schedule 1, Part I, Section 3, (b).

[357] Royal College of Nursing Research Society (2011) "Informed consent in health and social care research", available online from www.rcn.org.uk.

[358] Royal College of Nursing Research Society (2011) "Informed consent in health and social care research", available online from www.rcn.org.uk.

"informed consent" based on minimal parental understanding is next thereto for example accepted in neonatal intensive care as it may not be possible for parents to at that moment understand the full implications of the research quickly enough for recruitment to take place. Proper informed consent needs to be obtained as soon as possible[359].

- An implied informed consent is accepted when a participant for example implies their informed consent by returning a completed **anonymised** questionnaire. In this case however it will have to be impossible for researchers to identify the participants in any possible way[360].

3.5 Information to be addressed in the informed consent form

Each person giving consent, whether a participant himself or the representative of a child, should be provided with all necessary information in both written and verbal form. Time should be allowed for discussion of the aims, methods, benefits and risks of the clinical trial proposed. Time should also be allowed to consider the decision and if desired discuss the information with relatives, friends or healthcare professionals[361]. Parahoo therefore describes the informed consent as "the process of agreeing to take part in a study based on access to all relevant and easily digestible information about what participation means, in particular, in terms of harms and benefits"[362].

It is regarded good clinical practice is the UK to provide potential participants in clinical trials more specifically with information on:

- The purpose of the clinical trial;
- The duration of the participation;
- Who is involved in the clinical trial;
- The practicalities, procedures and expectations involved in participating;
- The possible benefits and risks of participation and when appropriate, the alternative therapies;
- How data about them will be managed and used;

[359] S. Andrew Spencer (2004) "Research governance regulations and paediatric research", Current Paediatrics, 14, 532-539.

[360] Royal College of Nursing Research Society (2011) "Informed consent in health and social care research", available online from www.rcn.org.uk.

[361] S. Andrew Spencer (2004) "Research governance regulations and paediatric research", Current Paediatrics, 14, 532-539.

[362] K. Parahoo (2006) Nursing research: principles, process and issues, Basingstoke: Palgrave Machmillan.

- How long and where the data will be stored;
- Why consent is requested;
- How further information will be provided to participants throughout the clinical trial and how and where questions can be addressed;
- The insurance indemnity arrangements for the conduct for the clinical trial where appropriate;
- That the clinical trial has been approved by a research ethics committee.

With regard to the description of the risks and benefits it should be stressed that potential participants should of course be informed of the potential benefits they may experience when taking part in the trial, but this may not lead to people being persuaded to participate for the wrong reasons. The benefits should be clearly balanced with not only the possible physical, but also the emotional, psychological and economical consequences of the trial[363]. Training for personnel obtaining informed consents is therefore also considered to be no needless luxury[364].

In Schedule 1, Part III of the Medicines for Human Use Regulations 2004 specific provisions are foreseen for the involvement of **minors in clinical trials**. These specific provision first of all stress that no minor can be included in a clinical trial before "a person with parental responsibility for the minor […] has had an interview with the investigator or another member of the investigating team, in which he has been given the opportunity to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted". Secondly it is stressed that a contact point for further questions should be available and made known. Next to the legal representative, the minor too has the right to be informed. Paragraph 6 more specifically states that the minor should receive "information according to his capacity of understanding, from staff with experience with minors, regarding the trial, its risks and its benefits".

3.6 Rights of the clinical trials subject

The most important right of the legal representative of the minor is the right to **withdraw** the minor from the trial at any time. The informed consent form should therefore explicitly describe that the person with parental responsibility or the legal representative may without the minor being subject to any resulting detriment, withdraw the minor from the trial at any

[363] Department of Health (2005) Research governance framework for health and social care, available online from www.dhgov/uk/en; Royal College of Nursing Research Society (2011) "Informed consent in health and social care research", available online from www.rcn.org.uk.

[364] S. Andrew Spencer (2004) "Research governance regulations and paediatric research", Current Paediatrics, 14, 532-539.

time by revoking his informed consent[365]. As indicated above, discussion does however exist in the UK on the right of the minor himself to leave the trial[366].

3.7 Authorisation of the informed consent forms (by ethic committees and competent authorities

In the UK a lot of criticism is expressed on the implication of the implementation of the Clinical Trials Directive. Data of notifications to competent authorities have shown a decrease in the overall number of clinical trials. From 2004 to 2005 for example (the time when the Medicines for Human Use Regulations was enacted) a 22% decrease in clinical trials was noted, affecting first and foremost academic trials. While commercial trials did recover from this decrease in the following years, academic trials continued to drop drastically, reaching a number in 2008 still only around half of that in 2004[367]. The main reason for this decrease is ought to be the overregulation of clinical trials since the deemed stringent implementation of the EU Clinical Trials Directive and more specifically on the one hand the monitoring of clinical trials by the Medicine and Healthcare products Regulatory Agency and on the other hand the multiplicity of ethical approvals the implementation brought along[368].

Ethical approval

All UK research should be approved by the relevant ethics committee before it is started. Independent scrutiny includes the consideration of the proposed process for gaining informed consent. The Ethics Committee will want to assure that all participants freely give informed consent and will therefore scrutinize carefully the participant information sheet and the proposed process relating to obtaining informed consent[369]. "Getting the information sheet right is an essential part of the process" Andrew Spencer states, "the lay membership of the committee will judge whether the average patient in the clinic or ward would be able to understand the project"[370]. For clinical trials involving minors this should include the advice of the relevant field of paediatric care.

[365] Schedule 1, Part III, 3. and 5.

[366] See: VI1.3

[367] K. Robinson and P. Andrews (2011) "'(More) trials and tribulations': the effect of the EU directive on clinical trials in intensive care and emergency medicine, five years after its implementation", JME, 36, 6, 322-325.

[368] M. Rawlins (2011) "A new era for UK clinical research?", The Lancet, vol 377.

[369] Royal College of Nursing Research Society (2011) "Informed consent in health and social care research", available online from www.rcn.org.uk.

[370] S. Andrew Spencer (2004) "Research governance regulations and paediatric research", Current Paediatrics, 14, 532-539.

The Ethics Committee competent to approve of the clinical trial, depends on the nature of the research and is determined by the United Kingdom Ethics Committees Authority. The Authority is responsible for establishing, recognizing and monitoring Ethics Committees that give opinions on clinical trials[371].

Consistent with the EU Clinical Trials Directive a single opinion for ethical review is installed in the UK. The sponsor or investigator has to apply to a main Research Ethics Committee for the review of the protocol, the information sheet and informed consent, questionnaires, advertisements etc. The Research Ethics Committee may be an NHS research ethics committee, a university or faculty research committee or any other independent research ethics committee[372]. In multi-centre trials this single opinion ethical review has however to be complemented with site-specific approval. Each investigator site applies for such a site-specific approval from their research and development department or their local ethics committee. "It is not a second review, but acts as a check on the local suitability of the trial documentation, investigator qualifications and site suitability", Dyson and Garrisi clarify[373].

Regulatory approval

Clinical trials involving investigational medicinal products need to be approved by the Licensing Authority consisting of the health ministers acting through the Medicines and Healthcare products Regulatory Agency[374].

4 Consent for data processing

4.1 Data protection framework in the UK

The EU Data Protection Directive 95/46/EC is implemented in UK law by the Data Protection Act 1998.

The Data Protection Act 1998 should however be read together with the common law on confidentiality as both sources of law influence each other. The common law duty of confidentiality is based on the action in contract, the tort of negligence and as a sui generis action.

- An **action in contract** can be used by private patients in their contractual relationship with their doctor[375].

[371] S. Shorthose (ed.) (2010) Guide to EU Pharmaceutical Regulatory Law, Kluwer International.
[372] K. Dyson and D. Garrisi (2011) "Research in the United Kingdom", Applied Clinical Trials, 44-49.
[373] K. Dyson and D. Garrisi (2011) "Research in the United Kingdom", Applied Clinical Trials, 44-49.
[374] S. Shorthose (ed.) (2010) Guide to EU Pharmaceutical Regulatory Law, Kluwer International.
[375] Reynolds v health First Medical Group, 2000 and Pfizer Corporation v Ministry of Health, 1965.

- The **tort of negligence** considers the duty to confidentiality to be part of the duty of care. The tort of negligence can however only be applied when actionable damage has been caused and this is not very frequent following an information breach.
- Finally an action for the breach of confidence could also be brought as a **sui generis action** derived from the law of equity[376].

The common law on confidentiality will sometimes apply where the Data Protection Act 1998 will not and vice versa. Not all misuse of confidential or private information will fall within the Data Protection Act and not all processing of personal data will constitute relevant misuse of confidential information. Pattinson illustrates this interaction with the following examples: Patients often divulge information about their personal lives to their healthcare professional, but this information is not necessarily recorded in an accessible record or as part of a relevant filing system; Medical information that is not held in connection with the care of an individual could fall out of the Data Protection Act when it is handwritten and not stored in a relevant filing system[377].

Many other legislative documents refer to these two sources of law for the protection of personal information. This is for example also the case for the Medicinal Products Use (Clinical Trials) Regulations 2004. In Schedule 1, Part II, 11 the Regulations state that: "The confidentiality of records that could identify subjects shall be protected, respecting the privacy and confidentiality rules in accordance with the requirements of the Data Protection Act 1998 and the law relating to confidentiality".

4.2 Data subject

Under the UK Data Protection Act 1998 data subjects are ought to be those individuals who are subject of the personal data collected. Only living individuals are protected under the Act[378].

4.3 Personal data and sensitive personal data

The concept of personal data is defined as widely in the UK Act as in the EU Directive. S.1(1) defines personal data as:

"data which relate to a living individual who can be identified (a) from those data; or (b) from those data and other information which is in the possession of or is likely to come into the possession of the data controller, and includes any expression or opinion about the individual and any indication of the intentions of the data controller or any other person in respect of the individual"

[376] S.D. Pattinson, Medical law and ethics, 2006, Thomson Sweet & Maxwell.
[377] S.D. Pattinson, Medical law and ethics, 2006, Thomson Sweet & Maxwell.
[378] S.1(1) Data Protection Act 1998.

Different from the EU Directive, the UK Act does however explicitly mention the patient's health record, whether kept electronically or in manual form, as a type of personal data[379]. S.68(2) defines a health record as: "any record consisting of information relating to the physical or mental health or condition of an individual that has been made by or on behalf of a health professional in connection with the care of that individual". The category of health professionals includes doctors, dentists, nurses and the like[380].

Health records as defined by the Act may contain both personal data and sensitive personal data. The processing of personal data is regulated under Schedule 2 of the Data Protection Act 1998, whereas the processing of sensitive personal data is regulated under Schedule 3. Sensitive personal data are defined as to include all information about a person's physical or mental health or condition: "In this Act "sensitive personal data" means personal data consisting of information as to— (e)his physical or mental health or condition"[381].

4.4 Consent

As indicated in the previous paragraph, schedule 2 regulates the use of **personal (non-sensitive) data**. One of the conditions under which these data may be processed is with the **consent** of the data subject[382]. Consent under this schedule is not required to be explicit but "lack of definitional detail does leave some ambiguity as to when consent can (as a matter of law) be taken to have been given in the absence of explicit words of acceptance or equivalent conduct" Pattinson signals[383]. Sometimes doctrine argued that consent could have been given when the patient has not opted out. However, the consistency of this interpretation with the original EU Directive could be questioned.

Sensitive personal data too may be processed after having obtained consent of the patient. However, in this case the consent needs to be given explicitly[384]. There is no requirement that the consent is made in writing. **Explicit oral consent** suffices. Nevertheless Jay argues that due to the fact it needs to be explicit, it is likely that it must be clear and unambiguous and therefore data controllers may prefer to "ensure that the explicit consent is signified in writing in order to fend off any criticism that the required consent was insufficiently clear and unambiguous"[385].

[379] Ss.1(1) and s.68 Data Protection Act 1998.
[380] S.69(1) Data Protection Act 1998.
[381] S.2(e) Data Protection Act 1998.
[382] Schedule 2, 1. Data Protection Act 1998.
[383] S.D. Pattinson, Medical law and ethics, 2006, Thomson Sweet & Maxwell.
[384] Schedule 3, 1. Data Protection Act 1998.
[385] R. Jay (2007) Data Protection Law and Practice, Sweet & Maxwell London.

In order for the consent to be considered valid it is furthermore presumed that the same requirements apply as described above with regard to the informed consent for care[386]. "Presumed", because no explicit definition is provided in the Data Protection Act 1998 and no clarification is made by courts[387]. One difference which should however not be forgotten is that, as explained in the beginning of this section, the Data Protection Act does not accept fictional consent for processing health data.

Schedule 1, part II does implicitly require the consent to always be informed. It foresees that when the processed data are obtained from the data subject directly, specific information has to be provided so far as is practicable. When the processed data are not obtained from the data subject, specific information must also be provided so far as practicable, but unless doing so would involve disproportionate effort. The information which must be provided includes:

- The use of the data
- The identity of the data controller
- The identity of any person to whom the data will be disclosed
- Any further information that is necessary to enable the processing to be fair[388].

When the patient validly consents to the disclosure of his information under the Data Protection Act, this will also prevent the legal duty of confidentiality from being breached. The patient's consent operates as a waiver of the duty.

4.5 Consent for the use of retrospective data

When personal data are processed for research purposes, the Data Protection Act does not breach the purpose based principle when (a) no measure or decision relating to a particular individual is based on it and (b) the use is unlikely to cause substantial damage or substantial distress to any data subject[389]. Following this principle, the Court of Appeal took in the Source Informatics case the view that properly anonymised data falls outside the scope of the Data Protection Act and the Data Protection Directive[390]. However, this interpretation could certainly be questioned. The Court of Appeal argued in the same case that even though confidential information does not lose all protection as soon as it is anonymised, patient information is no longer subject to a duty of confidentiality one it has been fully and effectively anonymised by a party who has lawfully obtained it.

[386] See: VI2.2
[387] R. Jay (2007) Data Protection Law and Practice, Sweet & Maxwell London.
[388] Schedule 1, Part II Data Protection Act 1998.
[389] S.33(1) and (2) Data Protection Act 1998.
[390] Ex p. Source Informatics, 2001, Q.B. 424.

It should however be noted that although the Data Protection Act 1998 does not expressly require it, there may be circumstances where fair obtaining of personal data requires the data subject to have the opportunity to opt out of additional uses and disclosures of the information he or she has provided beyond the primary purpose for which it was supplied. Also in situations where the individual does have this choice, it would constitute good practice to offer the same opt out option[391].

4.6 Supervisor Authorities and their role

In order to create transparency, UK law too requires a notification of every processing of personal data to the Data Protection Authorities[392]. A few exemptions on the duty to notify have been foreseen by the Data Protection Act, but since these are of minor importance to this country report, they will not be further discussed here.

[391] R. Jay (2007) Data Protection Law and Practice, Sweet & Maxwell London

[392] S.17(1) and s.21(1) Data Protection Act 1998.

Annexes

Annex 1: List of legislation used within the document

International documents

Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine Oviedo, 04.04.1997	
The Nuremberg Code	
Organisation for Economic Co-operation and Development Guidelines on the Protection of Privacy and Transborder Flows of Personal Data adopted on 23.09.1989	
Council of Europe Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data adopted on 28.01.1981	
The Convention for the Protection of Human Rights and Fundamental Freedoms Rome, 04.11.1950	

EU legislation

Charter of Fundamental Rights of the European Union 02.10.2000	
Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use	Directive 2003/94/EC
Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC	Directive 2001/18/EC
Directive 2001/20/EC of 4 April 2001, of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use	Clinical Trials Directive, or Directive 2001/20/EC
Directive 95/46/EC on the protection of individuals with	Data Protection Directive, or Directive

regard to the processing of personal data and on the free movement of such data	95/46/EC
Regulation 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004	Regulations EC 1901/2006

Belgian legislation

Belgische Grondwet	Belgian Constitution
Burgerlijk Wetboek	Belgian Civil Code
Wet van 22 augustus 2002 betreffende de rechten van de patiënt, BS 26 september 2002.	Law on Patient Rights or LPR
Wet van 7 mei 2004 betreffende experimenten op de menselijke persoon, BS 18 mei 2004.	Law concerning Experiments on the Human person or LEH
Wet van 29 april 1999 inzake de geneeskunde, de artsenijbereidkunde, de kinesitherapie, de verpleegkunde en de paramedische beroepen, BS 24 juni 1999	Law concerning healthcare, physiotherapy, nursing and paramedical professions
Wet van 8 december 1992 tot bescherming van de persoonlijke levenssfeer ten opzichte van de verwerking van persoonsgegevens, BS 18 maart 1993	Data Protection Act
Koninklijk besluit nr. 78 van 10 November 1967 betreffende de uitoefening van gezondheidszorgberoepen, BS 14 november 1967.	Royal Decree concerning the performance of health care professions
Koninklijk besluit van 30 juni 2004 tot bepaling van uitvoeringsmaatregelen van de wet van 7 mei 2004 inzake experimenten op de menselijke persoon voor wat betreft klinische proeven met geneesmiddelen voor menselijk gebruik, BS 2 juli 2004.	Royal Decree implementing the LEH for clinical trials involving medication for human use
Koninklijk besluit van 6 juni 1960 betreffende de fabricage, de distributie in het groot en de terhandstelling van geneesmiddelen zoals gewijzigd bij besluit van 30 juni 2004, BS 22 juni 1960.	Royal Decree on the production and distribution of medication
Koninklijk besluit van 15 juli 2004 tot bepaling van de bijdragen te betalen in het kader van een verzoek om advies of toelating voor het uitvoeren van een klinische proef of een experiment, BS 16 juli 2004 .	Royal Decree determining the retributions to be paid in the context of an application for a clinical trial or an experiment
Koninklijk besluit van 27 april 2007 betreffende de vergoedingen in de context van artikel 30§6 WEMP.	Royal Decree providing the fees to be paid in the context of Article 30§6 LEH

German legislation

Grundgesetz für die Bundesrepublik Deutschland in der im Bundesgesetzblatt Teil III, Gliederungsnummer 100-1, veröffentlichten bereinigten Fassung, das zuletzt durch Artikel 1 des Gesetzes vom 21. Juli 2010 (BGBl. I S. 944) geändert worden ist	German Constitution or GG
Bürgerliches Gesetzbuch in der Fassung der Bekanntmachung vom 2. Januar 2002 (BGBl. I S. 42, 2909; 2003 I S. 738), das zuletzt durch Artikel 1 des Gesetzes vom 27. Juli 2011 (BGBl. I S. 1600) geändert worden ist	German Civil Code or BGB
Strafgesetzbuch in der Fassung der Bekanntmachung vom 13. November 1998 (BGBl. I S. 3322), das zuletzt durch Artikel 1 des Gesetzes vom 6. Dezember 2011 (BGBl. I S. 2557) geändert worden ist	German Criminal Code or StGB
Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. I S. 3394), das zuletzt durch Artikel 1 der Verordnung vom 19. Juli 2011 (BGBl. I S. 1398) geändert worden ist, hereafter Arzneimittelgesetz	Medicinal Products Act or AMG
Medizinproduktegesetz in der Fassung der Bekanntmachung vom 7. August 2002 (BGBl. I S. 3146), das zuletzt durch Artikel 13 des Gesetzes vom 8. November 2011 (BGBl. I S. 2178) geändert worden ist	Medical Device Act or MPG
Transfusionsgesetz in der Fassung der Bekanntmachung vom 28. August 2007 (BGBl. I S. 2169), das durch Artikel 12 des Gesetzes vom 17. Juli 2009 (BGBl. I S. 1990) geändert worden ist	Transfusion Act or TFG
Bundesdatenschutzgesetz in der Fassung der Bekanntmachung vom 14. Januar 2003 (BGBl. I S. 66), das zuletzt durch Artikel 1 des Gesetzes vom 14. August 2009 (BGBl. I S. 2814) geändert worden ist	Bundesdatenschutzgesetz or Federal Data Protection Act or BDSG

Polish legislation

The Constitution of the Republic of Poland of 2 April 1997 Dz.U. 1997, NR 78 poz. 483.	Polish Constitution
Civil Code, Dz.U. 1964 nr 16 poz. 93.	Polish Civil Code
Polish Family and Guardianship Code of 25 February 1964 Dz.U. 1964 nr 9 poz. 5.	
Act from 6 November 2008 on Patients' Rights and the Commissioner for Patients' Rights Dz.U. 2009 nr 52 poz. 417.	

Act on doctor's profession of 5 December 1996
Dz.U. 1997 nr 28 poz. 152

Act on the Pharmaceutical Law of 6 September 2001
Dz.U. 2001 nr 126 poz. 1381

Pharmaceutical Law

Health Minister Order in matter of the Central Records of Clinical Trials of 29 November 2002

Health Minister Order in matter of specific requirements of Good Clinical Practice of 11 March 2005,

Health Minister Order in matter of way and range of inspection of clinical trials in range of accordance these trial with requirements of Good Clinical Practice of 10 December 2002,

Health Minister Order in matter of determination of detailed requirements of Good Clinical Practice of 10 December 2002,

Health Minister Order in matter of detailed principles of appointing and financing a bioethical commission of 11 May 1999,

Health Minister Order in matter of way of conduct clinical trials with part of juveniles of 30 April 2004

Act of 29 August 1997 on the Protection of Personal Data

UK legislation

Medicines for Human Use (Clinical Trials) Regulations 2004

Children Act 1989

Family Law Reform Act 1969

Mental Capacity Act 2005

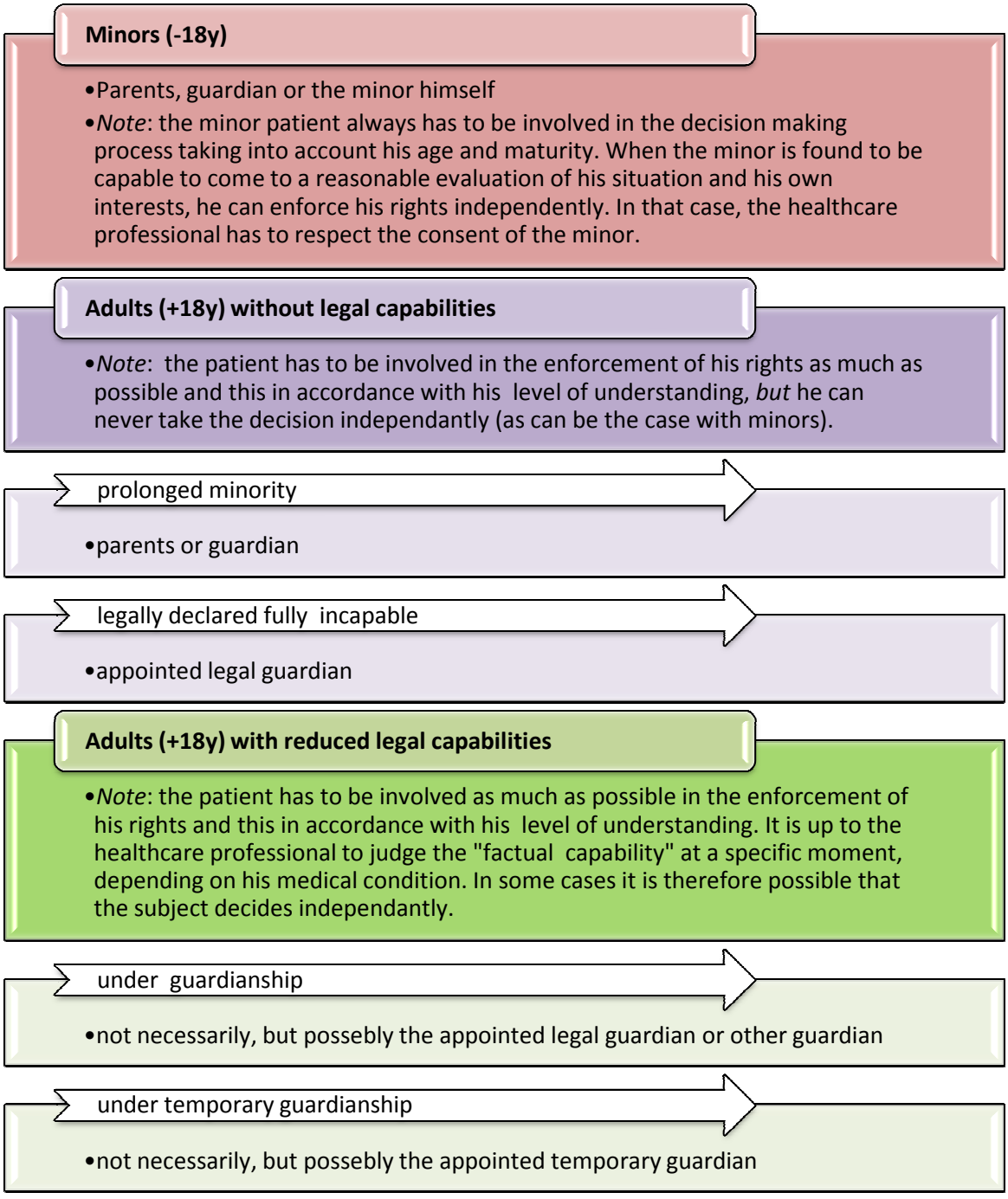
Adults with Incapacity (Scotland) Act 2000

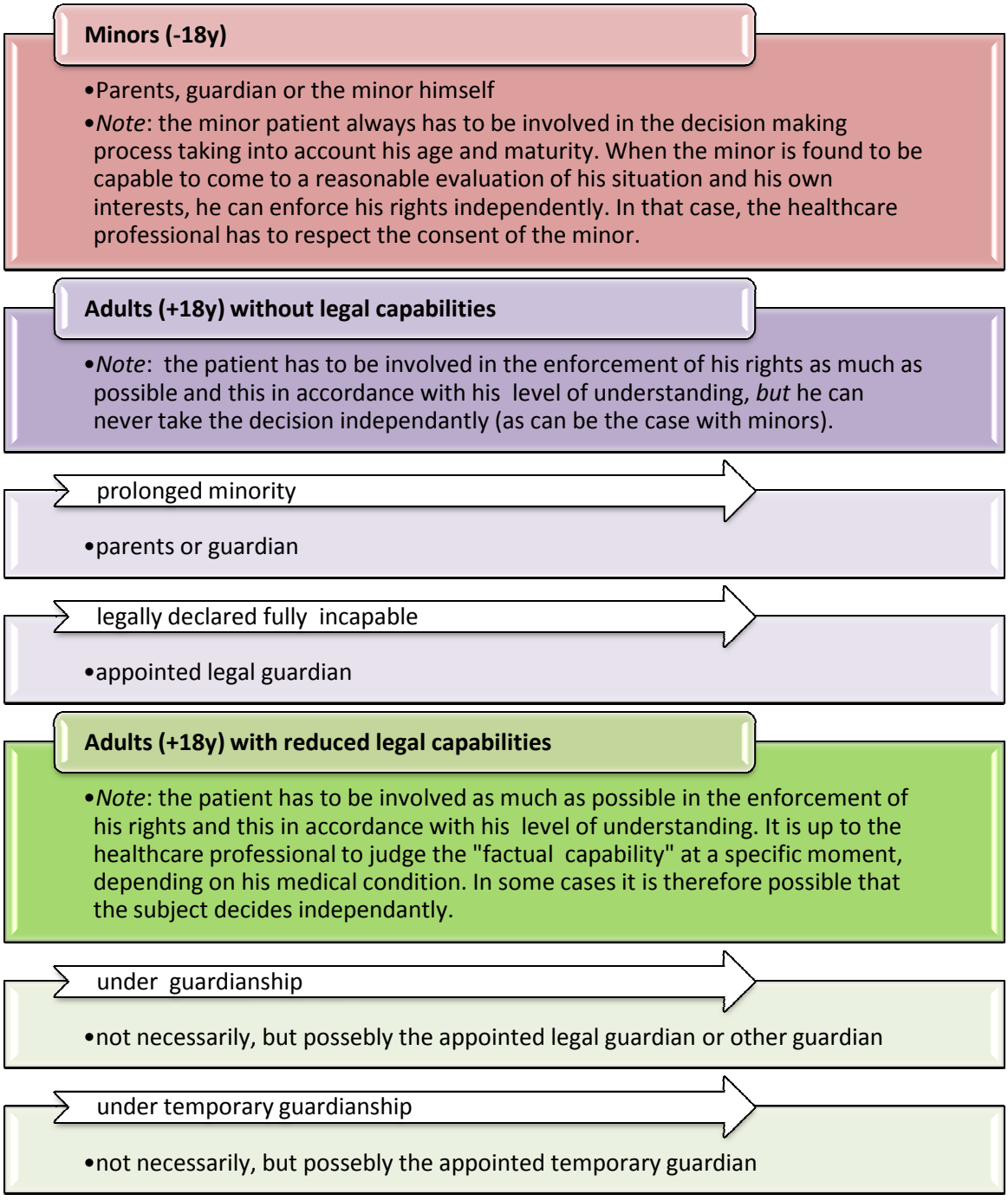
Age of Legal Capacity (Scotland) Act 2001

Data Protection Act 1998

Annex 2: Patient representation scheme

This table should help you recognise, who should sign the informed consent form in case the patient/ clinical trial subject cannot do it on his/ her behalf (based on Belgian law – national differences may apply)


Minors (-18y)
•Parents, guardian or the minor himself
•*Note*: the minor patient always has to be involved in the decision making process taking into account his age and maturity. When the minor is found to be capable to come to a reasonable evaluation of his situation and his own interests, he can enforce his rights independently. In that case, the healthcare professional has to respect the consent of the minor.
Adults (+18y) without legal capabilities
•*Note*: the patient has to be involved in the enforcement of his rights as much as possible and this in accordance with his level of understanding, *but* he can never take the decision independantly (as can be the case with minors).
prolonged minority
•parents or guardian
legally declared fully incapable
•appointed legal guardian
Adults (+18y) with reduced legal capabilities
•*Note*: the patient has to be involved as much as possible in the enforcement of his rights and this in accordance with his level of understanding. It is up to the healthcare professional to judge the "factual capability" at a specific moment, depending on his medical condition. In some cases it is therefore possible that the subject decides independantly.
under guardianship
•not necessarily, but possebly the appointed legal guardian or other guardian
under temporary guardianship
•not necessarily, but possebly the appointed temporary guardian


Minors (-18y)
•Parents, guardian or the minor himself
•*Note*: the minor patient always has to be involved in the decision making process taking into account his age and maturity. When the minor is found to be capable to come to a reasonable evaluation of his situation and his own interests, he can enforce his rights independently. In that case, the healthcare professional has to respect the consent of the minor.
Adults (+18y) without legal capabilities
•*Note*: the patient has to be involved in the enforcement of his rights as much as possible and this in accordance with his level of understanding, *but* he can never take the decision independantly (as can be the case with minors).
prolonged minority
•parents or guardian
legally declared fully incapable
•appointed legal guardian
Adults (+18y) with reduced legal capabilities
•*Note*: the patient has to be involved as much as possible in the enforcement of his rights and this in accordance with his level of understanding. It is up to the healthcare professional to judge the "factual capability" at a specific moment, depending on his medical condition. In some cases it is therefore possible that the subject decides independantly.
under guardianship
•not necessarily, but possebly the appointed legal guardian or other guardian
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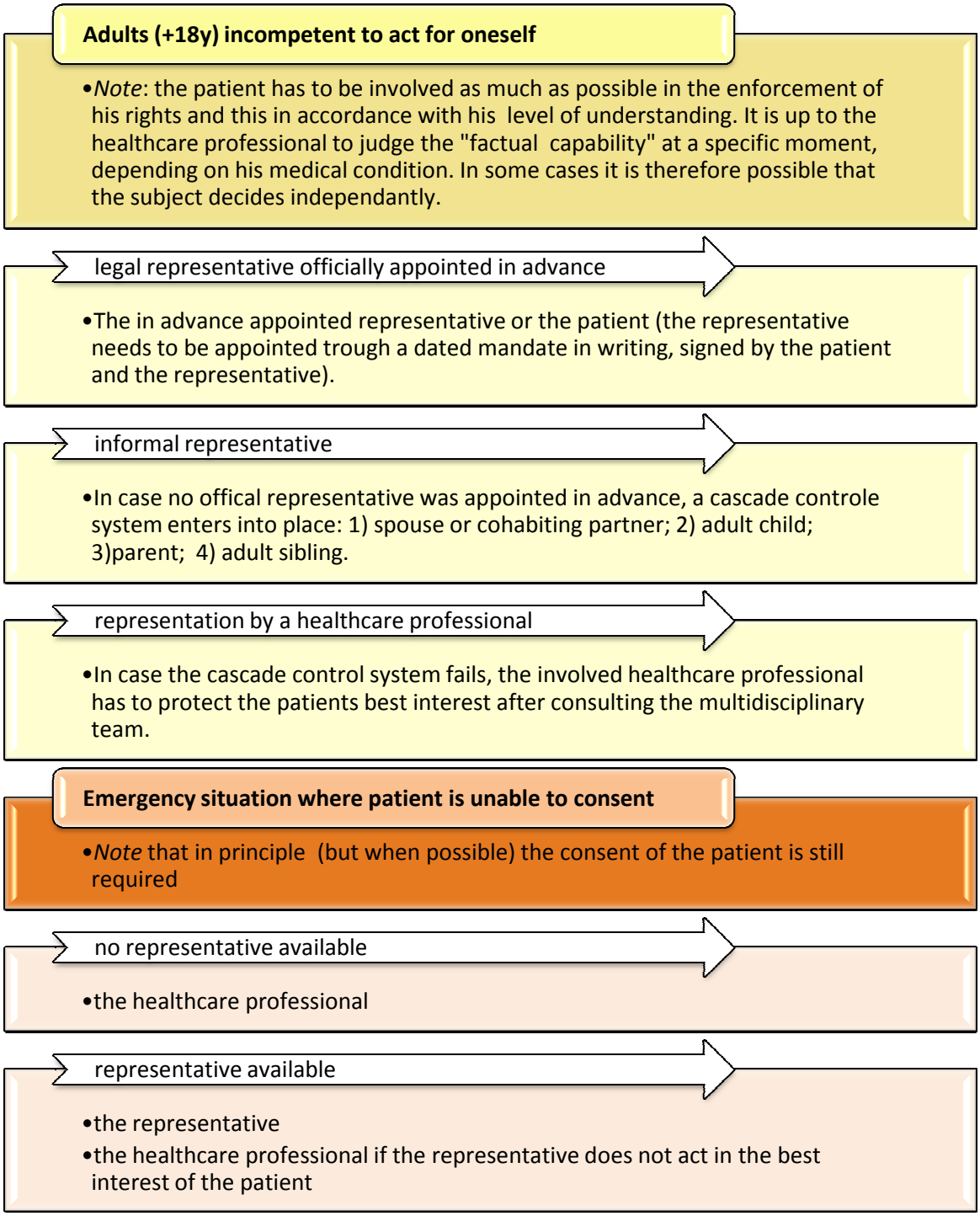
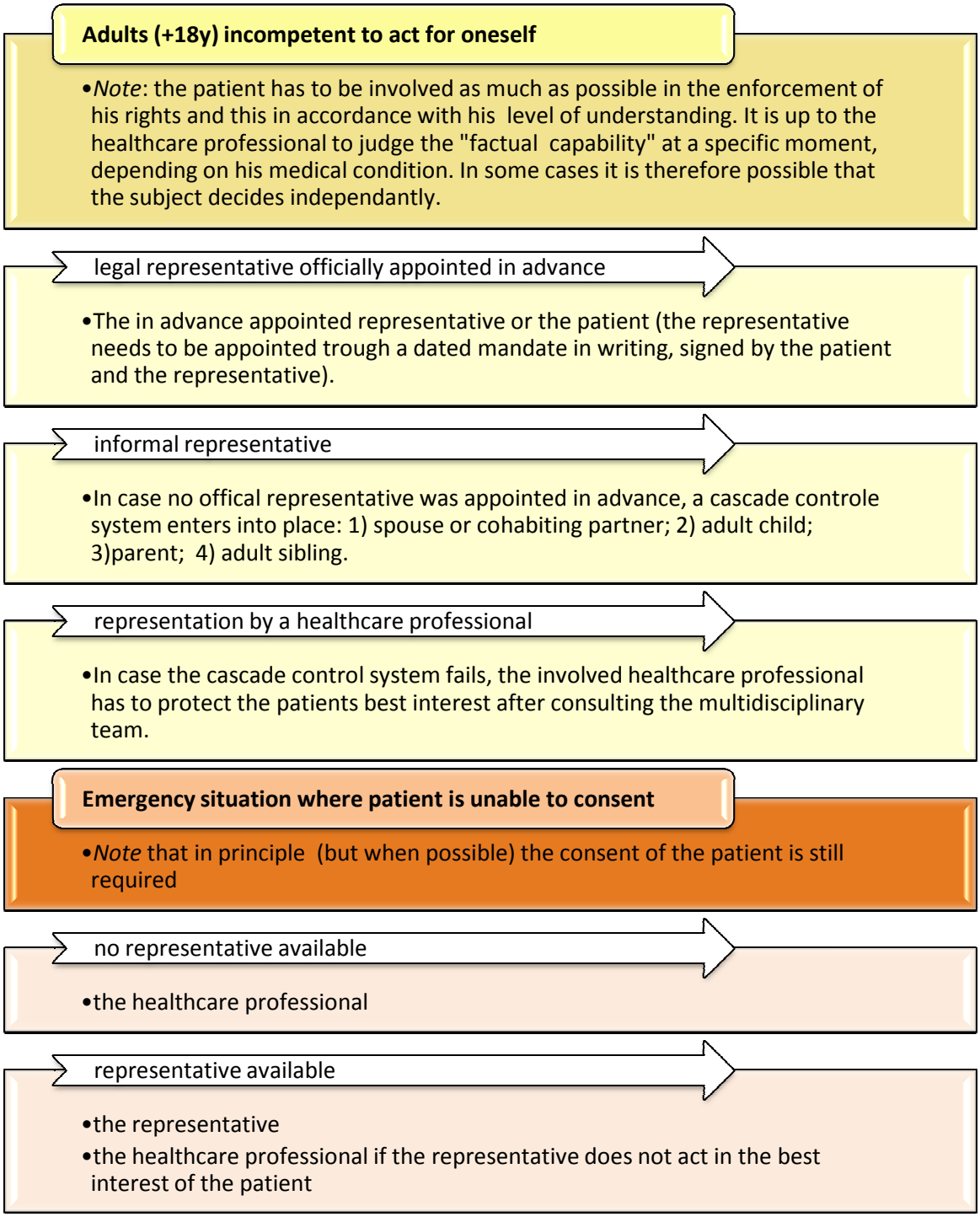

Adults (+18y) incompetent to act for oneself
•Note: the patient has to be involved as much as possible in the enforcement of his rights and this in accordance with his level of understanding. It is up to the healthcare professional to judge the "factual capability" at a specific moment, depending on his medical condition. In some cases it is therefore possible that the subject decides independantly.
legal representative officially appointed in advance
•The in advance appointed representative or the patient (the representative needs to be appointed trough a dated mandate in writing, signed by the patient and the representative).
informal representative
•In case no offical representative was appointed in advance, a cascade controle system enters into place: 1) spouse or cohabiting partner; 2) adult child; 3)parent; 4) adult sibling.
representation by a healthcare professional
•In case the cascade control system fails, the involved healthcare professional has to protect the patients best interest after consulting the multidisciplinary team.
Emergency situation where patient is unable to consent
•Note that in principle (but when possible) the consent of the patient is still required
no representative available
•the healthcare professional
representative available
•the representative
•the healthcare professional if the representative does not act in the best interest of the patient


Adults (+18y) incompetent to act for oneself
•Note: the patient has to be involved as much as possible in the enforcement of his rights and this in accordance with his level of understanding. It is up to the healthcare professional to judge the "factual capability" at a specific moment, depending on his medical condition. In some cases it is therefore possible that the subject decides independantly.
legal representative officially appointed in advance
•The in advance appointed representative or the patient (the representative needs to be appointed trough a dated mandate in writing, signed by the patient and the representative).
informal representative
•In case no offical representative was appointed in advance, a cascade controle system enters into place: 1) spouse or cohabiting partner; 2) adult child; 3)parent; 4) adult sibling.
representation by a healthcare professional
•In case the cascade control system fails, the involved healthcare professional has to protect the patients best interest after consulting the multidisciplinary team.
Emergency situation where patient is unable to consent
•Note that in principle (but when possible) the consent of the patient is still required
no representative available
•the healthcare professional
representative available
•the representative
•the healthcare professional if the representative does not act in the best interest of the patient

Annex 3: stakeholder interviews

First Interview

Role	*Investigator*
Main Trial Responsibilities	*Obtaining informed consent for a voluntary genetic sub study*
Clinical Trial Experience	*5 years*

1. Could you please describe the informed consent procedure for clinical trials in your hospital!
- Where does it take place?

Mainly in the visitor's room of the department for paediatric oncology / haematology

- Who is involved in the process?

The investigator and the parents/ legal representative(s)

- Oral conversation?

It is an oral conversation where the parents are informed about the trial objective(s), the trial procedures, the voluntary participation, and the possible health impacts of the invasive procedures. It is clearly stated that the trial is only carried out for research purposes and that it will have no direct effect on the child's recovery.

- Usage of information sheet or other tools?

At the beginning of the consent discussion the patient information sheet is handed out and the physician explains all information written there.

- How much time for decision is normally given?

Depends on the parents/ legal representative(s),as much time for consideration as required is given. Mainly the consent is signed directly after the conversation.

- Documentation of consent process?

The date of informed consent is noted in the patient's health records.

2. In which way are the minors/ adolescents integrated in the informed consent process?

- Who is involved in the process?

Normally, only the parents/ legal representative(s) together with the investigator are involved in the consent process. But the patients/ subjects are allowed to take part if they want.

- From what age onwards are minors involved?

From the age of 16, it is obligatory to take part in the consent procedures and patients/ subjects should also sign the consent form.

- Any measurements to judge minors capability to consent?

No

3. How do you make sure that the parents/ legal representative(s)/ patients have fully understood the content/ implications of the clinical trial and that the decision to participate has been taken fully knowingly and voluntarily?

There are no special methods/ measurements to check the comprehension of the trial and associated implications and the voluntariness of participation. Based on the patients/ subjects as well as parents'/ legal representatives' questions during and after the consent discussion the investigator get an impression of the understanding.

- How do you deal with patients (respective parents/ legal representative(s)) with lack of German language skills?

-There is a list of interpreters who can be asked to assist the informed consent discussion. But if the investigator feels, that parents/ legal representative(s) do not understand anything, no consent will be obtained.

4. What happens if a patient (or respective parents/ legal representative(s)) does not want to take part in a clinical trial or wants to withdraw from a clinical trial?

Trial participation is virtually never refused. But if a patient/subject, parent/ legal representative denies, then the normal standard treatment is continued.

5. a) How do you document and report the results of the clinical trials and especially adverse events/ serious adverse events? ((e)health records, paper CRF/ eCRF)

- AEs/ SAEs practically never occur. They will be reported by the treating physician.

6. In your opinion, what do you think is the biggest problem in clinical research with children?

Missing entries in the health records and on the CRFs. Often surgeons or pathologists who are treating the patients or the patient's tissue refuse to complete the respective CRFs or document the trial specific information.

Second Interview

Role	*Study documentalist*
Main Trial Responsibilities	*Preparation of informed consent documents, completion of CRFs, investigator site file management*
Clinical Trial Experience	*3 years*

1. Could you please describe the informed consent procedure for clinical trials in your hospital!
- Where does it take place?

Mainly in the visitor's room of the department for paediatric oncology / haematology

- Who is involved in the process?

At least one investigator and parents/ legal representative(s). But it is not known if a psychologist and/ or study nurse is also present.

- Oral conversation?

It's an oral conversation.

- Usage of information sheet or other tools?

The parents/ legal representative(s) are provided with patient information sheets. Sometimes there is a study specific checklist for the investigator, where all issues to be discussed are listed. Since about 2 years, there are also written assent documents for minor patients from the age of 8 and onwards which can be used to explain the main study procedures and implications.

- How much time for decision is normally given?

Not known

- Documentation of consent process?

Investigator site file, patient health records.

2. In which way are the minors/ adolescents integrated in the informed consent process?
- Who is involved in the process? From what age onwards are minors involved?

From the age of 16 it is obligatory for patients to sign the consent form. According to his/ her capacity of understanding, also minors younger than 16 may sign the consent form.

- Any measurements to judge minors capability to consent?

Not known.

3. How do you make sure that the parents/ legal representative(s)/ patients have fully understood the content/ implications of the clinical trial and that the decision to participate has been taken fully knowingly and voluntarily?

Not known

- How do you deal with patients (respective parents/ legal representative(s)) with lack of German language skills?)

Not known

4. What happens if a patient (or respective parents/ legal representative) does not want to take part in a clinical trial or wants to withdraw from a clinical trial?

Trial participation is virtually never refused. If participation in a therapy – optimization – study is denied than normally the patients are treated as 'observational patients'.

5. a) How do you document and report the results of the clinical trials and especially adverse events/ serious adverse events? ((e)health records, paper CRF/ eCRF)

SAEs are documented on SAE forms and in the patient's health records and reported to the sponsor exclusively by investigators. AEs are documented in health records by treating physicians/ nurses. Mainly study nurses/ study documentalist complete the CRFs, after review and signature by a responsible investigator they are reported to the sponsor.

6. In your opinion, what do you think is the biggest problem in clinical research with children?

Therapy – optimization – studies have the equal status than any other clinical trial. All regulations of the pharmaceutical legislation fully apply to this type of studies. Due to the high administrative burden (lot of different application forms and notification to different authorities, ethic committees) the start of the trial and the treatment of the patients are often delayed.

Third Interview

Role	*Principle investigator/ investigator*
Main Trial Responsibilities	*In general: Overall responsibility for the trial* *In particular: Obtaining informed consent, medical treatment of patients*
Clinical Trial Experience	*17 years*

1. Could you please describe the informed consent procedure for clinical trials in your hospital!
- Where does it take place?

On ward of the department for paediatric oncology / haematology

- *Who is involved in the process?*

Normally, only the investigator and the parents/ legal representative(s) are involved. It is consciously avoided involving more site staff (e. g. study nurses, psychologists, etc.) to ensure a trustworthy atmosphere and not put the parents/ legal representative(s) under pressure.

- Oral conversation?

The clinical trial and its objectives, implications, procedures are explained in detail during a face to face conversation.

- Usage of information sheet or other tools?

The parents/ legal representative(s) are provided with study specific information sheets.

- How much time for decision is normally given?

Several days

- Documentation of consent process?

The inform consent discussion is noted in the patient's medical records and in the investigator site file.

2. In which way are the minors/ adolescents integrated in the informed consent process?
- Who is involved in the process/ from what age onwards are minors involved?

The trial is also discussed with minors dependent of mental capacity and their will. Besides the patient and the investigator a psychologist is present. There are age specific written trial information available from the age of about 8 years.

- Any measurements to judge minors capability to consent?

No

3. How do you make sure that the parents/ legal representative(s)/ patients have fully understood the content/ implications of the clinical trial and that the decision to participate has been taken fully knowingly and voluntarily?

Empirically, only about 20% of the content of discussion is understood. But as the minors with oncological diseases are mainly treated as inpatients, the contact between the (study) physician and the parents/ legal representative(s) is always very close and parents/ legal representative(s) have the possibility to ask questions at any time. Regarding the treatment optimization studies, the voluntary nature of the consent is relative, as a real alternative treatment is often not available.

- How do you deal with patients (respective parents/ legal representative(s)) with lack of German language skills?)

This is a real problem due to the lack of competent (medical, ethical and socio-cultural) interpreters. Sometimes in multi – national trials, there are foreign language information sheets which are used.

4. What happens if a patient (or respective parents/ legal representative(s)) does not want to take part in a clinical trial or wants to withdraw from a clinical trial?

Of course this is accepted but practically never happens. Virtually, neither parents/ legal representative(s) nor minors refuse.

5.- How do you document and report the results of the clinical trials and especially adverse events/ serious adverse events? ((e)health records, paper CRF/ eCRF)

- Who is responsible for documentation/ reporting?

Informed consent conversation (date, result) is recorded in the patient's medical records, AEs/ SAEs are noted in the medical records and the care documentation by treating physicians and nurses. SAE forms are completed by investigators only, who are also responsible for reporting the SAE to the respective sponsor. CRFs (including AE forms) are mainly completed by study nurses or documentalists and signed by investigator.

6. In your opinion, what do you think is the biggest problem in clinical research with *children?*

It is sometimes very difficult to obtain informed consent from separated parents with joined custody; especially, when one parent lives abroad and is not available for consent process.

Furthermore, due to the small sample size in paediatric oncology studies, almost all studies are international multi–centred studies. All invasive procedures have to be justified in a totally different (more extensive) way than with adult patients. Also the requirements of the German Medicine Act are too stringent and paediatric trials are too costly. For the pharmaceutical industries, the costs are not justified for products used for minors for whom there is little commercial return and therefore, the number of paediatric research trials sponsored by the pharmaceutical industry is very low.

Fourth Interview

Role	*Study nurse*
Main Trial Responsibilities	*Completion of CRFs, nursing care of (study) patients, performance of non- medical study specific interventions*
Clinical Trial Experience	*12 years*

1. Could you please describe the informed consent procedure for clinical trials in your hospital!
- Where does it take place?

Mainly in the visitor's room of the department for paediatric oncology / haematology

- Who is involved in the process?

In general the investigator and the parents/ legal representative(s) are present. Depending on the situation, sometimes also a second investigator and/ or interpreter and/ or psychologists and/ or a witness (e.g. nurse) are also involved.

- Oral conversation?

It is always a face – to – face discussion.

- Usage of information sheet or other tools?

Study specific patient information sheet is provided and sometimes there is also a specific consent information protocol. No multimedia is used for consent purposes.

- How much time for decision is normally given?

Parents/ legal representative(s) are given the time they need to decide, on average it is 24 hours.

- Documentation of consent process?

The investigator records the day of consent discussion in the patient's medical records. A copy of the dated and signed consent form is also stored in the medical records.

2. In which way are the minors/ adolescents integrated in the informed consent process?
- Who is involved in the process?

Before the start of the clinical trial, all minors are informed, by a investigator, in so far as this is possible taking into account the minor's age and mental maturity. Sometimes also the parents are present. The psychologist is mainly present during the inform consent discussion with adolescents.

- Assent/ consent?

The minors are informed about the trial and its implications mainly orally sometimes also pictures and visual comparisons are used. From the age of 16, the patients have to consent on the consent form in writing.

- From what age onwards are minors involved?

In general, all minors are informed.

- Any measurements to judge minors capability to consent?

No

3. How do you make sure that the parents/ legal representative(s)/ patients have fully understood the content/ implications of the clinical trial and that the decision to participate has been taken fully knowingly and voluntarily?

The study staff gets an idea of the parents' comprehension by the parents/ legal representative(s) questions during and after the informed consent discussion. Especially in the area of paediatric oncology, parents/ legal representative(s) are in close contact to the physician this allows the building of mutual trust and allows for the possibility to ask any questions.

- How do you deal with patients (respective parents/ legal representative(s)) with lack of German language skills?)

Sometimes professional interpreters, sometimes former affected parents or relatives or other clinic staffs with the respective language skills are used to translate the oral/ written consent information. Sometimes there is also an English version of the consent form.

4. What happens if a patient (or respective parents/ legal representative(s)) does not want to take part in a clinical trial or wants to withdraw from a clinical trial?

This very rarely occurs. Refuse or withdrawal is accepted and alternative treatment is offered.

5.- How do you document and report the results of the clinical trials and especially adverse events/ serious adverse events? ((e)health records, paper CRF/ eCRF)

- Who is responsible for documentation/ reporting?

SAEs are recorded and reported on the (study specific) SAE forms only by the physicians. SAE/ AE symptoms, diagnosis, treatment and outcome is recorded in the patient file mainly by the treating physician. Incidents/ symptoms observed by the nursing staff are noted in the patients care documentation. CRFs are mainly completed by the study nurse or study documentalist and signed by the respective investigator.

6. In your opinion, what do you think is the biggest problem in clinical research with children?

There are very strict legal requirements in paediatric trials and there is too much bureaucracy. The focus is on the documents and not on the patients.

Fifth Interview

Role	*Investigator*
Main Trial Responsibilities	*In general: Conducting the trial (including recording and reporting)* *In particular: Obtaining informed consent, medical treatment of patients*
Clinical Trial Experience	*17 years*

1. Could you please describe the informed consent procedure for clinical trials in your hospital!

- Where does it take place?

In a room within the department for paediatric oncology / haematology but not in a patient's room

- Who is involved in the process?

The investigator and the parents/ legal representative(s), sometimes also patients from the age of about 15 are involved in the initial consent discussion.

- Oral conversation?

It's an oral, face –to - face discussion. The language used by the investigator is adapted to the parents'/ legal representative(s)' educational level.

- Usage of information sheet or other tools?

Study specific written information documents (if provided by the sponsor and if these documents are not too long and written in a simple and easily understandable language) are used.

- How much time for decision is normally given?

This is dependent of the patient's medical situation, physical and health condition. If the patient suffers from a life – threatening condition, consent or at least a preliminary consent is obtained immediately after the initial consent discussion. In general, the parents/ legal representative(s) are given as much time as needed, on average about 1 – 2 days.

- Documentation of consent process?

A copy of the dated and signed consent form is filed in the patient's medical records.

2. In which way are the minors/ adolescents integrated in the informed consent process?

- Who is involved in the process?

Mainly, the investigator and the patient, sometimes the parents/ legal representative(s) are also present. Also the psychologist, nurses and educators are involved but mainly after the initial consent discussion over the course of the study.

- From what age onwards are minors involved?

Depends on age and mental maturity, from the age of 5 to 6 onwards, all patients are consented. The minors are mainly consented orally, sometimes by using pictures. Infants are mainly informed about the disease and the treatment in general and to a lesser extent about trial specific interventions. From the age of 16, patient's consent signature is mandatory.

- Any measurements to judge minors capability to consent?

The investigator assesses the mental capacity to consent on the basis of the minor's behaviour and his/ her experience in working with children.

3. How do you make sure that the parents/ legal representative(s)/ patients have fully understood the content/ implications of the clinical trial and that the decision to participate has been taken fully knowingly and voluntarily?

The study staff get an idea of the parents'/ legal representative(s)' comprehension by the parents'/ legal representative(s)' questions during and after the informed consent discussion.

- How do you deal with patients (respective parents/ legal representative(s)) with lack of German language skills?

Sometimes professional interpreters are involved, sometimes clinic staffs with respective language skills translate all oral/ written information passed to the parents/ legal representative(s) and patients. If available foreign – language patient information sheets are used.

4. What happens if a patient (or respective parents/ legal representative(s)) does not want to take part in a clinical trial or wants to withdraw from a clinical trial?

This very rarely occurs. Refuse or withdrawal is accepted and alternative treatment is offered.

5. - How do you document and report the results of the clinical trials and especially adverse events/ serious adverse events? ((e)health records, paper CRF/ eCRF)

- Who is responsible for documentation/ reporting?

Study nurses and documentalists are mainly responsible for study specific recording and reporting. Investigators review and sign study specific documents. The CRF forms dealing with the initial diagnosis are mainly completed by the investigator.

6. In your opinion, what do you think is the biggest problem in clinical research with children?

Therapy – optimization – studies have the equal status than any other clinical trial. All regulations of the pharmaceutical legislation fully apply to this type of studies. The mandatory consent of all parents/ legal representative(s) who have custody makes the conduct of research difficult. The supposedly ethical concerns regarding research involving minors might deny children urgently needed therapies and innovations.

Sixth Interview

Role	*Investigator*
Main Trial Responsibilities	*In general: Conducting the trial (including recording and reporting)* *In particular: Obtaining informed consent, medical treatment of patients*
Clinical Trial Experience	*7 years*

1. Could you please describe the informed consent procedure for clinical trials in your hospital!
- Where does it take place?

Mainly in the visitor's room of the department for paediatric oncology / haematology. For smaller trials like sub studies, the consent discussion may also take place at bedside. It is also dependent on the patient's health condition.

- Who is involved in the process?

Mainly the investigator and the parents/ legal representative(s) are involved, sometimes relatives (above all, if parents/ patients do not understand German language), rarely psychosocial staff is present. Nursing staff is not involved.

- Oral conversation?

It is an oral, face –to – face discussion.

- Usage of information sheet or other tools?

The parents/ legal representative(s) are always provided with study specific patient information sheets. Depending on the urgency of the treatment start and the severity of the illness, the parents/ legal representative(s), patients receive the information sheets prior to the consent discussion.

- How much time for decision is normally given?

Depending on the urgency of the treatment start and scope of the study, but in general everybody is offered as many time as needed for consideration or second opinion, on average decision time is 1 to 2 days.

- Documentation of consent process?

Consent is documented on the consent form and sometimes also in the care documentation.

2. In which way are the minors/ adolescents integrated in the informed consent process?
- Who is involved in the process? *Investigator and patients and sometimes the parents/ legal representative(s) are involved.*

- From what age onwards are minors involved?

From school age, the patients are offered to take part in the consent discussion. From about 14, it is mandatory for the patients to take part in the discussion. If younger patients have questions regarding the study and its implications then of course these questions will be answered by the investigator but these patient group is not actively consented.

- Any measurements to judge minors capability to consent?

No, this depends on the investigator's experience and feeling.

3. How do you make sure that the parents/ legal representative(s)/ patients have fully understood the content/ implications of the clinical trial and that the decision to participate has been taken fully knowingly and voluntarily?

Due to the complexity of therapy optimization studies, it is almost impossible for patients/ parents/ legal representative(s) to understand the whole meaning, scope implications and procedures of the trial at the initial consent discussion. The investigator rather aims to explain the disease itself, the basic of the therapy, the most common side – effects and risks, what will happen if the disease will not be treated and alternative treatment options. Based on the patients/ subjects as well as parents'/ legal representatives' questions during and after the consent discussion the investigator get an impression of the understanding. Also sometimes the patient/ parents/ legal representative(s) are asked to summarize the main issues in their own words.

- How do you deal with patients (respective parents/ legal representative(s)) with lack of German language skills?)

An interpreter will translate.

4. What happens if a patient (or respective parents/ legal representative(s)) does not want to take part in a clinical trial or wants to withdraw from a clinical trial?

This very rarely occurs. Patients/ parents/ legal representative(s) are given more time to reconsider their decision and to ask for a second opinion. But if they refuse or withdraw participation, the latest officially recognized therapy is offered.

5. - How do you document and report the results of the clinical trials and especially adverse events/ serious adverse events? ((e)health records, paper CRF/ eCRF)

- Who is responsible for documentation/ reporting?

The recording and reporting of SAEs are carry out by investigators.

Completion of CRFs is mainly done by the study nurses and documentalist, except the CRFs dealing with the initial diagnosis; these are mainly completed by the investigator. Treating physicians and nurses make notes in the patient's medical records and care documentation regarding all incidents during the therapy of the patient.

6. In your opinion, what do you think is the biggest problem in clinical research with children?

In general, the treatment of minors is a highly emotional matter. It is often very difficult to convey the research/ experimental concept to the parents because the parents want safety and don't want their children to be used for experimental purposes. Injuries/ damages due to trial treatment may pose a substantially higher risk of persistent or significant disability/incapacity in minors. Furthermore, minors present a very heterogeneous patient group. And you have to adapt your research to the different age groups.

Seventh Interview

Role	*Principle investigator*
Main Trial Responsibilities	*In general: Overall responsibility for the trial (planning and conduct)* *In particular: Obtaining informed consent, medical treatment of patients*
Clinical Trial Experience	*30 years*

1. Could you please describe the informed consent procedure for clinical trials in your hospital!
- Where does it take place?

In a separate room in the department for paediatric oncology / haematology

- Who is involved in the process?

Investigator, patients and parents/ legal representative(s), sometimes also nurses, psychologist (mainly with difficult (family) situation) or other physicians involved in the treatment (e. g. surgeon) are present.

- Oral conversation?

It's an oral conversation.

- Usage of information sheet or other tools?

The parents/ legal representative(s) are always provided with study specific patient information sheets.

- How much time for decision is normally given?

The next day after the initial consent discussion, the patient and parents/ legal representative(s) return to hospital for a second conversation and for signing the consent form(s).

- Documentation of consent process?

Consent is documented on the consent form. A copy of the consent form is filed in the patient's medical records.

2. In which way are the minors/ adolescents integrated in the informed consent process?
- Who is involved in the process?

The investigator and the patient together with the parents/ legal representative(s)

- From what age onwards are minors involved?

All minors are always involved regardless of the age. The patient can decide if he/ she want to take part in the discussion. The investigator explains the trial using age –specific language, pictures and models, assent form (if available).

From the age of about 14 or even earlier (dependent on mental maturity), the patient also signs the consent form.

- Any measurements to judge minors capability to consent?

No

3. How do you make sure that the parents/ legal representative(s)/ patients have fully understood the content/ implications of the clinical trial and that the decision to participate has been taken fully knowingly and voluntarily?

The investigator encourages the patient/ parents/ legal representative(s) to ask questions at any time. The patient/ parents/ legal representative(s) are also asked to write down any questions. Sometimes they are also asked to summarize the trial and its procedures and implications in their own words. The investigator also uses open questions to evaluate the level of understanding.

- How do you deal with patients (respective parents/ legal representative(s)) with lack of German language skills?)

An interpreter will be present during the oral conversation. He/ she will also translate the written information provided.

4. What happens if a patient (or respective parents/ legal representative(s)) does not want to take part in a clinical trial or wants to withdraw from a clinical trial?

Refusal or withdrawal is of course accepted. Alternative standard therapy is offered.

5. - How do you document and report the results of the clinical trials and especially adverse events/ serious adverse events? ((e)health records, paper CRF/ eCRF)

- Who is responsible for documentation/ reporting?

Completion of CRFs is mainly done by the study nurses and documentalist, except the CRFs dealing with the initial diagnosis; these are mainly completed by the investigator. SAEs are recorded on the SAE forms and reported by the investigator according to the guidelines. Treating physicians and nurses make notes in the patient's medical records and care documentation regarding all incidents during the therapy of the patient.

6. In your opinion, what do you think is the biggest problem in clinical research with children?

Most of the medicinal products in clinical research with children are used off – label. Trial participation is a very emotional matter for parents; they often struggle whether to take the right decision for the child or not.