The donor as partner

How to involve patients and the public in the governance of biobanks and registries

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Foreword

This booklet contains a guideline that will help biobanks set up and maintain a donor participation and cooperation structure suited to both their situations and needs. The writing of this guidelines was one of the deliverables of the BBMRI-NL Rainbow project 6, "Towards a joint strategy for the return of results and optimal communication with biobank donors". BBMRI-NL, or Biobanking and Biomolecular Research Infrastructure for the Netherlands, is the biobanking collaborative effort of all Dutch UMC's and other institutions with biobanks for scientific research.
The need for this guideline became apparent when the project leaders sent out a questionnaire and conducted interviews with biobank coordinators in 2012 and 2013. The results showed that, although there are some initiatives to involve donors in biobanks, either by communicating with them or by actively involving them in the governance structure, participation is still a relatively scarce phenomenon, and there is no clarity as to which participation form works best for all parties in a given situation.
This guideline provides useful pointers for every biobank and the patient organizations involved, to find the form best suited and to prepare for mutual discussions on the subject.
The BBMRI-NL daily board therefore recommends this guideline wholeheartedly.

On behalf of the daily board,

Professor Gertjan van Ommen

Summary

Biobanks and patient registries require public trust and support. The views, concerns and experiences of patients, donors and the public are therefore important and should be taken seriously in decision making related to biobanks, patient registries and related research. A number of questions need be considered: What specific research is facilitated by the collection of datasets? How are donors recruited? And how will biospecimens and data be managed? These and other questions are central to participation in biobank governance, the subject of this guideline.
This guideline will not only focus on participation in biobanks and biobank research. Linked issues include the pursuit of a positive relationship of biobanks with patients, donors and the public, and an emphasis on the ethical and social aspects of research. Efforts to support biobank participation are also part of a broader program related to patient participation in research in a wider sense. Participation in biobanks and biobank research is therefore a crucial part of a broader vision on the societal embedding of medical research. Participation is related to the concept of socially responsible biobanks, or more generally to the idea of responsible research and innovation in research infrastructure. This guideline shows how biobanks, patient registries and the researchers who use them can achieve this in practice.

When is participation appropriate?

Each biobank, registry or related organization should develop its own participation strategy. The starting point for a strategy is the idea that relevant target audiences (directly or indirectly) are involved or have a say in decisions on issues that are relevant to them. This process begins with an exploration of the concerns that exist among various groups: the general public, (prospective) participants and donors, and patients as (potential) users of the results of biobank research.

The following questions are helpful in this process.

1. *What issues are relevant to the biobank, patient registry or biobank research?* Three themes are of interest here:

a. Research:
- Are *research priorities* related to issues that patients and consumers find relevant?
- Does biobank research, *in terms of design and results*, meet the practical needs and concerns of patients?
- Has sufficient consideration been given to issues surrounding the *ethical and societal implications* of research and research infrastructure?

b. The collection and management of biospecimens and data:
- Does the policy of the biobank meet the *concerns and expectations of donors*?
- Were *educational materials, recruitment strategy and management policy* prepared in consultation with donors?

c. Public support:
- How does the biobank (or organization) handle *public concerns and sensitivities* on matters that may be relevant to the biobank?
- How much *public support* is there for this type of biobanking in terms of health and science policy and related funding?

2. *Are the opinions of relevant target audiences already factored into decision making on biobanks and biobank research, and what are the weaknesses in this process? Choose a form of participation that fulfils these requirements.*

The following points are relevant to this:

a. How much *room for manoeuvre in policy* is available for each of the themes that emerged in the initial survey? Focus on participation, where necessary and feasible.

b. What opportunities are available to build on *participation initiatives elsewhere in the research chain*? To achieve efficiency and effectiveness, invest in joint participation efforts where possible. Ensure sufficient critical mass so that the voice of the public, patients and donors is heard more widely, and to ensure that research and infrastructure will benefit from any insights.

Due to the contextual and organizational diversity of biobanks and biobank research, themes that lend themselves to participation are clearly not a constant priority for biobanks. Some participation themes are particularly important to specific patient registries, biobanks or organizations, and different biobanks and associated researchers also deal with different target audiences. Recommendations for the various types of biobanks are therefore developed below:

- population biobanks and cohort studies: mainly relevant for the general public and participants, and to questions related to the collection and long-term management of data, public support, and the general direction and implications of research;
- clinical biobanks for rare and common diseases: have specific patient populations as their primary target audience. These patients act as donors, with interests related to the collection and management of data, and also act as spokesmen for the interests of future users of research;
- institutional biobanks and residual tissue biobanks: primarily concerned with patients in (academic) hospitals and a public of consumers of care with questions regarding the collection and management of and public support for this type of research infrastructure;
- patient registries: generally have a specific patient population as the main target audience, with questions about effective data management and sufficient and careful data use.

What form of participation is appropriate?

For concrete forms of participation, context is also important. The most appropriate form will vary per biobank and depend on several factors:

a. What level of participation (in decision making, contribution of ideas, cooperation) is most appropriate? Should participation be structural or incidental?
b. Which target audience should be involved? How can this group be best represented, given the required input and the availability of representatives?
c. How can participation initiatives be integrated into general decision making in terms of timing and responsibility?
d. When should participation commence? What is the available budget? How can participation be organized in concrete terms? And what specific concerns play a role?

A number of practical conditions should be taken into account during the developmental phase:

a. Provide public accountability of participation and the practical value of outcomes through a website, newsletters and annual reports;
b. Ensure that meetings are accessible and take place at times suitable for the participants;
c. Minimise the demand on participants' time, to make them stay on board;
d. Individuals active in participation initiatives should be kept regularly informed of progress. Provide feedback regarding the value of their contribution;
e. If necessary, provide adequate organizational support and training for participants;
f. Provide financial compensation to a participant (expenses, allowances) that is in reasonable proportion to their efforts;

g. Consider including these expenses as a component of the budget.

The table in chapter 3 provides an overview of the various forms of participation.

1. Introduction

Biospecimens and data from large groups of individuals are essential to biomedical research. The required infrastructure, in the form of biobanks and patient registries, depends on large groups of patients and participants who are willing to donate biospecimens and data that will form the basis of future research. Biobanks therefore depend on public trust and legitimacy among patients and donors.

Donors are more than just a source of raw materials, however: they wish to contribute to good research and have ideas, concerns and preferences regarding the use their data and tissues. This is part of the reason why donors have the right to decide on their own tissue and data.

Also, the involvement of donors is broader than just their own biospecimens. It is equally important to give the views, concerns and experiences of patients, donors and the public a voice in decisions on what happens to their biospecimens and data: thus facilitating a measure of control and influence over the conditions under which biospecimens and data are collected, over objectives, and the way specimens are utilized. That, in a nutshell, is the essence of participation in *biobank governance*. The aim of this guideline is to explain how biobanks and patient registries can achieve this goal.

Participation in decision making on biobanks, patient registries, and related research is generally believed to be important. The Dutch 'Code Goed Gebruik', or 'Code of conduct for responsible use of body materials', drawn up by researchers in collaboration with patient organizations for the ethical handling of biospecimens for scientific research, endorses this:

> 'Donors and/or patient organizations should be involved as much as possible in the management of and research with biospecimens' (Federation of Medical Scientific Societies (FEDERA) 2011, 24).

However, according to a survey conducted with coordinators of BBMRI-NL biobanks, participation is still limited in practice.[1] Only eleven respondents indicated that donors were involved in one form or another in executive matters concerning biobanks; seven respondents indicated that this was being considered. More than half of respondents felt that the involvement of donors contributed to an increase in public awareness and willingness to participate. Most biobanks appreciate the ambassadors' role played by donors. But other aspects, such as the organizational and financial feasibility of involving donors, and the contribution to more relevant research and resultant positive effects on quality, are mostly seen as neutral or even in a negative light. We can conclude that initial impressions are mixed, with doubts among researchers as to the value and feasibility of participation.

This guideline aims to remove those doubts, and show that participation is indeed substantively and strategically important for biobanks and biobank research. That is more than simply a claim: a number of examples will show that the involvement of donors in management is helpful for biobanks and registries. Biobanks should devote greater attention to participation; at the same time customized, tailored solutions are needed for the specific but diverse circumstances in which biospecimens and data are collected, managed and used.

The aim of this guideline is to assist biobanks, patient registries and related organizations in the formulation of a tailored participation strategy. Firstly, the characteristics of participation and *why* it is important for biobanks, patient registries and related research are

[1] Of the 144 representatives of BBMRI-NL affiliated biobanks contacted, 73 respondents answered some of the questions. Among these 73 respondents, 22 respondents answered a short questionnaire via a telephone interview. This survey provides an indication of attitudes to participation among biobank managers, but the low response precludes any firm conclusions on the basis of these results.

discussed. This is followed by an overview of *how* participation can be realized, and some of the associated main forms of participation are then discussed. This is followed by a discussion of the *conditions* that contribute to a sustainable embedding of participation initiatives.

Finally, participation strategies for *different types of* biobanks are outlined and illustrated with *concrete examples*. At the end of each section, biobanks, registries and researchers are provided with recommendations that can be followed when setting up their own participation strategies. A brief summary of this guideline is also appended for patients and patients' organizations.

2. Why participation is important for biobanks

Participation can contribute to better-informed and more broad-based decision making. Clearly, it is important to explain why a particular approach is chosen in a given situation: the reasons why certain publics should be involved in decision making and the concrete goals promoted by participation.

Participation is relevant to several issues: it aids the choice and development of the research goals facilitated by biobanks and patient registries. It also aids choices related to the collection and management of biospecimens and data, the conditions under which donors participate and how biospecimens and data are used. The relevant organizations and researchers can focus on different target audiences: patients with a stake in research, donors with concerns regarding the use of biospecimens and data, and a general public that ensures support for the work of biobanks.

Patients and research objectives

A number of players are involved in the dynamics of medical research: in addition to researchers, other interested parties include healthcare institutions, regulators, commercial interests, and not least, patients themselves. Originating from diverse sources, calls have been made for greater focus on demand-driven research: research based on the specific, urgent needs of patients in the short and longer terms. Assuming a demand-driven model of medical innovation, it seems obvious that end-users should be involved in the formulation of objectives and study design at an early stage (Boon et al. 2011).

Patients - the primary public concerned here - have basically the same interests as researchers: they want good research that will eventually help them and their peers in medical terms. Particularly in the case of rare diseases, biobanks embody the hope of a cure and

a better life, especially for future patients. Patient organizations are therefore a natural partner for many researchers. Organizations representing patients even argue for a *right to innovation*, the right to contribute to improving the outlook for patients in their particular field (Woods & McCormack, 2013). Patient organizations are often a driver of research, for example by actively raising and distributing funds, by stimulating cooperation between researchers (Panofsky 2011), or even by setting up their own biobanks.

Related to questions of research planning and the details of biobank and registry design, questions may also arise as to the use of cohorts of the biospecimens and data that organizations have under their management. Research priorities and terms of use are also relevant in this context. Possibilities for research can also change over the course of time. Patients and participants can therefore contribute to discussions of research priorities related to the use of existing collections.

In concrete terms, a contribution from patients can be expected in three areas: Firstly, patients have their own ideas regarding important directions for research and which questions deserve priority. These views are relevant for biobanks, for example in determining research priorities and the opportunities that a biobank should facilitate, and when evaluating research proposals that involve use of existing biobanks, cohort studies and registries (Abma & Broerse 2007; Elberse et al. 2012). Biobanks can profit from the participation initiatives in research programs: examples include the involvement of patient organizations in research on rare diseases (example 4, page 56), and more specifically the role of the Dutch CF Foundation in the Dutch CF registry (example 9, page 78).

A similar situation holds for the role patient organizations can play in management. That particular role may result from direct interests: patient organizations can act as financiers and/or owners of biobanks, and as active management partners in research. This supervisory role allows sanctions to be applied and can act to

balance and ensure the short and long-term interests of patients in research. Patient organizations often play this role in research on rare diseases (example 4, page 56).

Secondly, biobanks can engage patients in the development and improvement of their study designs, so that research better reflects the practical needs and views of patients themselves. For example, translational research and derived applications would benefit from early testing, adjustment and evaluation in relation to the needs and concerns of end users (Boon et al. 2011). Patient experience can also assist in the operationalization of research, an example of which is patient input in biobank research regarding appropriate outcome measures and effective, less invasive ways to collect biospecimens and data (De Wit et al. 2013). The role of patient knowledge in research will be explored in more detail later (example 5, page 62).

Thirdly, the involvement of patients may help researchers reflect on possible societal and ethical implications of their research. Contact with patients can help researchers develop a more palpable sense of the ultimate goal of fundamental research and may help them reflect on the unintended spin-offs of research: the 'soft impacts' of scientific developments on health and disease (Van der Burg 2009; Smit, Van der Valk & Weaver, 2011). This may encourage researchers to take a broader view of the nature of useful research and how it can best be performed. This contribution is especially prominent at the Radboud Biobank (example 8, page 75) and the Dutch Cancer Registry (example 10, page 80).

Donors and the collection of biospecimens and data

Participation can also contribute to issues related to the collection and management of biospecimens and data, and to the conditions of enrolment. This raises other issues such as ethical questions regarding ownership and privacy of donors, but also questions about how access and use of biospecimens and data are organized, how

long-term control by participants is guaranteed, and how the various claims on biospecimens and data are handled.

Laws and regulations governing biobanks are under discussion in both the Netherlands and in Europe, and these discussions include questions related to commercialization of research, control of use of residual material, privacy and *informed consent*. More recent discussions include the question of feedback of research results. Ethical and legal experts now regularly face researchers and patient organizations in these discussions (Geesink & Steegers 2009, Prince 2013 Skloot 2010). Donors often attach importance to matters other than those expected by ethicists and lawyers, and generally attach less importance to extensive prior informed consent than to sufficient information, updates on the research progress and long-term monitoring (Hoeyer 2010, Vermeulen et al. 2009).

This issue involves not only questions related to the collection of biospecimens and data managed by biobanks and registries, but also to their subsequent use. For example, opinion polls suggest that citizens wish to have more influence and information about how their data and biospecimens are used in research (Vermeulen et al. 2009; Hoeyer 2010, Hobbs et al. 2012). In addition, both the possibilities for use and public opinion can lead to changes in rules over time, which raises the question of how the initial conditions under which participants donated biospecimens can best be respected given these changing conditions.

The role of donors in biobanks - the main public - is similar to that of human subjects in clinical trials. But there are also differences: the specific objectives of clinical trials allow candidate-subjects to make a clearer assessment compared to the broadly-formulated objectives that biobanks stress when approaching potential donors. In addition, participation in a biobank is less intrusive than a clinical *trial*, and far more enduring. Balancing the relationship between biobanks and donors is therefore an ongoing concern. Where the *governance* of clinical research focuses on prior control, the emphasis of biobanks

is more focused on governance frameworks, the supply of regular updates to participants, and co-management – which doesn't influence or alter the participants' individual voice (Knoppers 2009; Federation of Medical Scientific Societies (FEDERA) 2011, 79-80).

There are two specific reasons to give donors a more direct say in decisions on the management of biobanks and biobank research, and on the collection of biospecimens and data. Firstly, donors can convey the expectations, needs and sensitivities that are involved in participation in biobanks. Donors are often willing to participate in biobanks, but biobank policy must accord with their ideas regarding control, scientific value, and the balance between science and personal health. Managing the relationship between biobanks and donors therefore requires ongoing attention. The involvement of donors and their views can help in the formulation and selection of policy options (Avard et al. 2009). This contribution played a role in the design of UK Biobank (example 1, page 43), the BC BioLibrary (example 2, page 47) and the Mayo Clinic Biobank (example 3, page 50).
Secondly, donors can help in the formulation, development and testing of the recruitment strategy and the information used to approach new donors. For example, they can indicate how donors can best be approached and the type of information they need. They can also act as a sounding board for a biobank's plans for informational activities or other participation initiatives. An example of this can be found at the Wales Cancer Bank (example 6, page 67) and the Nottingham Health Science Biobank (example 7, page 69).

Biobanks and public support

Biobanks ultimately depend on public support: not only the readiness to participate, but also for support in policy discussions. Current social controversies about privacy and control of data are reflected in how the public and policy makers view biobanks (see, eg, Geesink & Steegers 2009; Skloot 2010, Prince 2013, Gaskell et al. 2010). Despite high public confidence in biobanks in the Netherlands, rules and attitudes towards the commercialization of research, individual

control of biospecimens and the privacy of medical data and DNA are regularly the subject of policy discussions.

There is currently considerable interest in medical research. Ongoing discussions include the research agenda itself, whether research sufficiently meets the needs of patients and healthcare, and whether certain diseases are the focus of sufficient research. Discussions also regularly focus on issues of privacy and the control over data and biospecimens. And last but not least, trust in research is severely strained in relation to questions concerning commercial interests and fraud (Van Kolfschooten 2012; Goldacre 2012).

Compared with other sectors of society, trust in medical research and biobanks is relatively high, especially in the Netherlands (Gaskell et al. 2010, Gaskell et al. 2013; Tiemeijer & Young 2013). However, public support for biobanks cannot be taken for granted and many people are unfamiliar with biobanks and their activities (Geesink & Steegers 2009), evinced by the discussions that have taken place in several countries regarding the use of blood spot cards for research (Carmichael 2011). It is therefore important keep the general public well-informed about how and why biospecimens and data are used in research.

Biobanks would also do well to actively seek societal legitimacy. This requires policy making that is attentive to the exploration of scientific and social developments. It also requires the prioritizing of public support as a goal, providing accountability to both direct and indirect research stakeholders, and providing for participation and influence for those involved in biobank activities (O'Doherty et al. 2011). The participation of diverse publics plays an important role.

There are at least two practical reasons why the public should have a voice in the governance of biobanks and biobank research. Firstly, the involvement of public representatives may increase public support for decisions. This allows the channelling of public discussion of biobanks and allows biobanks to anticipate new concerns,

challenges and sensitivities amongst the public (O'Doherty et al. 2011). These factors motivated participation initiatives at the UK Biobank (example 1, page 43), the BC BioLibrary (example 2, page 47), the Mayo Clinic Biobank (example 3, page 50) and the Wales Cancer Bank (example 6, page 67).
Secondly, care and concern for public support and the interests of patients and donors can help biobanks obtain research funding and policy support. Participation creates legitimacy for decision making and thus offers strategic advantages during discussions with policy makers, for example. This issue played a role at the UK Biobank (example 1, page 43), the BC BioLibrary (example 2, page 47) and the Wales Cancer Bank (example 6, page 67).

Concrete contributions of participation in biobank decision making

- Research-related:
    - Patients have their own ideas regarding the importance of research priorities;
    - Patients can indicate whether and how research connects to the needs and experiences of patients themselves;
    - Patients can prompt researchers to reflect on the broader significance and implications of their work.

- In relation to the collection and management of biospecimens and data:
    - Donors can specify their expectations regarding participation and biobanks;
    - Donors can assist in the formulation, development and testing of patient information, recruitment strategies and management policies.

- Public support:
    - Participation can help biobanks to identify public concerns and sensitivities, and to learn to deal with them constructively;

- Participation can help increase support for biobanks in policy making and research funding.

Building blocks of a participation strategy

Drafting a specific participation strategy begins with an exploration of the potential concerns of the various groups central to biobanks and biobank research. Researchers and administrators can prepare a strategy based on a few simple rules:

- Identify issues relevant to the work of the biobank, registry or research. The following checklist of issues (based on the above) provides a brief guide.
- Determine how and whether the views of relevant publics are taken into account in decision making on biobanks and biobank research, and where this is lacking.
- Determine the available *room for manoeuvre* in policy for each of these themes - focus on participation, where necessary and possible.
- Explore, especially in the case of limited policy options, how the voice of publics is balanced in the *broader processing of data and biospecimens*. Speak to partners (biobanks, registries, fellow researchers, etc.) and thereafter invest, where needed, in joint efforts in the area of participation.
- In the interests of efficiency and effectiveness, ensure sufficient *critical mass* for participation initiatives, so that the voices of publics resound more widely, and research and infrastructure consequently receive greater benefit from new insights.

The previously discussed policy issues that deserve input from patients, donors and the public can be summarized in a brief checklist for administrators and researchers: subjects that must be checked to ensure that there is sufficient understanding of the needs, views and concerns of different publics, and reviewed for legitimacy of decision making in relation to the public.

- Research-related:
    - Ensure that research priorities are relevant from the perspective of patients;
    - Examine whether the development and design of biobank research meets the practical needs and concerns of patients themselves.
    - Explore whether broader ethical and societal implications also play a role in research considerations.

- Related to the collection and management of biospecimens and data:
    - Determine whether biobank policy matches the concerns and expectations of donors.
    - Examine whether patient information, recruitment strategy and management policies are formulated, developed and reviewed in consultation with donors.

- Related to public support:
    - Ensure that the biobank and dependent infrastructure is sufficiently responsive to anticipate new public concerns and sensitivities.
    - Explore societal support from the viewpoint of other *stakeholders*, for example, policy and research funding.

Clearly, not every theme is always topical and the research landscape within which biobanking and patient registries operate is diverse and variously organized. Some participation themes therefore play a greater role than others in the context of biospecimen and data collection and use. The publics for biobanks and researchers are also diverse, and a major determinant is the specific context of biobanks, patient registries and related research.

Various approaches to biospecimen & data collection and usage present additional challenges in the area of participation. Biobanks, patient registries and researchers would therefore do well to consider the usefulness and necessity of specific forms of

participation in the light of their own policy options, publics and goals.[2] Participation is meaningless without room for the contributions or influence of the public. Creating space for expression not only prevents misunderstandings regarding the impact of participation initiatives, but also more explicitly defines the available room for influence.

This also leads to understanding that participation is not the sole responsibility of biobanks and registries themselves. The ultimate goal is to ensure that participation becomes invested in the entire process of biospecimen and research data collection, from initial collection and management to innovation and medical research as a whole. The ultimate goal is to ensure that patients, donors and the public can influence the entire process. Researchers and research departments that use patient registries and biobanks have the responsibility to determine the extent to which their work takes sufficient account of the interests, concerns and needs of patients, donors and the public. If these issues are given insufficient weight in the research process, stakeholders should point out each other's failings, and if necessary, jointly ensure that these are rectified. In some cases, the organization of the entire process can also be the subject of discussion. Health funds and patient organizations for rare diseases (see the example below, page 56) are therefore committed to working for more centralized and more systematically accessible forms of biospecimen & data collection.

Finally, costly and inefficient forms of consultation and participation are in no one's interest if this is at the expense of good research. This should, however, not be an excuse to ignore these issues. In addition to focusing on *policy options* and *the organization of the process as a whole*, a *critical mass* of initiatives is therefore

[2] An example is a cohort study such as the PRIDE Study, which focuses on pregnant women: although this study is not disease-specific, pregnant women in particular may have interesting ideas about pregnancy-related research (http://www.pridestudy.nl/).

important in the design of a concrete participation strategy. While involving patients in decisions about every biobank project in a clinical department is probably inefficient, broad decision making on such projects in a way that makes sense of participation can be useful - for example, by organizing participation in determining the research priorities of the research department or thinking about a role for participation in national and international coordination and cooperation related to research and research infrastructure. The size of cohorts can also be of importance when determining whether participation is appropriate. A tailored participation strategy is of greater value to a population biobank such as Lifelines than to a small clinical cohort.

It may be better to organize participation in clinical biobanks at the level of research departments or even at the level of a research field. This is not to say that there is no way to involve patient representatives in aspects such as the assessment of individual research projects. One way to achieve critical mass could be by cooperating in existing forms of research evaluation.

Different types of biobanks and biobank research will therefore often have to emphasize participation linked to certain themes. *Research-related participation* is primarily relevant to researchers who use biospecimens and data. *Research departments* and researcher-led *research collaborations* on specific diseases are primarily responsible, but choices on the design of biobanks and patient registries and choices related to priorities for the use of collected biospecimens and data are also determined by similar considerations. Clinical biobanks and patient registries in particular should therefore consider how the views of patients can be incorporated into research decisions. In the case of disease-specific clinical biobanks, patients can represent both donor viewpoints and patients' interests in research. To a certain extent the same is true for patient registries.

Although *participation related to the collection and management of biospecimens and data* is a general concern for any biobank or registry, the room for decision making differs. This theme is therefore especially relevant to particular kinds of biobanks: *population biobanks* focus on healthy participants as donors, which may be a reason to more explicitly consider the concerns of donors in decision making on collection and management. As a rule, population biobanks do not serve a well-defined research area and therefore present fewer opportunities for participation in research decisions. While *residual tissue biobanks and institutional biobanks* generally do not carry out research, they are usually associated with healthcare institutions and via this route have a relationship with and responsibility towards donors.

Public support is also a concern. Due to their scale of operation and the greater efforts required to maintain a high participation rate long-term, public support for population biobanks is a major concern. While this theme is also relevant for other biobanks and registries, it can be considered a general problem for the research community as a whole, and an extension of patient and donor participation.
Although the variation and overlap of practices between different types of biobanks and patient registries is clearly substantial, these recommendations illustrate the main directions that researchers and administrators should explore when developing participation strategies. In chapter 5, the various participation strategy options are further established and illustrated.

3. Forms of participation

Depending on the specific issues for biobanks, registries and research, a variety of participation forms are available. Relevant questions include whether themes require structural or incidental participation, what kind of input is expected from a specific public, which publics are selected and represented, and how far should influence on decision making be extended.

Forms of participation can aim to include various types of input, such as those related to identifying problems and concerns, related to conveying knowledge and experiences, and related to creating support for decisions. In addition, differing levels of participation have to be considered, ranging from consultation with publics on pre-defined topics through advising and contributing ideas on specific decisions, to active involvement in policy and setting the agenda. The way in which groups and their views are mobilized also varies: a representative sample of donors provides insights that differ from those of a knowledgeable patient expert or a representative of a patient organization.

Levels of participation

- Consultation on predefined themes
- Cooperation and co-authorship of themes
- Contribution of ideas and advice
- Contribute new themes to the agenda
- Contribution to decision making on themes

Levels of participation are sometimes referred to in terms of a 'participation ladder'. But more or 'greater' participation does not necessarily lead to better or more legitimate decisions.[3]

[3] Some arguments against forms of participation that go too far include the following: based on the notion that professional expertise should be the most important factor in decisions about research, combined with the fact that researchers have a better overview of developments in their area of specialization than patients,

Efficiency, effectiveness and the question of what form of participation best serves the interests of the relevant public are also relevant (Trappenburg 2008; Bovenkamp, Trappenburg & Grit 2010; Bovenkamp & Zuiderent-Jerak 2013).The choice of a particular form of participation can best be tailored to the desired result and desired form of influence of a particular public, with basic principles and practical limitations simultaneously influencing the choice. We now briefly describe some of the main forms and practical concerns they raise.

Structural forms

Executive involvement of patient organizations

Patient organizations are often interested in the promotion of research. Provided they are well organized and have sufficient contact with their members, they can act as the representatives of patients and donors in relation to biobanks and registries, and can act as a full partner in biobank management and contribute to strategic decisions. An active executive role seems most appropriate when they themselves make organizational contributions to the biobank or patient registry.

Patient organizations can also be involved as guardians of patient and donor interests; they can mediate between a donor population and research, and can bring patient and donor perspectives to the attention of researchers and administrators. However, patients' organizations and affiliated funds often focus on the tangible, short-term results of research. They will therefore sometimes need to be convinced of the importance of intensive involvement in research

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it is sometimes concluded - rightly or wrongly - that patients should not have a voice in determining the research agenda (Caron-Flinterman, Broerse & Bunders 2007). In addition, at this moment public trust in medical research in the Netherlands is high; there is(at this time) no clear crisis of confidence in biobanks (Gaskell et al. 2010; Gaskell et al. 2013; Tiemeijer & De Jonge 2013). Even if donors can make contributions to the conditions under which biobanks operate, it does not follow that participation in determining the policy of each biobank is necessary and useful.

and the added value that long-term investment in research infrastructure can offer.

The extent of executive involvement of patient organizations varies. Representatives of patient organizations can serve in the executive board, but may also be members of the Board of Trustees. The role as partner played by patient organizations should also take a practical form. This means, among other things, that availability for meetings is an issue and that a budget must be reserved for travel and attendance costs. In terms of embedding, it is also advisable to establish the role of patient organizations in the statutes.
In the case of rare diseases in particular, patient organizations are heavily involved in biobanking and patient registries. Some examples related to rare diseases are detailed below (see pages 56 and 78).

Advisory boards

Establishing a separate advisory board may be useful when strategic or practical questions regularly arise that require input from donors, patients and/or the public. Advisory boards can contribute ideas on practical and strategic issues related to the participation of donors, in addition to also dealing with questions related to research. An advisory board may, for example, act as a focus group on questions facing the biobank management and can also act as a representative advisory board by identifying problems that should be on the agenda. The recruitment of members depends on the design of the biobank, the tasks of the advisory board and the contacts of the biobank. Recruitment can be implemented both via the biobank itself (e.g. by recruiting via a website or newsletter) and through patient organizations.

Advisory boards require effective factual and practical support from the biobank itself. In addition to organizational support, financial compensation for travel and other expenses is necessary. The practical limitations on members should also be taken into account, for example, regarding times and locations of meetings. In addition, meetings must be coordinated to coincide with other current

organizational activities, so that advice can make a timely contribution to decision making. Ensuring that advice is acted upon and followed up is also important: for example, include the Chairman of the Board of Trustees in the biobank's executive board, explicitly define the role and relationship to the board, and including the monitoring and implementation of advice as a regular feature on the agenda of both the executive board and the Advisory Board itself. In order to maintain momentum, it is sensible to convene an advisory board regularly. The selection and term of office of members are also important issues.

Members must understand the practice and interests of biobanks and research, but simultaneously also develop their own perspectives. Advisory board numbers can range from around five members on an informal board, to ten members when a reflection of a diverse donor population is required. Examples of advisory councils are to be found in UK Biobank (page 43), Mayo Clinic Biobank (page 50) and the Wales Cancer Bank (page 67).

Participatory bodies

Biobanks can sometimes link up with existing participatory bodies and (patient) organizations by keeping them regularly informed about the progress of the biobank. This helps promote support and awareness of biobanks and also helps create a lower threshold for further contact if there are questions that require advice or consultation. This is most likely to apply to residual tissue biobanks and institutional biobanks. The 'Code of conduct for responsible use of body materials' recommends, for example, that residual tissue biobanks send an annual report to the patient advisory council of their associated institution (Federation of Medical Scientific Societies (FEDERA) 2011). This approach need not be demanding in practical terms, requiring first and foremost a survey of relevant bodies in the vicinity of the biobank and the building and maintaining of contacts with them. The Radboud Biobank (page 75) already puts this form of participation into practice.

Incidental forms

In addition to structural forms of participation, there are various incidental forms of participation that allow the experiences and views of different groups to be explored and involved in decision making.

Collaborating with patient experts

The objectives and outcomes of research are relevant to patients and their quality of life. The same applies to discussions of the stress experienced by research participants, clear information and the relationship of conditions of participation to an individual's expectations. There are various ways in which patient experiences can be evaluated and used. For instance, biobanks and researchers can use social science research of patient attitudes or carry out this research themselves – such as by forming focus groups (see below). Another approach is to involve patients as patient experts or 'research partners' in the design and implementation of biobanks.

Patients can bring their personal experiences to the dialogue with researchers, and by so doing help researchers to reflect on the effects of research on participants and what it can mean in practical and more fundamental terms to patients and how they deal with their illness.
The practical value of such discussions and whether they take the form of advice or cooperation depends on several factors. Worthwhile dialogue requires the willingness of researchers to explain scientific and technical discussions in understandable terms. It also requires willingness on the part of patients and caregivers to translate personal experiences into insights that are of value in research practice. Building mutual understanding takes time and effort, especially when involving fundamental choices in research, and this dialogue should not be entered into entirely free of obligation. Some patient organizations encourage and support patient experts in their contacts with healthcare professionals and researchers, and some research areas have long-term projects that involve patient knowledge. When patient-experts participate on

behalf of patient organizations, a reasonable budget for the training and support costs of such organizations is appropriate. Specific examples of patient knowledge are discussed below (page 62).

Focus groups

When preparing strategic or practical choices, donors or patients views can also be surveyed by bringing together a select group of participants in a focus group. This form of participation is widely used in public administration as a way to give specific groups a say in policy deliberations (Leyenaar 2009). These groups can take a variety of forms and in some cases participants may be selected more or less systematically to reflect the study population or the range of views among stakeholders. The subjects included can also be more or less specifically defined depending on the topicality of questions. More intensive and systematically structured focus groups can help to develop policy in consultation with particular groups. Focus groups thus present a broad spectrum of opportunities for participation that extends from consultation on specific questions to deliberation on fundamental issues. The focus group is therefore a form of participation that can be deployed by a diverse selection of biobanks, registries and related research.

Focus groups are also a commonly used social science research method. The better-known international examples of focus groups related to biobanks are research projects in their own right (O'Doherty et al. 2011; Gaskell et al. 2013), but there are also variants that are more accessible and easier to establish (Abma & Broerse 2007). Expertise in the field of social science research into the life sciences (ELSA) is widely available in the Netherlands. Several variations on focus groups played a role in the design of UK Biobank (page 43), BC BioLibrary (page 47) and Mayo Clinic Biobank (page 50). A decision support tool for patient involvement in translational research, recently released by the Dutch CTMM and CSG (Garcia & Van der Scheer 2014), also includes a variety of specific forms of participation.

Consultation rounds

When specific questions are addressed to a specific audience, a closed consultation will sometimes suffice. This type of consultation can involve either representatives of the public or a selection of potential donors, and can be particularly useful in the case of very specific questions such as the assessment of intelligibility of consent forms and brochures. This type of validation step is customary prior to wider distribution of questionnaires. Consultation is only appropriate once strategic and practical issues have been resolved. Seen from the position of participation as a principle, this is a drawback as it fails to assume a far-reaching influence on decision making. One advantage is that consultations absorb little time and budget, but they should be tailored to ensure that the appropriate group is consulted at the appropriate stage of decision making, and via the appropriate channels of communication.

The results of consultation rounds can also be reported in newsletters and/or annual reports. The UK Biobank in particular (page 43) carried out extensive consultations rounds during the establishment phase.

Online Participation: Internet discussion and consultation

Many forms of participation can occur online. Consultation of specific publics is possible via Internet, especially when a biobank maintains contact with its donors (e.g. for general communications) via other electronic means. Patients can also be approached for advice or consultation using this channel, for example by launching discussions about a particular medical condition amongst online communities, whether or not in consultation with patients, moderators or site administrators. More intensive forms of participation can be considered, for example, the involvement of participants in work, in stages, on wiki pages on biobank policy (Dove, Joly, & Knoppers 2012). Policy concepts or forms that are still at the design stage can also be opened to public consultation on a website that allows feedback, similar to the approach that the Dutch

government uses when making draft legislation available for consultation (see http://www.internetconsultatie.nl).

Internet consultation raises issues similar to those for focus groups and regular consultation: preparation is required, the timing must be right, issues of how the intended audience can best be reached must be addressed (making documents available online is not enough), quality must be monitored by moderating feedback/comments, and the results of feedback must be transparently reported. The budget and time involved may be lower than 'offline' forms, depending on which approach is chosen. As self-contained web pages for one-off discussions are poorly visited in general, a more effective approach is to integrate consultations or discussions with existing discussion or communication channels such as local or patient-oriented online communities, or via the MyBiobank app currently under development by BBMRI-NL. The Dutch CF Foundation conducts, partly in relation to the CF registry it manages, an online consultation on research priorities via a focus group (see page 78).

Combination of forms of participation

The views of donors, patients and public can be solicited and used at various times and in a variety of ways. Ideally, the various forms of participation will synergize: structural and incidental forms of participation function best when combined intelligently. For example, patient organizations involved with biobanks at an executive level can organize consultations amongst members on research priorities. Biobanks themselves can also organize similarly layered forms of participation, for example, the social advisory board of the UK Biobank (page 43) provides public accountability, and at the Mayo Clinic Biobank (page 50) the chairman of the donor advisory board has a seat on the Board of Trustees. Decisions thereby gain legitimacy, the chairman is supported by the representation of donors, and the connection between the donor advisory board and the biobank board of directors improves.

In this context, larger biobanks and institutions can draw inspiration from patient participation in the healthcare field of patient safety policy. This states, for example, the central idea that criteria, rules and conditions of care must be continually re-evaluated. Patients deserve an important say in this. Furthermore, patient participation in patient safety policies is linked to the handling of complaints as well as to suggestions for improvements, done by the patients themselves.

Choosing a form of participation

The organizational context is clearly also important in the choice of a specific form of participation. Crucial points include:

- Try to achieve a particular level of participation and make a clear choice between a structural or incidental form. This will determine the choice of a specific form and provides clarity for participants.
- Define the specific public and determine how it can best be represented given the required input and the availability of representatives and representative bodies.
- Be aware of and explore, in a timely manner, the practical concerns that the chosen form of participation entails in terms of timing, budget and organization.
- Ensure that (results of) participation initiatives are well-embedded in all administrative decision making.

There are a variety of ways in which biobanks relate to donors and in which the voice of donors is registered and represented: Which public(s) are relevant to the biobank and the subjects on which participation is needed? Are there existing advocacy groups or forms of representation? And are these sufficiently legitimate and aware of issues important to the group(s) they claim to represent? Patients' organizations or patient experts may legitimately speak on behalf of donors, but sometimes no representatives are available, they are insufficiently knowledgeable, or do not have sufficient contact with donors and patients to be able to legitimately represent them. In

such cases, other legitimate representatives can be involved who can speak on behalf of donors or patients. This may include the involvement of parents of young or legally incompetent donors, or of caregivers and nursing staff who voice the concerns of patients.

Practical issues should also be taken into account when planning participation, such as reserving sufficient time and budget to organize practical involvement, and including this in funding applications. All forms of participation involve dealing with practical issues:

- Provide accountability for participation and the implementation of outcomes via a website, newsletters and annual reports.
- Keep those involved in participation initiatives regularly informed of progress and explain how their ideas and advice are put into practice.
- Ensure that meetings are open to all participants and take place at times appropriate for them - not necessarily in office hours.
- Make sure that the time demanded of participants is not excessive, causing them to drop out.
- If necessary, provide appropriate organizational support and training of participants.
- Provide financial compensation (expenses, attendance allowance) to participants in reasonable proportion to their efforts.
- Consider including this expense as a budget item in funding applications.

Resources with further practical information are discussed in examples below. A general resource for background information on the theory and practice of participation is the website - http://www.participatiekompas.nl.

Finally, participation strategies should be embedded in general decision-making processes. Where, when and by whom are decisions taken on issues that require consultation? Timing is important, but

the impact of participation initiatives and their results must also be guaranteed. It is important to clarify in advance how the outcomes of participation initiatives will be dealt with and to subsequently report back results to stakeholders and donors themselves. Also, it is important that biobanks' participation initiatives link to / build on projects and experiences with participation in their field of research and/or care – for instance, patient participation in research agendas.

The following table (see next page) provides an overview of the various forms of participation.

Form of participation	Suitable for	Level of participation	Variants	Support needed	Specific issues
Managerial involvement of patient organization	Research and infrastructure in areas with an active patient association	Involved in decision making	Direct involvement or indirect monitoring function	Limited	Agreements over extent of involvement
Advisory Board	Biobanks with strategic and practical questions regarding donor or patient perspectives	Advisory role	Donor and/or Patient Advisory Board	Requires considerable support	Organizational commitment, agreements on mandate
Direct influence	Residual tissue biobanks and institutional biobanks in particular	Consultation, contribution of ideas or indirect role in decision making	Diverse patient advisory boards	Relatively limited	Background knowledge of research of advisory board members
Patient knowledge	Clinical biobanks and biobank research	Cooperation, contribution of ideas, consultation	Contribution to strategy, involvement in design and development, consultation on methodology	Varying	Training of patient experts, willingness to engage in dialogue
Focus groups	Biobanks and research that require a systematic exploration of public attitudes	Consultation, contribution of ideas	Group interviews, methodologically- sound surveys	Varying	Timing, budget, organization
Consultation rounds	For review or feedback on specific proposals	Consultation	Limited (e.g. focus groups), large-scale surveys	Varying	Timing, budget, organization
Online engagement	Online variants of all of the above	Consultation, contribution of ideas	See above	Varying	Timing, budget, organization

4. Preconditions for sustainable participation

Although participation in *biobank governance* is important to ensure public and societal support for biobanks, patient registries and biobank research, investing in participation alone will not sustain this support. Successful participation initiatives are also supported by a research culture in which the concerns and wishes of patients, donors and the public are taken seriously in a broader sense. Ideally, participation stretches over all topics related to biobanking: from financing research and the research world to care. Biobanks can learn from and build on participation initiatives in those areas, and stimulate such initiatives where possible. Also, there are several preconditions, which can be realized by biobanks themselves, which are ultimately essential for successful 'socially responsible biobanking'.

The general relationship with patients, donors and the public

Participation in governance is an effective means of meeting the concerns and wishes of patients, donors and the wider public, but is not an end in itself. It therefore complements other ways in which biobanks and registries can interact responsibly with their publics. Ideally, this leads to a better relationship between biobank, biobank research and the stakeholders. Although this relationship is important regardless of participation, a good general relationship with patients, donors and the public is also a necessary condition for successful participation.

There are several issues that biobanks, registries and biobank researchers can and should consider if they wish to take their publics seriously. Specifically, issues such as good quality information, clear and accessible individual influence and accessibility for questions and comments, for example by keeping participants well-informed of procedures related to question and complaints. For biobanks in a hospital environment, integration of systems for providing and

withdrawing of consent in local electronic patient files is one possibility. Public accountability for current activities is also important, and biobanks and patient registries can report regularly on biospecimen & data collection and usage via websites, newsletters and annual reports. The 'Code of conduct for responsible use of body materials' goes into more detail on these aspects (Federation of Medical Scientific Societies (FEDERA) 2011, 74-80).

Online forms of communication such as local patient sites and *communities* (and the BBMRI-NL developed *MyBiobank* app) can also be used. Some biobanks and patient registries, one example being the Dutch Twin Register, have already implemented these approaches (http://www.tweelingenregister.org).
Public accountability and participation can thus complement each other. By providing accountability for participation and how outcomes have been implemented, biobanks and registries can demonstrate to a wide audience that the views of the involved parties are taken seriously, while at the same time encouraging donors and patients to actively participate.

ELSA research

Many of the questions that are central to participation initiatives relate to the ethical and societal aspects of biobanks and biobank research. These questions are the subject of so-called ELSA (ethical, legal and social aspects) research (Hoeyer 2012). This research is also important in creating fertile ground and support for participation. Consideration of ethical and societal challenges of biomedical research is an important foundation for participation initiatives primarily because it can help make the researchers and administrators involved aware of ethical and social issues. For example, as understanding of participation increases among researchers, this can form a starting point for an improved relationship with patients, donors and the public.

In addition, ELSA research often acts as an extension of participation. Because medical ethicists and social scientists still use forms of participation as a research method, they can be approached as collaborators or for assistance in setting up and supervising participation initiatives. Many Dutch research groups have in-house expertise and often have experience of research into developments related to biobanks and biobank research.
ELSA research is worthwhile in itself and is necessary for overall strategic reflection on societal developments related to data and biospecimen collection in and around biomedical research over the short and mid-term. For these reasons, it is prudent for biobanks and biobank research to invest in ELSA research, and cooperation should be sought with experts in the field. Biobanks, registries and researchers should not only seek involvement on an individual basis, this issue is also of importance for large-scale biobank/registry collaborations such as BBMRI-NL.

Support for patient knowledge

Participation requires that participants in initiatives have sufficient understanding of the subject matter. While the recommendations and preconditions in this guideline certainly help, the preparation of patients and donors requires wider support and an infrastructure of training for and by patient experts and patient organizations can assist in this.

Patient experts and patient organizations are clearly able to make a constructive contribution to discussions concerning medical research and biobanks. However, individual patients and the general public often require training before they can discuss developments in and around medical research. In addition, the ability to effectively contribute personal experiences to discussions without being intimidated by the professional authority of researchers is not present in all participants. Training opportunities for patient experts already exist in (some forms of) clinical research, but are generally not specifically tailored to biospecimen research. Training should also be supported both financially and practically, so that expertise

and contacts in the field of research can be maintained. Support from research and academic institutions is indispensable for patient organizations and their training infrastructure.

In concrete terms this means that biobanks should offer a joint training course tailored for patient experts, for example in the context of BBMRI-NL, with clear opportunities for collaboration with existing *patient-advocate* and *patient-partner* training programs. In the Netherlands, existing initiatives include supporting patient participation and patient advisory boards at various university medical centres through ZonMW and PGO Support, an organization that provides courses and manages information for patient organizations. In the European context, training of *patient advocates*, such as via the European Patients' Academy on Therapeutic Innovation (http://www.patientsacademy.eu/) and EURORDIS (http://www.eurordis.org/training resources) can also be considered. An appendix also includes a version of this guideline for patients and patients' organizations; this provides an accessible overview of their possible contributions to biobanks, patient registries and biobank research.

5. Participation strategies explained - suggestions and examples

Because biobanks come in a variety shapes and sizes, they regularly have to deal with different groups and challenges. Each biobank should therefore adapt recommendations to their own individual strategy. A number of suggestions, relevant to several different types of biobanks, may be of assistance: population biobanks, clinical biobanks, general biobank facilities at UMCs and hospitals (including residual tissue biobanks) and patient registries. For each type, successful examples of participation in biobanks, biobank research and patient registries are discussed.

Population biobanks

Population biobanks and longitudinal cohort studies sometimes spend decades collecting data and blood samples from large numbers of participants. The advent of genomics has provided these studies with new impetus. DNA is now part of the arsenal of data from stored biospecimens, and the isolation and genotyping of previously stored samples is now common. These cohorts are therefore highly versatile and the Netherlands has a long tradition of population cohorts and biobanks such as the Rotterdam Study (ERGO) and Dutch Twin Registry (NTR). More recently, large-scale biobanks such as the Icelandic deCODE Genetics, the British UK Biobank, and the Dutch Lifelines have been established.

Population biobanks require design choices that determine subsequent research opportunities and conditions for collection and management. All of these areas trigger a variety of questions: regarding the blending of public health research and basic research, but also about the conditions surrounding participation and utilization. Population biobanks rarely focus on a specific disease and therefore have no clear links to specific patient groups. Due to their size, they often have a clear geographical or group-related

public profile. The representation of publics should therefore be mostly sought outside the context of patient organizations.

Population biobanks have long-term goals, provide regular updates and make diverse use of data and biospecimens. Long-term public trust and support is therefore particularly important, and population biobank policy can be revised regularly or expanded as new opportunities or challenges arise around medical research. Structural forms of participation are therefore the most appropriate.

Early consultation of donors in relation to decisions on complex, large-scale research infrastructure is regarded internationally as best practice. The details vary from case to case: for example, some consultations are set up as a general exploration of public attitudes, while others focus on the discussion and formulation of concrete policy recommendations in intensive multi-day discussions with a select group of participants.

Although agencies or practitioners involved in the recruitment of donors can sometimes also act as spokespeople for the interests of donor populations, they are not always aware of how donors feel about new developments. In terms of structural forms of participation, population biobanks are well-advised to consider establishing their own advisory boards, with members recruited among biobank participants. The embedding of advisory boards is strengthened in cases where the Chairman also takes a seat in other fora, such as the Board of Trustees. Although requiring greater involvement, this is an effective way to ensure that current activities and the concerns of biobank and advisory board remain in close contact.

Because many population biobanks maintain regular contact with their members through newsletters, this offers them both a channel to recruit new candidate-participants and an opportunity to report results. Biobanks that already maintain contact with their members online, for example for questionnaires, can also use that

infrastructure to consult participants. The MyBiobank app developed by BBMRI-NL can also be adapted to allow this.
Participation can also be valuable during a review of objectives and designs, for example by determining, through consultation or exploratory focus groups, the objectives most favoured by participants or their needs and concerns associated with participation.

Example 1 - Public Consultation and public supervision: UK Biobank

UK Biobank has attracted international attention over the past decade. The project was set up by the British Wellcome Trust and the Medical Research Council as a publicly accessible infrastructure that is organized as a non-profit company. Since 2006, an estimated 500,000 participants scattered around the UK have been recruited as donors. Data and samples from participants are now available for use, and any researcher with a clear plan and sufficient resources can use the data and samples, provided that the new data generated are made available to the biobank.

Participation in UK Biobank: public consultations and the Ethics and Governance Council

The voice of donors influenced the formulation of policy for UK Biobank at various stages. During the set-up phase a series of consultations with the general public took place. A decision was then taken to establish a permanent 'social' board of trustees, the Ethics and Governance Council.

During the preparations, various concerns were raised related to public support for a project such as UK Biobank. Firstly, the public debate on genetic issues such as cloning and genetically modified foods had gone off the rails. At the end of the nineties, the Icelandic company deCODE Genetics triggered a global ethical and legal debate related to conditions of consent and commercialization of biospecimens and medical data. Due to the requirement of large-scale national participation, this crisis of confidence was seen as a

real threat to the project. Moreover, the initial plans were strongly criticized by researchers and the NGO GeneWatch, both in terms of methodological design and objectives, the benefits and need for a large-scale investment in a population biobank, and the ethical and legal aspects of participation (Barbour 2003; Wallace 2005).

Early 'upstream' involvement of the general public at the planning stage was seen as a way to accommodate these views (Levitt 2005). That took the form of an extensive consultation process among stakeholders from research, industry and the general public. The public consultations took place in the form of both widely-distributed surveys and as focus groups in which ideas could be explored in greater depth. These discussions were focused on all facets of biobanks: on exploring concerns about the kind of research that UK Biobank made possible, the way in which participation in UK Biobank would be organized, and management and supervision.

These consultations raised several general concerns about commercialization, the fairness of research priorities and the social consequences and adverse effects of widespread use of genetic techniques. More fundamental objections against certain types of genetic research and commercialization were not addressed. The project created the impression that the principles of future medical research would be up for discussion, whereas in practice only a limited consultation on details of the project took place. The researchers involved at the time have since criticized this process (Levitt 2005; Petersen 2005; Petersen 2007). Expectations regarding what exactly consultation could and would be allowed to contribute differed and were not clearly defined in advance.

However, the concerns about the conditions of participation and the importance of ongoing public accountability were picked up and

embedded in a governance framework, the *Ethics and Governance Framework* (EGF)[4].
This framework provides for an independent Ethics and Governance Council (EGC), a council which constantly monitors UK Biobank and provides both solicited and unsolicited advice. According to UK Biobank, the EGC is a 'strong and well-informed independent voice, speaking on behalf of participants and the public (…). It will ensure that the UK Biobank acts in the public interest and that the right safeguards are in place from the beginning.'

The EGC is charges experts from a variety of disciplines, including medical, legal, ethical, social science and social fields with the task of safeguarding the public interest. The EGC also provides public accountability through annual reports and public meetings. Graeme Laurie, former president of the EGC, sees the council as an example of 'reflexive governance': a way to increase the learning capacity, through reflection on the principles of research, organization and management, of an organization that operates in a complex and changing environment. A major achievement of the council is a revision of the Ethics and Governance Framework: when it appeared that complete destruction of all medical data on withdrawal of participation could not be guaranteed, this situation was modified in consultation with the EGC (Laurie 2011). Despite the fact that members of the EGC are largely unpaid, there are costs associated with the project and each year approximately one hundred thousand pounds is required, primarily as salary for a full-time secretary.

Broader relevance
During the establishment of UK Biobank little was known about the prevailing public attitudes to biobanks. It was unclear whether biobanks could count on public support - a problem not only for biobanks themselves, but also for the policy makers required to

[4] This issue has also led to criticism: it would result in fundamental political discussions on issues such as research commercialization being swept under the carpet (Klaus L. Hoeyer & Tutton 2005).

formulate the conditions under which biobanks operate. Today, public attitudes are broadly known and can be integrated into the charters of an organisation via literature reviews and expert consultation. Of course, it remains important to keep insights up-to-date and keep abreast of any new questions that may arise (recently the significance of unsolicited findings). Clearly explaining to the general public how outcomes of consultations are incorporated into policy is important, especially because this can avoid raising false expectations regarding the implementation of the outcomes of consultation.

The experience of UK Biobank shows that many strategic and practical questions about the organization of biobanks cannot be resolved during the setup phase. The Ethics and Governance Council is a way to introduce societal considerations into the discussion. A 'social advisory council' can thus play a mediating role for public concerns. This type of council must itself be accountable if it wishes to maintain public legitimacy. The elaborate form chosen by UK Biobank is particularly relevant for large-scale biobank initiatives such BBMRI-NL and Life Lines.

Further reading

- UK Biobank website: http://www.ukbiobank.ac.uk/
- Public consultation: see in particular Levitt (2005) and http://www.ukbiobank.ac.uk/public-consultation/.
- About the Ethics and Governance Council: see Laurie (2011) and http://www.egcukbiobank.org.uk/.

UK Biobank

- A nationwide population biobank with 500,000 participants from the general population
- Governance: independent company with the Medical Research Council (government) and the Wellcome Trust (private foundation) as shareholders; bound by the Ethics and Governance Framework and independent supervision by the Ethics and Governance Council

- Participation themes: unfamiliarity with attitudes among the public on biobanks in general; concerns about public support
- Forms of participation: public consultations during the design phase aimed at gauging attitudes and creating executive support; Ethics and Governance Council, board with a structural supervisory and advisory role that contributes expertise on ethical and social discussions on all aspects of biobanks
- Conditions: management of expectations regarding consultation; independence of the Advisory Board; adequate financial and secretarial support

Example 2 - Public deliberation: BC BioLibrary

The goal of the BC BioLibrary is to streamline the supply of biospecimens to research, a task that involves supporting and mediating between researchers and medical practitioners in the collection of tissue from patients undergoing surgery in the Canadian British Columbia region (Watson et al. 2009). The participation initiative at the BC BioLibrary doubles as a social science research project.

Participation at the BC BioLibrary: the deliberative forum

Based at the W. Maurice Young Centre for Applied Ethics at the University of British Columbia, Michael Burgess and Kieran O'Doherty were responsible for a public participation project carried out in the context of ELSA research on developments in the life sciences. Because biobanks were an emerging subject of social, ethical and legal debate, they decided to organize public discussions of the subject together with researchers involved in the BC BioLibrary, a project then at the development phase. This approach also ensured that any recommendations were addressed towards a concrete project. Public participation was in keeping with the objectives of the BC BioLibrary: to increase public confidence in and familiarity with biobank activities in British Columbia, and to avoid misunderstandings about how biobanks operate.

Stakeholders attempted, for example, “to correct the persistent assumption that biobanking can continue as a ‘cottage industry’ and the misconception that the BC BioLibrary exists to create a single ‘BC Biobank’” (Watson et al. 2009). Specific questions about the acceptability of the proposed consent procedure, which required permission for the further use of surgically removed tissue only after surgery, also arose.

These issues triggered the exploration of the concerns and wishes of the general public regarding the conditions for collection and management of biospecimens and data, and resulted in changes to the facility’s policy. Based on theories of participation in political decision making related to deliberative democracy, Burgess and O'Doherty developed a participation form in which participants themselves formulated the principles of policy. The basic principle is that legitimate decisions arise through consultation via an as open as possible discussion with citizens who are as well-informed as possible.

Deliberation requires a setting in which citizens with diverse backgrounds and beliefs are first fully briefed on the subject to be discussed, followed by a period of reflection on the various principles of policy. Creating this type of deliberative forum, referred to as a mini-public, requires methodological elaboration and substantiation to ensure worthwhile and trustworthy results. A small group of citizens is selected based on diversity of background and perspective on the issue (using criteria such as age, political affiliation, relationship to medical research, etc.). The group is fully briefed on the subject, followed by an intensive and structured discussion of the type of approach to the subject they wish to see. Consensus on outcomes is possible, but is not essential: a clearer view of the most problematic issues and conflicts is also an acceptable result. It is therefore crucial to define the agenda under discussion (O'Doherty & Hawkins 2010).

Clearly, there is some tension between the pursuit of democratic openness and allowing the public to highlight important issues, and the need for concrete policy recommendations. The agenda of the deliberative forum was therefore prepared, in consultation with stakeholders in BC BioLibrary (O'Doherty, Hawkins & Burgess 2012), by inviting experts as both contributors and spectators but without a dominant position in the discussion (MacLean & Burgess 2010), and by selecting citizens on the basis of a constructive attitude towards medical research (Longstaff & Burgess 2010). The results were positive: participants supported biobanks and endorsed an open consent form. However, the group expressed concerns about commercialization and attached great importance to structural monitoring and public accountability. The BC BioLibrary responded by extending conditions of consent. One of the participants in the forum now serves on the *Governance Oversight Committee* (O'Doherty, Hawkins & Burgess 2012). The forum increased the support for the project amongst ethics committees, physicians and researchers (Watson et al. 2009), and the participatory model developed is now used in similar projects, including the Mayo Clinic Biobank discussed below (Luque et al. 2012).

Broader relevance

Deliberative forums are an effective means by which to generate robust and democratically legitimate policy advice. They thus constitute an example of a form of participation in which the public, via a carefully designed, comprehensive focus group, can actively reflect and advise on the conditions under which biobanks operate. Similar approaches can also be used in interactive sessions to develop more specific practical results (e.g. for the development of consent forms) and for the exploration of ideas about research priorities among patient experts. Endless variations regarding the form and focus of discussion are possible (Abma & Broerse 2007) and a number of examples will be separately discussed later.

Further reading

- On the BC BioLibrary: see Watson et al. (2009) and http://www.bcbiolibrary.ca/.
- On the deliberative forum: See for example O'Doherty, Hawkins & Burgess (2012) and http://flyingturtles09.wordpress.com/. The vision for participation that is the foundation of the forum is explained in O'Doherty et al. (2011).

BC BioLibrary and ELSA research on life sciences

- An intermediary between researchers and managers of biospecimens and the clinicians who collect tissue removed during surgery
- Governance: Board under the direction of a policy advisory board
- Participation themes: public trust, legitimacy of the organizational strategy followed, support from other stakeholders
- Forms of participation: deliberative forum, organized incidentally during the design phase, focus on in-depth exploration of attitudes among a section of the general public
- Conditions: methodological underpinning of project, financial and organizational support, ensure formulation of concrete recommendations and their translation into policy

Example 3 – A local advisory board: The Mayo Clinic Biobank

The Mayo Clinic is a leading referral centre, headquartered in Rochester, Minnesota. As the Mayo Clinic is investing heavily in clinical research in the field of personalized healthcare, the integration of care and research, and the associated data infrastructure are prominent issues. This led to the creation of the Mayo Clinic Biobank in 2009, driven by the Center for Clinical and Translational Science (CCATS).

Rather than focus on specific disorders, the Mayo Clinic Biobank instead collects biospecimens and data from about 50,000 (English

speaking, adult) donor-patients at Mayo Clinic who have volunteered to participate in the biobank and related research. Upon participation, donors give blood, complete a number of questionnaires and give the biobank permission to access and use their medical records in research. Over 30,000 participants have registered to date and the biobank is now used in a wide spectrum of research, in particular as a reference cohort for clinical research at the Mayo Clinic.

In addition to medical ethical oversight via the local ethics committee, the Mayo Clinic Biobank has other governance bodies: the Biospecimen Trust Oversight Group, a type of Board of Trustees in which a team of scientists, clinicians, ethicists and lawyers serves, an Access Committee that determines access to the biobank, and a Community Advisory Board to advise on matters that effect participants and their communities. The latter issue is also the most important.

Participation at the Mayo Clinic Biobank: the Community Advisory Board (CAB)

Prior to the launch of the Mayo Clinic Biobank, the bioethics department involved in founding the biobank arranged a 'deliberative forum' over several days for a select group of members of the Mayo Clinic patient community, in a manner similar to that described earlier for the BC BioLibrary (see above). The participants and organizers quickly realized that many subjects would require on-going discussion and that biobank policy would regularly result in new discussion. The forum therefore suggested a form of structural participation, which led directly to the establishment of the Community Advisory Board (CAB) in 2010. Similar biobanks have since been established at annexes of the Mayo Clinic in Arizona and Florida, and these also include a local CAB as part of the management structure.

The CAB is an example of an advisory board and focuses primarily on issues related to the role of donors as research subjects. Recruitment to the CAB is based on a number of criteria, such as

diversity of ethnic and socio-economic backgrounds and various links that members have with the Mayo Clinic. Members of the CAB participate in a personal capacity. The deliberative forum organized in the early phase also acted as an introduction for future CAB members, and during meetings time is still devoted to introducing members to specialized subjects. The regular rotation of members is considered advisable (e.g. after five years) because members sometimes begin to overly identify with the biobank after extended periods and are thus less able to clearly express personal views during discussions.

In practice, the CAB acts as a sounding board and advisory body on several general themes facing the biobank. Topics in recent years have included feedback on new findings, access policies and review of research protocols, sharing data with researchers outside the Mayo Clinic, communication and public relations, challenges surrounding *whole genome sequencing*, the inclusion of children and young people, and dealing with commercial research partners.

The CAB receives considerable support from the Department of Bioethics at the Mayo Clinic. The stakeholders at the department contribute to the CAB agenda and, where necessary, establish contact with other stakeholders who can brief the CAB on particular issues. Until recently, the head of the department of bioethics was a dual chairman, together with a 'lay member', of the CAB. This intensive support also ensures that advice given by the CAB is embedded in the decision making of the biobank and in the themes that determine the agenda. This embedding is further reinforced by the participation of the CAB chairman in the *Biospecimen Trust and Oversight Group* (BTOG), the policy advisory board that advises the CAB. In some cases, requests for access received by the *Access Committee* are discussed by the CAB.

Broader relevance

The Community Advisory Board (CAB) of the Mayo Clinic Biobank is a textbook example of an advisory board for long term organizational

issues and challenges. The selection of members and their actual contribution as relative laymen have both been a focus, as was the embedding of this advice in biobank decision making. The CAB does illustrate that the practical support of this type of advisory body also requires organizational skills and expertise in the field of ethical and social issues related to biobank research. This requires both long-term commitment to this form of participation and adequate financial resources. For that reason, this model is more suitable for large-scale population biobanks, biobank organizations and UMC-wide biobank facilities. However, simpler versions with less extensive support are also conceivable.

Further reading

- The website of the Mayo Clinic Biobank: http://www.mayo.edu/research/centers-programs/mayo-clinic-biobank.
- Olson et al. (2013) examines the structure and objectives of the Mayo Clinic Biobank.
- Efforts related to participation were part of eMERGE, a project aimed at systematic integration of genomics data in patient records. Several review articles summarize the main findings (Hartzler et al. 2013; Lemke et al. 2010).

Mayo Clinic Biobank

- A biobank for volunteers recruited from the patient population of the Mayo Clinic, with more than 30,000 participants
- Governance: medical ethical review, a central policy advisory board (the Biospecimen Trust and Oversight Group), an executive Access Committee, and a separate advisory board for donors (Community Advisory Board)
- Participation themes: ethical and social issues related to the organization of biobanks, practical and personal conditions of participation, and monitoring of use of materials and data
- Forms of participation:

    - o 'Deliberative community engagement': a multi-day deliberative forum that generated advice on biobank policy related to organization and supervision
    - o The Community Advisory Board (CAB): an advisory board that meets regularly to advise on practical issues and future challenges in the management and organization of the biobank
    - o The CAB is supported in terms of information and organization by the Department of Bioethics at the Mayo Clinic. The role of chairman is a dual function: one chairman is a bioethicist and staff member, while the other is a lay member
- Conditions: Integration of CAB work with other fora (CAB chairmen are members of Board of Trustees; Access Committee and BTOG submit questions to CAB)

Clinical biobanks

The increase in biomarker research and pharmacogenomics has led to greater demand for biospecimens and associated data, which are collected in a variety of ways: from research cohorts, from collections associated with clinical trials, and also in collections interwoven with the healthcare infrastructure. Such research also requires systematization and scaling of biospecimen & data collection and management, and therefore cooperation and coordination between clinicians and researchers. Various alliances are currently working to streamline the basic infrastructure that makes this possible.

Within the UMC's, this is carried out by the Parelsnoer Institute; similarly, these issues are coordinated for rare diseases under the National Plan for Rare Diseases.
Clinical biobanks facilitate translational research that ultimately aims at practical application. Whether such research is relevant to patients is therefore a relevant consideration. Also important are questions about the type of influence over biospecimens that is best suited to donors. One opinion is that the integration of biobanks with healthcare opens the door to innovative, 'dynamic' forms of influence. Finally, public support for the use of biospecimens and data for clinical research is an on-going issue in a partially commercialized sector that is also intertwined with the privacy-sensitive data infrastructure in healthcare.

In general, clinical biobanks target quite specific groups: patients with a particular disease. In many cases, patient organizations are a point of contact for researchers, both on matters affecting donors and matters relating to the objectives and outcomes of research. Such organizations - or individual patients - can also act as a link between a biobank and patients in the recruitment of donors. Biobanks can themselves approach donors or patients or can make use of contacts within the institution - and they may even be more effective in this than patient organizations.

Taken together, a variety of forms of participation are open to clinical biobanks. Depending on the specific needs and policies of a biobank, various structural or more incidental forms are possible, and these may relate to both the research objectives and design and to issues surrounding collection, management and recruitment. Some patient organizations are active in research and can act as an administrative partner to biobanks. This is especially common in rare diseases, but some patient organizations dedicated to common diseases may also play an executive role in research infrastructure. They may also act as an intermediary, for example by bringing researchers and patient experts together. For long-term, large-scale projects, a local advisory board may also be useful. These advisory boards can act as a sounding board for changes in policy and can express the concerns and needs of participants.

Incidental forms of participation are also relevant. For example, through focus groups or consultation, patient or donor groups can help set the agenda on research priorities. Patient experts can contribute ideas or even cooperate in matters such as research design and public relations. In the UK, in some instances, patient experts even act as volunteers in public relations and recruitment.

Example 4 - An active role for patient organizations: rare disease biobanks

Rare diseases were once in a no-man's land: they received only marginal attention as a public health problem and were of little interest to the pharmaceutical industry. Fortunately that situation has changed and governments now have policies related to orphan diseases. The emergence of biotechnology and genomics has also created new opportunities for research and development of therapies, to which biobanks can make important contributions.

However, this did not happen without assistance. Patient organizations waged a decades-long battle for recognition of the

importance of orphan diseases, a battle that in the light of the newly adopted National Plan for Rare Diseases is still continuing. Patients and their representatives, often parents of affected children, have struggled together with the emerging biotechnology industry for attention for their distressing situation. But even in basic genetic research, patient organizations sometimes take the role of stimulator, investor and even organizer, and their tendency to focus on preclinical, basic research is related to the fact that this type of research holds the greatest promise for diagnosis and treatment. Due to the rarity of these diseases and the fragmented nature of patient care, cooperation related to biobanks and registries for the collection, management and analysis of biospecimens and data is crucial. Patient organizations have also taken steps in this direction.

Participation in biobanks for rare diseases: executive participation of patient organizations

Professionally organized patient organizations play an active role in driving, organizing and running biobanks and patient registries. The traditional division of roles between patient and researcher is now becoming blurred: patient organizations are developing professional expertise on medical developments in their field, are mixing in research networks, and are trying to influence the direction of research, thus participating in 'evidence-based activism'. This also happens on a smaller scale, for example, when patients or other stakeholders see new connections and hypotheses about diseases and communicate these to researchers. In addition, patients' organizations can act as an important link, via the patient contact groups that they organize, between research and patients.

Patient organizations for rare diseases are not remote financiers: they contribute to an efficient and effective organization of the research itself, actively striving to influence its direction and thereby demanding attention for issues that are important to patients and research such as provision of clear information. There are several examples of patient organizations that are closely

involved in the governance of biobanks in their field of interest. Two well-known examples are the French *Association Française contre les Myopathies* (AFM), and the American *PXE International*.

The AFM, a French patient organization focused on muscular dystrophy, is a prime example of a new form of profoundly involved patient activism in research. The AFM has an in-house biobank, with a board on which representatives of the patient organization have a controlling voice. In formal terms, scientists have a purely advisory role. The AFM also works with the European umbrella organization for orphan diseases, EURORDIS, which is involved in Eurobiobank, collaboration for the exchange of biospecimens and data on various rare diseases. The close relationship between patients and research organization not only influences research strategy, but also ensures that researchers remain aware of the severity of the conditions that they work on in the laboratory.

PXE International is an American association of and for patients with a rare genetic condition, *pseudoxanthoma elasticum*. When Sharon and Patrick Terry noticed that there was little good quality research on their children's condition, they began to raise funds themselves and bring together patients and researchers from all over the world (including the Netherlands). An in-house biobank played an important role, with the in-house collection, standardization and coordinated use of biospecimens and data from as many patients as possible allowing researchers to collaborate effectively. The patent on the subsequently discovered gene was awarded to PXE International and gave the organisation the means to remain active in research. Similarly to the AFM, PXE International is now also active in the field of drug development. PXE International has also offered their organizational model as an example for other rare diseases, including the establishment of the *Genetic Alliance Biobank*, an umbrella facility of biobanks for different rare diseases.

Patient organizations in the Netherlands are also actively involved in the organization and conduct of research with biobanks and patient

registries. An example is the Netherlands Neuromuscular Diseases Association (VSN). The VSN views basic research as an activity that requires planning, policy and a long-term strategy, and which can benefit from the difference that the additional stimulus and input a patient organization can make. To achieve this, the VSN has helped establish various partnerships for research on muscular diseases. VSN is also a fully-fledged strategic partner in European muscular dystrophy registries.

As a professionally managed patient organization that has good contacts with both patients and researchers, the involvement of the VSN is mutually advantageous: they ensure that the individual and general interests of patients in research are respected and, where necessary, temper the exaggerated expectations of patients and researchers regarding new therapies. This also allows greater focus on appropriate patient education and well thought-out consent conditions that do not unduly hinder the study. To do this properly, the VSN requires sufficient knowledge and expertise to assess developments in research on their merits. Maintaining this level of expertise is an ongoing challenge in times when public funding for patient organizations is under pressure and links to commercial parties are potentially controversial. Support from the research community is therefore very welcome. Similar organizations for other rare diseases have not all been successful but where they have been, the value of biobanks and registries is clear.

Broader relevance

Successful collaborations between patient organizations and researchers in the field of rare diseases have contributed significantly to all aspects of biobanks and patient registries, improving research, organization and management. At the same time, patient organizations help in collecting patient feedback and ensure continuing support.

While collecting and maintaining expertise and financial resources is a challenge for patient organizations, at the same time huge gains can be achieved for many diseases through improved data

organization and supply of biospecimens. Driven by their direct involvement in the disease, the contribution of patient organizations can provide an important stimulus. Patient organizations would therefore do well to learn from each other regarding how developments in their field can be influenced, a process that also take place with umbrella organizations such as the Dutch VSOP and the European EURORDIS.

Conversely, clinical biobanks and researchers who wish to establish a biobank can also take this as an example and take steps to involve patient organizations. Other clinical specialties are struggling with similar questions of availability of sufficient biospecimens and data. Involving patient organizations at an executive level in the design and development of biobank strategy can help, although patient organizations and health funds quite often develop policies that focus on research that yields concrete results in the short term. They will therefore have to be convinced of the importance of intensive involvement in research and the added value of long-term investments in research infrastructure, just as researchers will have to be open to discussion about the organization of their research. Long-term benefits may require the temporary sacrifice of individual research output in the short term.

Current developments surrounding the organization of care and research also affect the field of rare diseases. The National Plan for Rare Diseases (NPZZ) was recently launched by the government, and registries and biobanks are included as a major focus. Active patient organizations can become involved, where possible, in the governance of biobanks and patient registries in their field. Currently, a broader discussion is underway on the designation of centres of excellence for treatment of and research into a variety of rare diseases, and umbrella organizations in the field of rare diseases can contribute useful expertise. As part of a nationwide network of centres of expertise, an overall registry(form) could be set up and possibly supplemented with biobanks. In a European context there are several examples of this type of collaboration that

were partly established by patient organizations, such as Eurobiobank.

Further reading

- About the AFM: For further explanation of the AFM and its new form of patient empowerment, see Rabeharisoa (2003). A broader reflection on the rise of patients as active partners in the governance of research, using the example of the AFM, can be found in (Callon & Rabeharisoa 2008; Callon & Rabeharisoa 2003; Rabeharisoa, Moreira & Akrich 2013).
  The AFM website: http://www.afm-telethon.com/.
- About PXE International: an explanation of the ambitions and organization of the PXE organizational model can be found in (Terry & Boyd 2001, Terry et al. 2007). For a short Dutch exposition, see (Van der Valk & Smit 2011). The PXE International website: http://www.pxe.org/.
- About the VSN: The VSN's mission is explained in Boon & Broekgaarden (2010). A more extensive public administrational analysis can be found in Boon et al. (2011). The VSN website: http://vsn.nl/.
- The National Plan for Rare Diseases is available via http://www.npzz.nl/.
- For interesting examples of cross-fertilization between basic researchers, patients and patient organizations, see for example the useful booklet by Cees Smit: http://www.vsop.nl/nl/publicaties/downloads/fundamenteel-onderzoek-en-patientenorganisaties-een-verrassende-combinatie/.
- For the contribution of patient organizations in genomics research, see Koay & Sharp (2013).

Initiatives in the field of biobanks and rare diseases: AFM and Eurobiobank, PXE International and the Genetic Alliance Biobank, VSN

- Type of biobank: biobanks for rare diseases

- Governance: diverse; patient organization may have a leading role, or as an executive partner
- Participation themes: research strategy and bottlenecks in the collection of sufficient information and material; short-term interests of individual researchers
- Forms of participation: professionalised, active patient organizations that encourage research and act as a full executive partner in strategic, and occasionally, in practical questions on research, organization and management
- Conditions: expertise and financing of patient organizations; reorganization of research fields with more emphasis on cooperation

Example 5 - Patient knowledge: research priorities and outcome measures in clinical trials

In clinical trials, patients are not simply passive objects of research – their personal experiences of their illness are equally important. These experiences are of great importance for the design and management of clinical research, with patients involved in this process acting as research partners or patient-partners. Various specialties rely on the expertise of patients in determining forms and directions for relevant and valid research, and for the design and testing of effective ways to approach patients.

Patient participation in research is encouraged as a matter of policy, especially by ZonMW, and is sometimes a condition for the submission of research proposals. Participation is more developed in some fields of study than in others and while there are no explicit examples of participation of patient-partners focused on clinical biobanks, this form of participation can have specific value for these biobanks.

<u>Patient knowledge at various research stages</u>

Patient participation in research is now seen as the next step in the empowerment of patients. Patient movements advocate greater control by patients and call for greater awareness of their

perspectives on medical needs. Exercising influence over research so that these medical needs are addressed is therefore an obvious next step.

Patients are not alone and, ideally, all medical research should aim to improve the lot of patients. However, the scientific problems that researchers consider most important and most prestigious are not necessarily the issues that best address the concerns of patients. Conversely, it is also important for patients that researchers and medical professionals address their concerns, and that patients understand how science works and how and within what time period research yields (or often fails to yield) results. It is therefore important that a dialogue on equal terms takes place between patient and investigator which can lead to mutual understanding and acceptance.

Research partners often place great stead in the involvement of patient knowledge in all phases of research. The most optimal approach varies and depends on the precise objectives and practical possibilities. One possible form is that of a survey or consultation among patients as to which topics deserve to be research priorities: a small group of patients can be fully briefed on developments in their clinical field of interest, followed by a structured and moderated discussion of how these issues relate to their own needs or those of their group. This type of discussion may then result in a list of issues on which research should be encouraged. Online variants are, of course, also possible. For example, the Dutch Cystic Fibrosis Foundation (NCFS, see page 79) regularly organizes consultations on research priorities amongst a large group of members. The themes that emerge are then used by the NCFS as a guide when formulating its own research priorities.

Patients can also make specific contributions to research and can advise, develop ideas and where possible, help determine relevant outcome measures. Considerable attention has been devoted to this issue in the field of rheumatology, with patient experts involved

since the nineties in OMERACT, a regular international conference focused on the definition of validated outcome measures for clinical trials. Patient contributions have included defining and developing outcome measures for fatigue, pain and sleep problems, indicators that make a greater contribution to research on the quality of life of patients than the usual outcome measures. These indicators are now part of the standard parameters for clinical trials in the field of RA. There are also follow-up initiatives focused on questions concerning preconditions for participation in research.
These types of initiatives are often focused on strategic and principled choices in and around research at the level of the field as a whole. But patient experts can also contribute to discussions at the local level in the planning and implementation of individual research projects. For example, they can act as a sounding board for researchers or brainstorm with them about the best way to carry out research. Some may also have a useful network, for example, due to contacts with organizations or other patient experts who may be interested in collaboration with the researchers. These collaborations can be developed in both informal and formal contexts.

The success of patient expert -researcher *partnerships* often depends on the individual, personal efforts of both. Good contacts with research partners have to be built and maintained. Patient experts must understand research and need to learn how they can contribute their personal experience constructively to general discussions. There is thus not only an issue of sufficient knowledge but also a psychological component: patients need to be able to cope with the professional authority of clinicians and researchers. Training patient experts can help with this issue. Conversely, collaborations are only worthwhile for researchers if they are willing to make efforts to explain their research to patients in understandable terms, and if they themselves are aware of the limitations of their research perspective. Achieving mutual understanding of each other's viewpoint is certainly helped, in the

early stages, by support from professionals who can guide these collaborations.

Broader relevance

The concrete needs of patients and the practical preconditions and needs that they have regarding participation should play a central role in clinical research. Collaborations between researchers and patients that aim to introduce patients' experiences can help. This can be both at a strategic level through consultation and requests for advice on goals, and on a practical level through discussion with individual patients about the development of protocols and the way research efforts are focused. While these discussions require preparation and effort by both researchers and patient experts, there are good reasons to include these discussions in the standard organizational routines of medical research: research eventually becomes more relevant and valid. These issues are as equally relevant to clinical, disease-oriented biobanks as they are to clinical research.

Further reading

- The recently published thesis by Maarten de Wit (2014) provides both insight into the personal perspective of patient experts and an evaluation of ten years of patient participation at various levels in rheumatology research.
- Tineke Abma and Jacqueline Broerse (2007), two leading experts in the field of participation in medical research, have written a comprehensive, practical guide to patient participation in research. For an example of a survey carried out by Broerse and her team of the research needs of patients and caregivers, see the background study for the 'Health Council Report on Medical products: new and needed!' (Health Council 2010).
- ZonMW supports patient participation in research, development and implementation. This has yielded several accessible publications and manuals, such as a manual of patient participation in research, a book with background studies and reflections on participation, and a useful list of tips and tricks

related to participation that should be kept in mind. These can be found on the ZonMW website: http://www.zonmw.nl/nl/programmas/programma-detail/patientenparticipatie-in-onderzoek-kwaliteit-en-beleid/publicaties/.
- The Centre for Translational Medicine has recently launched a useful guide to patient participation. The included participation checklists for translational research are a very useful supplement to the general questions developed in the present guideline. The guide also provides an overview of specific forms of participation and related practical and logistical concerns. The manual can be found on the CTMM website: http://www.ctmm.nl/nl/nieuws/keuzehulp-en-gespreksmethode-hoe-patienten-te-betrekken-bij-translationeel-onderzoek.
- A general resource for background information on the theory and practice of participation is the website http://www.participatiekompas.nl.

Patient knowledge in clinical research

- Patients are involved as patient experts in prioritizing, designing, developing and implementing patient-related research
- Examples in research include rheumatology and oncology. Patient knowledge can, in principle, also be used by clinical biobanks
- Participation themes: the experiences of patients may shed light on the relevance, feasibility and impact on quality of life of research priorities, design, development, implementation, recruitment and information about research
- Forms of participation: diverse; incl. closely supervised focus groups, as well as intensive individual contacts
- Conditions: Guidance of and contact with patients, training and education of patient experts, room for dialogue between research and patient experience

Example 6 - Consultation and communication through a local patient advisory board: the Wales Cancer Bank

The *Wales Cancer Bank* (WCB) collects various types of tumour tissue from hospitals distributed across Wales, and the bank has been recruiting cancer patients for the donation of tissue remaining after surgery since 2004. Around eleven percent of all cancer patients in Wales have been asked to participate and most have agreed. The WCB also has other tissue collections under their management, for example from clinical trials. Tumour samples and associated clinical data are available for all researchers with a legitimate research question, which is evaluated by an external scientific committee. An advisory board with representation from a range of stakeholders (financiers, pathologists, institutions, researchers) oversees the affairs of the biobank as a whole. In addition, there is a separate donor advisory board, the *Lay Liaison and Ethics Group* (LLEG).

Participation at the WCB: the Lay Liaison Ethics Group (LLEG)

Around the time that WCB was established, several public scandals related to the collection of biospecimens (including the Alder Hey scandal, in which several thousand organs from deceased children were found stored in a British hospital) were still fresh in the minds of the public, politicians and policy makers. Convincing and involving patients was therefore considered crucial to the success of the biobank. Although the actual work of the WCB takes place in institutions and is relatively low-profile, a decision was taken to launch the project in a very public fashion.

Patient advocates from cancer patient organizations were involved at an early stage of the project, both in order to present a widely-accessible story to the press and as a voice in discussions with policymakers. These (former)patients actively lobbied for the bank and called for a flexible approach to commercial use of tissue, with the needs of research as their first priority.

The participation of (former)patients was permanently secured by creating an advisory board, the *Lay Liaison and Ethics Group* (LLEG). This group, which consists of former patients who support cancer

research and who became involved with the WCB informally or via patient-patient contact, is involved in such activities as the drafting of consent forms and information for potential donors. The advisory board acts mainly as an advisory group on ethics and communication with patients and (potential) donors, but is also kept informed of the general progress of the WCB.

The structural involvement of former patients has helped the WCB in a variety of ways. Most importantly, these patients have provided the project with publicity: their personal experience with cancer guarantees a credible and accessible story about the importance of contributing to cancer research. Secondly, their personal stories inspire researchers working with the tissue and they have helped to create support for the WCB amongst policymakers and ethics committees.

While the durable, structural participation of a small, fairly cohesive group of patient experts is valuable to the WCB, this is not always necessarily the case. The WCB also has had the experience that not everyone is effective in representing the interests of patients: a constructive and professional approach to scientific authority is crucial to the proper functioning of the members of the advisory board. The advisory board itself also needs momentum. General questions about financing and public communication continually appear on the administrative agenda, and while the input and participation of lay individuals is important, they must be regularly updated if their involvement is to be guaranteed. That is one reason why the WCB calls regular meetings of the advisory board about 3 to 4 times each year.

Broader relevance

The WCB demonstrates that a permanent advisory board with patient experts can represent a valuable source of information and can be helpful in generating publicly for biobanks. The composition of the membership and maintaining an enduring relationship with the advisory board is important.

Further reading

- The Wales Cancer Bank website: http://www.walescancerbank.com
- More background about the project can be found in (Anon 2007).

Wales Cancer Bank

- Type of Biobank: Biobank for the collection and storage of postoperatively collected tissue and clinical data from different types of cancer
- Governance: WCB is funded by the government and healthcare of Wales; oversight by an advisory board with representation from all stakeholders; in addition, an external scientific committee to assess applications and a patient advisory council (LLEG)
- Participation themes: public trust, public awareness of the project, advice on policy choices
- Forms of participation: Patient expert patient-advocates act as spokesmen for the bank in the media and in the direction of policy and provide regular input on new developments in their own advisory council (LLEG), particularly on organizational and information issues
- Conditions: Selection and training of volunteers based on professionalism and communication skills; structural support of advisory council needed to maintain participation

Example 7 – Public relations and consent procedures involving patient experts: the Nottingham Health Science Biobank

The Nottingham Health Science Biobank (NHSB) focuses on streamlining the collection and management for research purposes of surgically removed tissue and associated clinical data. Several local projects for the collection of tissue fall under the responsibility and/or management of the bank. The integration of healthcare and research is paramount, thus clinical data are collected through a patient information system in which data on research and healthcare are integrated. A similar approach is used for tissue: permission for the collection of tissue for the NHSB is requested at the beginning of

the care process, even before a definitive diagnosis is established. In organizational terms, the NHSB also falls under healthcare (the NHS Trust), with the pathology department acting as an operational base.

Patient participation in the NHSB: the role for former patients in publicity and consent

The NHSB attaches importance to the involvement of donors in biobanks. Due to the long-term storage and use of personal data and tissue, donor trust and providing executive accountability are serious concerns. Involving patients and public through *Patient and Public Involvement* (PPI) is also a policy priority in the British healthcare system organized through policy programs such as INVOLVE. Nottingham University Hospital, home to the NHSB, has its own PPI department and a facilitator, who manages a card catalogue of approximately 1,500 *patient advocates*. This resource allows panels and individual volunteers to be regularly recruited.

The participation of donors in the NHSB is currently focused on public relations and seeking permission for the donation of biospecimens to the biobank. A number of volunteers play a major role, handling public relations and asking patients to consent to the storage of research biospecimens. The British legal requirements surrounding residual tissue were an important impetus to revise consent procedures. Generic informed consent from each separate patient is a requirement: each patient should be well-informed. Normally, research nurses are responsible, but due to the selective collection of tissue around treatment schedules and the distance from daily care (due to the location of pathology), this was not financially realistic for the NHSB. Volunteers with personal experience of the disease (currently breast cancer in particular) have therefore taken on this task.

The task of volunteers is not without obligation. They are therefore subject to strict selection and follow a specially designed training program designed to provide communication skills and background

knowledge of biobanks. They are part of the biobank team in an explicit sense, both formally through an appointment process for volunteers and informally through participation in staff meetings. Selection and training are particularly important to maintaining respect for the rules and customs associated with obtaining permission (not being too pushy, avoiding personal involvement, etc.).

The involvement of former patients and volunteers in the consent procedure has been successful. The program developed by the NHSB is considered by the local coordinator of patient participation as a perfect example of good quality training for volunteers. Some volunteers are also active in patient movements, including the *Independent Cancer Patients' Voice*. And because they are well-versed in the ins and outs of the biobank, these volunteers can also provide the NHSB with advice on strategy.

Broader relevance

The Nottingham Health Science Biobank demonstrates that former patients can also play an active role in approaching potential donors. Even though this solution evolved due to financial constraints, it is far from being a poor man's solution. One could even argue that patients as patient experts might be better able to explain, from the patient viewpoint, what participation in a biobank means and why it matters - provided they are sufficiently well-prepared and do not proceed in too directive a manner. While this role hinges on appropriate preparation and support, including via the selection and training infrastructure, this can be arranged. Finally, there are also indirect benefits of practical participation: patient experts are well-versed in the subject and may therefore, in time, become biobank advisors.

Nottingham Health Science Biobank

- Type of Biobank: Biobank for storage of postoperatively collected tissue with related blood samples collected during diagnostics

and clinical data on various diseases, currently primarily (breast)cancer
- Governance: NHSB is the responsibility of the NUH Trust (government hospital); specific data access committee
- Participation themes: Informed consent
- Forms of participation: Patient experts obtain consent from new patients to include data and tissue in biobank
- Conditions: Selection and training volunteers in communication skills and background knowledge

Institutional biobanks and residual tissue biobanks

Residual material and data from healthcare have traditionally been used for research purposes. Today this takes place to a much greater extent: in teaching hospitals in particular infrastructure for data and biospecimen collection is geared to creating research opportunities. This results in a lowering of the threshold for use of biospecimens and data from healthcare in research. Biospecimens are also available through the pathology departments of hospitals, which manage residual tissue banks and register tissue and related data via PALGA, the national pathology registration system.

Furthermore, in recent years many UMC's have established new institutional biobanks that facilitate the collection and management of data and biospecimens in clinical settings. Although these facilities manage biospecimens specially collected for research, these biobanks are similar in terms of both their public and their position within organizations: they are responsible for the handling of biospecimens and data for research purposes within institutions, but operate at arm's length from (academic) healthcare and usually have no direct contact with patients whose biospecimens and data are stored.

In the Netherlands it is generally not mandatory to explicitly ask patients for consent for the use of biospecimens in research. This practice is, however, a subject of both national and international discussion. The 'Code of conduct for responsible use of body materials' provides guidelines for the handling of biospecimens in research, but these are not often followed. It is often unclear whether patients are sufficiently well-informed about the use of biospecimens and data for research purposes. This is the responsibility of not only doctors and researchers, but also of institutions as patients have a relationship of trust with the hospital where they are treated.

Public support for biobanks with a distinct role within (academic) institutions is therefore an important issue. Informing and obtaining consent from donors deserves a more prominent place in the overall institutional information architecture in healthcare. The ability to withdraw consent could, for example, be built into the institutional electronic patient file. Medical research, and need for data and biospecimens from patients and donors, could be promoted within local patient communities. The participation of donors and patients can be seen as an extension of the general challenge to engage patients as a partner in the healthcare process.

Although the policy flexibility of institutional biobanks does not usually extend directly to questions of research priorities, other matters including issuance procedures, patient information and the establishment of infrastructure within institutions are agenda items. Client advisory boards may have a role to play: for example, the 'Code of conduct for responsible use of body materials' prescribes that biobanks prepare a brief report that should be made publicly available and which should be supplied to the patient advisory council. This thus creates a (otherwise fairly minimal) supervisory role for the interests of patients in the use of residual material. A representative advisory board can also help biobanks to raise issues of importance to patients with the appropriate individuals and bodies within the institution. These issues could certainly include subjects such as provision of information and publicity related to use of residual material.

Institutional biobanks can also consider a self-contained form of participation. This could be via an approach similar to a 'lay member' of medical ethics committee, a member that is expected to represent the interests of research subjects. Besides understanding the interests of patients, these representatives must also have an adequate overview of issues within the institution. There are several available recruitment options, with examples including the volunteer pool linked to the institution or via patient movements. Incidental forms of participation are sometimes useful, especially when related

to issues such as the provision of information to patients and on issuance policies. One example could be the arranging of a patient panel as sounding board or test audience for newly-developed educational materials.

Example 8 – User influence in UMC-wide biobank facilities: Radboud Biobank

Clinical research biobanks are increasing in scale, organization and reliability. This requires increasing professional support and collaboration in the design of shared facilities and methods, and nationally, the Parelsnoer Institute now has a central role. At the institutional level, UMC's are also committed to streamlining collection of biospecimens and data, and the Radboud Biobank, a management facility for (sub)collections of tissue and data for researchers in various departments, is an example of this trend. Local departments can delegate the work-up and management of biospecimens and data to the Radboud Biobank, thus achieving higher quality and other efficiencies of scale. However, due to this intervening management, departmental biobanks also partly lose control over use of biospecimens and data. The Radboud Biobank thus acts as an intermediary who brings together external interested parties and the researchers involved in the collection of biospecimens. The board of the Radboud Biobank is controlled by a policy advisory board that determines the strategy of the facility and oversees its implementation. The policy advisory board includes all parties involved in the biobank (researchers, institution and patient), under the chairmanship of a patient representative.

<u>Participation at the Radboud Biobank: representation in the Policy Advisory Board and institutional user participation</u>

Further integration of research and healthcare is seen as a prerequisite for clinical biobanks. Components of clinical care, such as electronic patient files and healthcare pathways, are now being revised with a view to this goal. Particularly in an academic setting, clinical biobanks are dependent on the willingness of patients to donate biospecimens and data for research. But this also means that

collecting research material is now a shared responsibility of institutions, departments and researchers.

While public trust is a requirement, a more fundamental issue facing research participation is the active influence of patients and donors themselves. How should the voice of the patient be reflected in the academic decision-making of UMC's regarding the integration of care and research? These questions underlie the participation-related activities of the Radboud Biobank. With its participation model, the Radboud Biobank joins with other local initiatives to give 'the patient as partner' a voice in academic healthcare.

Two representatives of patients and donors are members of the central policy-making body of the biobank, the Policy Advisory Board. Both are nominated by representative bodies, the national patient advisory council for academic hospitals (CRAZ) and the Nijmegen Patient Advisory Board (PAR), with one member acting as chairman of the Policy Advisory Board. The underlying philosophy is that patients, with their interests in innovation in healthcare, are the unifying factor driving the efforts of all those involved in biobanks.
The Policy Advisory Board is a central point for the introduction of additional participation strategies, and patient representation at a high strategic level in the biobank infrastructure of the UMC also serves to disseminate the theme to other UMCs. Among other things, this helps increase the visibility of themes such as improved information on biobanks and the further use of biospecimens and data. The participation of patient organizations in determining the research agenda of the departments participating in Radboud Biobank also plays an informal role in discussions on the inclusion of these biobanks in the management facility.

In addition to patient representation on the Policy Advisory Board of the Radboud Biobank, the Radboud UMC also has other representative bodies, in particular the Patient Advisory Board (PAR), which advises the Board of Directors on patient issues. This

board is also indirectly involved in the biobank, including provision of annual reports and participation in issues that affect all patients entering the Radboud UMC, such as the handling of and information on further use of biospecimens and data obtained from healthcare. The idea behind this tiered approach to participation is to stimulate the involvement of researchers and administrators as the interests of patients are often rapidly submerged by the routine tasks associated with research and infrastructure.

Broader relevance

Although the Radboud Biobank is still under development, this example illustrates the importance of participation and influence at all institutional levels of the clinical research process: both in relation to collection and management, and in relation to research and oversight. The tiered model of participation and influence developed in Nijmegen can serve as inspiration for other UMCs and UMC facilities.

Further reading

- The website of the Radboud Biobank: http://www.radboudbiobank.nl.

Radboud Biobank

- Type biobank: institutional management facility for clinical (sub) biobanks
- Governance: medical ethical review (via a lighter ethical review process, CMO-Light), interdisciplinary policy advisory board for strategic policy, chaired by patient representative
- Participation themes: integrating research and healthcare requires a constructive approach and a voice for patients and donors
- Forms of participation: patient representation as president of policy advisory board; In addition, contributions from Patient Advisory Board (PAR) on relevant topics; stimulate strategic consultation between patient representatives and disease-specific (sub)biobanks

Patient registries

Patient registries mainly focus on collecting a single - if possible nationwide - dataset including as many patients as possible with a specific disease. Registries can help in identifying trends in health and disease for specific disorders or in monitoring the quality of healthcare. They can also serve as a starting point for the selection and recruitment of patients for further research. In addition, data from patient registries can be linked to data sets to allow more specific research. The organization of patient registries varies: while they usually gather their data via healthcare facilities, they may also act independently through direct contact with patients.

Similarly to biobanks, registries can also encourage research. This is particularly true for research into rare diseases, because without registries reliable data are not always available on the incidence and prevalence of such diseases and on the efficacy of (orphan) drugs. However, since data from large groups of patients are not usually stored completely anonymously, registries can raise concerns about privacy.

Patient organizations can play an active role in the management of patient registries, including both a role in daily management and in mediating between patients and the registry itself. Patient organizations or patient-donors designated by such organizations can also act as an advisor or (co)supervisor. The continuity of the registry and the partnerships needed to achieve nationwide coverage can also benefit from patient representation.

Example 9 - Patient organizations as administrator-coordinator: the CF registry

The Dutch CF Registry has a dual purpose: to monitor the quality of care in a way that allows comparison between treatment centres, and to support research into CF. All centres specialized in CF treatment jointly participate in the registry, together with the Dutch Cystic Fibrosis Foundation (NCFS), which actually manages the

registry. Almost all Dutch CF patients are included in the Dutch registry. Some data are collected for the purpose of drug research and drug registration. Work is also ongoing to link these data with biospecimens in a fungal repository partly established with the support of the NCFS. Thanks to the registry, treatment options and their effects can be compared and discussed in so-called benchmark meetings. The CF registry also publishes an annual public report and another aim is to finance the registry through the regular costs for CF treatment.

Participation in the CF-registry: the Dutch Cystic Fibrosis Foundation at the helm

The CF registry is coordinated, managed and currently structurally funded by the NCFS itself. Previous attempts to create a CF registry foundered due to disputes over funding and the relative responsibility of different treatment centres. As an independent party (at least independent of the treating centres), the NCFS changed this situation and played a crucial strategic role in the success of the collaboration that established the registry. The registry quickly allowed comparisons of care outcomes and thus fostered awareness of room for improvements in care. In addition to an executive role, the NCFS carries out focus group research that contributes to determining research priorities for CF every four years. The active role of the NCFS in the CF registry serves these priorities.

Broader relevance

Professionalized patient organizations with expertise and ambitions in research can play an important role in the organization of research in their field, a role that can act as both a motivator and as a stimulator. The example of the CF registry shows that this can also be a mediating role that enables collaboration between different centres in the area of data and biospecimen collection, an example that can be instructive for researchers pursuing the harmonization of data and biospecimen collection.

Further reading

- The Dutch CF registry: http://www.cfonderzoek.nl/cf-registratie
- The Dutch Cystic Fibrosis Foundation (NCFS): http://www.ncfs.nl/

The Dutch CF registry

- Type biobank: National registry of Dutch CF patients
- Governance: data management under the responsibility of the NCFS; participating treatment centres and the NCFS both sit in the steering committee
- Themes for participation: coordinate data collection between centres
- Forms of participation: coordination, daily management and maintenance are carried out by the NCFS; link to focus group research NCFS
- Conditions: self-financing, professional organization

Example 10 - Advocacy in the monitoring of privacy: the Dutch Cancer Registry

The IKNL records the data of all Dutch cancer patients in the Dutch Cancer Registry (NKR). Once institutions provide consent, IKNL registry employees enter the data in the database using hospital medical records. The NKR is remote from the patients themselves: IKNL makes educational materials available to hospitals, but the arrangement is that doctors and the institutions themselves inform patients about the inclusion of patient data in the NKR. They do this by providing patients with the IKNL folder or by including a passage in their own patient folder. Researchers can apply to use data available in the basic NKR dataset and additional data that are collected separately.

Applications are reviewed by the four-member Supervisory Committee (CvT). This assesses whether the privacy of the parties involved is sufficiently safeguarded, an issue that is not only relevant to patient privacy, but also to hospital confidentiality and

the privacy of doctors. The CvT has an (influential) advisory role. An agreement was reached with the CvT that fully anonymised data may be provided without prior approval.

In addition to abiding by Dutch laws and regulations (in particular, the Wbp, Wgbo and Gedragscode Gezondheidsonderzoek), the CvT assesses applications using an assessment framework for privacy safeguards prepared by the NKR. Ensuring academic quality and methodology is clearly the responsibility of researchers themselves. In addition to individual requests, broader discussions are conducted concerning the criteria to be used in areas still lacking well-defined regulations, such as requests from *trusted third parties*.

Participation in the Dutch Cancer Registry: representation in the Supervisory Committee

The composition and functioning of the CvT is bound by statutes that allow the participation in the commission of a member nominated by an organization representing the interests of patients, the Dutch Federation of Cancer Patients (NFK). The appointed members are expected to empathize with patient perspectives; they themselves see their contributions in those terms. At the same time, their input has value in proportion to their understanding of relevant laws and regulations, the work of the cancer registry and in terms of the research that this facilitates.

Broader relevance

In the NKR participation focuses on a specific question: establishing the sensitivity of the privacy issues related to requests for use of data with identifiable personal information. While the specific input of representatives is certainly important, the NKR assessment framework is primary. Another issue for the NKR is that the registration of data must be able to rely on the legitimacy of the parties involved, and this form of engagement ensures this. The NKR can thus serve as an example for biobanks and patient registries that explicitly seek support among donors.

The involvement of delegates who represent the perspective of patients in the supervision of national registries is an increasingly commonly used form of participation. PALGA, the national registry of pathology results, uses a similar approach and a representative of the Dutch Patients Association (NPV), a general patient organization based on Christian principles, participates in the privacy commission.

Dutch Cancer Registry

- Type biobank: Registration of data on all cancer patients in the Netherlands
- Governance: data collection and management responsibility of the Comprehensive Cancer Centre the Netherlands (IKNL); In addition, a Supervisory Committee (PMC), which decides on issuance and/or collection of additional data in compliance with legal and institutional privacy framework
- Participation themes: privacy - not only for patients, but also for the doctors and institutions involved
- Forms of participations: participation of members who oversee enforcement of privacy from the perspective of patients, physicians and institutions. Appointment of members through associations for patient advocacy through the Dutch Federation of Cancer Patients (NFK)
- Conditions: The Supervisory Committee was established by the IKNL and operates within frameworks adopted and enforced by the IKNL

6. Context

This guideline was prepared in the context of BBMRI-NL Rainbow Project 6: "Towards a joint strategy for the return of results and optimal communication with biobank donors", more specifically Work Package 3 on the involvement of donors in biobank governance. The project was carried out between January 2012 and May 2014. Professor Gerhard Zielhuis and Dr Rob Reuzel led the work program; Martin Boeckhout, MSc. was the postdoc/researcher for this part of the project. Other project members are Dr Eric Vermeulen, Dr Marjanka K. Schmidt (Work Package 2), Professor A. Cecile J.W. Janssens, Dr Rachel Bakker (until April 2013) (Work Package 1) and Dr Florianne Bauer (Work Package 3, to December 2012).

This guideline was developed based on qualitative research of participation in decision making related to biobanks and medical research. That study consists of the following:

- Literature review and interviews on the principles and experiences of participation in and around medical research;
- Literature review and interviews focussed on the evidence base for various forms of participation - in order to gain insight into the effects of participation and how these can be achieved, especially with regard to biobanks;
- Literature, interviews and *site visits* to biobanks where participation plays or has played a role in *governance* - developed into studies of so-called best *practices*.

In addition, within the framework of this project two meetings were organized with representatives in the field. On May 13, 2013, a meeting took place with representatives of patient organizations, with the objective of exploring the role that patient organizations can play in the governance of biobanks in the Netherlands and as a first step towards structural discussions between Dutch biobanks and patient organizations. Those present were:

- Dinant Bekkenkamp, staff member research Alzheimer Nederland
- Daphne Bloemkolk, staff member Heart & Vascular Group (Hart & Vaatgroep)
- Ria Broekgaarden, Netherlands Neuromuscular Diseases Association (Vereniging Spierziekten Nederland - VSN), also involved in various national, European and international initiatives in the field of research and biobanking for neuromuscular disorders
- Karin Eizema, research manager Heart Foundation (Hartstichting) involved (formerly) in Concor, the Durrercentrum and TRAIT-CTMM
- Vincent Gulmans, coordinator for research and the CF registry, Dutch CF Foundation (NCFS)
- Margreet Jonker, volunteer at the Dutch Breast Cancer Society (Borstkanker Vereniging Nederland - BVN)
- Dorothee Laan, research coordinator (Longfonds)
- Sue Peterse, volunteer at the Dutch Breast Cancer Society (Borstkanker Vereniging Nederland - BVN)
- Bob Roukema, a member of the Committee of Patient experts of the Heart & Vascular Group (Hart & Vaatgroep)
- Cees Smit, former chairman VSOP (Chairman)
- Ton den Teuling, independent consultant, board member Heart & Vascular Group (Hart & Vaatgroep) and deputy in the Patient Advisory Council Academic Hospitals (Cliëntenraad Academische Ziekenhuizen - CRAZ)
- Tessa van der Valk, staff member VSOP

On March 4, 2014, a final *meeting of experts* was organized as part of the validation of this guideline. Present were:

- Koos Cramer, staff member Lifelines/UMCG and public relations advisor LifeLines, Parelsnoer Institute and BBMRI-NL
- Martina Cornel, EMGO/VUmc, professor of community genetics and program committee heel prick screening

- Elisa Garcia Gonzalez, researcher bioethics, IQ Healthcare, Radboud UMC, coauthor of a manual on patient participation in translational research CTMM
- Nella Groenewegen, Lifelines/UMCG, manager buildings and medical affairs
- Gerard van Grootheest, GGZ ingest, NESDA study coordinator
- Vincent Gulmans, Dutch CF Foundation (Nederlandse CF-Stichting), Coordinator Dutch CF registry
- Tineke Markus, Director, Netherlands Crohn's & Colitis Ulcerosa Association (Crohn & Colitis Ulcerosa Vereniging Nederland (CCUVN)
- Petra van Overveld, program manager BBMRI-NL
- Lina van der Ploeg, business director, Lifelines/UMCG
- Peter Riegman, Erasmus MC, Erasmus MC Tissue Bank manager, former chairman of ISBER
- Ger Olthof, ethics section, Ministry of Health, Welfare and Sport, (Ministerie van Volksgezondheid, Welzijn en Sport)
- Chantal Steegers, VUmc, program manager Dutch National Tissue Portal (DNTP)
- Ton den Teuling, independent consultant, board member Heart & Vascular Group (Hart & Vaatgroep) and deputy in the Patient Advisory Council Academic Hospitals (Cliëntenraad Academische Ziekenhuizen - CRAZ)
- Evert-Ben van Veen, Medlaw, lawyer for the Federation of Medical Scientific Societies (Federatie medisch-wetenschappelijke verenigingen - Federa)

During the development of the guideline the following experts were also consulted:

- Greta Antuma, staff member, patient participation UMCG
- Ineke Bos, adviser registration & research IKNL
- Koos Cramer, staff member, Lifelines, also involved in communication and support of several advisory boards

- Elisa Garcia Gonzalez, researcher bioethics, IQ Healthcare, Radboud UMC, coauthor of a manual on patient participation in translational research CTMM
- Barbara Koenig, professor of medical anthropology and bioethics, University College San Francisco, previously associated with the Department of Bioethics at the Mayo Clinic, Chairman, Community Advisory Board, Mayo Clinic Biobank
- Peggy Manders, coordinator, Radboud Biobank, Radboud UMC
- Malcolm Mason, Director, Wales Cancer Bank
- Balwir Matharoo-Ball, manager, Nottingham Health Science Biobank
- Jennifer McCormick, assistant professor of biomedical ethics, coordinator CAB Mayo Clinic Biobank
- Alison Parry-Jones, Manager, Wales Cancer Bank
- Maud Radstake, former program manager Centre for Society and the Life Sciences, Radboud University Nijmegen and Secretary, Patient Advisory Board Radboud UMC
- Melanie Schmidt, Secretary, Patient Advisory Council Academic Hospitals (Cliëntenraad Academische Ziekenhuizen - CRAZ)
- Salome Scholtens, data coordinator and secretary of the Scientific Board Lifelines
- Marieke Snijder, Helius Study, AMC
- Richard Sharp, Professor of Biomedical Ethics, Mayo Clinic, an expert in the field of participation in genomics research and involved with Mayo Clinic Biobank
- Cees Smit, Chairman, Policy Advisory Board Radboud Biobank and active in the patient movement
- Ronald Stolk, scientific director Lifelines and Professor of Clinical Epidemiology
- Peter Thomas, Lay Liaison and Ethics Group, Wales Cancer Bank
- Brian Thomson, Director of Nottingham Health Science Biobank and Director of Research & Innovation, Nottingham University Hospital
- Suzanne Williams, Lead Nurse, Wales Cancer Bank
- Tessa van der Valk, staff member VSOP

- Maarten de Wit, patient-partner and patient expert on arthritis research, including a role in department of Metamedica at the VUmc
- Caroline Woolston, senior biobank scientist, Nottingham Health Science Biobank

The project team would like to thank all participants for their contributions.

Appendix 1: explanation of biobanks and participation for patients and patients' organizations

Participation and voice of the patient in biobank research and patient registries

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Afdeling Health Evidence, Radboud UMC, April 2014

Introduction

The volume of research into the genetic basis of health and disease is increasing, research that opens the way to prevention and the development of treatments. Doctors now hope to fulfil the dream of personalized medicine, developing treatments that are truly individually tailored to the person and his or her illness. However, to accomplish this goal increasingly larger groups of patients and healthy participants will be required who are prepared to donate a little of their time, biospecimens and data to science.

Patients and participants are an important source of information for medical research. In this sense research is similar to the organization of blood donation: the confidence and willingness of donors to take part in research are crucial to improving healthcare. But patients are more than just a source of data: they have ideas, concerns and wishes concerning what should happen to their data and biospecimens.

On the initiative of BBMRI-NL, the Dutch biobank umbrella organization, a guideline was therefore developed to actively encourage biobanks, biobank research and patient registries to explore these issues. It explains how and why researchers, biobanks and patient registries should give their patients and donors a voice in decision making and the selection of research goals. As this issue is equally important to patients and patient organizations, this section

is an adaptation of the guideline that separately discusses the contribution of actively-involved patients themselves.

Biobanks and patient registries in a nutshell

Our ability to analyse DNA and related molecules in detail has increased enormously in recent years, leading to an explosion in the number of samples and the amount of data processed in research. Many more diseases can now be investigated using the new techniques of genetics and bioinformatics. This research focuses on the relationship between genetics, environment and behaviour in the onset and course of disease, but also involves the development of new therapies that are better tailored to the biology of diseases and human physiology, and involves attempts to identify new factors that aid in the diagnosis or prevention of disorders.

This type of research requires data and biospecimens from large groups of individuals. Rather than focus on research into very specific questions, researchers today often work with Big Data, gathering data and biospecimens in a non-specific manner and then searching for interesting patterns in the data. This approach means that data and biospecimens must be collected over a long period of time and stored for later research.

Biobanks are responsible for the collection, storage and management of biospecimens and data. Some are created specifically for research, but researchers also use so-called residual material that was originally obtained via healthcare. There are different types of biobanks: for example, population biobanks focus on collecting biospecimens and data from healthy participants, whereas clinical biobanks focus on patients with a particular medical condition. Residual tissue biobanks manage biospecimens and data from patients that was initially collected for diagnosis or treatment. Patient registries are similar to biobanks, with the difference that they only collect data; data that can sometimes later be linked to other data and biospecimens collected elsewhere.

Biospecimens and research data are also used and distributed in a variety of different ways. Research may be carried out by the biobanks themselves, but biobanks also often provide biospecimens and data to researchers elsewhere. For example, international collaborations and exchange of biospecimens and data across borders is common.
The most important laws and regulations governing biobanks, patient registries and biobank research relate to privacy (the Data Protection Act, Wbp) and to the rules governing medical research (the Medical Research Involving Human Subjects Act, Wmo). In addition, researchers have developed, together with patient organizations, codes of conduct for dealing with biospecimens and data, known as the Code of conduct for responsible use (Code Goed Gebruik) and Code of Behaviour on privacy matters (Code Goed Gedrag). No prior consent is required from patients for the further use of biospecimens obtained from medical procedures, but patients can register an objection. If biospecimens are obtained specifically for research, ethical review and the consent of participants is required.

Patients as partners in biobanking and patient registries

While biobanks, patient registries and related research appear to be complex, technical matters, this is no reason for patients to remain on the side-lines. There are several issues that require their input and in which the can collaboration with biobanks and researchers. The guideline that is the basis of this summary discusses several ways in which biobanks and researchers can achieve this. All these forms of participation have one thing in common: they give patients the opportunity to collaborate in biobank research as partners. This can be achieved in various ways, a few of which are discussed here.

Patient organizations can stimulate and financially support biobank research.
Firstly, *patients and patient organizations can encourage biobanks and biobank research*. Biobanking and patient registries provide insight into the disease process and represent a possibility for the

development of new treatments. Many patient organizations feel that they are entitled to contribute to improving the prospects for (future) patients with similar conditions.

Patient organizations, especially those for rare diseases, encourage and financially-support collaborations for the collection, management and investigation of biospecimens and data. Some organizations even shoulder the role of organizer and manager themselves.
Patients can provide input to identify the best and most important research, but patients can also contribute their knowledge to biobank research. Good research follows from the concrete, urgent needs of patients in the short and longer term, and understanding of these needs might help in the set-up and use of biobanks and registries. As patients and their families have a better understanding of what it is like to live with a disease, their so-called experiential experience is useful when developing and conducting research. For example, they can help in the development of indicators to measure whether new treatments actually lead to an improvement in their condition. Patients can also help identify the moral dilemmas and social consequences that may result from research.

Patients have a voice in how biospecimens and data should be donated and managed, and patient contributions are also important in the practical affairs of a biobank or patient registry. For example, patient expectations regarding participation and their ideas about ethical conditions for management and use can contribute to the formulation of policy. This is important not only because it is a just state of affairs, but also because research can consequently expect greater support - and thus is more likely to reach a wider group of donors. Patients can also help researchers in the preparation or presentation of public relations material and in the recruitment of new participants.
Patients are the social antennae of biobank research, and biobanks and registries need the help of patients to keep track of social trends. Patients can also support researchers and administrators in

the discussion of political and social policies, such as changes in laws and regulations.

What can you as a patient or patient organization do?

What can you, as a concerned patient or patient organization, do to support biobank research and essential infrastructure?

Get involved in discussions with researchers actively working on your condition.

Involvement in research often starts with a simple interest or need; for more information or for prospects for better treatment or cure. Once you have a better understanding, you can then contribute to discussion of research-related issues or join ongoing initiatives. You can begin by talking to your patient organization and perhaps discuss their contacts with scientific research, biobanking and patient registries and the initiatives they participate in. For example, you could discuss important issues requiring further research and how the needs of patients are included in ongoing research.

Act as patient expert and patient-partner.

You can also contribute ideas in a more systematic way to research and the provision of data. In such diseases as arthritis, cancer and heart disease, initiatives already exist to bring researchers and patients together. This dialogue is important for mutual understanding and recognition of the importance of the patient perspective in research, even when it comes to fundamental research in biospecimens. The scientific problems that researchers consider most important and most prestigious do not always coincide with the concerns of patients themselves. Conversely, it is important for patients that researchers and medical professionals can respond with their concerns. Before this can happen, patients also need to understand how science works and how and within what period of research may (or may not) yield results.

This dialogue may take various forms. The discussion could focus on research priorities important to you and your fellow patients, but you can also contribute ideas on research priorities. For example, rheumatoid arthritis patients have helped in the development of instruments that determine whether patients themselves benefit from new treatments. Patients may also contribute to individual research projects, such as acting as a focus group for researchers in the development of research proposals or in handling publicity aimed at other patients.
Collaboration between researchers and patient-partners is clearly dependent on good personal contacts between patient experts and researchers. Patient experts need to understand how research works and how they can best contribute their personal experience to discussions. Training of patient experts can help and although training specifically aimed at biobank research is not yet available, it is available in relation to other research subjects.

Encourage and support the establishment of a biobank or registry in your area of interest.

The study of some diseases is hampered not only by a lack of financial resources, but also in terms of availability of data and biospecimens. Data and biospecimens are sometimes only fragmentally available - joining forces can make all the difference. However, this will not happen without action from patient organizations and health funds, which can help fill the void by setting up a good infrastructure. Although this requires long-term investment and coordination, it can bring significant benefits for research and development. Professionally organized patient organizations can play an important role in stimulating, organizing and managing biobanks and patient registries, and so place the perspective and interests of patients at the centre of research. Patient organizations can thus form an important link in the contact between research and patients.

There are a number of examples of patient organizations that are closely involved in the governance of biobanks. Two well-known examples are the French *Association Française contre les myopathies* (AFM), and the *American PXE International*. In the Netherlands, patients' organizations actively involved in the management of biobanks and patient registries, include the Netherlands Neuromuscular Diseases Association (VSN) and the Dutch Cystic Fibrosis Foundation (NCFS).

More information

For more information about biobanks and biobank research, the websites biobanken.org and biobanken.nl are a good starting point. BBMRI-NL includes information about ongoing collaborations between biobanks in the Netherlands. Some examples of Dutch biobanks and patient registries are the Groningen population biobank, LifeLines, the Rotterdam ERGO study, the national Parelsnoer Institute, the Erasmus MC tissue bank, the Dutch Cancer Registry and the Dutch CF registry.

There is still plenty of room for progress regarding the laws and regulations affecting biobank research. The documentary 'Your life in the freezer' (2012) provides more information. Further information on the 'Code of conduct for responsible use of body materials' can be found on the website of the Federation of Medical Scientific Societies (Federa). The code itself can be found elsewhere online.
You can also find more information on patient participation in biobank research in the guideline on which this summary is based, including discussions of various examples of participation, and references to other background literature and organizations. The guideline is available from the undersigned or through the BBMRI-NL office.

Conclusion

Patients and donors have an important role to play in the governance and strategy of medical research, biobanking and

patient registries. While many patients feel involved in and understand the importance of biobank research, it is perhaps even more important that patients and patient organizations help stimulate and improve research in their own field of interest because the active involvement of patients as partner is likely to lead to improvements in medical research. Patient movements can make a difference in biobank research and thus help improve prospects for future patients - the guideline and this summary should hopefully act as a further inspiration in this goal.

Appendix 2: a list of key factors contributing to the success or failure of donor involvement in biobank governance

BBMRI-NL Rainbow Project 6, April 2014

This deliverable offers a succinct overview of key factors involved in organizing participation in biobank governance. It is based on the project's central deliverable *Participation in Biobank Governance: A Guideline for Patient and Public Engagement*, a summary of which is also available in English. The guideline itself is aimed at biobanks, patient registrations as well as researchers making use of such research infrastructures. For the sake of brevity, we simply refer to all of these activities simultaneously with the term 'biobanking' in this list of key factors. Pointers to the relevant sections in the guideline are provided for each factor.

Premises and principles

Patient and public engagement in biobank governance relies on a number of general premises and principles undergirding all successful engagement initiatives:

- First and foremost, a serious, durable commitment to and positive attitude towards engagement is a prerequisite;
- Second, committing to a strategy for engagement requires clear, well-articulated ideas of why engagement is needed and what it might achieve in a particular setting;
- Third, strategies for engagement need to be operationalized into a reliable and sustainable form with sufficient practical and financial support;
- Fourth, engagement initiatives need to be integrated into general mechanisms and processes of governance;
- Fifth, achieving the goals of engagement requires attending to a number of general conditions pertaining to the societal embedding of biobanking.

Each of these principles involves a number of specific key factors involved in devising a successful form of participation. These are discussed in turn hereafter.

Commitment and attitude

A serious, durable commitment to and positive attitude towards engagement is a prerequisite.

Key factors include:

- Basic commitment to the goal of engaging patients and publics not simply as objects of research, but as subjects whose views and concerns need to be taken into account when designing, prioritizing and conducting research, and as partners with a stake in making research move forward;
- Understanding why engagement matters to biobanking, a goal to which this guideline may also contribute;
- Commitment to the Dutch Code of Conduct for responsible use of human tissue in medical research, which prescribes that 'donors and/or patient organizations should be involved as far as possible with the governance over and the research with human tissue (Federa 2011: 24)'.

These factors are addressed throughout the entire guideline, particularly in section 2, on why participation matters.

The idea of engagement

Committing to a strategy for engagement requires clear, well-articulated ideas of why engagement is needed and what it might achieve in a particular setting.

Key factors involved in articulating those ideas include:

- A good understanding of the issues pertaining to biobanking to which patients and publics have something to contribute. The guideline distinguishes between three themes and publics in this respect: research and future patients; procurement and donors; legitimacy and general publics;

- An exploration of what issues are particularly pertinent to biobanking in a particular setting;
- An exploration of how the voice and concerns of relevant publics has been taken up in governance processes, and where such voices have remained un- or underexplored;
- A good view on where and when patient engagement should be organized in the broader context of governance processes pertaining to biobanking.

The guideline features checklists which provide guidance in these explorations. The factors are discussed further in section 2 on why participation matters, as well as in a series of more specific recommendations developed for various types of biobanking efforts, such as population-based biobanks, clinical biobanks, biobanks dedicated to residual use of human tissue and data and patient registrations.

Tailoring engagement to a specific form

Strategies for engagement need to be operationalized into a reliable and sustainable form with sufficient practical and financial support.

Key factors involved in tailoring engagement to a form suitable for particular issues and settings are the following:

- Selection of a suitable form: defining and demarcating the issues at stake, the level and intensity of participation involved, and the duration of the initiative;
- Recruiting suitable participants: defining and demarcating the publics which should be targeted and selecting spokespersons capable of participating;
- Exploring practical and financial needs: attending to issues such as timing, budgeting and practical organization of participatory initiatives;
- Maintaining necessary organizational ties and support.

Together with the overview of examples of engagement in biobank governance discussed in relation to the specific recommendations, section 3 of the guideline provides an overview of different forms as well as guidance in selecting and maintaining them.

Integrating engagement into governance

Engagement initiatives need to be integrated and fed into general mechanisms and processes of governance.

Key factors involved in this respect include:

- Timing: engagement should ideally be organized 'upstream' – at an early stage at which principled decisions still need to be decided on and engagement initiatives can still make a substantial contribution;
- Impact and follow-up: procedures for following up on outcomes of engagement initiatives should be established and communicated transparently at an early stage. These procedures typically also involve accountability about how outcomes are taken up by those involved, both to participants in engagement exercises as well as to the public at large.

These factors are discussed in section 3 as well.

Societal embedding

Achieving the goals of engagement also requires attending to a number of general conditions pertaining to the broader societal embedding of biobanking.

Key factors include:

- Attending to good ties with publics and patients overall: informing the public and participants about biobanking activities, investing in active involvement of donors more generally, maintaining procedures for complaints and questions, attending to accountability through yearly reports and a website, et cetera;

- Supporting patient participation in biobanking: investing in ties with patient organizations and aid in maintaining an education infrastructure for patient advocates engaged in biobanking;
- Attending to ethical, legal and social aspects (ELSA) of biobanking more generally: setting up and supporting awareness of and research projects dedicated to ethics and the relationships between science and society.

These factors are discussed in section 4, while also figuring large in the various examples of successful engagement exercises in biobank governance.

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