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RD-Connect

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bioinformatics for rare disease research

Collaborative project

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[Databases, biobanks and 'clinical bio-informatics' hub for rare diseases]

Work Package 6

D6.05

Guidelines for Informed Consent

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Abstract: The increased exchange and sharing of data inside and outside international research consortia raises new complexities in the informed consent process as it adds new ethical and legal considerations for potential donors/participants and requires coordination and harmonisation between different research centres worldwide.

Previous work on data sharing in international consortia¹ suggests that to increase consistency and harmonisation in the practices of collecting informed consent in different research centres there must be: clear principles, flexible guidelines, modifiable model language and governance procedures to resolve ambiguities that inevitably will arise.

In RD-Connect the Guidelines on Informed Consent must consider the needs of EuRenOmics and NeurOmics, other rare disease projects, and of other candidate registries and biobanks that will be integrated in the RD-Connect platform in the future, most of which already have in place forms and templates for the informed consent process.

Guidance and clear principles are hence needed to be applied to different situations:

- 1) new research projects (biobanks and registries) for which the information sheets and consent templates can be created ex-novo.
- 2) new collections using the informed consent forms of existing study projects which include specific information on international data sharing
- 3) old collections obtained with / without informed consent where data sharing is not addressed or even specifically excluded

In the present work, an analysis of the values and principles particularly relevant in RD research is made in order to define core principles. This will enable us to provide guidance in different situations and list core information elements that must be integrated into a model informed consent document that may be used and adapted by RD-Connect partners.

The present guidelines do not deal with special cases like vulnerable subjects requiring surrogate consent: minors, incapacitated adults and deceased persons. These will be the subjects of specific deliverables (D6.5, D6.9, D6.10).

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Dissemination Level		
PU	Public	X
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

¹ Wallace SE, Knoppers BM. Harmonised consent in international research consortia: an impossible dream? *Genomics, Society and Policy* 2011;(7):35-46.

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1. Introduction:

Informed consent guidelines in the era of data sharing

Fostering data-sharing is an ethical imperative where such sharing is required for the achievement of important aims and the common benefit of patients. Data sharing is necessary for scientific benefit, economic growth and the progression of knowledge. For people living with rare diseases there is the additional necessity for data sharing which comes from the fact that progress on diagnosis, understanding the natural history of a condition, and the translation of research into treatment, can only happen if there are sufficient data to support the science. Indeed, data sharing is proving essential to study complex disease aetiology even in more common conditions². However, people living with rare diseases are also faced with additional risks in terms of personal identification and discrimination. Therefore, a careful balance in ethical principles is even more critical for this vulnerable population. International scientific research consortia are being created worldwide bringing together diverse groups of researchers who may represent different countries, cultures and scientific methodologies³, most notably those generating –omics data.

Such international consortia are encouraged to share data intra-consortia, inter-consortia and with the wider scientific community⁴. In fact, those research projects which have received funding under the IRDiRC banner are required to share data under the terms of the funding award.

This creates new complexities in the informed consent process as it adds new ethical and legal considerations for potential donors/participants and requires coordination among research projects and harmonisation of the processes and documents they use to inform and involve research participants. It has been proposed that in order to harmonise current practices of obtaining informed consent international research consortia establish:

- core principles upon which all members agree and core elements in the consent materials
- flexible guidelines able to accommodate the differing ethical, legal and cultural norms of their members
- model consent forms in different languages to increase consistency across consents
- governance structures in order to solve the ambiguities and inconsistencies that inevitably will arise⁵.

Here we try to address the first point.

In agreement with the European Convention for the Protection of Human Rights and Fundamental Freedoms, the Social Charters adopted by the Union and by the Council of Europe, the Charter of Fundamental Rights of the European Union (2010/C 83/02) emphasizes the right of each individual to integrity within the fields of medicine and biology, implying a free and informed consent according to the procedures laid down by law (Article 3). Article 8 grants the individual the right to the protection of personal data concerning him or her, implying that processing of such data requires consent of the

² Weitzman ER, Adida B, Kelemen S, D. Mandl K. Sharing Data for Public Health Research by Members of an International Online Diabetes Social Network. Plos One. 2011;6(4):1-8. DOI: 10.1371/journal.pone.0019256

³ Wallace S, Knoppers BM. op. cit. note 1.

⁴ Budin-ljøsne I, Isaeva J, Maria KB, et al. Data sharing in large research consortia: experiences and recommendations from enGaGe. Eur J Hum Genet 2014;22:317–321. DOI:10.1038/ejhg.2013.131

⁵ Wallace SE, Knoppers BM. Harmonised consent in international research consortia: an impossible dream? Genomics, Society and Policy 2011;(7):35-46.

person concerned or some other legitimate basis laid down by law. These and other rights in the charter may be motivated by a fundamental respect of each individual's autonomy and right to have control of matters related to oneself, e.g. the processing of personal data. They may imply a right to know about genetic and other medical information about oneself but also, as has been frequently discussed in the ethical and legal literature, the right not to know such information. In addition to these autonomy rights the Charter of Fundamental Rights of the European Union also lays down rights of each individual to social security benefits and social services in cases of illness (Article 34) and the rights of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices (Article 35).

Commonly the interests of the individual in matters like this have been framed as standing in need of balancing against societal interests, e.g. interests related to public health or development of health care. However, as described, the charter of the European Union recognizes both the autonomy right and the right to health care and social services in cases of illness as fundamental individual rights, notwithstanding that there may also be societal and public health related interests concerned. The right to health care as described in the EU Charter implies a concern in information and consent procedures to promote research that is conducive to this end while respecting autonomy and integrity of those who give access to their biospecimens and personal data.

Informed consent is usually discussed in terms of its function as a means to ensuring respect for personal autonomy and preserving the right to self determination and the right to privacy.

In RD research however, the requests to preserve the identity and the privacy of participants may be particularly challenging. In certain cases it would suffice to link basic information like the name of the diagnosis and the name of the treating physician to identify individual patients⁶⁷.

Also, to conduct successful research it may be essential to go back to the families and, according to some authors this is likely to be what they would want, for it is only through the promotion of research that they will gain understanding on the disease and eventually can have hope of making progress towards a cure⁸.

From the perspective of the rare disease patient there are at least three additional important values worth emphasising (though these do not exhaust all the values engaged here). The first and perhaps foundational value is:

1. The right to benefit from research. From its place within the EU Charter of Fundamental Human Rights as described there is a recognition of a right to medical treatment and prevention, entailing a social commitment to allow good science to happen, which would improve the understanding, the diagnosis and treatment for rare (and all) diseases. Since rare diseases face the additional challenge in research because of their rarity this fundamental right takes on a particular significance since rare disease research has been neglected in the past⁹. Enabling research for rare disease is not a luxury or an optional activity but is then to be recognized as a fundamental human right connected to the value and well-being of those affected by such conditions.

⁶ McGuire AL1, Gibbs RA. Genetics. No longer de-identified. *Science*. 2006 Apr 21;312(5772):370-1.

⁷ Lowrance WW, Collins FS. Ethics. Identifiability in genomic research. *Science*. 2007 Aug 3;317(5838):600-2.

⁸ Kent A. Consent and confidentiality: whose information is it anyway? *J Med Ethics* 2003;29:16-18. doi: 10.1136/jme.29.1.16

⁹ Mascalzoni D, Paradiso A, Hansson MG. Rare disease research: Breaking the privacy barrier. *Applied & Translational Genomics* 2014; DOI:10.1016/j.atg.2014.04.003

This same right seems to have been founding the new EU Regulation on clinical trials¹⁰ which is aimed, among other things, at facilitating cross-border cooperation to make clinical trials larger, more viable and more reliable. In the intentions of the legislator this should boost efforts to develop special treatments, e.g. for rare diseases.

2. Altruism, or the expectation that people will make some sacrifice for the benefit of others, is a much disputed concept but its basic appeal is very clear to see in the context of rare disease where patients and families can all easily recognise the needs of others, appreciate that there are others worse off than themselves with the same disease or with other rare diseases. The desire to act altruistically is important to value but it should not be exploited in the research context.

3. Related to altruism is the concept of solidarity, that sense of shared purpose which makes people inclined to act in a collaborative way. Solidarity is evident in the way that patients with rare disease have organised themselves in ways to cooperate and work together with physicians and with the scientific community in order to make research progress.

In rare genetic diseases, solidarity plays a strong role in the decision to participate to clinical and genetic research. Family members share genes, and there are moral considerations in favour of sharing information that could benefit the whole group or family, even if the people providing information or samples cannot benefit themselves¹¹. Also, some genetic diseases are so rare that the only way to gain new knowledge is through examination of very few families across the world. Therefore solidarity may concern family relation as well as the relation with other persons affected by the same rare disease¹².

Broad consent

In the last decades, especially in biobank research there has been a shift from an informed consent paradigm based only on the principle of respect for autonomy and self determination to a paradigm adding the values of beneficence, solidarity, justice, reciprocity, mutuality, citizenry and universality^{13,14,15,16,17}.

Drawing upon the biobanking experience, models such as broad consent have been proposed as a solution to some of the ethical challenges of data sharing. At the time of the collection of data and bio-

¹⁰ European Parliament. Clinical trials: clearer rules, better protection for patients. 2014. www.europarl.europa.eu/news/en/news-room/content/20140331IPR41186/html/Clinical-trials-clearer-rules-better-protection-for-patients.

¹¹ Kent A. Consent and confidentiality in genetics: whose information is it anyway? *J Med Ethics* 2003;29:16-18. doi: 10.1136/jme.29.1.16

¹² Chadwick R, Berg K, Solidarity and equity: new ethical frameworks for genetic databases. *Nat Rev Gen* 2001;2:318-321. doi:10.1038/35066094

¹³ Graeme L. Genetic Databases: Assessing the Benefits and the Impact on Human and Patient Rights – A World Health Organisation Report. *European Journal of Health Law* 2004;11:79-84.

¹⁴ Knoppers BM1, Chadwick R. Human genetic research: emerging trends in ethics. *Nat Rev Genet* 2005 Jan;6(1):75-9.

¹⁵ Hoedemaekers R1, Gordijn B, Pijnenburg M. Solidarity and justice as guiding principles in genomic research. *Bioethics*. 2007 Jul;21(6):342-50.

¹⁶ Gottweis H, Gaskell G, Starkbaum J. Connecting the public with biobank research: reciprocity matters *Nature Rev Genetics*2001;12:738-739 DOI:10.1038/nrg3083

¹⁷ Praisnack B, Buyx A. A solidarity-based approach to the governance of research biobanks. *Med Law Rev* 2013;21(1): 71-91. DOI: 10.1093/medlaw/fws040

specimens, their future specific use may be difficult to anticipate or may only be described in very broad general terms, e.g. for cancer research, rare disease research or medical research.

In broad consent, an individual gives consent to widely specified research, which allows for many future uses of tissue and data rather than just the one (or more) use(s) specified by known researchers. Once individuals give consent, they are not usually re-contacted concerning new uses. In projects that contain uncertainty about the scope of the consent, authorization for the use of coded samples and data may be given by a research ethics committee.

According to a recent review¹⁸ the shift towards a new paradigm, allowing a more broad and flexible interpretation of consent, occurred in 1995, following the publication of the Statement on Human Genomic Databases of the Human Genome Organization's Ethics Committee¹⁹.

Following this document, other guidelines have proposed the use of a broad or even a blanket consent^{20,21,22} especially in genomics research that would allow "use of a sample for genetic research in general, including future as yet unspecified projects"¹⁷. Thus, a new consent would be required only if a research project is different from the ambit of the original broad/blanket consent²³.

The question about the acceptability of broad consent^{24,25} has been deeply debated in the ethics and legal literature^{26,27,28,29}, and there is some consensus on its acceptability³⁰ provided proper on-going ethical and legal oversight are in place and timely, e.g. in the form of approval by ethical review boards/research ethics committees for new projects. There should also be regular and comprehensive mechanisms to update research participants wishing to be updated on the use of their samples. Given the increased informational risks that rare disease patients take in sharing data the principle of

¹⁸ Budin-Ljøsne I, Tassé AM, Knoppers BM et al. Bridging consent: from toll bridges to lift bridges? *BMC Medical Genomics* 2011, 4:69. doi:10.1186/1755-8794-4-69

¹⁹ Human Genome Organization Ethics Committee. Statement on Human Genomic Databases. Vol. 15. *Eubios J Asian Int Bioeth*; 2003. p. 99.

²⁰ United Nations Educational, Scientific and Cultural Organisation (UNESCO) Human Genetic Data: Preliminary Study by the IBC on its Collection, Processing, Storage and Use. Paris: United Nations Educational, Scientific and Cultural Organisation; 2002.

²¹ World Health Organisation (WHO) Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services. Geneva: World Health Organisation; 1998.

²² Human Genome Organisation (HUGO) Ethics Committee Statement on Human Genomic Databases London: *Eubios Journal of Asian and International Bioethics*; 2003. 13: 99.

²³ Vayena E, Ganguli-Mitra A, Biller-Andorno N. Guidelines on biobanks: emerging consensus and unresolved controversies. In Elger B, Biller-Andorno N, Mauron A, Capron A (dir.) (eds): *Ethical Issues in Governing Biobanks: Global Perspectives* Hampshire: Ashgate Publishing Limited; 2008. 23–35.35.

²⁴ Lunshof JE, Chadwick R, Vorhaus DB, Church GM, From genetic privacy to open consent, *Nat Rev Genetics* 2008;9:406-411.

²⁵ Hansson MG, Dillner J, Bartram CR, Carlsson J, Helgesson G, Should donors be allowed to give broad consent to future biobank research? *Lancet Oncol* 2006;7: 266–269

²⁶ Caulfield T, Biobanks and blanket consent: The proper place of the public good and public perception rationales. *Kings Law J* 2007;18: 209 – 226

²⁷ Arnason V, Coding and consent: moral challenges of the database project in Iceland. *Bioethics* 2004;18: 27–49

²⁸ Mascalzoni D, Hicks A, Pramstaller P, Wjst M (2008) Informed Consent in the Genomics Era. *PLoS Med* 5(9): e192. doi:10.1371/journal.pmed.0050192

²⁹ Kaye, J. Broad consent is informed consent, *Br Med Journal* 2011;343 doi: <http://dx.doi.org/10.1136/bmj.d6900>

³⁰ Sheehan M, Martin J, Can broad consent be informed consent? *Public Health Ethics* 2011; Epub, doi:10.1093/phe/phr020.

reciprocity should be even more emphasized through comprehensive and readily available (though actively sought) information about research progress using their samples.

2. Presentation of results

Informed consent as a process

To become real, ethical values must be translated into processes and procedures.

Informed consent is usually described as a "process of informing and sharing information and addressing questions and concerns, rather than simply obtaining a signature on a prescribed form"³¹.

Informed consent can take many forms but we would advocate that in order to share procedural consistency and good practice it should consist of two fundamental components: a document and a process. The informed consent document provides a summary of the research project (including the study's purpose, research procedures, potential risks and benefits, etc.) and explains the individual's rights as a research participant.

The document is part of an informed consent process, which consists of conversations between the research team and the participant and may include other supporting material such as study brochures.

In certain cases informed consent to participate in research may be overlooked by patients/participants especially when research is seen as a continuation of a process already started in the clinic and the person inviting participants/donors to participate is the clinician responsible for their care with whom they have a trusting relationship. Clinicians and clinician-researchers should therefore ensure that they have discussed the research project³².

The informed consent process provides research participants with ongoing explanations that will help them make informed decisions about whether to begin or, if they so wish, continue participating in the research project, including therefore a possibility for a participant to ask questions.

The process of obtaining informed consent is the only way to allow research participants to have some control over how their information is used. However, this procedure is problematic when it is applied in a data sharing context because there are several challenges³³. First, it is often difficult to explain genomics research in simple language^{34,35}. Second, it is difficult if not impossible to provide information about all the potential uses of such data nor who will have access.

³¹ World Health Organisation Research Ethics Review Committee. The Process of Obtaining Informed Consent.

³² Ponder M, Statham H, Hallowell N, et al. Genetic research on rare familial disorders: consent and the blurred boundaries between clinical service and research. *J Med Ethics* 2008;34:690-694 doi:10.1136/jme.2006.018564

³³ Kaye J, Heeney C, Hawkins N, de Vries J, Boddington P. Data sharing in genomics: re-shaping scientific practice. *Nat Rev Genet.* 2009 May;10(5):331-5. doi: 10.1038/nrg2573.

³⁴ Lunshof JE, Chadwick R, Vorhaus DB, Church GM. From genetic privacy to open consent. *Nature Rev. Genet* 2008; 9:406–411.

³⁵ McGuire AL, Caulfield T, Cho MK. Research ethics and the challenge of whole-genome sequencing. *Nature Rev. Genet* 2008;9:152–156.

We recommend that:

- researchers make a sincere attempt to provide as much information about a project in as many accessible forms.
- Information may be provided on several occasions, but without over-burdening participants.
- It can employ different means (brochure, colloquium, internet pages).
- The formal decision (consent) should happen after the informing process, allowing participants appropriate time to think, reflect and ask questions.
- A description of the communication of information strategy flowing from the project should be provided, and should include the general development of project timelines and newsletters or website updates dedicated to the participants.
- Wherever possible patient/ participant representatives should be consulted on the quality and detail of the information in advance of the study commencing.

It is acknowledged that within RD-Connect and related projects the informed consent process will be different according to different situations:

- 1) new collections using the informed consent forms of existing study projects which integrate RD-Connect specific information (including the possibility of large scale sequencing techniques , a personal unique identifier, international data sharing inside and outside the consortium, including sharing with commercial companies).
- 2) new research projects (biobanks and registries) for which the information sheets and consent templates can be created ex-novo.
- 3) old collections obtained with / without informed consent

In all such situations the concept of broad consent for, as yet undetermined, future uses of data and samples should be explained.

Prospective consent

Essential information elements

According to most guidelines dedicated to informed consent in human research, informed consent must clearly describe the research objectives, procedures, risks, and benefits to potential participants^{36,37,38,39,40,41,42,43}. Also, there are basic principles in research ethics, including the voluntariness of participation

³⁶ World Medical Association (WMA) World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Helsinki, Finland, World Medical Association (WMA); 1964.

³⁷ Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva, CIOMS publications; 2002.

³⁸ Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Epidemiological studies. Geneva, CIOMS Publications; 2009.

³⁹ Council of Europe. 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, Spain, Council of Europe; 1997.

and the right to withdraw, the right to decide without coercion, the right to have one's medical treatment not affected by a decision to not participate.

Most of these principles are derived from clinical research ethics and have been translated to the context of observational, biobank and genomics research. However, some information elements are differently described in the latter, in particular:

Reasonably Anticipated Benefits—participants are made aware that, as compared to certain kind of clinical research, there will probably be no direct personal benefits associated with their participation. In this type of research benefits are most likely foreseen for future patients though it might be reasonable to describe potential secondary benefits, for example, in the case of registries used for recruitment for clinical trials.

Foreseeable Risks—they include the potential loss of confidentiality caused by misuse of data, misconduct, hacking, and the chance of information about a family member possibly being divulged.

According to some authors these risks are low, as technologies and models currently exist that facilitate data sharing without sacrificing privacy⁴⁴.

The current evidence however do not allow to draw conclusions about the efficacy of de-identification methods⁴⁵.

Although the risks associated with the dissemination of data are very much socially and culturally situated; in certain countries, for example, individuals may not want their data to be freely shared for the purposes of research. Identification and stigmatization are sensitive issues in certain societies.

In order to "widen" the scope of existing informed consent documents it has been proposed to specify, in the sections describing the risks and benefits that there are no additional risks or benefits to be expected, except those "related to expansion of scope of research". However, the benefits and risks deriving from such a broadening are not easily foreseeable and they are not easy to explain⁴⁶.

As regarding the risks of re-identification donors/participants should be made aware that their data can be and will likely be accessed, shared and linked to other sets of information, and that the full purpose

⁴⁰ United Nations Educational Scientific and Cultural Organisation. Human Genetic Data: Preliminary Study by the IBC on its Collection, Processing, Storage and Use. Paris, France; 2002.

⁴¹ United Nations Educational Scientific and Cultural Organisation International Bioethics Committee. United Nations Educational, Scientific and Cultural Organisation International Bioethics Committee: International Declaration on Human Genetic Data. Paris, France; 2003.

⁴² Organisation for Economic Co-operation and Development (OECD) Draft Guidelines for Human Biobanks and Genetic Research Databases: Text for Comment. Paris, France, Organisation for Economic Co-operation and Development; 2008.

⁴³ Human Genome Organization. Statement on the Principled Conduct of Genetics Research. Vol. 6. Eubios J Asian Int Bioeth; 1995. pp. 59–60.

⁴⁴ Knoppers BM, Dove ES, Litton JE, et al. Questioning the limits of genomic privacy. Am J Med Genet 2012;91:577-8. DOI: 10.1016/j.ajhg.2012.05.027.

⁴⁵ El Emam K, Jonker E, Arbuckle L, et al. A systematic review of re-identification attacks on health data. PlosOne2011;2. DOI: 10.1371/journal.pone.0028071

⁴⁶ Budin-Ljøsne I, Tassé AM, Knoppers BM et al. Bridging consent: from toll bridges to lift bridges? BMC Medical Genomics 2011, 4:69. doi:10.1186/1755-8794-4-69

and the extent of further usage cannot be foreseen. Donors/participants should realize that they are potentially identifiable even if all efforts will be made to protect their identity.

Study procedures - in observational and biobank studies they are not bodily "invasive" procedures and may include: storage and conservation of samples; steps for data entry; submission of medical records; allowances for participation by a patient surrogate (when applicable); provision of updates to patients; methods of future contact from staff; access to data by researchers; the use and sharing of the data for research; and information on or options for future uses⁴⁷.

Other core elements usually found in observational and biobank studies are: kinds of samples and data that will be collected; Coding system and protections in place locally to ensure the confidentiality of samples and data; Return of incidental findings, if any; Compensation/reimbursement; Withdrawal procedures, such as sample retrieval and/or destruction; Ownership of samples; Prospects for third-party commercialization and intellectual property procedures; Study dissemination⁴⁸.

In a research scenario where the data are shared more widely and frequently, additional core elements should be included into the informed consent documents, describing specific research domain and simultaneously anticipating cross-domain data sharing. Several studies demonstrate that research participants across a range of populations and disease groups wish to be informed if wide data-sharing procedures are implemented⁴⁹. In their paper, McGuire et al. show that patients would feel deceived and angry if they found out that their data was shared without their knowledge and consent⁵⁰; even where patients would have gladly shared their data if they had been asked to do so or had been adequately informed⁵¹. In a study by Ludman and colleagues⁵² the majority of respondents (90%) stated it was very important or somewhat important to be asked for their permission to add their health and genetic information to a databank. In contrast an opt-out approach was much less acceptable to respondents, and a notification-only approach even less acceptable. Thus, information and transparency seems to play a significant role according to this study in maintaining the trust of individuals that are included in registries and biobanks.

In RD-Connect potential participants should be informed of the likelihood of international data sharing and the fact that data and samples will be used for RD research. Also, they should be notified that their data will be coded within the consortium and the coded data will be placed in an open access database, the European Genome-Phenome Archive (EGA), where access to data will be overseen and decided by a data access committee according to established principles .

⁴⁷ Rubinstein YR, Groft SC, Hull S, et al. Informed consent process for patient participation in rare disease registries linked to biorepositories. *Contemp Clin Trials* 2011;33(1):5-11. doi:10.1016/j.cct.2011.10.004

⁴⁸ Mallette A, Tassé AM. P3G generic Information Pamphlet and Consent Form (2014). Available at: http://www.p3g.org/system/files/biobank_toolkit_documents/P3G%20Generic%20Info%20Pamphlet%20and%20Consent%20Form%20for%20Biobanks.pdf . Accessed last March 24, 2014.

⁴⁹ Tabor HK, Berkman BE, Hull SC, et al. Genomics really gets personal: how exome and whole genome sequencing challenge the ethical framework of human genetics research. *Am. J. Med. Genet. A*, 155 (12) (2011), pp. 2916–24. DOI: 10.1002/ajmg.a.34357

⁵⁰ McGuire AL, Gibbs RA. No longer de-identified. *Science* 2006;312 (5772):370–371. DOI: 10.1126/science.1125339

⁵¹ Oliver JM, Slashinski MJ, Wang T. et al. Balancing the risks and benefits of genomic data sharing: genome research participants' perspectives. *Pub. Health Gen* 2012;2:106–114.

⁵² Ludman EJ, Fullerton SM, Spangler L. et al. Glad you asked: Participants' Opinions of Re-Consent for dbGaP Data Submission. *J Empir Res Hum Res Ethics*. Sep 2010; 5(3): 9–16. DOI: 10.1525/jer.2010.5.3.9

Consortium specific elements must also include details of the procedures for data access and the persons entitled to access the data, including commercial partners.

The wide sharing and open research programme does create a problem for the execution of the right to withdraw. Because participants are unlikely to know the exact uses of their data and samples they will not be able to judge whether the research is something to which they approve or not. It must be acknowledged therefore that there may be some practical limitations in respecting the right to withdraw. In the context of global data sharing, better methods of informing participants about the use of their personal information for different research purposes need to be developed⁵³.

"Flexible" elements

There are elements that deserve flexibility in the informed consent process, in order to allow adaptability to the local context.

Some of these elements are:

- the policy for return of incidental findings,
- the destination of data and bio-specimens after death or in the case of the termination of the project,
- the involvement of relatives in research.

Participants should be allowed to have some options to express choices, or at least be provided clear information on these elements and where there are likely to be restrictions on, or limitations to the usual rights of autonomy, then these should be explained and justified by the researcher. All policies and governance protocols should be open to scrutiny, have developed from an appropriate process of participant consultation, and have been given ethics approval.

⁵³ Kaye J, Heeney C, Hawkins N, de Vries J, Boddington P. Data sharing in genomics: re-shaping scientific practice. *Nat Rev Genet.* 2009 May;10(5):331-5. doi: 10.1038/nrg2573.

BOX1: Essential elements for the informed consent of biobanks and observational studies

- General (name of the PI, Institution, funding, duration, oversight, contact persons)
- Aims, research uses of data (e.g cancer research, RD research)
- Voluntariness of participation and possibility to withdraw
- Procedures involved in participation, including interviews, blood taking, etc.
- kinds of samples and data that will be collected;
- Potential physical, psychological and social risks
- Potential benefits
- Description of the coding system
- Protections in place locally to ensure the confidentiality of samples and data;
- Access to data/samples for research purposes: who will have access who should control and what the procedures in place (data access committee)
- Access to data/samples for purposes such as validation, quality control, etc.
- Study oversight
- Compensation/reimbursement
- Custodianship of samples;
- Study dissemination.

Core elements for the informed consent of studies participating to RD-Connect

- Hosting of the data in an open access database
- Access by industry if foreseen
- Possible linkage to different data (registries, medical records, etc)
- Possibility of large scale genome sequencing techniques
- Possibility of data sharing across research groups and national borders
- Return of incidental findings
- Withdrawal procedures, such as sample retrieval and/or destruction
- Prospects for third-party commercialization and intellectual property procedures;

Retrospective consent

The use of biological samples and data outside the range described in the consent form is usually considered as a 'secondary use'⁵⁴.

For most studies using "secondary" data, the original informed consent did not contemplate the possibility of international data sharing.

In some jurisdictions institutional review boards/research ethics committees (IRBs/ REC) can determine if the sharing of a participants data for research purposes is “consistent with” the informed consent of study participants from whom the data were originally obtained. However, where there is no national guidance or legislation IRBs/ REC can differ in their decisions⁵⁵.

In most jurisdictions, secondary use of old collections is not legal in the absence of a new consent, an ethics waiver, or other legal provisions⁵⁶. Therefore, the use of samples and data in different research domains is highly problematic and the current interpretation of consent in existing international and national ethics guidelines does not facilitate data sharing in general.

A sizeable number of samples currently exist in clinical biobanks as well as patient data registries for which there is little or no expressed consent for research, data/material sharing to other groups especially industry, or where the scope of the consent may be unclear. These samples may have been collected at a time when research ethics were not developed to the standard they are now and before the advent of modern research technologies such as next-generation sequencing.

Given that there are a limited number of biospecimens for most RDs and it may be difficult or impossible to obtain a new sample, and thus existing samples are extremely precious. As such every effort should be made to use existing data and samples.

Rules and recommendations regarding information and consent procedures need to take into account the complexity of patient perceptions as well as the different characteristics of different cohorts and collections^{57,58}, with a view to preserve and maximise the use of the most rare data and samples.

To enable researchers to share samples and data of this kind a common framework of how to manage informed consent concerns is needed. Legal frameworks do differ between countries making it possible in some countries to use archived samples and data without explicit consent while researchers in other countries are obliged to obtain new consent. Approval of these single projects by an IRB/REC is always required.

According to some national legal requirements either re-contact and re-consent or a notification with opt-out schemes should be required in order to enable the institution to use and share internationally. This is especially important where minors (at the time of the collection) are involved. In some cases -

⁵⁴ P3G Observatory, Lexicon, online: <<http://www.p3gobservatory.org/lexicon/list.htm>>

⁵⁵ Ludman EJ, Fullerton SM, Spangler L. et al. Glad you asked: Participants' Opinions of Re-Consent for dbGaP Data Submission. *J Empir Res Hum Res Ethics*. Sep 2010; 5(3): 9–16. DOI: 10.1525/jer.2010.5.3.9

⁵⁶ Budin-Ljøsne I, Tassé AM, Knoppers BM et al. Bridging consent: from toll bridges to lift bridges? *BMC Medical Genomics* 2011, 4:69. doi:10.1186/1755-8794-4-69.

⁵⁷ Høyer, K. Donors perceptions of consent to and feedback from biobank research: time to acknowledge diversity? *Public Health Genomics* 2009;13:345–352.

⁵⁸ Steinsbekk KS, Solberg B. Biobanks—when is re-consent necessary? *Public Health Ethics* 2011;4:236–50.

where re-contact of patients is unfeasible and disproportionate to benefits (very old collections) - a waiver for re-consent can be granted by an ethics review board. In this case a clear outline of the reasons for requiring the waiver should be provided to the ethics board.

In RD-Connect we suggest that the original informed consent document be revised by the local P.I. and subject to IRB/ REC approval, and if core elements listed in BOX1 are missing a new informed consent (through re-consent or opt out procedure) is needed.

A clear distinction should be made between collections in which a previous consent was obtained and where a question was not asked, and one where a patient actively declined an option or in which the information provided excluded some options (e.g. “your data will not be shared with any commercial organizations”). In these instances, re-consenting or notification with opt out should always be pursued.

For some older cohorts the researcher may still find re-consent achievable within reasonable efforts, using this also as an opportunity to update or collect new data. Other projects may be particularly vulnerable to drop outs and one may want to use a scheme with notification and opt-out, thus still respecting the autonomy of participants.

Re-consent

Respect for autonomy in the sense of having a direct say on how one’s samples and data will be used implies re-consent in cases where the scope of the consent is unclear. This is particularly relevant where the development of new techniques could not have been anticipated when the samples were first collected.

While ethical review is always requested for every single project, a general requirement to obtain new informed consent in all cases may be disproportionate to the potential benefits resulting in use of data and samples and would also involve a potential for selection bias due to drop outs. Rare disease research may be particularly vulnerable to selection bias because the number of available samples and data is intrinsically low for each condition, ultimately jeopardising research which is in the interests of all parties. However, careful consideration of the time, effort and other resources required to adequately re-consent patients should be given, as re-consent may also result in benefits if drop-out rates are low and donors participants become more motivated to participate in the research project. The actual balance and trade-off between respect for autonomy and optimizing provision of new treatment opportunities should be sensitive to and recognise the needs of the rare disease community and the wider public.

An analysis of the costs associated with consent should also include an examination of the costs of “no consent” for the use of samples and information such as loss of public trust in research, loss of participation in future studies, loss of opportunity for follow up and loss of patient organisation support in research projects. . The benefits of re-contact in order to re-consent should also not be underestimated. Establishing a better dialogue about research with a patient cohort may lead to a motivated, informed and proactive patient community. Trust and transparency may be increased and drop-out rates reduce.

Opt out

Opt out methods are designed to minimize the burdens of eliciting voluntary participation from a large number of patients while providing those who do not wish to contribute the opportunity to exercise that preference⁵⁹.

However, as already mentioned, studies show that donors/participants are not always favourable to opt-out schemes⁶⁰.

Before using an opt-out method researchers should be able to demonstrate that all reasonable efforts were made to make contact with a patient.

The fact that opt out options do not affect research is supported by the report of a Swedish study revealing that, even with an especially elaborate system for opting out of consent (where detailed information and consent forms were offered at sampling that patients could take home and fill in), only 1 in 19,000 actually did opt out⁶¹. Recent legislation in Finland also supports this view, and foresees the implementation of opt out options for registries and biobanks⁶².

Waiver of consent

While it is clear that having a proper consent in place is the most ethical option and should be pursued whenever possible in order to pay respect to participant's autonomy and improve active participation in research, there may be instances in which a waiver may be requested to ethical boards. This waiver should contain an explanation why participants should not be re-contacted. New consent procedures may ensure that this occurrence will be minimized in the future by asking specific permission to look up contact information for re-contacting patients.

E-mail, telephone contacts and strategies to keep contact are especially relevant for studies that involve minors. The need to re-contact and involve patients in research may also lead to the development of patient centric approaches to consent that provide a dynamic interaction.

Where it is determined that re-contacting patients is unfeasible or when inclusion of small sample numbers from across a large number of collections and registries are of outmost importance or when samples are held in older collections, an acceptable option could be a waiver on re-consent. This option is not feasible in every legal system and requires an adequate assessment of the reasons for asking for a waiver to the ethics review board.

Optional re-consent as well as notification with an opt-out clause or general waiver of re-consent for specific cases may create some efficiencies and still maintain ethically responsible and practical ways to access samples an data spread across many sites globally. A permission by the ethics board to use

⁵⁹ Brothers KB, Westbrook MJ, Wright MF, et al. Patient awareness and approval for an opt-out genomic biorepository. *Per Med*. 2013 Jun;10(4). doi: 10.2217/pme.13.34.

⁶⁰ Ludman EJ, Fullerton SM, Spangler L. et al. Glad you asked: Participants' Opinions of Re-Consent for dbGaP Data Submission. *J Empir Res Hum Res Ethics*. Sep 2010; 5(3): 9–16. DOI: 10.1525/jer.2010.5.3.9

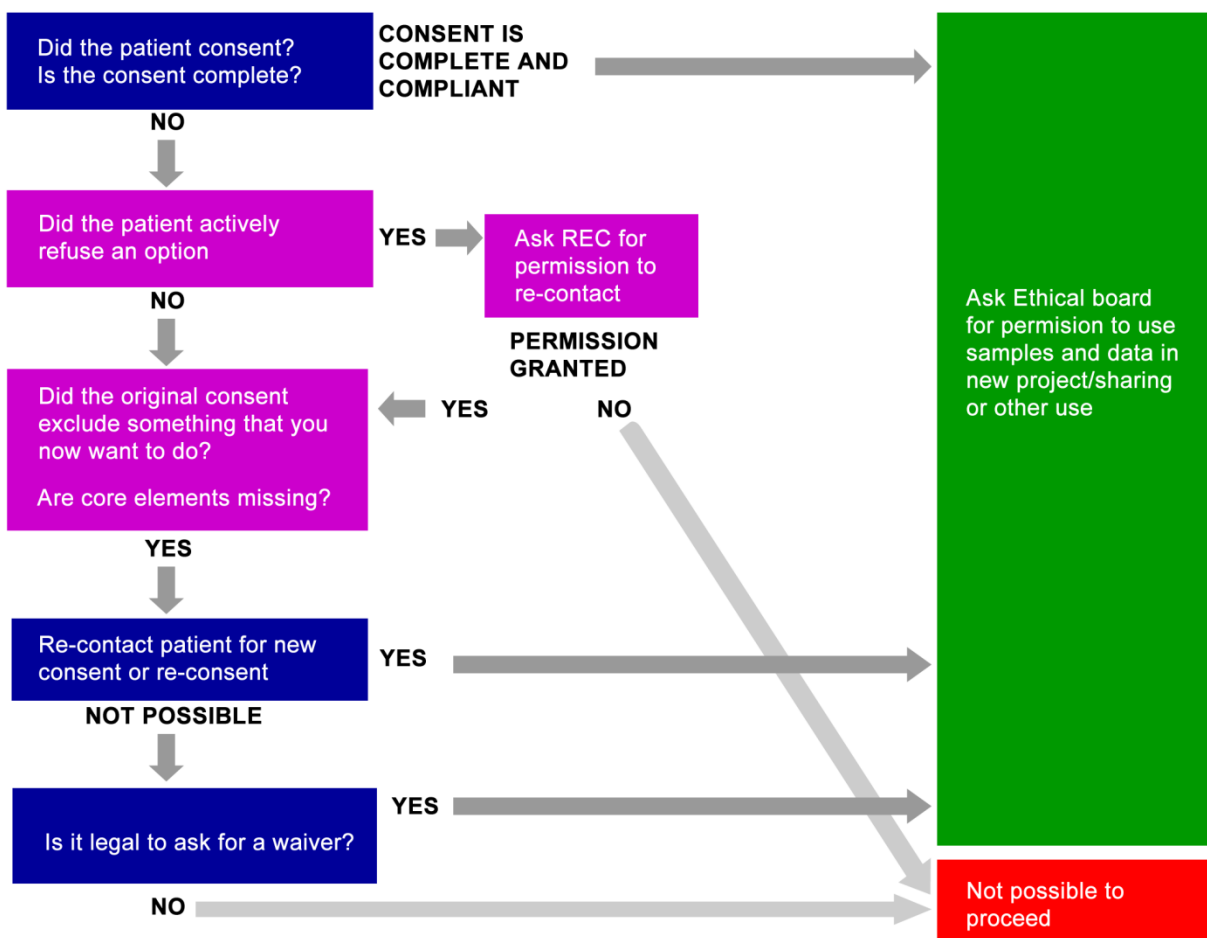
⁶¹ Johnsson L, Hansson MG, Eriksson S, et al. Patients' refusal to consent to storage and use of samples in Swedish biobanks: cross sectional study. *Br Med Journal* 2008;337:p. a345. doi: 10.1136/bmj.a345

⁶² Forsberg JS, Soini S. A big step for Finnish biobanking. *Nat Rev Gen* 2014;15:6. doi: 10.1038/nrg3646

previously collected samples should specifically state the permission to share abroad and foresee genetic analysis where appropriate.

Besides permission of the IRB/REC to use patients data and samples for a specific research project without asking participants re-consent, the "moral endorsement" of patient organizations may be sought in order to ensure that the patient community agrees with certain uses of data and samples related to their diseases. The sharing of data and bio-specimens without consent needs to be compliant with the appropriate legal framework.

Figure 1: Procedures for using already collected samples.



3. Critical analysis of results

In RD-Connect the Guidelines on Informed Consent have to consider the needs and specificities of the data-generating projects (NeurOmics and EURenOmics), and of other candidate registries and biobanks that will ultimately use the platform, most of which may already have in place forms and templates for the informed consent process.

Guidance and clear principles are therefore needed to be applied to different situations:

- 1) new research projects (biobanks and registries) for which the information sheets and consent templates can be created ex-novo.
- 2) new collections using the informed consent forms of existing study projects which should include specific information on the new challenges of international data sharing
- 3) old collections obtained with / without informed consent

In the first part of the work we described the most important values in RD research: the right to integrity within the fields of medicine and biology, implying a free and informed consent according to the procedures laid down by law, the individual right to the protection of personal data concerning him or her, but also the right to benefit from research, and the duty to altruism and solidarity with other rare disease patients. All these values provide a strong ethical foundation to the sharing of data across countries and disciplines for the sake of the RD patients and for the search of new diagnostic and therapeutic possibilities.

We then described the process of informed consent in RD Connect and the core elements that must be explained to research participants in order to involve them as much as possible in the process of creation of new knowledge.

The main ethical challenge here is that of obtaining an informed consent that is perceived as ethically equivalent to specific and detailed consent but in a data sharing context which is necessarily broad⁶³, and the difficulty to achieve the level of understanding that is required for meaningfully informed consent^{64,65}, especially for data sharing in genomics. Also, there is a difficulty in providing information about all the potential users of shared data, without a constantly updated system to inform participants.

Broad consent is probably the only possible kind of consent that one can be obtained in a data sharing context without rendering the procedure burdensome and complex.

However we propose that, if broad consent is used:

- regular updates on the development and the aggregated results of the project/biobank are given to participants, as they serve as reminders of on-going participation and keep the participants involved.
- Also, patient participation should be promoted at a more institutional level by involving patient organisations in governance, developing policies, practices and documentation.

A number of patient-centric consent strategies exploiting online technologies have been developed to help address the limits of a pure broad consent approach. For example longitudinal population projects are in constant contact with their participants⁶⁶ but dynamic consent models⁶⁷ offer an alternative way to

⁶³ Kaye J, Heeney C, Hawkins N, de Vries J, Boddington P. Data sharing in genomics: re-shaping scientific practice. *Nat Rev Genet.* 2009 May;10(5):331-5. doi: 10.1038/nrg2573.

⁶⁴ Lunshof JE, Chadwick R, Vorhaus DB, Church GM. From genetic privacy to open consent. *Nature Rev. Genet* 2008; 9:406–411.

⁶⁵ McGuire AL, Caulfield T, Cho MK. Research ethics and the challenge of whole-genome sequencing. *Nature Rev. Genet* 2008;9:152–156.

⁶⁶ Golding J, Pembrey M, Jones R; et al. ALSPAC--the Avon Longitudinal Study of Parents and Children. I. Study methodology. *Paediatr Perinat Epidemiol* 2001;15(1):74-87.

⁶⁷ Kaye J, Curren L, Anderson N, et al. From patients to partners: participant-centric initiatives in biomedical research. *Nat. Rev. Genet* 2012;13 (5): 371–376.

overcome the tension between broad and specific consent also in non-longitudinal research such as clinical trials, by ensuring on-going information and participant involvement after general consent has been provided at the time of bio-specimens collection.

- New forms of consent should be implemented for research that have a special social or “public good” value (excluding highly sensitive research)^{68,69}.
- In such cases, a thick opt out procedure would provide for higher-than-normal participation and would simultaneously acknowledge the rights of individuals to make decisions in respect of their own private spheres.

A thick opt-out procedure is "an opt-out procedure with the fulfilment of the following conditions: (1) awareness is raised about the opt-out procedure (2) adequate information is provided (3) a genuine possibility to object is presented and objections are adequately registered"⁷⁰.

In a thick opt out procedure, patients should be well informed about research but they should not actively agree to participate. In fact, the default position would be agreement to be into research and patients who do not want to participate could actively disagree by opting out.

- So to overcome the lack of detailed research information at the time of consent, we suggest an integrated approach entailing obtaining broad consent integrated with providing on-going information over time about the general development of project, for instance by proper communication with the participants/donors through email, phone, a newsletter, patient organizations contacts and regular website updates dedicated to them.

A need to re-contact and re-consent patients calls for something different than traditional consent, and would be best served (from a patient and scientific perspective) by a dynamic consent procedure. Such a procedure would make it possible to be specific and individual about how much information is desired as well as to allow for choice in terms of the level of participation and communication up front. This approach also constitutes a tool for a thick opt out procedure over time.

4. Conclusion

The increased exchange of data inside and outside international research consortia raises additional complexities in the informed consent process as it adds new needs for potential donors/participants and requires coordination and comparability between different research centres worldwide.

Also, the complexity and unpredictability of research in the new context of data sharing makes real informed consent more difficult to achieve without an adequate system of updating for participants.

The involvement of participants in research will improve trust towards the research enterprise.

⁶⁸ Rothstein MA, Shoben AB. An unbiased response to the open peer commentaries on “does consent bias research?” *Am. J. Bioeth* 2013;13 (4):W1–W4. DOI:10.1080/15265161.2013.769824

⁶⁹ Giesbertz NA, Bredenoord AL, Van Delden JJ. A thick opt-out is often sufficient. *Am. J. Bioeth.* 2013;13(4):44–46

⁷⁰ Giesbertz NAA, Bredenoord AN, van Delden JJM. Inclusion of Residual Tissue in Biobanks: Opt-In or Opt-Out? *Plos Biology* 2012;10(8): e1001373. DOI: 10.1371/journal.pbio.1001373