

ARTICLE

Improving the informed consent process in international collaborative rare disease research: effective consent for effective research

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The increased international sharing of data in research consortia and the introduction of new technologies for sequencing challenge the informed consent (IC) process, adding complexities that require coordination between research centres worldwide. Rare disease consortia present special challenges since available data and samples may be very limited. Thus, it is especially relevant to ensure the best use of available resources but at the same time protect patients' right to integrity. To achieve this aim, there is an ethical duty to plan in advance the best possible consent procedure in order to address possible ethical and legal hurdles that could hamper research in the future. Therefore, it is especially important to identify key core elements (CEs) to be addressed in the IC documents for international collaborative research in two different situations: (1) new research collections (biobanks and registries) for which information documents can be created according to current guidelines and (2) established collections obtained without IC or with a previous consent that does not cover all CEs. We propose here a strategy to deal with consent in these situations. The principles have been applied and are in current practice within the RD-Connect consortia – a global research infrastructure funded by the European Commission Seventh Framework program but forward looking in terms of issues addressed. However, the principles established, the lessons learned and the implications for future research are of direct relevance to all internationally collaborative rare-disease projects.

European Journal of Human Genetics (2016) **24**, 1248–1254; doi:10.1038/ejhg.2016.2; published online 10 February 2016

INFORMED CONSENT FOR RARE DISEASE RESEARCH IN THE ERA OF GLOBAL DATA SHARING AND NEXT-GENERATION SEQUENCING

Fostering global data sharing that allows collaborative work on scarce and disparate resources is essential for research into rare diseases (RDs).¹

The challenges posed by new sequencing technologies and the world-wide dimension of data sharing require research consortia to adapt existing informed consent (IC) procedures to a new reality and ensure that consent processes are relevant and useful for ongoing and new collections.

For RD patients, research is often the only hope for future treatments and in some cases the only possibility for getting a diagnosis. This creates a status of special vulnerability in RD patients that could lead them to accept conditions which they might not in other circumstances. Therefore, it is especially important to identify guidance that will foster the right to enjoy the benefits of scientific progress for RD patients and at the same time respect patients' rights and values:^{2–7} we regard it as an ethical duty to plan ahead the best possible consent procedures in order to anticipate and avoid ethical and legal hurdles that could hamper research in the future.

RD-Connect is a global research infrastructure⁸ aimed at developing an integrated platform in which omics data will be combined with

clinical phenotype information and biomaterial from multiple RD projects including EUReOmics⁹ and NeurOmics.¹⁰

We suggest that RD-Connect poses relevant ethical challenges, which are common to other international research projects focused on omics research and can therefore be used to learn common lessons. There are sensitive topics that need special consideration in the consent process such as return of incidental findings to participants; the ties to family members and possible obligations arising from research results; the future use of samples; the limits or the foreseen sharing of data derived from next-generation sequencing (NGS);¹¹ as well as the difficulty to explain and enforce the right to withdraw from research in the light of global sharing. The very nature of genomic research promotes a widespread dissemination and ongoing reuse of data and participants should be made aware that different actors and bodies (ie, research ethics committees (RECs), internal governing boards and external reviewers) will be responsible to decide on their behalf for future uses and for reviewing and evaluating access requests from external researchers.^{12–14} This means that the protection of their integrity is delegated to a system that should be explained and disclosed.^{12–14}

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Received 7 August 2015; revised 23 November 2015; accepted 8 December 2015; published online 10 February 2016

In fact specific features of omics research, and in this case of the global RD-Connect platform, raise particular challenges for the IC process as they add new ethical and legal complexities and require coordination and harmonisation between different research centres worldwide.^{15–17}

IC is traditionally discussed in terms of its function as a means to ensuring respect for personal autonomy, integrity, self determination and the right to privacy.¹⁸

In RD research respecting privacy can be especially challenging since, in certain cases, it would suffice to link basic information like the name of the disease and the name of the treating physician or the specific ultra-rare sequence change and the place of origin to trace back individual patients.^{19–22} In ‘undiagnosed cases’ clinical and genetic data (and occasionally also patient images) are often entered into databases expressly conceived to facilitate the matching of cases with similar phenotypic and genotypic profiles (eg, the Matchmaker Exchange project <http://www.matchmakerexchange.org/>).

Family contact and therefore re-identification is common practice to build a full data set, and it is often necessary to be able to re-contact and re-identify patients. This is usually accepted by patients and relatives because it is only through the promotion of research that they will progress towards a diagnosis or a cure,²³ but requires that participants are carefully informed of the risk as codification cannot ensure a zero risk of re-identification.²²

To address those special concerns we tried to determine the kind of information that should be required for this type of research in international consortia in the form of core elements (CEs) required for informing patients in research.

The CEs recommended in our guidelines are in response to particular legal and ethical requirements identified through an extensive literature analysis and on the values identified through stakeholder involvement.

Key values identified by stakeholders at a workshop held in Rome in April 2014 with patients, scientists, industry and ethicists include:

1. Respect for patients’ and patients’ families’ integrity;
2. The right to enjoy the benefits of scientific advancement;
3. Altruism and solidarity.²⁴

All such values are assumed to hold within an environment where trust is well-placed.²⁵ RD research is often conducted in a context in which the research is closely tied to patient care and is merged in the route to diagnosis. The current request made by key funders for research to be conducted in the international context of data sharing, possibly with unspecified partners, may not always be clear enough to patients. The link between research and this close, clinical relationship should be made transparent and explicit so respecting the special trust granted by participants.²⁶

Also, participants should be offered the possibility to decide the level of accessibility of their data, especially in matchmaking databases where researchers must decide to make a case ‘private’ (visible and accessible only by themselves), ‘matchable’ (visible by all users and accessible upon request) and ‘public’ (visible and accessible by all users).

The discussed sharing practice can get really problematic if it does not also include an explicit sharing of responsibilities, which could be facilitated through the adoption of a ‘Code of Conduct’ and a system of unique identifiers for researchers.²⁷ Researchers not directly involved in a caring relationship with the RD patient might perceive that they are not bound by the same medical or deontological framework as are treating clinicians.

INFORMED CONSENT FOR NEW RESEARCH COLLECTIONS

In the last decade, there has been a shift from a specific IC paradigm to a paradigm that tries to take into account the values of beneficence, solidarity, justice, reciprocity, mutuality, citizenship and universality.^{28–33}

Different models such as broad consent and dynamic consent have been proposed as possible solutions to some of the ethical challenges described above, like future uses and international sharing of samples and data derived from NGS, return of incidental findings to participants and family members and difficulty to enforce the right to withdraw from research.^{34–37}

Focus groups carried out with RD patient representatives (<http://rd-connect.eu/platform/ethics/rd-pec/>)³⁸ highlighted that RD patients generally find acceptable broadly described purposes for the use of biomaterials and data for biobanks. However, many would prefer to see access to their data more strictly controlled. Also, RD patients foresaw a number of possible risks for themselves, their children and/or other family members; most notably discrimination in such areas as employment, health-care access and financial matters.

Therefore, we propose that if broadly descriptive consent is to be adopted, then this should be supplemented by providing participants with additional safeguards and opportunities for being updated.³⁹ Patients may accept data sharing and find broadly described purposes of a research acceptable, provided there is clarity about governance of data and samples, re-contact policies, privacy measures, ethical oversight, clear withdrawal policy and a commitment to keep participants informed if major changes in these areas occur.

For RD patients, research is often the only hope for future treatments and in some cases the only possibility for getting a diagnosis, and RD patients and their families are usually highly motivated to participate and have a significant role in the research process. The need to re-contact and involve patients in research takes advantage of patient-centric approaches to consent that provide dynamic interaction exploiting online technologies to help address new challenges. Online tools can assist with ongoing information and participant involvement regarding new studies.^{40,41}

During the IC process, new research participants as well as participants who are re-consenting are entitled to understand to what extent they are involved in research and the kind of control that is granted to them on the use of their data and samples.

The challenges of this procedure are on many levels and include the need to explain genomic research in simple language as well as to provide information about the potential foreseeable uses of data and samples.^{11,42,43}

It is therefore important that:

- Researchers make a sincere attempt to provide clear information in patient friendly form and include the CEs (as defined below);
- Information is provided to patients at least when major changes occur and by sharing general results (brochures, colloquium, internet pages, mass media);
- The formal decision (consent) should take place after the information process, allowing participants appropriate time to think, reflect and ask questions;
- A description of the communication of information strategy for the future (after the collection) is provided to the participant;
- Wherever possible patient/participant representatives are consulted on the quality, detail and clarity of the information provided before a study starts.

CORE INFORMATION ELEMENTS

There are some essential requirements for a valid IC,^{17,44,45} including age and legal capacity of the participant, freedom of choice and voluntariness – implying the right to withdraw from research at any moment without prejudice. IC in human research must clearly describe research objectives, procedures, risks involved and expected benefits to potential participants. As voluntariness is a precondition of participation in research and IC aims to support a free informed decision, the elements that mostly impact the risk/benefit ratio of the project should always be disclosed.

A broad description of the kind of research expected at the time of the collection is acceptable, provided transparent information about the CEs is provided.

CEs should be included in the IC material for ongoing and future collections occurring in global consortia^{46,47} (Box 1):

1. *Study procedure*: descriptions should address how and for how long the storage and conservation of samples and data is planned; access policies; security measures; the use and sharing of the data for research; and information on options for future uses.
2. *Reasonably anticipated benefits*: participants are made aware that there will probably be no direct personal benefits, though it might be reasonable to describe potential secondary benefits, for example, in the case of registries, participants may be kept up-to-date about ongoing clinical trials for their RD. Also, participants without a clear diagnosis may benefit in terms of advancing knowledge on the causes of their condition and possibly find the causative gene.
3. *Foreseeable informational risks*: these include the potential loss of confidentiality caused by misuse of data, misconduct, hacking, the chance of information about a family member being divulged in one's country and abroad, also in jurisdictions that may have different data protection provisions in place. The current evidence does not allow us to draw conclusions about the efficacy of de-identification methods;⁴⁸ therefore, participants should be aware that their data will be accessed, shared and linked to other sets of information, that there exist different data protection regulations in different countries and that, while all reasonable efforts will be made to protect confidentiality, the purpose and extent of further usage cannot be foreseen. Participants should be made aware specifically if their medical records will be accessed and how these may be used alongside data from research studies.
4. *International data sharing*: in a research scenario where the data are shared widely and frequently, the sharing process must be clearly described. Several studies show that research participants across a range of populations and disease groups wish to be informed whether wide data-sharing procedures are implemented.^{49,50} Participants should be informed that their coded data will be placed in international archives such as the European Genome-phenome Archive (EGA), where access to data will be overseen and decided by a data access committee according to established principles and criteria. Information on the use of interoperable identifiers allowing matching between different databases also needs to be provided. Interoperable identifiers, created by using the same data elements in different databases with different algorithms will enable researchers to follow patients over time and across diseases, registries, studies and countries and avoid duplicating efforts by matching data collected at different times and by different entities, including linking patients' clinical information recorded in registries to biological samples available in one or more biobanks.
5. *Use of NGS techniques*: participants must be informed that their samples are likely to be analysed using large-scale genome

Box 1 Essential elements of IC documents for International Consortia on RD

Information elements that are relevant in IC documents for biobank and observational studies in RD Research

- General (name of the PI, Institution, funding, duration, oversight, contact persons)
- Aims, research uses of data (eg, cancer research and RD research)
- Voluntariness of participation and possibility to withdraw
- Procedures involved in participation, including interviews and blood taking
- Kinds of samples and data that will be collected
- Potential physical, psychological and social risks (informational risks)
- Potential benefits of participation
- 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 and quality control
- Study oversight
- Compensation/reimbursement
- Custodianship of samples
- Study dissemination plans (professional journals/lay versions/codified or aggregated results only/specific results/patient pictures and occasionally short professional video sequences).

CEs for the IC of studies participating to international RD research

- Possibility of data sharing across research groups and national borders
- Possibility of large-scale genome sequencing techniques
- Return of secondary findings
- Hosting of the data in open access database (eg, in RD-Connect the European Genome-Phenome Archive)
- Use of interoperable identifiers for the de-identification of participants
- Access by industry if foreseen and prospects for third-party commercialisation and intellectual property
- Possible linkage to different data (registries, medical records, etc.)
- Withdrawal procedures, such as sample retrieval and/or destruction and difficulties in ensuring the right to withdraw for the data already shared
- Permission to re-contact

sequencing techniques that carry potential for clinically relevant discoveries for individuals and families. A brief description of the techniques used should be given and the aim of the analysis explained, including the possibility of discovering previously unknown mutations relating to their condition as well as 'disease modifier' genes which do not directly cause the condition but might affect its severity and its course.

6. *Return of secondary findings and access to sequences*: this is a very sensitive issue that needs to be addressed.⁵¹ As there are no shared guidelines on this matter the IC should at least state if return is

planned or not. If not, when sequencing is performed, it should be clear whether individuals may ask permission to access their sequencing in order to seek advice elsewhere. If return is planned, then it should be detailed how the re-contact will occur; if the health-care system will be involved, then what are the researchers' options if results have implications for family members. Return of secondary findings should always be optional and not forced. As it is unclear to what extent or how secondary findings may impact individuals in future discoveries, this is a strong argument for asking the participants if they want to be re-contacted or not.

7. *Procedures for data access*: Core elements should also include details of the procedures for data access⁵² and the persons entitled to access the data, *including industry access* with prospects for third-party commercialisation and intellectual property procedures.⁵³
8. *Right to withdraw*: a research participant holds a right to withdraw from research at any time,¹⁸ but wide sharing and an open research programme create a problem for the execution of the right to withdraw. It must be acknowledged therefore that there may be some practical limitations in respecting the right to withdraw, in particular that while it is always possible to withdraw and deny access for future research projects, it may be impossible to withdraw from a specific research project for which one's data may have already been accessed.¹² The name of the person legally responsible for data as well as specimen custodianship must be available.
9. *Permission to re-contact*: permission to re-contact should always be pursued in order to allow unexpected events to be addressed in the future. If the project does not ask permission then this may lead to the impossibility of re-contact in the future.
10. *The information strategy on a general level should be described*: the strategy may vary greatly from project to project but it should be clear whether the plan foresees individual information being returned or whether the study is planning to publish newsletters, or information on a webpage dedicated to patients.

We suggest the inclusion of the following items in the IC, as it seems reasonable and will provide greater flexibility to researchers and participants:

11. Destination of data and biospecimens after death or in the case of the termination of the project;
12. Access to research results by family members if foreseen, or after death.

Participants should preferably be allowed to express choices with regard to the CEs. CEs are moving targets and the need to re-contact patients in the future is foreseeable. Therefore, we strongly recommend that permission is sought to be able to re-contact participants and ask them for contact details. Of course they may freely refuse this option.

USE OF EXISTING BIOSPECIMENS COLLECTION

The use of biological samples and data outside the purpose originally described in the consent form is usually considered as 'secondary use'.⁵⁴ The original consent, usually describing the aims of the 'primary use' of donation and/or data collection may not contemplate one or more CEs previously defined.¹⁷

Given the scarcity of biospecimens in RDs, existing collections are extremely precious. As such, every effort should be made to use

existing data and samples by looking at feasible ways for preserving and maximising their use in the future.^{55,56}

In some jurisdictions, institutional review boards/research ethics committees (IRBs/RECs) can determine whether sharing a participant's data for research purposes is consistent with the IC of study participants from whom the data were originally obtained. However, IRBs/REC can differ in their decisions even in countries where there is guidance or legislation.¹⁵

In international consortia using RD data and samples we suggest that, whenever possible, the original IC document used in existing collections be revised by the local investigator subject to IRB/REC approval to ensure that IC is compliant. If CEs are missing and re-contact is feasible (as in the case of regular follow-up visits with the researcher), then a re-consent is required. This may be done by actively asking participants' permission (opt-in) or by sending participants a notification and a description of the research project and presuming his/her consent unless s/he declines participation (opt-out).

Although the 'opt-in' option is always preferable, there may be instances in which the request may not be highly sensitive (few CEs missing in the original IC document), the costs of re-consent may be considered as too high for researchers in terms of possible drop outs, the re-contact may involve very old cohorts or the number of people to be re-consented may be very high. However, this is not likely to be the case in RD research.

For some 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 here one may want to use a scheme with notification and opt-out.

A clear distinction should be made between collections in which a previous consent was obtained and a question was not asked, and one where a patient actively declined an option or in which the information provided excluded some options (eg, 'your data will not be shared with any commercial organisations'). In the last instances, opt-in re-consenting should always be pursued in order to verify whether these options are now acceptable to the participant.

OPT-IN RE-CONSENT

Opt-in procedures require the participant/donor to actively give permission. Rare disease research may be particularly vulnerable to selection bias because the number of available samples and data is intrinsically low for each condition. 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 the benefits of better patient engagement, reducing drop-out rates and increasing donors' motivation to participate in research projects. Also, re-consent would be the occasion to effectively broaden the scope of participants' consent, thus ensuring its broad validity in future research projects.

An analysis of the costs associated with consent should also include an examination of the costs of 'no consent' or badly designed consent for the use of samples and information. If research participants feel that relevant information has been withheld from them, then this may result in a loss of public trust in research; and therefore, a reduction in participation in future studies, loss of opportunity for follow-up and loss of patient organisation support in research projects.⁵⁷ Some studies indicate that patients are more willing to share their data when procedures are in place that give them more control over the way their data are used.⁵⁸ Establishing a better dialogue about research with a patient cohort may lead to a more motivated, informed and proactive patient community.⁵⁹ Trust and transparency

may be increased and drop-out rates may reduce, as the NeurOmics experience illustrates below.

OPT-OUT STRATEGIES

In an opt-out procedure, the participant/donor receives a notification and a description of the research project and consent is presumed unless he/she declines participation. Opt-out methods are designed to minimise the burdens of eliciting IC from a large number of patients while providing those who do not wish to contribute the opportunity to exercise that preference⁶⁰ although studies show that donors/participants are not always favourable to opt-out schemes.^{61–63} Therefore, this option may only be justified when re-contact is not achievable with reasonable efforts.

The fact that opt-out options do not affect research in terms of drop outs is supported by the report of a Swedish study.⁶⁴ Recent legislation in Finland also supports this view, and foresees the implementation of opt-out options for registries and biobanks.⁶⁵

WAIVER OF CONSENT

Although having a valid consent in place is the most ethical option, there are instances in which a waiver may be requested to ethical boards, especially where it is determined that re-contacting patients requires disproportionate effort or is impossible (perhaps because of lack of contact details or patients lost to follow-up). This waiver should contain an explanation why participants should or could not be re-contacted. New consent procedures may ensure that this occurrence will be minimised in the future by asking specific permission to look up contact information for re-contacting patients.

This option is not feasible in every legal system and requires an adequate assessment of the reasons for asking for a waiver from the ethics review board.

The ‘moral endorsement’ of patient organisations could be sought in order to ensure that the patient community is aware of, and agrees with, certain uses of data and samples related to their diseases.⁶⁶

Indeed patient associations often have an educational role, and patient representatives dedicate a lot of time and efforts to explain to other RD patients the kind of research that is conducted and highlighting the importance of participating in clinical and observational research.

Even if re-consent is perceived as burdensome and detrimental to research by many researchers, positive outcomes can come by its practice.

THE NEUROMICS EXPERIENCE

The NeurOmics project is facing many of these consent and re-contact issues now. As a partner project of RD-Connect,¹⁰ NeurOmics is undertaking whole-exome sequencing and deep phenotyping of 1100 genetically-undiagnosed rare neuromuscular and neurodegenerative disease patients.

NeurOmics has therefore worked closely with RD-Connect in order to recommend CEs to be included in any consent forms used by partners contributing samples. Templates were circulated to all partners collecting samples and data in January 2013. This template included permission to have samples included in genetic research, specified how data would be accessed – including by international and commercial partners, made clear that unrelated findings would not be returned, asked for permission to re-contact and made clear the right to withdraw from the research. Partners were asked to check existing consent forms against this template.

NeurOmics investigators are requested to confirm that the consent necessary to share data is in place when entering phenotype data into the project’s clinical database, PhenoTips.⁶⁷ Where this consent is not yet obtained, it is expected that patients will be re-contacted and re-consented following the guidelines proposed here (Figure 1) and drawn up by RD-Connect, NeurOmics and patient groups.

This has now resulted in the confirmed consent and therefore possible sharing of data for 976 of 1065 patients entered into the PhenoTips system. In the meantime, those remaining 89 patients are being re-contacted according to the proposed guidelines. In spite

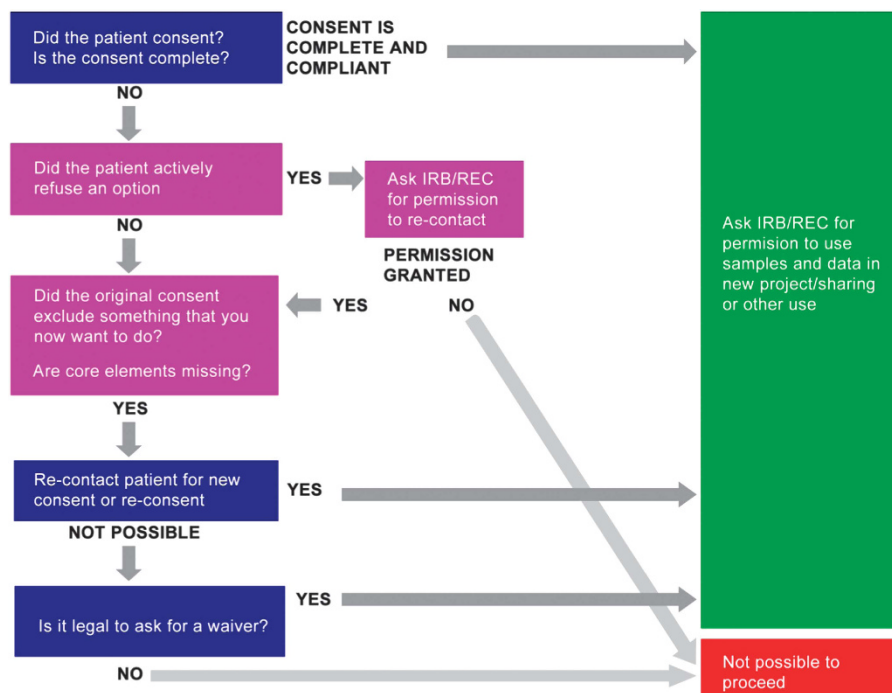


Figure 1 Procedures for using already collected samples.

of time and resource implications, which have understandably been a concern for partners, this re-contact has worked well and has had benefits beyond the obtaining of consent.

At the University of Newcastle, patients for whom consent was incomplete were contacted by telephone and/or letter in order to explain the changing research needs, data-sharing intentions and to request consent. This resulted in only one patient declining the request, around 80% returning new consents and 20% with no response so far – (still ongoing). Clinicians involved reported added benefits – up-to-date clinical and family information could be obtained, patients and their families were generally motivated to be involved in research, hear more about it and give further samples if required. Several patients reported that it was good to know that their (historic) sample was still being used and that they had not been forgotten. The clinicians were also able to use the contact to answer questions or concerns and manage patient expectations where required. The team at Newcastle University feel that this has resulted in a more engaged patient cohort and have reported this as a very positive outcome of investing the resources needed to undertake this updating of consent.

CONCLUDING REMARKS

In the era of genomic research and global data sharing, participants must deal with an unprecedented mass of information and complexity. Moreover, the information given today may be obsolete in the near future. The risks and the aims of research and the benefits of participation are not always completely foreseeable at the time the data and/or samples are collected.

In this current work we propose that, for the IC of prospective cases, broadly described research purposes with ongoing updates for participants is the best current solution. This allows for the requirement of research to have a flexible tool as well as the need for transparency and good ethical standards. Achieving a good balance between the level of understanding that is required for meaningful IC,^{11,68} especially for data sharing in genomics, and the need for practical solutions, is burdensome without a system in place to engage participants. Therefore, dynamic options may be the future of research, especially in projects where a share of funding is devoted to the development of IT platforms.

If this option is not yet implementable, then we propose that at least:

- Regular updates on development and aggregated results of the project/biobank are given to participants;
- Patient participation is promoted at a more institutional level by involving patient organisations in governance, developing policies, practices and documentation.

Regarding established collections, the decision to ask for re-consent through active opt-in or opt-out procedures, or to ask for a waiver of consent from the IRB/REC, should be guided by a careful evaluation of the following elements:

- Possibility of re-contact and re-consent of patients within a reasonable effort (also dependent on researchers' resources, eg, availability of contact details and possibility to meet the patient during follow-up visits);
- Specificity of the original IC and number of CEs missing;
- Rarity of the collection and the disease under study;
- Endorsement by patient associations directly involved with the research and collections at stake.

The process of IC that we propose here is intended to enhance the involvement of participants, but we are aware that there are instances for which the applicability is not certain, for example, in very old collections.

The effort to create a good ethical framework for prospective use, including clear governance and good IC procedures, is an ethical obligation in the light of good, sound, well-thought procedures that allow scientific research to happen. Although our emphasis is on good ethical guidance, we understand that different legal jurisdictions may require different standards, even though the ethical principles are broadly applicable across different contexts. But, without doubt, it is necessary to plan ahead for better consent and ethical practices in future collections.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work has been supported by the European Union Seventh Framework Programme (FP7/2007–2013) under grant agreements no. 305444 (RD-Connect), 305121 (Neuromics), and no. 305608 (EUREnOmics) and RD-Connect from the Australian National Health and Medical Research Council APP1055319 under the 'NHMRC-European Union Collaborative Research Grants scheme' as well as the IMI project BTCure (grant agreement number 115142-1), the BioBanking and Molecular Resource Infrastructure of Sweden project, Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)LPC. We thank the RD-Connect Patient Ethics Council and RD-Connect Patient Advisory Council (Jean Jacques Cassiman, Tracy Dudding, Muriel Gevrey, Emma Heslop, Joseph Irwin, Julian Isla, Sigurður Jóhannesson, Lydia Lemonnier, Chantal Loirat, Dorthe Lykke, Milan Macek, Caron Molster, Kay Parkinson, Odile Perrousseau, Marita Pohlschmidt, Daniel Renault, Peter Reussner, Françoise Roualt, Balthasar Schaap, Inge Schwersenz, Chris Sotirelis, Oliver Timmis, Johannes van Delden, Marieke van Meel, Elizabeth Vroom and Urban Wiesing) and all RD-connect partners for their valuable inputs. We also thank RD researchers and patient representatives who participated to the workshop on informed consent held in Rome in 23–24 April 2014: Marco Crimi, Erica Daina, Fabrizio Farnetani, Vera Frankova, Elisabeth Hulier Ammar, Javier Judez, Daniel Renault, Françoise Roualt, Chris Sotileris, Virgilia Toccaceli and Paola Torrerri.

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Supplementary Information accompanies this paper on European Journal of Human Genetics website (<http://www.nature.com/ejhg>)