CONTRACT

CONSENT IN A TRIAL & CARE ENVIRONMENT

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Project Overview

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Abstract

The CONTRACT consortium held the second stakeholder Workshop in Hannover, Germany on 6 September 2012. CONTRACT analyses the impact of the European Data Protection Directive and the Clinical Trials Directive on translational research by focusing on informed consent as a fundamental precondition for the legal processing of personal data and for conducting legally admissible trials. The main aims of CONTRACT are to document how on-going and upcoming European and national translational projects deal with consent issues, define good practices, provide policy recommendations, and to offer a helpdesk on consent issues for partner projects.

The aim of the Workshop on the other hand was to present the outcomes of the CONTRACT project, to reveal and discuss current hurdles in informed consent (IC) practice, and to elaborate the main message, which should be delivered at the joint conference of AcademicGMP and CONTRACT titled “The Impact of EU legislation on Therapeutic Advance“, which will take place in Brussels, 11 October 2012. This Deliverable reports on the outcomes of this Workshop.

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Executive summary

The second CONTRACT stakeholder Workshop took place in Hannover, Germany, on the 6th of September 2011.

The Workshop aimed to present the outcomes of the CONTRACT project, to reveal and discuss current hurdles in informed consent (IC) practice, and to elaborate the main message, which should be delivered at the joint conference of AcademicGMP and CONTRACT titled “The Impact of EU legislation on Therapeutic Advance“, which will take place in Brussels, 11 October 2012.

Experts from the legal, medical and ICT academic community, as well as representatives of major organizations, industry and EU projects gathered to express and evaluate which main changes they would expect from policy makers to facilitate the process of obtaining informed consent, and how different models of consent could improve their experience with IC. Two sessions were held in series. The first encompassed presentations on the outcomes of CONTRACT:

One of the project’s main outcomes is the Helpdesk, a help forum for legal, ethical, IT-related and clinical questions related to IC and data protection in translational research. The helpdesk contains comprehensive best practice guides that are structured so that the transfer of knowledge is easy and effective. It also encompasses the informed consent generator, a tool that helps the organisers of a clinical trial to compose IC forms addressing the intended patients of the trial (or their guardians). Finally, a set of case studies as practical examples of how to deal with consent in common situations are included within the helpdesk and efficiently linked to the informed consent generator. The IC generator is a customised IC template set based on the specific characteristics of a trial and supports observational & interventional trials, prospective and retrospective data usage, as well as dealing with IC for minors and adults without full legal capacity (a.o. generating assent form). The helpdesk is initially available for partner projects and will be available for the general public at the end of the project.

As identified early within CONTRACT, e-consent is one of the most anticipated technical solutions to managing informed consent documents and to gaining informed consent, as it can provide a more flexible and dynamic way of informing participants, while enhancing the feeling of trust.

CONTRACT investigated legal and practical aspect of six possible informed consent scenarios. The audit/monitor scenario, the reminder scenario, the re-consent scenario, the consent for screening scenario, the conditional consent scenario and the opt-in/ opt-out scenario. These scenarios could be ideally supported by e-consent models, but raised specific legal issues, especially with respect to the Data Protection Directive, resulting the fact that there are more than just the three known types consent (to treatment, for research and for data processing), which are defined by the purpose for which personal data is being processed, as each e-consent solution poses different demands in terms of data protection.

The second session within the Workshop consisted of guest presentations on informed consent experience, followed by an in-depth discussion on actual recommendations for policy makers. Among the guests were representatives of Katholieke Universiteit Leuven, the Institute Curie (ENCCA project), Hannover Medical School (Centre for Ethics and Law in the Life Sciences, AcademicGMP project), the European Clinical Research Infrastructures Network and London's Global University.

All participants agreed on the need for harmonization between the different legal entities within and between the EU member states. Furthermore, the fact that the CTD is more on the side of protecting the physician rather than the patient, focus on the patient must be set, especially when the patient or person legally entitled to take a decision is in a stressful situation caused by the health condition of the patient. This situation furthermore might ask for informed consent to be seen as a procedure of multiple decisions taken gradually over time, as the patient or legal representative becomes better and better informed and more aware of the situation. For this, e-consent is obviously a possible solution that has to be considered seriously; also supporting gradual information delivery in contrast to long overwhelming IC forms. Of course a change in the clinical trial regulation might be necessary in terms of allowing the acquisition a full IC also after a clinical trial starts, especially in emergency cases. Finally, the value of technology in terms of the above mentioned helpdesk is highly appreciated, making the composition of a consent form easier.

Acronyms

ATMPs	Advanced Therapy Medicinal Products
BBMRI	Biobanking and Biomolecular Resources Research Infrastructure
CCLG	Children's cancer and leukaemia group
CT	Clinical trial
CTD	Clinical Trials Directive
DPD	Data Protection Directive
DPR	Data Protection Regulation
EC	Ethics committee
ECRIN	European Clinical Research Infrastructures Network
EHR	Electronic Health Record
ENCCA	European Network for Cancer Research In Children and Adolescents
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
GCP	Good clinical practices
HTA	Human tissue act
IC	Informed consent
ICH-GCP	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use Good Clinical Practice
IRI	Institute for Legal Informatics
IT	Information technology
LUH	Leibniz Universität Hannover
PDMC	Patient decision making capacity
SOP	Standard operating procedures
UK	United Kingdom

Terms of reference

The second CONTRACT Workshop had three major objectives: the first was to present the outcomes of the CONTRACT project, the second to reveal and discuss current hurdles in informed consent practice, and the third to elaborate the main message, which should be delivered at the joint conference of AcademicGMP and CONTRACT titled “The Impact of EU legislation on Therapeutic Advance“, which will take place in Brussels, 11 October 2012. The current report compiles the collected stakeholder and consortium member views.

Acknowledgements

The CONTRACT consortium wishes to thank all participants for their contributions and the valuable discussions.

Disclaimer

This report summarizes stakeholders’ views collected during the second CONTRACT Workshop and does not necessarily at all points reflect the opinion of the CONTRACT consortium and the authors. The collected comments and recommendations will be considered during the future work of the CONTRACT project. The authors are not responsible for any errors, misinterpretations or omissions.

1 Welcome address, Nikolaus Forgó

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

2 CONTRACT presentation: "Overview of the CONTRACT project" by Magdalena Góralczyk

2.1 Summary

When starting up a new trial, researchers need to consider the requirements of the Clinical Trials Directive (2001/20/EC), legislative requirements for treatment and care and, as they work with sensitive patient information, also the obligations arising from the Data Protection Directive (1995/46/EC).

The question of informed consent is at the nexus of this complex framework; on one hand as the essential basis of a successful patient–researcher relationship, on the other hand, a possibly serious impediment resulting from uncertainty surrounding legal requirements.

It is at this juncture that CONTRACT (CONsent in a TRial And Care EnvironmenT) seeks to find solutions to support researchers in both today's and future work. The project's focus was put on analysing how the legal (and underlying ethical) concepts of informed consent in the European Data Protection Directive and in the Clinical Trials Directive have had and continue to have an impact on the success of translational research

The concept of informed consent in the two mentioned Directives was closely monitored from a legal, ethical, IT-related and clinical point of view. The European approach on the matter was compared with national concepts of informed consent in chosen Member States.

3 CONTRACT presentation: “Informed Consent Scenarios” by Norbert Graf, Magdalena Góralczyk and Yvonne Braun

3.1 Summary

“Informed consent” is a legal concept used to indicate that the wishes of a person have to be respected before acting. Unfortunately, our study showed that the concept is used by different regulatory and legal documents in different ways. Requirements to a legal informed consent differ as there is not one generally accepted definition of “informed consent”. Instead the concept of “informed consent” is defined in each legal or regulatory instrument separately. Differences in the requirements often concern the form of the consent and the elements of information which have to be provided to the subject. Consequently, it has become a necessity for every practitioner compiling an informed consent form to check for each situation which type of informed consent is required, which rules apply and which exact requirements are imposed by this rule.

CONTRACT investigated legal and practical aspect of six possible informed consent scenarios. This legal analysis advises on whether such scenarios could be possible in current European legal framework and to what special attention has to be paid. The practical views are focusing rather on whether in daily clinical setting it would be possible to handle issues in a way foreseen in the scenarios, or rather due to their impracticability the e-consent solutions could not be used.

Scenario 1: Control Scenario

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.

Legal requirements:

- Who can access personal information in the patient file (Data Protection Directive)?
- Electronic signatures for use in clinical trials (Clinical Trials Directive and E-signatures Directive)

What has to be considered from the legal point of view that 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 e.g. eConsent solutions makes this an even more important issue). Three different situations of access to personal data are relevant and of different legal consequences.

Scenario 2: Reminder

Peter hears about abuse of data by an insurance company. Peter remembers signing consent, but cannot recall what the content was. Peter turns on his computer and logs in to the system (e.g. central national consent register). To log in Peter must provide a unique identifier (UUID) and password. This UUID can be a social security number, an eID, etc. After login, Peter has read-only access to all of his given IC forms.

Legal requirements:

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

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

Chris is a 15-year-old leukaemia patient. Consent of both parents has been given for their son to participate in a trial. The trial will run for a very long time (>10 years). To further guarantee Chris' voluntary participation in the trial, consent from Chris himself will be needed when he legally gets adult.

An alerting system can offer a solution to notify the trial manager when consent from Chris is needed.

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. It tries to encourage its patient to allow access to their data if it's for recruitment purposes. This also implies that patient data will only be viewed by local hospital employees. This way trial recruitment is significantly easier. Peter is a patient at the hospital, and allows access to his data, only for recruitment purposes.

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.

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

a) Opt-out

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.

b) Opt-in

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.

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) .

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.

4 CONTRACT presentation: “The Informed Consent Generator and the concept of the Center of Data Protection” by Brecht Claerhout

The Center for Data Protection is a non-profit organisation under Belgian law and was founded in August 2007 as spin-off from the ACGT ("Advancing Clinico-Genomic Trials on Cancer") project. Its objectives are to serve as a “home” for the ethical and data protection issues, to offer services to EU projects and other research collaborations as a contract party - data controller the sense of the European 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.

During the CONTRACT project, the “CONTRACT Helpdesk”, a help forum for legal, ethical, IT-related and clinical questions related to informed consent and data protection in translational research has evolved. One of its core services is the informed consent (IC) generator.

The IC generator is a tool that helps the organisers of a clinical trial to compose IC forms for the intended patients of the trial (or their guardians). The IC Generator creates tailor-made consent forms that are specific to the procedure as well as including country-specific requirements. The IC generator will take the language of the patients involved into account, as well as the national legislation of where the trial is held, so that every IC form will be in the correct language and conformity of national legislation. The template IC forms, produced by the IC generator, are tailored to the specific needs of the end-user. They do not only contain template text, but also include guidelines and tips for creating correct (legal) IC forms, ready to be used in the trial.

The user is guided through a wizard style questionnaire, which captures the specific characteristics of the trial that influence the content of an IC form. The questionnaire consists of a list of questions, each providing one or more possible answers. For this, CONTRACT partner Custodix used modules from an in-house data capture product and extended them so that they can cope with conditional rendering, meaning that certain questions will only be asked (or shown) when a certain answer to a previous question was selected or not, hereby eliminating contradictions in the answers provided.

Depending on the given answers, the IC Generator creates a set of IC forms. These forms are derived from a set of basic IC forms for:

Prospective interventional trials; Prospective observational trials; Trials using retrospective data; Trials where biomaterial is used; Assent

These forms are complementary (modular) in a sense that a single trial might require consent for more than one topic (consent for trial participation, consent for data processing, consent for biobanking etc.). For each generated basic IC form, the IC Generator adds certain content that is defined by specific rules. These rules are of the form “when question A is answered with answer X, then add this paragraph in section Y”. There are different types of paragraphs that can be added to the form :

- Form text: text that will be literally used in the final consent document (but could still need some editing).
- Descriptions: placeholders for descriptions that still need to be provided by the organisers (e.g. the purpose of the trial).
- Explanations: text that provides an explanation to why a certain section is in the final IC form. These could be excerpts from a law, or just additional information for the person that should sign the IC form. This text is displayed in a gray box in italic.
- Tips: these are guidelines or tips that inform the people issuing the IC forms about certain actions they might have to undertake in order for the form to be valid (e.g. when collecting data in a trial, this can require a notification to a national protection authority). These guidelines are displayed in a blue box.

When all rules are evaluated, the basic IC form is completed with a set of paragraphs, and the result is shown to the user. The resulting IC forms are returned to the user in two ways: in xml-format or as an rtf-file. The reason why these formats are chosen is simple: xml is a structured format that allows easy transformation to any given format, and rtf is a rich text format that can be opened in almost every text editor.

It is clear that the eventual documents generated by the IC form generator still require additional editing. Certain tips require actions from the organiser of the trial and can be removed afterwards. Certain other fields are still occupied by a placeholder and should be replaced correctly as well. For example, fields describing the trial should be filled out in the correct language. This need for editing the text after form generation cannot be avoided. It is not practically possible to ask all missing information directly at the questionnaire stage. This would require one person to be able to complete all text, determined by different national legislation, in different languages. Hence, the choice was made to only have selectable answers in the questionnaire part of the wizard and not give the user the ability to formulate an answer as free-text.

However, note that the tool could easily be further developed so that it also includes editing these free-text parts online (after template generation) so that the management of the different consent forms gets further simplified.

In the end, the user will be offered the necessary IC forms in the correct language, containing not only legal text, but also tips and explanations for producing a correct IC form, ready to be used in a trial.

5 Guest presentation: "Consent in data protection: the Directive and the Draft Regulation" by Eleni Kosta (K.U. Leuven)

Dr. Eleni Kosta from K.U. Leuven presented a thorough analysis on the concept of consent in data protection a result of the current DPD (1995/46/EC) in comparison to the new Draft Regulation (COM(2012) 11 final).

5.1 Summary

The presentation was structured in four parts. Initially, a description of consent, as given in the Data Protection Directive, was presented:

In the current DPD "**consent** is defined as any **freely given, specific** and informed **indication of his wishes** by which the data subject signifies his **agreement** to personal data relating to him being processed"[1]. Furthermore "Member States shall provide that personal data may be processed only if: (a) the data subject has unambiguously given his consent (…)"[2] and the processing of sensitive data is in principle prohibited, unless "(a) the data subject has given his explicit consent to the processing of those data (…)"[3]. Moreover, "Member states shall provide that a transfer or a set of transfers of personal data to a third country which does not ensure an adequate level of protection may take place on condition that (a) the data subject has given his consent **unambiguously** to the proposed transfer (…)"[4]

This presentation was followed by an analysis of opt-in vs. opt-out methods in consent:

With the opt-in method, the wishes of the data subject are expressed in an **affirmative** action, while the opt-out method offers the possibility to the data subject to **express his objection** to the processing of his personal data. This it is not a freely given indication of the wishes of the data subject and it should not be understood as consent in the understanding of Data Protection Directive, it only expresses the data subject's right to object.

The third part of the presentation analysed the contents of the new Draft Regulation of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data (COM(2012) 11 final).).

In this draft "Consent means any freely given specific, informed and **explicit** indication of his or her wishes by which the data subject, **either by a statement or by a clear affirmative action**, signifies agreement to personal data relating to them being processed"[5]. Furthermore "Processing of personal data shall be lawful only if and to the

[1] Art 2(h) DPD

[2] Art 7(a) DPD

[3] Art 8(2)(a) DPD

[4] Art 26(1)(a) DPD

[5] Art4(8) draft DPR

extent that: (a) the data subject has given **consent** to the processing of their personal data for one or more specific purposes (…)"[6].The processing of sensitive data is in principle prohibited, unless "(a) the data subject has given **consent** to the processing of those personal data (…)"[7]. Considering the transfer of personal data, the draft directive states that "(…) a transfer or a set of transfers of personal data to a third country or an international organisation may take place only on condition that: (a) the data subject has **consented** to the proposed transfer, after having been informed of the risks of such transfers due to the absence of an adequacy decision and appropriate safeguards (…)"[8]. In the description of the conditions for consent, the following points are highlighted:

- "The controller shall bear the burden of proof for the data subject's consent"
- "(…) consent is to be given in the context of a written declaration (…)" and must be "(…) presented distinguishable in its appearance from other matter."
- "Consent shall not provide a legal basis for the processing, where there is a significant imbalance between the position of the subject and the controller."

The last part of the presentation dealt with the competence of minors to consent to processing personal data:

Consent for a minor is generally given by its legal representatives. A minor is any person below the age of 18 years. The draft of General Data Protection Regulation contains a rule, where "in relation to the offering of information society services directly to a child, the processing of personal data of a child below the age of 13 years shall only be lawful if and to extend that consent is given or authorized by the child's parent or custodian" (Article 8.1).

As a final comment, it is not yet known, whether and when and in what shape the new Data Protection Regulation will come in force.

[6] Art 6(1)(a) draft DPR

[7] Art 9(2)(a) draft DPR

[8] Art 44(1)(a) draft DPR

6 Guest presentation: "Consent settings in biobanks for children and adolescents with cancer" by Jean-Claude Dupont (Institut Curie)

The presentation was held by Dr. Jean-Claude K. Dupont from the Institut Curie. Dr. Dupont is working on the ENCCA project, work package 18, which is dedicated to the ethics of research with children and adolescents with cancer.

6.1 Summary

Amongst other tasks in WP 18 of the ENCCA project, guidelines on the issue of confidentiality in biobanks will be created. These guidelines are based on a two-tier consultation process. At first parents' representatives are addressed, in order to collect their expectations and concerns towards confidentiality in biobanks. In a second stage, patients and young people will join the consultation process in order to confront their own views to those of the parents group.

This presentation reported on the results of the consultation with parents using typology of contract theory.

Contemporary bioethics deal with confidentiality in a quite legalistic and contractualist way. To put it in a nutshell, patient's authorisation to know some private information is the event causing professionals to enter a confidential relationship with this patient. Such confidential relationship entails the promise not to re-disclose such information improperly.

Following this view, it is possible to analyse the confidential relationship between patients and professionals in research biobanking environment in the light of Randy Barnett's work "A Consent Theory of Contract"[9]. Paediatric biobanks have special features, however. First, consenters are not the right holders; parents are surrogate consenters. Second, it is impossible to predict what intimate information will be retrieved from biological samples in the future.

As a consequence, parents have to face two uncertainties at the time they have do decide whether or not to bank samples from their children. Using core concepts of contract theory, the way parents negotiate these uncertainties and what terms they are offering for consenting to enrol their children in genetic research was analysed.

a) *Will-related aspects:*

Will, or intention, is a very important aspect for parents. They want to get early general information about biobanks, thus allowing people to refuse to be approached to that end. They further expect transparency about selection criteria of "suitable" research projects and about the categories of research to be performed with the samples.

Further, time-extension of participation is a key concern for them. Parents don't want samples and data to be available without limitations. When left blank in the consent

[9] Barnett, 1986, p. 270 (86 Columbia Law Review 269); also see Barnett, 2011: "contract as consent"

form, they would value the possibility to agree with professionals on categories of research and time extension.

Clearly, parents value making the decision and expressing their will, or intention. They endorse the view of consent as the very starting point allowing professionals outside medical staff to access private and medical information about their children. They also expect that what they agreed on in consent forms will be scrupulously respected and narrowly interpreted.

b) Reliance-related aspects:

When parents talk about Ethics Committees, in their view, these committees must serve sick children and adolescents' interests. They must act as gatekeepers, not as surrogates.

Conversely, parents recognise that research must be facilitated. In this view, they conceptualise samples as "gifts", endorsing that biobanks become their legitimate owners. Reliance is a matter of reciprocal relationship in this sense.

Interestingly, parents put emphasis on will or intention, but not on reliance. Explicitly, they refuse to base confidential relationships with professionals on mistrust. They rather expect to establish a mutual commitment in the best interests of sick children. For instance, they endorse the altruistic nature of research participation, accepting as a reason for participating that "it may help sick children in the future", but would like professionals to undertake, also in consent forms, the converse commitment to "use banked samples and attached data to try to help children with cancer in the future".

However, there remains a difference in appreciation between public research and private research. Parents seem quite cautious towards genetic research performed in the private sector.

The consultation process further on revealed interesting results about the limits of what parents are ready to agree upon in the name of their children:

a) Fairness-related aspects

Parents want their agreements with professionals to be subjected to normative standards. Three standards can be related to expectations concerning the fairness of these agreements.

First, although research biobanking does not entail any physical risk for their children, confidentiality risks must be held as real research risks. As a consequence, some objective limits should exist for agreements to be valid. They reject the idea that people might individually accept greater confidentiality risks in return for greater benefits, whatever such benefits may be.

Second, they expect that researchers (and legislators) to act AS IF in case of confidentiality breach, the younger the victim the greater the damages. In one sence they expect higher level of protection for children.

Third, in their view, it would be unfair to agree to confidentiality risks without the prospect of a possible return of clinically significant results, if any. A fair counterpart of children enrolment in research would also be to improve the role and involvement of associations in research biobanking.

b) Process-related aspects

Other important standards conditioning what parents can validly consent for their children are process-related.

In the process of seeking their consent, their agreement should be sought at distance from diagnosis and from medical procedures. They also want people's right not to know to be respected, so individual results should be returned to donors only on their request. It is also important for parents to have the possibility to contact professionals for further information over the long term, and not only at the time when they have to give consent.

Indeed, it is important for parents, that children know who to address if they need information. Further, parents expect professionals to involve children in the decision-making, respecting their views according age and maturity. Finally, parents agreed that children should re-consent after they reach their legal maturity age.

c) Efficiency-related aspects

Efficiency is also an important standard allowing parents to validly consent to confidentiality risks in the name of their children. As already mentioned they expect from professionals to "promise" to make good use of the samples. Parents are fully aware that paediatric tumour samples are rare resources. As a matter of efficiency, they consider that these samples should be used in priority for research benefiting children (although paediatric samples are common goods like biological samples from adult donors).

As a consequence, consent procedures must respect autonomy while minimising loss. For instance, parents want professionals to inform and to re-consent young people after 18 years of age, for they are concerned with the risk of some parents omitting to inform their child or some young people omitting to re-consent, thus depriving research from valuable resources.

Another condition for an efficient use of paediatric samples consists in limiting claims to confidentiality. Parents don't want confidentiality to be over-protected, or too broad a constraint on research. Confidentiality is not an absolute value, it has to be balanced with other fundamental rights of sick-children and adolescents, especially their right to self-determination and their right to appropriate access to research and innovation. As a result, confidentiality is narrowly defined in relation with the possibility to uniquely identify a donor.

In conclusion, the issue of whether confidential relationships within a biobank can be interpreted uniquely in the terms of a contract between the parents and the professionals was discussed:

In the 1970s, the question was posed whether informed consent is causing patients and professionals to enter a contractual or a coventual relationship. A contract is a formal agreement, whose content (the “promise”) creates reliance interests by the promisee. For promisor and promisee don’t trust each other, they want their agreement to be enforceable by legal means. A contract is an agreement made in mistrust. By contrast, a covenant is defined as a solemn agreement, based on oath and personal commitment, by which the doctor declares to be loyal and to care the patient. A covenant is an agreement made in trust.

To tell a long story short, debates about managed care and cost-containment led ethicists to view informed consent in healthcare environment as causing doctors and patients to enter a coventual relationship while informed consent in clinical trials settings is viewed as causing professionals and participants to enter contractual relationships. In research environment, contract-based relationships are conceived as protecting research participants from deception and misconception.

The situation is however not that clear in a biobanking-research environment.

Obviously, there is no covenant: one cannot build a trust-based relationship with an institution (the biobank). Conversely, if mistrust was the leading word, parents would simply not consent to bank the samples of their children.

Dr. Dupont’s hypothesis is that a more subtle and sophisticated view is needed on the contract/ covenant divide to interpret parents’ views about consent in a research biobanking environment.

Certainly, they rely on people operating biobanks to compel to contractual obligations, especially towards data security. They also acknowledge that researchers have reliance interests, by rejecting ambivalence about ownership of samples.

By consenting to bank samples of their children they surrender a parcel of the rights of their children but also of their own rights as parents. For instance they transfer to biobanks the power to evaluate which research projects will be deemed suitable. B. Hofmann and colleagues suggest that, by doing so, consent causes parents to enter a civil covenant with researchers, but – we can add – also with the State, for they expect law-maker to facilitate research and access to innovation while protecting privacy interests of young people.

Finally, parents’ views reflect another covenant determining to what they can validly consent for their children. Familial covenant is not a product of consent, it is a product of natural roles and obligations between intimates. Such a covenant confers rights to parents over their children, and inappropriate consent settings may interfere with these

rights. However, parents recognise that these rights are limited in scope and time. Re-consent after 18 might be uneasy, but it may also constitute a vital ethical requirement.

7 Guest presentation: "Empirical consent research. With an outlook on biobanks" by Dr. Daniel Strech (Medizinische Hochschule Hannover)

In his presentation, Dr. Strech from the Medizinische Hochschule Hannover described empirical consent research, the associated challenges and strategies on how to deal with them. Additionally an outlook on research regarding biobanks was given.

7.1 Summary

Informed consent is considered a requirement of ethical clinical research, but getting valid informed consent requires that people not only decide freely whether to participate in clinical research, but decide with an understanding of the relevant facts. Since research participants can have significant misconceptions about the nature of research (even when researchers think that sufficient information has been provided), IC is difficult to realize in practice. Empirical informed consent research incorporates a set of questions (empirical questions), whose answers help to address the issue of misconception. Such questions are:

- How well do participants understand their research participation?
- Is there any way to predict who will have the most trouble in understanding?
- Which interventions can improve participants' understanding?

To answer these, adequate questions in IC research have to be posed to the participant. They include questions about **purpose, voluntariness and prospect of benefit**.

Within this context the timing of posing the questions and getting the answer is important, since delayed data collection makes it hard to distinguish understanding from retention. For this reason, consent research is added to and goes along with existing research projects, which on the other hand might discourage patients from participating in a trial or study. Moreover heterogeneity due to questionnaire results from different studies and settings poses a further challenge.

As an example, the MacArthur Competence Assessment Tool[10] enables to assess the patient decision making capacity (PDMC) as a psychological/cognitive trait. It includes a structured disclosure of information about the study, followed by questions that assess four domains of PDMC: **understanding, appreciation, reasoning, choice.**

The understanding of IC, can be improved with interventions in the IC giving process such as multimedia, enhanced consent form (e.g. leaving out passages that are not relevant), extended discussion, test/feedback etc. A study[11] that assessed these

[10] Appelbaum, P. and T. Grisso, MacCAT-CR: MacArthur Competence Assessment Tool for Clinical Research2001, Sarasota: Professional Resource Press.

[11] Flory J & Emanuel E (2004) *Interventions to improve research participants' understanding in informed consent for research: a systematic review.* JAMA, 2004

interventions showed that multimedia and enhanced consent form interventions do not consistently improve research participants' understanding but person-to-person interactions, especially the extended discussion interventions, may be more effective.

Regarding empirical IC research in biobanks, the results of a systematic review were presented:

A total of 12 studies were included. 9 references reported research on attitudes about (hypothetical) consent for biobank research and 3 references reported research with (experienced) biobank research participants.

The three existing studies indicate:

- The majority (65-93%) understands purpose of tissue-/biobank (n=3)
- There is a lack of knowledge about right to withdraw (n=1)
- The majority (>75%) accepts surrogate decision making by RECs (n=2)

The review indicated that the current intense debate about adequate consent procedures for participation of tissue donors in biobank research (e.g. informed vs. broad consent) still lacks substantial support through empirical studies that investigate participants' understanding (consent validity).

The general conclusion of the presentation showed that conceptual research on how to improve informed consent procedures should explicitly acknowledge the best available evidence (concept/theory/regulation/law), based on which works in practice and which not.

Ethical and judicial recommendations on adequate IC procedures should at least be transparent about their empirical background assumptions.

8 Guest presentation 3: "ECRIN and Informed Consent – Our approach" by Wolfgang Kuchinke (Universitätsklinikum Düsseldorf)

The presentation was held by Dr. Wolfgang Kuchinke from the Universitätsklinikum Düsseldorf, describing ECRIN's (European Clinical Research Infrastructure Network) approach to informed consent.

8.1 Summary

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

ECRIN has standard operating procedures (SOP) for preparing an IC form which cover all participants entering into a trial with a medicinal product. The patient must have given informed consent prior to participating in any procedure. Additional requirements are given by the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use Good Clinical Practice (ICH-GCP), which includes the definition of IC (EC approval; No influence; All pertinent aspects of the trial; Language; etc.) and the definition of vulnerable subjects.

The SOP covers the EU Directive 2001/20/EC (CTD) and 2005/28/EC (Guidelines for good clinical practice). The Clinical Trials Units have up-to-date SOPs for all the phases of clinical trials including informed consent.

Problem areas for international ERCIN clinical trials include the legal fragmentation in Europe on the national level, the fragmentation and heterogeneity of Ethics Committees in Europe and the additional costs, burden of additional documentation, trial management.

Based on its experience, ECRIN poses the following recommendations for Informed Consent in clinical trials:

IC should be better harmonised, with common templates and common content.

Lengthy and complicated documents should be avoided.

The risk assessment for an individual trial should include risk to patient rights, to patient integrity and to trial results.

Risk to patient rights assessment should include the patient information sheet and the collection of informed consent.

Mitigating procedures (e.g. monitoring) should consider these aspects whenever there is a particular risk (vulnerable subjects, children, emergency situation etc.).

9 Guest presentation: "The Institute of Child Health Harmonised Consent in International Research in Relation to UK Governance" by Mark Weeks (University College London)

Dr. Mark Weeks from the University College London presented the legal framework and common practices governing over informed consent in the UK for tissue banking.

9.1 Summary

The obtainment, storage, and use of human tissue taken from children for research purposes is an area that is notable for its complexity and legal uncertainties. In the UK, the controversy surrounding organ retention prompted radical legislative change in the form of the Human Tissue Act 2004, which came into force in September 2006.

Human Tissue Act (HTA):

1) A legal framework for regulating the storage and use of human tissue from the living, and the removal, storage and use of tissue from the deceased.

2) Defined as material which has come from the human body which consists of, or includes, human cells.

3) Consent IS REQUIRED for research involving both identifiable and anonymous samples of human tissue, including histology blocks and slides.

The consent is not required when:

1. Using surplus surgical material that has been anonymized (includes linked-anonymized samples) to the researcher, providing the research project has received ethics approval from a Research Ethics Committee (REC) recognised by the United Kingdom Ethics Committee Authority (UKECA) and the rationale for not obtaining explicit or retrospective consent is justified and approved.
2. Existing holdings are exempt from the Act's consent provisions. An existing holding is defined material held before the day on which the HT Act commenced (1 September 2006).
3. In most circumstances, it is an offence to hold material with the intent of analysing DNA without qualifying consent. However, the offence does not apply if the results of the analysis are intended to be used for 'excepted' purposes.

When designing an IC form for tissue collecting, the following aspects are considered:

a) Parental input (Arch Dis Child. 2012 Jul;97(7):632-6. Epub 2012 May 18)

Families' views inform valuable to optimise the experience of consent for tissue banking. They are supportive of tissue banking and typically detailed information is not important when consent is sought. They prefer to see tissue-banking as part of routine practice and are content to give consent based on their understanding at the time (not being fully informed).

b) Clinical Input

Clinicians and point of care physicians and nurses must comment on feasibility, cost and patient impact.

c) CCLG - UK national tissue bank

The CCLG (Children's Cancer and Leukaemia Group) Tissue Bank was set up in 1998 to provide a resource of human tissue for scientists studying the biology of childhood cancers

d) Competency - age relevant material

In the UK age divisions are arbitrary but the legal requirement in the HTA is to consider the competency of a child to consent for use for their tissues in research

e) Retrospective consent

Research conducted in UK shows us that retrospective consent is neither welcome or often given (Patient may have died; Patient may have recovered and has no interest in revisiting experience; No longer 'in system' or contact details have changed)

In the UK for new national studies with prospective AND retrospective data ethics have accepted our contention that where consent has previously been given, it is implicit in that consent that research and clinical data 'in anonymised/coded format' can be used in subsequent analysis whether or not further use of such data was initially specifically mentioned unless specific withdrawal of consent to use data has been stated.

10 Guest presentation: "About the AcademicGMP Project" by Eva Mischak-Weissinger (Medizinische Hoschschule Hannover)

Prof. Dr. Eva M. Weissinger presented the AcademicGMP Project and its legal aspects.

10.1 Summary

Academic GMP is a research project, funded by the European Commission, to investigate the impact of EU Regulation on the development of Advanced Therapy Medicinal Products in academia.

Advanced Therapy Medicinal Products (ATMPs) are medicinal products based on gene therapy, somatic cell therapy or tissue engineering. Regulation (EC) No 1394/2007 has been designed to ensure the free movement of ATMPs within the European Union (EU), to facilitate their access to the EU market and to foster the competitiveness of European pharmaceutical companies while guaranteeing the highest level of health protection for patients.

Academic GMP are "clean laboratories" at the campus of an University/Hospital or in close vicinity to the campus. They are major contributors to the development of ATMPs (bench to bedside).

Academic GMP facilities are major contributors to the development of ATMPs. They respond to clinical needs and foster therapeutic innovation in an environment which is not industrial by definition nor by intention. European investigator-initiated multicenter trials on ATMPs critically depend on academic GMP facilities.

The impact of Regulation (EC) No 1394/2007 and related Directives on academic GMP facilities has been investigated by: a) conducting a European survey among non-industry facilities in this sector; b) organising workshops for a targeted, collaborative discourse; c) establishing a web-based platform for information exchange; d) analysing publications and guidance from the perspective of better regulation principles; e) analysing innovation statistics in relation to ATMPs.

By accessibility sampling, 747 European contact points in academic and non-industrial facilities were identified. Of these, 85 responded to a first, short survey and 50 to a longer questionnaire. Experienced centers were selected in every member state and approached with a semi-structured interview.

Distinct subgroups of Academic and Hospital GMP facilities can be identified in terms of successful development and manufacture of ATMPs, independent of the country of origin. However, the responses to the surveys showed highly heterogeneous implementation of EU Regulation between member states, with evidence of substantial differences in the criteria used to define ATMPs and in the approved manufacturing environment.

Current regulation does not address Academia as a major contributor to ATMP Development and Manufacture. Moreover, there is uncertainty about the regulatory process and little harmonisation at the level of delivery across the Member States which

are stifling development and commercialisation of these promising therapies. Most disturbing appears to be the detrimental effect on translation to early phase trials which remain largely academic investigator-led. However, current regulation appears to offer space for further exploitation to meet academic needs.

Expected final results and potential impacts:

- A comprehensive report reviewing the success of the ATMP regulation, drawing out important trends, potential unforeseen consequences, benefits and opportunities.
- The regulatory landscape will be delineated in which the Directive 1394/2007/EC will be placed in context.
- With Academia emerging as the major contributor to ATMP Development and Manufacture, the academic perspective that has been laid down in the title of our project is expected to shed light on the developmental trajectory and obstacles to successful manufacture of ATMPs.

11 Conclusion

All participants agreed on the need for harmonization between the different legal entities within and between the EU member states. Furthermore, the fact that the CTD is more on the side of protecting the physician rather than the patient, focus on the patient must be set, especially when the patient or person legally entitled to take a decision is in a stressful situation caused by the health condition of the patient. This situation furthermore might ask for informed consent to be seen as a procedure of multiple decisions taken gradually over time, as the patient or legal representative becomes better and better informed and more aware of the situation. For this, e-consent is obviously a possible solution that has to be considered seriously; also supporting gradual information delivery in contrast to long overwhelming IC forms. Of course a change in the clinical trial regulation might be necessary in terms of allowing the acquisition a full IC also after a clinical trial starts, especially in emergency cases. Finally, the value of technology in terms of the above mentioned helpdesk is highly appreciated, making the composition of a consent form easier.

Finally the following three key messages for policy makers have been distilled as aroused from the results of the CONTRACT questionnaire, discussions during the CONTRACT Workshop, the build-up of the CONTRACT informed consent generator and the study of legal and medical literature:

- **The regulatory framework on informed consent needs harmonization;**
- **The patient's view should be reflected in these regulations;**
- **An electronic consent should be supported.**

CONTRACT second Workshop participants

Appendix

Workshop participants

CONTRACT project consortium:

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