The Ethics and Governance of Health Research Infrastructure
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The Ethics and Governance of Health Research Infrastructure

Ethiek en beleid van gezondheidsonderzoeksinfrastructuur
(met een samenvatting in het Nederlands)

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Chapter 3

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GENERAL INTRODUCTION

INTRODUCTION

Large-scale data processing and analysis offers the promise of personalizing health and biomedicine. In order to realize this promise, growing numbers of patients and citizens are contributing data to health research in many different ways: through participation in trials and studies, by being monitored and tracked in their daily lives, as well as through repurposing of personal data from health care. Making and keeping personal data and tissue samples available through careful curation, storage, management and distribution is becoming an ever more important element of health research. The health research infrastructures facilitating these processes raise multiple ethical challenges. Focusing on (clinical) biobanking infrastructures, this thesis aims to identify and evaluate the emerging ethical challenges raised by health research infrastructures.

PERSONALIZED MEDICINE, DATA-CENTRIC RESEARCH

Personalized medicine (along with near-synonyms such as precision medicine) aims at understanding, managing and intervening in health and disease tailored to small patient subgroups, and at times individual patients, using biomarker-based risk-factors and advanced molecular and data-intensive analytical tools and techniques (1–3). Human genetics and genomics have been leading the charge, together with associated developments in molecular biology and information technology. For instance, pharmacogenetics offers the promise of pharmaceuticals that are designed and prescribed to fit patients' profiles, improving the efficacy of drug therapies (4). A growing number of therapies in oncology and rare diseases are being tailored to personal DNA or tumor characteristics. Therapies for breast cancer, for example, are organized around patients' genetic carrier status and tumor characteristics which indicate sensitivity to hormone therapy (5). Many other molecular markers in areas such as genomics, proteomics and metabolomics, in combination with data on aspects such as personal diet, lifestyle, and environmental data such as exposure to toxicity, are being investigated for their role in understanding disease risk, their prognostic value for health and disease course, and their usefulness for designing and determining accompanying interventions (6).

The aim of capturing processes of health and disease in and through data so as to make them amenable to analysis, management and intervention is a defining feature of personalized medicine. The life sciences are also becoming more and more 'data-centric': scientific research is increasingly organized around the trajectories of collecting, maintaining, structuring and curating data and faculitating its subsequent use and reuse over time (7). In turn, health research requires many more participants to contribute personal data and samples (8,9). In result, more and more patients and citizens, health care institutions and even aspects of social life are being enrolled in the personalized medicine research enterprise.

Personalized medicine is not without its detractors. It remains contentious whether molecular and large-scale 'big data' analysis will ever live up to their promise (10,11). Current progress and uptake of genomics in biomedicine beyond clinical genetics is far more limited than expected (12). 'Personalization' may not even be a correct term, since research into meaningful stratification of patients and treatments and attention to the specificity of individuals' health and disease traditionally stand at the heart of biomedicine already. Such criticisms notwithstanding, targeted molecular and data-intensive exploration play a prominent role in present-day biomedicine and health care. Personalized medicine functions as a paradigm around which the world of biomedicine and health research are being reorganized (13).

HEALTH RESEARCH INFRASTRUCTURES

A whole host of preparatory actions are required in order to generate and make fine-grained, relevant data available and useable for personalized medicine research. For instance, participants or participating health care settings need to be approached; data needs to be collected following particular standards and formats; tissue samples need to be maintained under specific controlled conditions; data may need to be generated from samples; data and samples need to be maintained over time in order to be able to amass sufficient cases, to gather follow-up data and to allow for a longitudinal view on health and disease progression; data requires curation in order to allow for interpretation and analysis. Only after these and countless other steps have been followed can data and samples be accessed, used and re-used for research purposes in meaningful ways. Making data available to research therefore requires complex research infrastructure, an umbrella term for the 'robust networks of people, artifacts, and institutions that generate, share, and maintain specific knowledge about the human and natural worlds' (14). In an era of increasing scale, sophistication and reliance on 'big data', these occupy a central position in the organization of scientific life (15).

This thesis will center on the infrastructures for the long-term, open-ended, large-scale collection, management, processing and distribution of personal data and tissue samples in personalized medicine research. For the sake of simplicity, these will simply be refered to as health research infrastructures. These come in many different forms as well. Many have a long pedigree in observational health research, such as in public health registries, pathology collections, and longitudinal epidemiological cohort studies. Personalized medicine research builds on such long-running resources and data collections, by drawing on available data, by incorporating design aspects, as well as by building on the institutional arrangements involved (16).

Previously, many such arrangements were used for research on a relatively small scale, set up to serve specific disciplinary purposes, and used mostly by researchers directly involved in their set-up. Health research infrastructures mount a step change in each of these respects. These often incorporate and draw together initiatives across multiple sites and settings, and are designed or repurposed to be widely accessible while catering to multiple, open-ended

research objectives. Ambitions to set them up have quickly spread across biomedicine and health care over the last two decades. Health research infrastructures are considered to offer a more efficient approach to data collection compared to approaches collecting prospective follow-up data for each specific research objective or health concern anew. Moreover, prospective collection of data on large populations may be a prerequisite to identify small patient subgroups to focus subsequent research on (17,18). This is not just a matter of setting up new infrastructures for research: it often involves reforming the health care contexts and practices in and through which data and samples are collected, processed and managed (19). Finally, personal data and tissue samples are often distributed widely in order to pool data to increase sample sizes or in data linkage in order to enrich the data available for analysis. Efforts to make so-called metadata about data and samples available and efforts aimed at facilitating analysis on distributed data are part and parcel of this movement as well (20,21). Together, these efforts make up a complex, layered and networked infrastructural ecology aimed at generating, preserving and using health data (22).

The main empirical focus in this thesis will be on a subset of health research infrastructures: those associated with biobanking. These also come in a number of different forms. Population-based biobanks such as UK Biobank (with about 500.000 participants) and the Lifelines Cohort Study (about 165.000 participants) aim at facilitating the study of health and disease as they emerge and develop in the general population over an extended period of time (23,24). These initiatives in many respects mount a step change in terms of the number of participants followed over time, the intensity with which their health is monitored, and the scope of research objectives they aim to facilitate. Although similar in set-up to long-running population-based cohort studies such as the Framingham Heart Study, these biobanks are considered to involve a fundamental change in 'the philosophy of how [epidemiological] science is implemented' by providing 'powerful platforms for biomedical and epidemiological science that will enable future research to be undertaken more effectively and at lower cost' (17). An example of research cutting across domains facilitated by population-based biobanks is the Genome of the Netherlands, a map of human genetic variation in The Netherlands which provides both fundamental insights into genetic variation as well as a set of reference data with which disease-specific studies can be enhanced and compared (25).

Pathology collections are an example of existing collections in health care transformed by the infrastructural revolution. Existing collections of data and tissue are considered a huge asset to molecular pathology. Across Europe and the United States, many tissue banks have amassed hundreds of thousands and associated data over long periods of time (26). Such resources can also be repurposed for novel research objectives in the era of genomics (27). In The Netherlands, efforts to make pathological specimens more easily available for research are underway. PALGA, the Dutch nationwide pathology network and registry, operates the Public Pathology Database, through which tissue specimens can be retrieved and distributed for research purposes (28,29).

Next to the repurposing of existing collections, health research infrastructures often involve significant reforms in health care settings and associated data collection and

management. For instance, initiatives aimed at reshaping, linking and harmonizing electronic health care records for large-scale genomics research have emerged across the globe (30). The clinical biobanking collaborations set up in the context of the Parelsnoer Institute (PSI) provide a case in point. PSI, which will be investigated in more detail in subsequent chapters, provided a catalyst to the set-up and renewal of clinical care protocols, logistical procedures and consensus data standards for Dutch academic care in a number of clinical subfields to accommodate future research (31).

Health research infrastructures are also increasingly collaborating on efforts aimed at deeper technical and organizational integration. Such integration can be aimed at facilitating linking personal data from diverse sources in order to enrich data sets, at facilitating interoperability of data across sites, as well as at facilitating smooth access to samples, specimens and data managed by different infrastructures. Biobanking initiatives in The Netherlands collaborate through the biobanking network BBMRI-NL and its European counterpart BBMRI-ERIC – with BBMRI standing for Biobanking and Bio-Molecular resources Research Infrastructure (32,33). Many other initiatives in the Dutch Health-RI initiative are involved in facilitating integration, such as through the development of shared data standards and collaborations in data stewardship and access governance (34).

Many infrastructural developments take place outside of the confines of (academic) health research and (clinical) health care as well. Through health data platforms such as PatientsLikeMe and the US-based Genetic Alliance Platform for Engaging Everyone Responsibly, patient advocacy organizations and commercial companies aim to drive health research forward (35). Commercial companies such as 23andMe are also conducting long-term health research using their customers' data, privately as well as through public-private partnerships (36).

ETHICAL CHALLENGES OF HEALTH RESEARCH INFRASTRUCTURE

Clinical research ethics provides the predominant lens for assessing health research more generally, structuring the problems which are considered to be at stake, the ethical requirements to be fulfilled as well as the directions for operationalizing solutions (37). According to Emanuel and others, the central focus of clinical research ethics is on protecting human subjects who participate in research against exploitation (38,39). Three core elements of this approach to research ethics and regulation are:

- Respect for the rights, interests and autonomy of research participants, enacted in particular through informed consent;
- The social and scientific value of research, which should be made explicit through specific research protocols;
- Ethics review of these aspects, focused on weighing the risks, burdens and benefits of the research involved, a judgement typically made through a process of independent, project-by-project ethics review.

Clinical research ethics focuses mostly on the research model of clinical trials. It thereby

assumes and reinforces a model of research with clear boundaries between individual research projects, and between research on the one hand and other societal domains such as the provision of health care on the other. Yet this approach may be problematic for other areas and forms of research. In public health research, for instance, the values at stake may differ, as well as the ways of conducting research and different ways of making and keeping personal data available (40). The same arguably goes for health research infrastructures. Although a number of recent updates and supplements to regulatory frameworks, such as the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Health-Related Research Involving Humans and the World Medical Association (WMA) Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks provide guidance, health research infrastructures still raise ethical and regulatory anomalies (41,42). These cannot be articulated and addressed properly through direct application of the principles and frameworks of clinical research ethics. The leading paradigms of research ethics and oversight for health research infrastructures are shifting in response to and evolving with scientific and societal challenges (38). Three themes for ethical attention stand out in particular.

THE ETHICS OF RESEARCH DATA STEWARDSHIP

The collection and management of personal data and biosamples for ongoing research use requires work. This work, generally referred to as research data stewardship, is becoming more specialist, professionalized and organized at some distance from specific research projects and objectives (20). This raises a number of distinct ethical challenges. Health research infrastructures are designed to facilitate multiple, initially undefined research objectives over long time stretches. This is often considered a strength and even a prerequisite for developing insights into many aspects of health and disease, such as multimorbidity, the emergence and slow progression of diseases over longer periods of time, and the sifting out of small-scale risks and contributions of rare variants of otherwise more common disorders (17). However, open-ended research data stewardship sits uneasily with the principle of purpose limitation that is central to clinical research ethics and data protection regulation. Project-specific ethics review, an evaluation of expected risks and benefits, and specific informed consent: each hinges on clearly defined research goals to be specified in advance.

Informed consent is regarded as one of the chief ways by which research participants' personal autonomy is protected and respected. Without specification of specific research objectives, participants are generally not considered to have provided valid consent. Open-ended data use cannot live up to this norm. Questions about what should count as valid consent under these circumstances have been discussed over and over again (43,44). A common approach is to adopt 'broad' consent which allow future uses to particular areas of research, along with ongoing oversight (45,46). Yet although international regulatory frameworks condone this form of consent, no ethical consensus about it seems to have emerged, nor about the extent to which consent should be considered an obligation in all circumstances (43,47).

Responsible research data stewardship requires more than just participants' consent. Particularly since terms of use cannot be specified in advance of data collection, normative safeguards need to be provided in other ways: through organization and technical design, and through enduring governance arrangements (46,47). 'Governance' in this context can refer to any and all rules and mechanisms for decisionmaking relating to the management, maintenance and use of infrastructures (48). International normative frameworks provide basic guidance in this respect. The Taipei Declaration, for instance, posits that governance should be based on principles regarding the protection of individuals, transparency, participation and inclusion, and accountability (42). In practice, however, governance considerations are multiple and messy: biobank governance is typically the temporary outcome of heterogeneous and at times conflicting technoscientific, biomedical and health-related, economic, legal, ethical and sociopolitical perspectives and interests, with responsibilities distributed among various parties along the winded trajectories through which data and samples are collected, managed, distributed and linked (48–50). Managing these differences in responsible ways can be challenging.

Health research infrastructures also relate closely to the Open Science movement. Enhanced data stewardship and data sharing are considered crucial components of 'open' scientific research practice. Health research infrastructures embody and share many of the ambitions that come with calls for opening up science, along with the challenges these raise (20). Chief dilemmas in this respect relate to the extent to which data should be made 'as open as possible, as closed as necessary'. Extensive data sharing may be indispensible in order to achieve many research objectives in health research, for instance to amass sufficient number of cases when investigating patients suffering from rare diseases, or when extremely large sample sizes are required in order to achieve statistical significance for the subtle phenomena under study. Data sharing practices in human genomics mounted pioneering efforts in this area (51). Yet 'openness' relates problematically to privacy as well as commercial interests and claims to intellectual property (52,53). Moreover, the distribution of credit and credibility in science is not always conducive to data sharing and and may not always provide researchers with sufficient 'incentives to share' (54,55). The challenge is to adjudicate between competing values and requirements of openness, privacy and intellectual property and to come up with responsible, workable and context-sensitive ways to cope with the dilemmas arising from them (56).

THE INTEGRATION OF RESEARCH AND CARE

Health research infrastructures often facilitate data-driven integration of health research into health care practice. Several factors are driving this change: systematic data reuse promises to make data collection more expedient; real-world evidence from real-world data is often considered as a supplement to (and in some cases: a short-cut for) evidence gathered from randomized controlled trials; many aspects of health and disease such as detailed data related to diet and lifestyle can be monitored more accurately in real-world

settings; and harmonizing research and health care data may help to facilitate smooth translation of evidence into health-related decision support (19).

The integration of health research infrastructures into health care blurs the boundaries between health and research. Particularly in the context of academic hospitals, data and tissue collected from patients is systematically collected to cater to potential research purposes: clinical care routines are changed to accommodate these collection practices, while patients are appealed to contribute to research enterprises on a regular basis as well. However, the so-called received view in research ethics presupposes a clear distinction between research and care (57). This underpins informed consent processes and risk-benefit assessment in research ethics review, and also marks differences in professional responsibilities. Yet in hybrid practices of research and care, the distinction does not always hold up (58).

The blurring of boundaries between research and care raises the question according to which norms responsible integration should be set up and evaluated. Regulatory frameworks guiding clinical research, such as the Dutch Medical Research Involving Human Subjects Act (Wet medisch-wetenschappelijk onderzoek met mensen, WMO), either do not apply to infrastructural arrangements or impose too stringent requirements (59,60). When patients become enrolled routinely in the research enterprise, this puts them in a double role which should be made clear to them and about which expectations may need to be managed (58). And while direct physical risks of participation will usually be limited, data protection and informational risks to participants require closer scrutiny. Health research infrastructures form a kind of exchange zone between research which should help mask patients' individual identity while still allowing for linkability and traceability of data in research (61).

Another prominent example of blurring boundaries relates to secondary findings emerging from data-driven health research, and the professional obligations for selecting and reporting these back to patients and research participants (62–64). Conventionally such obligations were considered to be limited to cases in which direct harm to research participants could clearly be prevented, i.e. instances in which the 'rule of rescue' applied unequivocally. This is only the point of departure for reflecting on the avalanche of findings of potential personal significance emerging from genetics researchthis (65). Genetics research routinely leads to uncertain findings of unclear, yet sometimes great personal significance, without necessarily having a connection to the original context of treatment or research from which DNA was procured, such as when research into genetic predisposition for asthma generates insights into highly elevated risks for cancer.

Moreover, some health research infrastructures involve new forms of behavioural interventions informed by data-driven analysis, an area of interventions which is not routinely covered by regulations applying to intervention studies. 'Digital nudges' aim at influencing people's choices and standpoints in subtle ways which cannot always be discerned clearly by those being subjected to them. Informed consent and advance ethics review offer only limited protections against the long-term effects of such interventions,

particularly when such effects manifest themselves at the group level. The potential for harm resulting from the use of insights through unwarranted profiling, discrimination or stigmatization needs to be considered as well (66,67).

CHANGING FORMS OF RESEARCH PARTICIPATION

Health research infrastructures mediate the relation between research participants and research. This changes the roles that participants are expected to play. Research-specific interventions to which participants are being subjected no longer take center stage: instead, the focus is on monitoring, tracking and analyzing digital traces of participants' actions, bodies and biological samples. The ethical issues raised relate less to direct physical harm run by participants, and more to risks and opportunities related to the management of information flows (68). While protection of autonomy remains important, it cannot and should not be the sole focus of principles and approaches to research ethics when participants figure as 'connected selves', whose identity and agency is also a result of data-driven connections (69). The role of research participants thereby changes in a number of ways: participants not only figure as research subjects to be protected from harm, but also as active data subjects with rights, interests and a voice in how their data is being used and what it is used for (38,68).

Autonomy and privacy are traditionally protected through informed consent or anonymization. However, where long-term follow-up and data linkage are involved, data usually cannot be considered anonymous; instead, it remains variably identifiable to a greater or lesser extent. Keeping data identifiable to a certain degree can be a prerequisite for many research purposes, such as for constructing traces of health and disease as they emerge over time in participants. Moreover, data-intensive genomics and imaging techniques and samples allow for reconstructing individual characteristics to such a degree that anonymity can often no longer be fully guaranteed. Moreover, anonymization may also prevent participants from exercising personal rights over the data they contributed to research (70).

Conventional forms of informed consent also fall short of protecting individuals' rights in this context. In response, some scholars have proposed a 'dynamic' model of consent, involving ongoing online notifications and updating opportunities, as well as more extensive engagement with research participants over time (71). Various perspectives and ideals of engagement coexist. Patient advocates stress that patients and participants should become actively involved throughout the research process (35). Some ethicists and social scientists stress the extent to which health research and accompanying infrastructures embody and give shape to collective values of community, solidarity and reciprocity between and among patients and generations (72). Still others stress patient empowerment and its relation to questions of the distribution of power and expertise in health research (73).

Although patient partnerships are relevant to health research in general, health research infrastructures play a particular role: these are responsible for enrolling and managing long-term enduring relationships with participants. Some patient organizations have also

taken the lead in bringing together data and tissue samples and research groups related to their disease (74). The question is how participation in health research infrastructures should be shaped in responsible ways, through partnerships and governance arrangements which can lead to beneficial forms of coproduction of knowledge (75). The diversity of infrastructural arrangements involved in health research also makes this a complex societal challenge: public health registries, screening programmes and pathology archives are being repurposed and interconnected for more and novel research objectives. Ethics debates and safeguards will also need to take heed of this merging of infrastructural arrangements into an increasingly interconnected web, in which conventional boundaries of purposes and objectives are no longer always upheld.

RESEARCH AIM AND SCOPE

Taken together, the themes discussed above make clear that ethical norms, safeguards and instruments require reconsideration for health research infrastructures. This thesis aims to examine the main emerging ethical challenges and proposes a number of directions for development. Specifically, the aims to be addressed in this thesis are:

1. To identify and ethically evaluate efforts to improve research data stewardship;
2. To identify and ethically evaluate the challenges and opportunities of integrating health research infrastructures into health care;
3. To identify and ethically evaluate novel models and instruments for actively engaging participants.

Although the issues under investigation are relevant to health research infrastructures generally, the empirical focus will be on how these issues play out in relation to (clinical) biobanking networks and initiatives and their integration in health care. Over the last two decades, biobanking initiatives provided pioneering efforts in the large-scale collection, storage and exchange of human tissue and data for personalized medicine research. Biobanking initiatives have also been the subject of a wealth of studies in research ethics and Science and Technology Studies (43,76,77). These provide a backdrop to draw from in reflecting on the ethical challenges associated with health research infrastructures.

RESEARCH APPROACH

The research approach of this thesis can be described as ethics parallel research (78). Driving this approach is the idea that philosophy and ethics should be conducted in conjunction with the study of the practices to which the analysis pertains; ethics and philosophy should be understood not simply as a way of 'thinking about' but rather as a way of 'thinking with' practice. The approach takes its cue from constructivist perspectives on science and technology, which assume that science and normative orders are co-produced (79). Following this perspective, scientific and social developments are deeply intertwined; scientific progress is anything but an amoral force, and ethics, society and politics do not play a separate, 'external' role in such development. For this reason, ethics research can both

inform and be informed by the sociotechnical developments at issue, and proactively engage with social and ethical dilemmas during the design and construction of infrastructure. In this way, ethics work can also help change the design and course of development of emerging health research infrastructure. The focus in this respect will be on analyzing, evaluating, and – in part – shaping the 'midstream' activities concerning the organization, governance and operation of health research infrastructures (80). The arguments and manuscripts in this thesis were developed in connection with the development of Dutch and European biobanking infrastructures. I have conducted case studies of the Parelsnoer Institute from 2009 onwards, and have been involved with BBMRI-NL in different capacities from 2013 until 2017. The upcoming chapters, particularly chapter 7 on tissue donors as partners in biobanking, provide examples of coproduction in these settings.

The normative positions defended in this thesis are informed and substantiated by combinations of conceptual analysis and case-based empirical (qualitative social-scientific) research. Several chapters draw on case studies of health research infrastructures, particularly the national research infrastructures in the area of biobanking set up since 2006 by the Parelsnoer Institute (75) and BBMRI-NL (32). The Parelsnoer Institute and BBMRI-NL provided rich material to understand and come to terms with the many facets of emerging health research infrastructure at the interface of biomedical research, clinical care and society. The empirical research involved a mixed-methods approach, combining qualitative research as well as desk research involving structured and semi-structured document analysis (82). These empirical insights inform the normative evaluations and considerations provided. Drawing inspiration from the argumentative model of the wide reflective equilibrium, these evaluations strive to incorporate and weigh as much of the different perspectives brought to bear on the issues at hand as possible (83). The robustness of the moral arguments provided should be understood as a 'provisionally fixed point', amenable to change following further insights and reflection, though one in which most reasonable parties affected by the matter at hand should be able to recognize their perspectives. More details of the methods employed can be found in each chapter separately.

STRUCTURE OF THE THESIS

With the exception of chapter 7 and chapter 8 (the general discussion), each of the following chapters consists of an article which has been published or submitted for publication.

The ethical challenges with respect to data stewardship are addressed primarily in **chapter 2**. **Chapter 2** discusses the challenges of fostering and facilitating wider data sharing while also taking heed of privacy considerations, claims of proprietary control and practical constraints. The FAIR guiding principles for research data stewardship have risen to the forefront of research policy for open science. The chapter assesses whether and how the FAIR principles can provide a way forward for responsible research data stewardship.

The ethical challenges and opportunities of integrating health research infrastructures into health care are addressed in **chapters 3**, **4** and **5**. Drawing on case-based research into

the Dutch Parelsnoer Institute, **Chapter 3** investigates how relationships between research and clinical care are changing in the context of clinical biobanking and assesses how these challenge research-care distinctions as they are enshrined in the ethics and governance of health research. **Chapter 4** explores how health care and research in academic medicine could be organized to serve as a dual engine for treatment and scientific discovery and assesses the directions for change in research ethics and governance. **Chapter 5** makes a case for extending the notion of ancillary care obligations beyond its traditional domain of health research to other domains and actors involved in the research process, including social media platforms.

Novel models and instruments for actively engaging participants are addressed primarily in **chapters 6** and **7**. **Chapter 6** explores the right to data portability, a right which has recently emerged as a significant addition to normative frameworks for data control, focusing in particular on the ramifications and ethical impact for health research. **Chapter 7** presents an abridged version of the guideline 'The Donor as Partner', drawn up for Dutch national biobanking infrastructure BBMRI-NL, providing guidance with respect to how and why biobanking initiatives can and should engage participants as partners in governance.

Chapter 8 recapitulates the main findings and places the findings into a wider perspective, reflecting on future directions for ethics research and guidance.

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THE FAIR GUIDING PRINCIPLES FOR DATA STEWARDSHIP: FAIR ENOUGH?

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ABSTRACT

The FAIR guiding principles for research data stewardship (Findability, Accessibility, Interoperability and Reusability) look set to become a cornerstone of research in the life sciences. A critical appraisal of these principles in light of ongoing discussions and developments about data sharing is in order. The FAIR principles point the way forward for facilitating data sharing more systematically – provided that a number of ethical, methodological and organisational challenges are addressed as well.

INTRODUCTION

Calls for facilitating wider access and reuse of research data have rapidly gained traction across health and biomedical research for multiple reasons: because of concerns over research integrity, reproducibility and accountability as well as new needs and opportunities of large-scale data analysis and reanalysis (1–3). More and more research gatekeepers, particularly journals and funding organisations, now mandate data sharing to various degrees (4). In most cases, however, data sharing remains conditional on privacy considerations, claims of proprietary control and practical constraints. It is often unclear how these can legitimately be combined with the goals of fostering and facilitating wider data sharing (5).

The FAIR guiding principles for research data stewardship, with FAIR standing for Findability, Accessibility, Interoperability and Reusability could provide a way forward (6). The principles were coined in 2014 as a set of minimal guiding principles and practices for research data stewardship in the life sciences. Since then the principles have quickly gained traction in research and research policy. They are set to become a cornerstone of research policy and requirements for research data management plans, notably for research under the new EU Framework Programme (3,7). Now that adherence to the principles may quickly become mandatory for a wide body of research, the FAIR principles clearly warrant further scrutiny.

Based on a critical appraisal of the literature on data sharing in health research, and focusing on human genomics, this article assesses the challenges and opportunities raised by the FAIR principles and the conditions to be taken into account to enact them in a responsible manner. The first section provides an explanation of the FAIR guiding principles and a number of cross-cutting focal points. The second section argues that even though the principles create a powerful platform for furthering data sharing and improving data stewardship, they do not address the normative issues and challenges associated with data sharing. Addressing the issues connected to the organization of data sharing, design choices in data, participants' rights, and ways of valuing data sharing, while supplementing, supporting and enhancing the FAIR guiding principles, points to a way forward for responsible data stewardship.

WHAT FAIR DATA STEWARDSHIP IS ABOUT

Human genomics research is a pioneering discipline in setting norms and standards for data sharing. At the same time, systematic data sharing in human genetics and genomics is still hampered by numerous challenges, as testified by the initiatives assembled under the Global Alliance for Genomics and Health (8). The FAIR principles stress a number of crucial preconditions for data sharing, urging researchers to take the possibility of subsequent data sharing and reuse into account from the outset. Given that all researchers working

in a European research environment are increasingly required to specify how they will implement these principles in data management plans, an explanation of the acronym in non-specialist terms seems in order (table 1) (3,7,9).

The principle of Findability stipulates that data should be identified, described and registered or indexed in a clear and unequivocal manner. This entails in particular that datasets are assigned a unique and persistent identifier; that the main characteristics of data are systematically specified, ideally using standard formats; and that these are stored or indexed in a public resource such as a data archive or institutional repository. One example is the BBMRI-ERIC Directory for biobank collections (10).

The principle of Accessibility stipulates that datasets should be accessible through a clearly defined access procedure, ideally by automated means. This entails the establishment of authentication and authorisation procedures for access as well as the implementation of automated data retrieval protocols where appropriate. Metadata should always be accessible even if the underlying data is not or no longer available. One example in the area of human genomics is the access procedure of the European Genome-phenome Archive (11).

The principle of Interoperability stipulates that data and metadata are conceptualised, expressed and structured using common, published standards. This entails drawing on standard technical and semantic data formats, variables, ontologies and the like. Moreover, such standards should themselves be made FAIR, meaning at the very least that they are published, traceable and accessible. The Genomic Data Toolkit developed by the Global Alliance for Genomics & Health (GA4GH) provides an example of this principle in action (12).

Finally, the principle of Reusability further specifies the gist of the other principles: characteristics of the data, including their provenance, should be described in detail according to domain-relevant community standards, with clear and accessible conditions for use. This entails providing and publishing accurate and relevant data descriptions, access and usage licenses, the community standards which have been employed in the process as well as the associated provenance for each and every dataset. The BRCA Exchange, which enables public circulation and classification of actual and suspected pathogenic BRCA variants, is an example of an open-access implementation of this principle (13).

Table 1: The meaning of the FAIR principles, based on Wilkinson et al. and Mons et al. (6, 14)

Principle	Explanation	Example in human genetics and genomics
Findability	Datasets should be described, identified and registered or indexed in a clear and unequivocal manner.	BBMRI-ERIC Directory
Accessibility	Datasets should be accessible through a clearly defined access procedure, ideally using automated means. Metadata should always remain accessible.	European Genome-phenome archive
Interoperability	Data and metadata are conceptualised, expressed and structured using common, published standards.	GA4GH Genomic Data Toolkit
Reusability	Characteristics of data and their provenance are described in detail according to domain-relevant community standards, with clear and accessible conditions for use.	BRCA Exchange

FAIR IS ABOUT DATA AND METADATA

A number of focal points cut across the individual FAIR principles. Three stand out in particular. First of all, the FAIR principles stress the importance of metadata and metadata standards in data stewardship. This emphasis extends the methodological and transparency requirements in reporting scientific research into the domain of data stewardship. Metadata is an umbrella term for information and attributes applying to datasets and the data contained therein. A key message of the FAIR principles is that metadata and metadata standards should be articulated and made publicly available to the greatest extent possible. Narrowly defined, metadata is usually understood to refer to systematic descriptions and attributes of datasets relevant to interpret what the data is about, similar to bibliographic information about publications. More broadly, the term refers to all data about data, such as data about theoretical assumptions, methods and techniques used, as well as provenance and context relevant to proper interpretation and meaningful reuse. The FAIR principles thereby dovetail with calls for enhancing reproducibility in science (1).

FAIR IS ABOUT MACHINE-ACTIONABILITY

Second, many if not most aspects of data stewardship, such as data indexation, retrieval and analysis, are assisted and executed by computers. Facilitating automation is therefore a crucial prerequisite for large-scale data-intensive research. One may think here about reliable processing of sensor data, as well as about automating data retrieval from data repositories through APIs. Computers and computer-assisted data stewardship and analysis have a role to play in realising each of the FAIR principles. Machine-actionability is

relevant on all levels of data aggregation, applying equally to genome-level variant calling and to aggregate-level data and biobank catalogues.

FAIR IS ABOUT CONTROLLED DATA ACCESS

Thirdly, the FAIR principles call for explicit, well-defined and readily available terms and conditions under which data are shared or made accessible. The FAIR principles chiefly aim for background conditions for facilitating data sharing to be made explicit, including conditions for gaining and granting data access, privacy, publication and use embargos (14). In this sense, the FAIR principles are compatible with models of controlled data access and release.

Calls for open data have frequently involved appeals to make data publicly available to the greatest extent possible, with mixed success (5). For one, sharing individual-level genomic data, particularly with corresponding health data, will often raise privacy concerns. Moreover, open data and data sharing policies often seem to be adopted selectively. For instance, genomic reference data has become much more widely available over the past decade than specific research data sets. And commercial investments in data sharing have often been made with an eye on the development or expansion of novel, privatised and closed-source R&D-driven markets (15).

The FAIR principles offer a way out of the conundrums of combining open science with the values and interests of privacy and intellectual property, by offering a middle ground to which more parties can adhere. Instead of arguing for open and free availability per se, the aim is to settle on legitimate and effective means of controlling access while facilitating bona fide research for all data. This is in line with recent community standards on data sharing in human genomics (16).

APPLYING FAIR RESPONSIBLY

The FAIR principles were coined as a set of widely applicable 'permissive guidelines' offering a basis for developing flexible community standards (14). The principles thereby create a powerful platform for furthering data sharing and improving data stewardship. In so doing, however, the principles do not address the normative issues and challenges associated with data sharing. In order to apply the FAIR principles responsibly, a number of further conditions will therefore need to be met (table 2).

Table 2: Conditions for enacting FAIR principles for data stewardship responsibly

Facilitating data sharing and reuse	Organising and governing data sharing initiatives in specific communities of practice Fair and impartial assessment of requests for data sharing
Keeping design choices in mind	Explicating, formalising and continuous updating of data and metadata standards Additional methodological checks, statistical innovations and active monitoring and correction of inadvertent biases Ongoing vigilance and transparency when reusing data
Respecting participants' rights	Developing frameworks and methods for privacy and data protection 'by design' New governance frameworks capable of fostering trust and participation
Valuing data sharing	Frameworks and metrics for justifying the value of investments in systematic reuse and sustainable infrastructure Systems for scientific credit for reuse which do not reproduce current 'publish or perish' reward systems

FACILITATING DATA SHARING AND REUSE

First of all, the FAIR principles only call for explication of access conditions, without specifying how data sharing should be facilitated. The FAIR principles do not specify what would constitute legitimate means of controlling access. More extensive guidance within open science frameworks and policies about how data should be made available 'as open as possible, as closed as necessary' is urgently needed (3).

For one, effective ways of facilitating and organising data sharing initiatives in ways that further the ends of relevant and responsible research will need to be developed. The formalisation and publication of discipline-specific data and metadata standards is one step towards this end; metrics and incentives to stimulate adherence to such standards is another. Successful data sharing platforms in genomics and infectious disease research are usually carried forward by closely-knit communities of practice which collaborate on more than just standards. Replicating the success of such platforms in other areas will likely also require organisation and governance, collective oversight and reward mechanisms, as well as coordination of research efforts (17).

Moreover, due to privacy concerns, many forms of individual-level genomics data cannot simply be made publicly available for download without some form of access

control. Responsible ways of facilitating data sharing require fair and impartial assessment of requests for data sharing (18,19). Privacy and data protection are likely to remain at the forefront of ethical and legal debate over human genomics, not least because of the advent of the novel European legal framework for privacy and data protection, the General Data Protection Regulation (GDPR). The ramifications of the GDPR for scientific research cannot be assessed in any detail in the scope of this article (20). Nevertheless, it is worthwhile to shortly touch on the issues the GDPR could raise by the FAIR principles and 'FAIRified' research data stewardship practice. Overall, the GDPR leaves more leeway for scientific research than for other forms of data processing, provided that 'technical and organisational measures are in place in particular in order to ensure respect for the principle of data minimisation' (cf. recital 156, article 89.1). Exemptions afforded to scientific research with respect to further processing, a wider scope of consent, and storage limitation, could in principle help facilitate reuse. Moreover, FAIR data and metadata standards could help facilitate compliance with the principle of data minimisation, by allowing for an assessment of which data to reuse on the basis of an analysis of (by and large non-personal) metadata. On the other hand, however, the GDPR also aims to ensure that any data use is stipulated as clearly as possible in advance, providing data subjects with more rights in further processing. In practice, these provisions run against the drive for systematic and automated data reuse. How these different legal considerations should interpreted and weighed together will likely remain contentious for years to come. More clarity about legitimate and illegitimate ways of controlling access is therefore urgently needed. Multiple parties involved in supporting and facilitating research have a role to play in enforcing and facilitating this on multiple policy levels, for instance through standardised structured access conditions, mandatory data management plans, data sharing policies on behalf of funders and journals, and ethical and legal guideline development (21). Endeavours in this area, such as the drafting of a code of conduct led by BBMRI-ERIC, are much to be welcomed in this respect (22). At the same time, coordination and synchronisation of policies is an issue that will need to be addressed as well.

KEEPING DESIGN CHOICES IN MIND

Second, research data incorporates design choices, such as decisions on research focus, sampling frames, choices about categorising and measuring phenomena, as well as particular details involved in how the analytical technologies actually work.

The FAIR principles encourage researchers to make their choices explicit through the adoption of data and metadata standards. At the same time, systematic reuse may also facilitate the introduction and perpetuation of errors, bias and questionable interpretations, also because of lack of familiarity with the details and limitations of the original study (23). Moreover, systematic reuse of multiple datasets of varying provenance and quality could also facilitate data dredging, thereby exacerbating methodological and statistical concerns. Although the FAIR principles could help improve data stewardship, responsible data-driven

science will therefore also require additional checks on research quality and integrity – especially when drawing from diverse data sources (24).

Genetics and genomics researchers have been dealing with such issues for a long time already (25). The FAIR principles offer a stimulus for ongoing work on this, by raising questions concerning community metadata standards to the fore. Achieving FAIR data stewardship is as much a collective effort involving standard-setting as it is an individual requirement on the part of researchers and data producers. Individually, researchers reusing existing datasets will have to remain vigilant and transparent about the kinds of data they reuse, the ways in which they do so and the purposes to which they put them. Collectively, researchers will have to invest in explicating, formalising and regularly updating data and metadata standards. Additional methodological checks, statistical innovations and active monitoring and correction of inadvertent biases will also be needed in order to tame issues of research waste and reproducibility (26).

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RESPECTING PARTICIPANTS' RIGHTS

Third, in order to realise FAIR data stewardship in health research, concerns relating to privacy and the protection of personal data will need to be addressed vigorously. Facilitating reuse of data also stands to enhance and raise new risks related to privacy, confidentiality and informational harm. The paradigm of 'consent or anonymisation' is increasingly considered to fall short: anonymisation of personal data in research is neither feasible nor always desirable, whereas informed consent can often not be provided meaningfully for open-ended data collection (27). Additional safeguards are needed in this respect, with privacy and data protection being taken on board 'by design', at every stage of the research cycle (28). For example, complex automated personal data processing arrangements will require structured consent protocols, rigorous access controls, as well as accountability measures. Ethics review boards and data access committees will keep on playing a role in assessing the risks, benefits and appropriateness of such research in the foreseeable future (21,29). Adopting FAIR data stewardship and data sharing more widely will also need to go hand in hand with attention to the rights and roles of research participants and new governance frameworks. Even if the increasing separation in space and time between data subjects and researchers complicates a direct say for participants, a larger and more frequent role for participant participation in governance across the board could help foster accountability, trust and participation in the long run (30–32).

VALUING DATA SHARING

Questions relating to the value of data sharing constitute a fourth issue. Ultimately, data stewardship and data sharing are not ends in themselves, but means to more and better research. Preparing, organising and maintaining data and infrastructure for data sharing and reuse requires ongoing investment. Questions about how to provide and distribute credit and funding fairly both for those reusing data and those generating, collecting, and/or maintaining it will have to be tackled. In part, investments into FAIR data stewardship and research data

management could be covered as an element of overhead in research funding. Norms for redistributing scientific credit for reuse should also be developed. Furthermore, frameworks and metrics for justifying the investments in systematic reuse over and against other research opportunities will need to be developed, including opportunities for conducting novel studies. All the same, incentives for data sharing should be introduced with caution, as these risk reproducing the 'publish or perish' reward system in scientific research and its concomitant problems relating to research integrity and reproducibility (33).

CONCLUSION: MAKING FAIR WORK

Facilitating data sharing and reuse may be a prerequisite to reap the benefits of new forms of data-driven research. At the same time, the scientific and normative challenges this raises will need to be addressed head-on. The FAIR principles are a powerful way of making true on the ideal of a more open science, which could stimulate researchers to take issues related to data stewardship and wider accessibility and reusability on board in an early stage. Their strength also rests in their simplicity and flexibility, providing common ground for developing shared agendas and courses of action in research data stewardship and the development of community-wide data and metadata standards. The FAIR principles thereby provide a necessary stimulus to a data-driven research culture for actually facilitating reuse of data in a transparent fashion. The articulation of standards for data, metadata and access conditions is a core principle in this regard.

At the same time, the FAIR guiding principles on their own are unlikely to lead to responsible forms of data sharing. Although they provide a much-needed step forward for furthering the cause of data stewardship, they do not provide a complete set of guiding principles for improving data-driven science. On top of problems related to insufficient or incomplete adherence, unqualified application of the FAIR guiding principles could create additional issues. The FAIR guiding principles will therefore need to be supplemented with other principles and applied responsibly, taking additional normative considerations into account. This is particularly relevant now that the FAIR principles are occasionally framed in research policy circles as the predominant means to realize and improve open and data-driven science more generally (3).

In order for FAIR data stewardship to actually lead to better data and better science, research communities as well as individual researchers and research groups will need to rise to the challenge. Human genomics, with its rich history of collaborative research and data sharing and advancing data stewardship, could be leading the charge for life sciences writ large – a position which however requires ongoing work.

The FAIR guiding principles constitute necessary, even if not sufficient, principles for responsible research data stewardship. By sketching out in clear terms the key dimensions to be addressed, the FAIR guiding principles for data stewardship could help move the practice of data sharing into a more advanced stage, provided that a number of additional conditions are met. Four strands of action stand out in this regard (table 2): facilitating

and organising for data sharing and reuse; remaining vigilant about all the design choices embodied in data; developing new modes for respecting participants' rights; and coming up with robust measures for valuing data sharing which do not reproduce the problems related to current scientific reward systems. Addressing the issues connected to these areas while supplementing, supporting and enhancing the FAIR guiding principles points to a way forward for responsible data stewardship.

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AUTHOR CONTRIBUTIONS

MB came up with the initial idea for this paper. The idea was elaborated on in discussion with GZ and ALB. MB led the drafting process, to which GZ and ALB contributed with revisions, additions and comments in a number of iterations. The authors provide complimentary expertise to the topic: MB is a philosopher and sociologist of science by training; GZ is an epidemiologist and biobanker; ALB is professor in the ethics of biomedical innovation. MB is the guarantor of the article.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest: The authors declare that they have no conflict of interest.

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3

GOVERNING THE RESEARCH-CARE DIVIDE IN CLINICAL BIOBANKING: DUTCH PERSPECTIVES

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ABSTRACT

Biobanking, the large-scale, systematic collection of data and tissue for open-ended research purposes, is on the rise, particularly in clinical research. The infrastructures for the systematic procurement, management and eventual use of human tissue and data are positioned between healthcare and research. However, the positioning of biobanking infrastructures and transfer of tissue and data between research and care is not an innocuous go-between. Instead, it involves changes in both domains and raises issues about how distinctions between research and care are drawn and policed. Based on an analysis of the emergence and development of clinical biobanking in the Netherlands, this article explores how processes of bio-objectification associated with biobanking arise, redefining the ways in which distinctions between research and clinical care are governed.

INTRODUCTION

Biomedicine is frequently framed as standing at the cusp of an era of personalized medicine, an era ushered in and enabled by increasing capacities to collect and analyse huge amounts of data (1). Yet achieving that transformation will first require huge infrastructural changes in biomedical research, particularly in collecting, managing and using human tissue and data in large-scale, systematic fashion (2–6). Changes related to the collection of tissue and data do not solely implicate research processes, but also the provision of healthcare itself. The realization of personalized medicine is considered to require forms of biobanking that reconfigure the relationships between research and care.

In this article, we show how resources of clinical biobanking (i.e. human tissue and health data) link up and transgress commonly held distinctions between research and care in multiple ways. Recent scholarly work within science and technology studies (STS) has sought to develop a series of analytical tools for recognizing how such reconfigurations are taking place, and understanding their implications for current understandings of life (7–15). Drawing on the concepts and interpretive toolkit of bio-objectification (7–9), we trace how relationships and boundaries between research and clinical care are reconfigured through changes in the resources, their associated practices and the way these are governed in biomedical research. The notion of 'bio-objectification' calls attention to the ranges of work devoted to the exploration and fashioning of new forms of life. As these novel configurations disturb previously established boundaries, labour is undertaken to render bio-objects stable and both demarcate them and associate them with other forms and aspects of life (7). Such labour, involving many different practical, technical, legal and social aspects, can lead to 'bio-objects' such as frozen gametes that sit on the boundary of the living and non-living as they are simultaneously inanimate and sources of vitality (16), or microRNA that challenges the boundary between human and non-humans as it migrates from plants to regulate mammalian genes (17).

Our investigation of bio-objectification processes related to clinical biobanking draws on qualitative research based in the Netherlands over a five year time period (2008-2013). Data collection consisted of semi-structured interviews with key researchers, policymakers, and others involved in establishing Dutch biobanking infrastructures and policies pertaining to them, participant observation at professional conferences, alongside analysis of public and internal documentation of a prominent large-scale national initiative in clinical biobanking – the Parelsnoer Instituut (PSI). PSI is a large initiative aimed at providing a model for collaborative clinical biobanking across clinical disciplines and medical institutions, in which University Medical Centres (UMCs) coordinate and account for the lion's share of (relatively high-impact) biomedical research (18–20). UMCs also play a pivotal role in Dutch healthcare by providing specialized clinical care.

We use the term 'clinical care' loosely as a general term referring to settings and institutions of care in clinical medicine, particularly (though not exclusively) as it relates to diagnosis

and health monitoring, as these are the areas most directly affected by the emergence of clinical biobanking. Our use of the bio-objectification toolkit allows for an investigation of the most salient reconfigurations involved in emergent clinical biobanking infrastructure in the Netherlands. After showing how clinical biobanking has emerged over the last decades, and how it has given rise to concerns over the relationship between research and clinical care, we turn to an analysis of associated relationships of governance. By describing how distinctions between research and clinical care are enshrined into research governance we demonstrate how bio-objectification in clinical biobanking challenges these assumptions. Finally, we investigate the implications of these challenges, and show a number of possible directions taken in policies and governance pertaining to biobanking. Specificities of the Dutch institutional landscape notwithstanding, we believe our analysis also offers broader insights into the dynamics at work at the interface of research and care in clinical biobanking. We will link up our discussion of general trends, tensions and approaches taken to academic discussions on changes in biomedical research governance more broadly.

TISSUE AND DATA FOR RESEARCH AND ITS RELATIONSHIPS TO CARE

The emergence of clinical biobanking is associated with general shifts in biomedical research towards an investigation of the molecular level to understand and intervene in mechanisms of disease, particularly with the uptake of genomics in in clinical research and medicine. In turn, those shifts bring with them a hugely different role for human tissue and data as well as major changes in the ways in which tissue and data moves between research and care. These shifts provide a novel occasion for investigating relationships between research and care. In medical sociology and STS the relationships between research and care have been explored in a number of ways, particularly through addressing the ways in which medical uncertainties are dealt with by practitioners and researchers (21–23); the consequences of intertwining research and care at the level of clinical practice (24–26); the role of clinical trials as a constitutive component of clinical cancer care (27); as well as the ways in which changing practices and processes of research and drug development affect the organization and practice of clinical care and public health (28,29). Our research touches on the latter focus in particular. Analogously to the 'experimentalization' of clinical care for drug development, the reconfiguration of clinical care to accommodate biobanking can be understood as a way in which care practices are changed in order to feed into and accommodate broader research objectives.

Healthcare traditionally serves as the prime resource for biomedical research as a setting for recruiting patients as research subjects as well as a source of tissue and data. The interweaving of research and care also played a role in the emergence of modern medicine, as Michel Foucault argues in his classic study on the emergence of the modern clinic in which patients suffering from similar symptoms were assembled in a way that enabled them to be submitted more systematically to a 'clinical gaze' (30). Foucault shows how distinct constitutions of the patient emerge with new ways of thinking about medicine and sickness

as well as new technologies and techniques for investigating and recording the body. The emergence of new tools and techniques for examining particular organs went hand-in-glove with an associated disciplinary compartmentalization of the body, as well as an institutional sequestration of bodies in the clinic. In this respect, collection of -and research on- human tissue and data in relation to clinical medicine is far from novel as such. For instance, there is a long history of changing techniques and forms of research building on isolating, banking and manipulating human tissue for research purposes (31), and residual use of human tissue and data procured for medical purposes is common in modern medicine as well. Such uses involve medical files, but also blood leftover from diagnostic tests or excised tumor tissue. These are facilitated by infrastructures such as tissue archives in pathology that are set up for healthcare purposes, disease-related patient registries, and archives of dried blood spot cards collected through newborn screening for congenital defects.

The role played by human tissue and data, and the value attached to it, in research is now shifting along with novel approaches and techniques of biomedicine. Instead of focusing on causal mechanisms, health and disease are frequently understood nowadays in terms of risks and aiming for differentiation and stratification of diseases and disease populations. In order to accommodate that shift, resource provision for research has changed dramatically in scale, scope and systematic nature over the last decades. In seeking to exploit the potential of genomics and other molecular analytical techniques, increasing emphases on differentiation and stratification of target objectives and populations have emerged, while challenges in establishing statistically significant associations between diseases and disease markers require data of ever larger target populations – both healthy subjects as well as patients (32). While often grouped together under the heading of 'personalized medicine', current approaches to biomedical research therefore involve more than just individualized, stratified and differentiated forms of intervention, but also new forms of population-level surveillance (33). The emergence of biobanking is considered a chief enabling factor for these shifts.

Population-based biobanking set up specifically for research purposes have received considerable attention in studies devoted to ethical, legal and social aspects of biobanking (34–38). However, equally large changes in relation to biobanking are afoot in the practices and institutional settings of healthcare. The advent of molecular medicine both builds on and transforms existing ways in which body parts and data derived from them are procured, stored and used. Systematic, so-called, 'repurposing strategies' are now considered for most retrospective collections of tissue and data collected for purposes of healthcare (39). Prominent examples in the Netherlands include proposals for systematic use of dried blood spot cards for research, efforts aimed at increasing research opportunities from pathology archives and infrastructure, as well as initiatives in clinical biobanking (18,40–44). The Dutch branch of the European biobanking platform BBMRI has been providing funding to projects aimed at systematizing and upgrading existing collections for genomics research since 2009 (45). The project is now in its second phase, which will run until at least 2017.

Therefore, while human tissue, data, and the bodies of patients they are derived from

have traditionally served as boundary objects between research and care, those linkages are now formalized, systemized, and institutionalized on a much larger scale into basic routines of clinical care and molecular medicine. This is particularly true of healthcare taking place in academic centres or university teaching hospitals. PSI is a particularly prominent national initiative in the Netherlands in this respect, linking all eight UMCs with the goal of standardizing the procurement, management and distribution of samples from patients in academic hospitals for a number of different areas of disease. At present, over thirteen clinical specialties have joined up in this model to collaborate in the coordinated provision of human tissue and data for research purposes. Through PSI, these medical centres are taking up the task of professionalizing and systematizing the ways in which tissue and data are managed locally for subsequent research. This has also stimulated the establishment of new institution-wide biobanking facilities that dovetail with existing pathology and clinical chemistry facilities (cf. for instance the Radboud biobank (46)).

These Dutch initiatives are by no means unique in the world. In Denmark, for instance, opportunities for exploiting leftover dried blood spot cards from neonatal screening for genomics research are being considered (47). Other initiatives for coordinating provision and access (particularly tumor) samples in the United States and across Europe as well (39,48,49). Prospective initiatives with comparable aims are emerging at academic healthcare institutions across the globe as well as at the field level around specific diseases (50,51).

Below we detail how the emergence of clinical biobanking is reconfiguring relationships and interactions within and between research and care. By examining the procurement of research material in care settings, the alteration in clinical practice due to research protocols, and the routinization of patient participation in research through the analytical lens of bio-objectification, we show how these reconfigurations are currently taking place. With that description in place we will then move to a discussion of the socio-political and governance implications of those shifts.

PROCESSES OF BIO-OBJECTIFICATION IN CLINICAL BIOBANKING

The emergence of clinical biobanking has gone hand in hand with a blurring of the boundaries between clinical care and medical research. Specific components of that blurring can be understood as bio-objectification, a process through which novel personal and biological entities (in our case tissue and data) come into being and result in a reframing of the roles, responsibilities and agency of other parties, entities and institutions involved (52). In particular, we see three forms of bio-objectification taking place in clinical biobanking, each of which is challenging conventional boundaries between biomedical research and clinical care.

First of all, data and tissue initially procured for and circulating in contexts of academic clinical care is now often framed and systematically formatted as also catering to potential research purposes. For instance, according to one of the chief instigators of PSI, Daniel Hommes, the integration of care and research on the level of data is a chief imperative for clinical researchers working in academia (53). Hommes' vision subsequently became

a driving force in the establishment of PSI as well as related local initiatives in clinical biobanking. For clinical biobanking, facilitating such integration involves huge amounts of work aimed at standardization and harmonization of data and tissue provision as well as efforts aimed at establishing quality control, certification of workflows, substantial and procedural benchmarks for data and tissue collection and management and evidence-based data models (19,54)). Slightly different attempts at integrating healthcare data for research are made in projects aiming at large-scale systematic integration of medical data infrastructure into biomedical research, such as the controversial UK care.data project (55).

In order to achieve such close integration and harmonization, a second, related process of bio-objectification is also involved. The integration of care and research at the level of data and tissue does not just involve changes in the ways in which data and tissue are collected for research; rather, it also implies changes in the uses of tissue and data for purposes of care. For instance, in the context of PSI, clinician-researchers established so-called minimal datasets which specify how and what kinds of data would be collected of what patients. These were subsequently institutionalized into all clinical routines across participating UMCs. Settling on minimal datasets for purposes of research also involved settling details of how data would be collected in the context of care. Clinician-researchers across different institutions had to settle on questions such as whether blood samples would be collected from sober patients only. While many such changes may seem mundane (even if complex to change in a coordinated fashion), other changes also involved the establishment of novel and state-of-the-art invasive routines across multiple care settings. For instance, PSI catalyzed the introduction of routine collection of cerebro-spinal fluid for the purposes of Alzheimer diagnostics in UMCs (56). In cases such as this one, research processes are impacting the provision of clinical care, through novel standardized routines for the collection and storage of biomaterial and data on a nation-wide scale.

A third process of bio-objectification relates to the patients participating in these clinical biobanking endeavors and the roles they are expected to take up vis-à-vis the tissue and data procured from them. Through large-scale forms of resource provision embedded into practical routines and infrastructures for healthcare, patients are turned into regular contributors to the clinical research enterprise. This is reflected in terminology involved to describe their role. Instead of the use of language such as 'research subjects', contributing human tissue and data is now often framed as an act of 'donating', which a term previously reserved for more tangible donations dedicated to others' well-being such as through blood donations (57). A case in point is that in 2011 Dutch professional guidelines for responsible use of human tissue in biomedical research routinely speak of 'donors' and 'donations'; yet, in 2001 terminology used was 'betrokkene' (i.e. someone who's involved) (58,59). Some scholars have referred to this process as involving new forms of 'clinical' and 'immaterial labor'. At the same time, the labour performed by most donors is also minimized and made invisible by integrating it into routine aspects of care (39,60). In order to achieve high rates of donation, the success of clinical biobanking is considered to depend

on its unobtrusiveness and on not being seen to overburden patients in their donations. This is reflected in concerted efforts in PSI to minimize the work and time expended on biobanking for patients, research nurses and clinicians by integrating tissue and data procurement as efficiently as possible in day-to-day clinical care. These adjustments in clinical routines, which also involve mundane aspects such as training of research nurses and timing of clinical appointments, are forms of bio-objectification that allow for patients' data and tissue to be swiftly transformed into "workable epistemic objects" (52).

HOW CLINICAL BIOBANKING CHALLENGES RESEARCH GOVERNANCE

Through these processes, clinical biobanking poses challenges to clinical research governance. In a number of ways, such governance assumes and is aimed at enacting and enforcing distinctions and boundaries between research and care. As we have noted elsewhere, "Establishing and maintaining firm boundaries in biomedical practices are crucially important activities for establishing legal rights and responsibilities, as well as the navigation of routes to regulatory approval of new medicines and products. Classifications delineate what is and is not acceptable within biomedicine, which has knock-on effects in terms of how science, health care, and biomedical research will be structured, organized and funded. However, when such boundaries are breached and classifications begin to breakdown, questions are raised about how biomedicine will be governed." (12)

The first issue raised by the bio-objectification of clinical biobanking relates to the core principle underpinning the ethics of human subjects research: the protection of the autonomy of research participants. Distinguishing sharply between research participation and receiving care is widely considered part and parcel of such protection. The Dutch Law on Research Involving Human Subjects, for one, imposes a regulatory check on medical research on a project-by-project basis according to three basic criteria:

- human subjects research needs to be aimed at a specific, circumscribed goal, laid down in a protocol;
- each research subject needs to be free to decide about participation informed about and consent to potential risks and benefits in advance of their participation, through providing informed consent;
- research projects require ethics review, involving approval of protocol and consent procedure of an ethics review board (ERB) before the start of research as well as more marginal monitoring of possible safety breaches throughout the project.

Each of these criteria presuppose and serve to reinforce distinctions between research and care, which are destabilized by the objects and collection routines emergent in clinical biobanking. For instance, research protocols are directed at delimiting the scope of research in both substance and time, while explicating and justifying potential risks associated with that research to participants. Informed consent is a way of framing participation in research as an issue of individual choice made on a well-informed basis related to circumscribed research objectives. Finally, ethics approval of both aspects serves as a check

of the specific risks and research potential of each research objective taken on its own. The institutionalization of clinical biobanking into practices and infrastructures of healthcare challenges the project-based modes of research ethics regulation, and hence represent a significant governance challenge. The open-ended nature of biobanking is considered a crucial concern in this respect, and is a point that is raised time and again in discussions over the nature of informed consent, (e.g. 61–64).

This issue has also provided a powerful catalyst for the development of models of governance that would look to endure over longer periods of time (Knoppers 2009). However, such models of governance are complicated by the extent to which clinical biobanking initiatives are organized as complex nested arrangements, often involving overlapping organizational responsibilities for various aspects of tissue and data processing. This is a second challenge mounted by processes of bio-objectification. PSI, for one, draws together multiple departments located in different institutions collaborating on a number of specific disease areas. Clinical specialties from different academic hospitals collaborate in disease-specific entities called 'Pearls', while each academic hospital separately provides institution-specific logistical and technical facilities to its participating departments. The need for coordination between disease areas, medical institutions, as well as individual departments leaves considerable leeway for variation and conflict on many aspects of the initiative as a whole with respect to aspects such as the formats in which data is collected, issuance of data and tissue requests from the biobank, ethical and legal affairs, quality control, communications, finance, information communication technology and information security. The governance relationships between all these organizational entities are complex, diverse and subject to ongoing negotiation and modification. Such complex, nested organizational arrangements complicate project-based model of research ethics regulation, since ethics review for clinical research traditionally stresses the need to review the proportionality of research potential and risks upfront. In the case of clinical biobanking, ERBs find such a check on proportionality complicated by the time span passing between procurement and use of data and tissue for specific research projects. This became an issue when PSI sought ethics approval. ERBs and policymakers considered there to be a lack of legal basis for ethics review for projects lacking specific research objectives. Moreover, the fact that local standards of care provide an informal benchmark for both researchers and ERB members against which to compare the invasiveness of research interventions also complicates checks on proportionality. Several components of PSI involved not just the procurement of additional tissue and data for research, but also extensive changes in local standards and procedures of care, complicating the allocation of the burden of procedures to either research (in which case proportionality is an issue for ERBs) or care (in which case it technically is not). The previously mentioned example of cerebro-spinal fluid (CSF) provides a case in point. Procurement of such fluid, which had been incorporated into one leading institution's diagnostic routines for neurodegenerative diseases for a while already, was adopted by other clinician-researchers in the course of participating in PSI (56). After protracted discussions, local ERBs eventually settled on compromises which allowed the initiative to continue, but with additional liability insurance for

human subjects research in place in a number of the locations where diagnosis using CSF had not previously been included in clinical routines.

Thirdly, practices of residual use of human tissue and data procured in the context of healthcare often do not directly fall under the remit of most clinical research legislation. Historically, human tissue and data were often regarded as a kind of waste which could be regarded as an impersonal good (66). Even where personal rights in such resources were involved, current privacy legislation often contains provisos for so-called research exemptions. In this way, a distinction between research and care is upheld by depersonalizing the use of residual tissue and data in research and processing such resources only in aggregate form. As discussed above, such ways of drawing boundaries between research and care no longer apply in clinical biobanking. The boundaries are blurred by design, undercutting any sharp division between data for research and data for care. One area in which this blurring plays up clearly is in current debates over how to deal with the feedback of incidental findings. Many ethicists and legal scholars have argued that researchers and biobanks have duties and responsibilities towards participants and donors with regards to incidental findings generated from banked tissue and data. For instance, Wolf and others consider that "findings that are analytically valid, reveal an established and substantial risk of a serious health condition, and are clinically actionable should generally be offered to consenting contributors"(67). However, it is often unclear on whom this responsibility specifically falls, and this may require altering conventional roles and duties of researchers. This could extend researchers' medical responsibilities and would consequently also raise further governance challenges concerning the delineation of their role and remit in research and care. Even the question whether findings should still be considered 'incidental' given the systematic exploration of data and tissue will come up for debate. Irrespective of if most genomic variants may currently by-and-large seem of unclear significance, such findings are likely to be commonplace in some clinical settings (i.e. genetic diagnostics) and will eventually become more commonplace as similar analytical techniques are adopted in other clinical areas as well. Moreover, once personal tissue and data collected in care settings are processed for open-ended purposes over indeterminate time frames, research data may become a source of data with potential clinical significance as well. Once healthcare practices are modified to accommodate the provision of clinical data for research purposes, qualitative distinctions between clinical and research data are less likely to form a barrier to such feedback.

Fourthly, challenges related to the blurred boundary between research and care in clinical biobanking also emerge with respect to the rights of participants and the vexed issue of informed consent. An avalanche of academic literature on informed consent in biobanking has appeared over the last decade (63,68–72). Research legislation is often considered an impediment to, or safeguard against (as some ethicists would hold), 'broad' and generic forms of informed consent. This challenge is further compounded by the fact that consent is designed to regulate the rights of research participants and the obligations of researchers vis-a-vis them. Clinical biobanking often involves fairly diffuse relationships, relating to responsibilities to safeguard privacy over time as well as responsibilities relating to the integration of research into care. Consent serves a

different role in such a constellation and it becomes a placeholder for a much more diffuse set of entitlements and expectations regarding the control individuals should hold over their data and tissue within clinical biobanking infrastructures. In the Netherlands these issues were raised during ethics review of PSI. ERBs delimited the scope of consent, particularly by requiring subsequent ethics approval of projects applying for the use of tissue and data from PSI. At the same time, patients' role in such consent procedures remained restricted to a generic approval at the point of collection of tissue and data (73).

CHALLENGES TO GOVERNANCE: REINSTITUTING OR FLEXIBLY MANAGING DISTINCTIONS BETWEEN RESEARCH AND CARE?

Clinical biobanks, and the tissue and data brought into circulation through them, uncomfortably straddle governance regimes of clinical medicine and biomedical research and are facing renegotiations of the terms under which biological material and data are collected. Divergent approaches to dealing with these challenges of bio-objectification can be discerned. While some approaches aim at purification and the re-establishment of boundaries between research and care through updates and extensions of existing modes of governance, others aim at hybridization, flexibly managing the traffic across the divide. In practice, both are coined next to one another, providing an additional source of conflict.

One particularly salient challenge in this respect relates to the individual feedback of findings. At stake in such discussions are a series of ethical, legal, economic and medical questions about what kinds of outcomes of research should be reported back to individual contributors of data and tissue and under what circumstances. Considering the diversity of kinds of data and tissue, contexts of procurement and kinds of research involved, this makes for a fraught discussion (67,74–76). The issue is complicated further by the fact that similar debates on the issue of reporting back results from techniques such as imaging and whole-genome sequencing in clinical and diagnostic settings remain unresolved in the Netherlands as elsewhere (77,78). Various proposals to establish protocols and guidelines to deal with the issue have been made. A consensus document by the Public Population Project in Genomics and Society (P3G) proposed that every biobank should at least have established some policy on how incidental findings would be handled, but the content of such policies remains very much a matter of dispute (79,80). Although some biobanks have developed preliminary policies, the majority of biobanks in the Netherlands have not done so up to now (81). Some lawyers and ethicists argue forcefully for policies limited to only the most clear-cut, acute 'clinically actionable' cases, minimizing the medical responsibilities involved (82). Dutch researchers have argued publicly and in academic debate for substantive restrictions on the clinical relevance of data. Genetic epidemiologist Cecile Janssens pointed to the limited quality control for research data and interpretation of genomics data (83). Community geneticists involved in the European Society for Human Genetics (ESHG) have suggested that researchers employ data filters designed to screen off potentially significant clinical findings for particular research investigations (84). Others,

such as medical ethicist Annelien Bredenoord, advocate and experiment with more hybrid policies for dealing with and reporting back different ranges of findings to those who are interested, including findings of only potential personal significance such as slight changes in genetic risk susceptibility or findings which might inform reproductive decisions (85). Dutch population-based biobanking initiatives such as LifeLines and the Netherlands Twin Registry are also experimenting with reporting back preliminary screening results and survey findings over time as a means to engage with their participants. Responding to a keynote lecture of 23AndMe's then senior medical director at a major biobanking conference (Hands On Biobanks) in November 2013, multiple researchers considered 23AndMe's policy on data sharing an example to be followed. The severe ethical and legal conundrums surrounding 23AndMe's ways of feeding back findings notwithstanding, many considered their model to be attractive, not least because of the kind of involvement and interest on the part of 'citizen scientists' such feedback of data may invoke (86,87).

'Purification' measures aimed at disentangling effects and attachments of tissue and data in care and research are also taken to adapt existing modes of ethics review to the regulation of organizational forms of clinical biobanking. Uncertainties regarding the legal status of biobanking vis-a-vis medical research legislation notwithstanding, Dutch ERBs have gone ahead in reviewing proposals for biobanking on a project-by-project basis similar to ethics review of clinical trials. Clinical biobanking initiatives are now required by ERBs to explicate their research methods and objectives in a more or less circumscribed way in a protocol, with informed consent specific to the terms laid down in such a protocol. ERB monitoring of such projects then extends to subsequent use through ethics review of projects drawing on collected tissue and data. This way of holding biobanking initiatives to account by circumscribing research objectives and monitoring of progress brings clinical biobanking back into the fold of research ethics (73). In practice, however, such regulatory strategies leave considerable leeway in the manner in which clinical biobanking initiatives are governed. Within PSI many aspects of governance, such as those relating to access policies and substantive choices with respect to the kinds of data to be collected, are dealt with through consultation and management at the organizational level, with ERBs playing a minor oversight role. Such hybrid forms of self-governance imply more flexible forms of governance of the boundaries between research and care.

Similarly, both purification and hybridization approaches are at work in relation to the donors' rights and entitlements to tissue and data. Clinical biobanking initiatives require informed consent of their participants of varying scope and specificity. Blanket consent is generally not accepted by ERBs. Instead, ERBs require the scope of consent to be circumscribed to a particular research area, while remaining linked to ongoing oversight in actual research uses. Within such a framework of ethics approval, consent still by and large serves the same role that it does in clinical research more generally (i.e. as a means to state upfront what research is about and as a device to circumscribe and delimit subsequent entitlements and expectations of patients in contributing to a research endeavor).

Subsequent control of human tissue and data in such a model of consent is usually limited to a right to withdraw data and tissue for further use. More recently, however, proposals for so-called 'dynamic consent' have also been made that take a more hybrid approach (61,88). According to its proponents, dynamic consent may serve a role in programmes to make research more 'patient-centric', enabling patients to engage more actively in the research process themselves as well as granting them more authority over their tissue and data over time. Arguments for such active models of patient participation in research often dovetail with arguments for participatory healthcare supported by contemporary information communication technology-driven healthcare capable of facilitating both at the same time (89). At the same time, however, fierce protests in Europe from the medical research camps over proposed new data privacy legislation have emerged (64,90). The protests are aimed particularly against explicit, detailed consent requirements for secondary use of medical data for medical research. According to medical researchers, limiting the scope of research exemptions in data protection legislation would severely hamper biomedical research. Such exemptions thereby enact a principally different way of policing the traffic between biomedical research and healthcare. Instead of blurring the boundary on the level of individual donors, these arguments consider research as a public good relying on care for resources: 'In many studies that will be affected [by new data privacy legislation], individuals have voluntarily given broad consent for their data to be used in research to further our understanding of society, health and disease' (91). The chief value put in play to justify such broad forms of consent, oriented as these are towards enhancing purported collective benefits of research, is not autonomy but a form of solidarity with patients mediated through biobanking research – solidarity which serves to shield biomedical research from overly grand responsibilities vis-à-vis individual donors.

CONCLUSION: CLINICAL BIOBANKING, BIO-OBJECTIFICATION AND THE GOVERNANCE OF THE RESEARCH-CARE BOUNDARY

Generally, changing relationships between research and care have received relatively little explicit consideration in academic reflection on biobank governance. One of the central values of the bio-objectification toolkit is that it helps us make visible in-between forms of life, or entities such as tissue and data – or clinical biobanking infrastructure more generally – that straddle conventional conceptual distinctions and practical and institutional boundaries. Our analysis shows that a number of bio-objectification processes are ongoing and actively pursued, resulting in new 'epistemic objects' which mediate between practices of research and clinical care The formatting of data and tissue collected in contexts of care in order to cater to potential research purposes; the entanglement of new forms of resource provision in existing processes and practices of clinical care; and the routinization of turning patients into contributors to the clinical research enterprise: each of these processes present important issues of governance pertaining to the relationships between research and care. As we have outlined here, these challenges emanate from the fact that dominant modes of

clinical research governance assume research and care as morally and practically distinct sets of activities, and attempt to constitute them as such. As a consequence, diverse approaches have been deployed in an attempt to address these challenges and "establish a stabilized field of inquiry that addresses regulatory and wider challenges" (52).

We have shown here how clinical biobanking is accompanied by changes in the constitution of healthcare leading to novel, systematic infrastructural couplings between research and care mediated by human tissue and data. Clinical biobanking infrastructures underpinning data-driven research are accompanied with medical responsibilities for those involved in using and managing the data and tissue circulating therein. The tensions raised are dealt with in different, at times conflicting ways: by re-establishing and re-purifying distinctions between research and care within the novel setting of clinical biobanking, but also by actively embracing the hybrid nature of clinical biobanking between research and care by flexibly managing the intermingling of both domains. Given the multiple ways in which the governance issues related to the bio-objectification of clinical biobanks can be and are in practice addressed, governance for clinical biobanking is likely to remain a dynamic and heterogeneous field. While different approaches to processes of bio-objectification may be compatible at times, they depart from opposing philosophies. Underlying these different responses are questions and visions of how healthcare and research should be related, as well as questions about how the contribution research makes to healthcare should be understood. Is it a common good contributing to the well-being of anonymous others over the longer term, or as a good closely linked to the fate of patient-participants? In consequence, moving the debates outlined here forward also requires asking political and social questions about what goals biobanking and biobank governance should serve, and the kinds of accountability required to foster them. From various angles, scholars have proposed alternative understandings and principles underpinning biobank governance based more overtly on concepts of solidarity and the public good (92,93).

In this sense, clinical biobanking is but one example of broader challenges in contemporary biomedicine. The ongoing transformation of academic clinical care through -and for- biobanking research represents another way in which biomedicine is increasingly turned into an 'experimental field' (29). Instead of clinical trials moving to countries in which access to healthcare is a relatively scarce commodity, however, it is medicine in affluent societies which may be transformed primarily for data- and tissue-intensive clinical research. This is a further way in which relationships between science and society become ever more complex and intermingled, a process accompanied by uncertainties, conflicts, new political fault lines and challenges, but also by new forms of governance. We believe that issues of governance pertaining to the relationships between research and care in clinical biobanking and beyond should be explored further in that direction.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

All authors have made substantial contributions to research, analysis and drafting of this manuscript. MB coordinated and led the drafting process. Both MB and CD have conceptualised the study, provided key data on PSI, delivered analysis of the data and have contributed substantially to revising drafts. Both authors read and approved the final manuscript.

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PATIENTS TO LEARN FROM: ON THE NEED FOR SYSTEMATIC INTEGRATION OF RESEARCH AND CARE IN ACADEMIC HEALTH CARE

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ABSTRACT

Patients suffering from rare, extreme or extremely complex sets of symptoms have something to expect from efforts to improve care through research. Biomedical research and care have often been approached as distinct worlds which are and should be only loosely connected. For observational research focusing on data drawn from real-world settings, however, that approach is found wanting. Integrating research and care responsibly is the main challenge instead. Integrated IT infrastructures facilitating Personalized medicine and Big Data are crucial components of a learning health care system, in which patients regularly play a double role: as individuals to be treated and as cases to learn from. Drawing on the example of the Dutch Parelsnoer Institute (PSI), a national biobanking and IT infrastructure integrated with clinical care procedures, this article outlines the reforms that are needed.

Systematic integration of research and care offers a promising avenue, provided that a number of conditions are met: data and IT infrastructures will require overhauls in order to facilitate secure, high-quality data integration between research and care; institutional focus is needed to bring patient populations and expertise together; ethical frameworks and approaches for integrating research and care responsibly require further elaboration; clinical procedures and professional responsibilities may need to be adapted in order to accommodate research requirements in clinical processes; and involvement of patients and other stakeholders in design and research priority setting is needed to further the goals of real-world and patient relevance. Integrating research and care in academic medicine in a more systematic fashion offers a promising perspective to current and future patients. In order to live up to these promises, research and care should be integrated more systematically in academic health science, with patients being included as research participants by default. Data and tissue infrastructures and facilities can provide a platform for doing so. At the same time, many issues remain to be settled. New ethical ways and means for protecting and respecting patient-participants in such a double role are also needed in this respect. In this way a deeper transformation is at stake as well: a change towards a setting in which patients fully take center stage in debate and action on the future of biomedicine.

INTRODUCTION

Biomedical research and care have often been approached as distinct, only loosely connected worlds. That approach has served patients, medicine and health care well in many ways. For instance, the approach has helped to protect patients from potential harms associated with participation while facilitating methodologically sound hypothesis-driven research. Currently, however, the approach is often found wanting. Moreover, research participants are only marginally subject to risks of physical burden and harm. Data-driven research efforts do not need to interfere with the provision of individual care, which was the prime ethical rationale for keeping health care and research apart. Research is turning to data-driven methodologies and approaches which draw on high-quality real-world data in health research collected in clinical settings.

Patients play a double role in such approaches: as individuals to be treated and as cases to learn from (1,2). Research focusing on patients' 'data doubles' is associated with different risks and concerns about transparency, rights and informational harm. Tackling such risks does not call for a sharp separation as it does for responsible integration. Advanced data and IT infrastructures make such integration both necessary and possible. How can health care and research be organized in order to serve as a dual engine for treatment and scientific discovery? In our view, patients suffering from rare diseases, along with other 'exceptional' patients, merit particular attention when pursuing integration of research and care. Academic medicine, which often focuses on such patients, should take the lead in developing such integration. Drawing in particular on the Dutch example of the Parelsnoer Institute (PSI), this article outlines the reforms that we believe are needed.

IT INFRASTRUCTURE, HEALTH CARE DATA AND THE INTEGRATION OF RESEARCH AND CARE: INSTITUTIONALIZING THE CONNECTION BETWEEN PERSONALIZED MEDICINE AND THE LEARNING HEALTHCARE SYSTEM

The integration of research and health care plays a central role in contemporary overarching models of biomedicine. In relation to Personalized or Precision Medicine, research and care are considered to be integrated at the level of (small groups of) patients. By adding an experimental dimension to diagnosis and treatment, data-driven innovations could help to differentiate therapeutic regimes to suit more specific patients and patient groups. In visions of learning health care systems, the integration of research and care is understood to be forged at a systemic level, by studying real-world patterns, drawing scientific insights and evidence from these and implementing these in health care practice. In such a model, data-driven innovations are more closely associated with the tools and research approaches of epidemiology. Both perspectives ultimately feed into one another: clinical decision-making relies on epidemiological evidence, while population-level insights can only emerge from carefully crafted standardized data

collection efforts. That being said, good institional and infrastructural arrangements are required in order to enable the translation efforts between both perspectives on health and disease. Academic health care is a crucial site for achieving this, provided that academic health care settings are turned into local learning healthcare systems (1,3).

For integration of research and care into their mission and daily activities, institutions have to be equipped and organized in such a way that uncertainties of biomedical knowledge and interventions pertaining to their patients can be systematically explored. Clinical data, for one, should be collected in ways which allow for further exploration and integration into research databases. Biobanking infrastructure and advanced electronic health record systems collecting comprehensive clinical data and capable of catering to research and care simultaneously should stand at the heart of such integration (4). These infrastructures can help to feed the discovery phase of translational research (for instance by facilitating the search for novel biomarkers), allowing for more systematic and far-reaching exploration of patient needs and how to meet them. Given the need for systematic data integration between research and care, meeting the highest informational privacy and data security standards in such infrastructures is a requisite.

EXAMPLE: THE PARELSNOER INSTITUTE

Many initiatives in which aspects of research and care are integrated are ongoing. One prominent initiative in The Netherlands which could serve as a source of inspiration is the Parelsnoer Institute (PSI). PSI was established in 2007 by the Netherlands Federation of University Medical Centers (NFU) in order to improve diagnosis, prevention and treatment of complex disorders and to facilitate personalized medicine. Here we explain the aspects of PSI that are most relevant. More details are available in a recently published PSI marker paper as well as on the PSI website, where PSI protocols and model regulations are available for download (5,6).

Parelsnoer Institute
Established in 2007
A collaboration involving 8 University Medical Centers and 15 clinical specialties
Prospective collection of biomaterials and data through shared clinical and data standards, information models and SOPs
Data and sample collection integrated into routine health care and electronic health record systems
Patients provide broad consent for use of their samples and data
Overview of available data and samples through https://catalogue.bbmri.nl
For more information, see (5) or http://www.parelsnoer.org/page/en/

PSI provides a national research infrastructure integrated with clinical care procedures, in which clinical researchers from all University Medical Centers (UMCs) collaborate and prospectively collect and store biomaterial such as DNA and serum and associated data from large cohorts of clinically documented patients. It develops and offers ready-to-use harmonized procedures in compliance with recognized national and international standards to ensure uniform collections. Standard operating procedures throughout the phases of the biobanking process are developed and implemented to ensure quality and uniformity of the collections.

Cohorts of disease-specific collections of biomaterials and data, the so-called Pearls, are collectively managed by clinician-researchers in multiple UMCs. Data in each Pearl is set up according to definitions, standards and procedures which are specified in information models drawn up by clinician-researchers according to international standards. The models are closely integrated into Electronic Health Records (EHRs) and routine care procedures, thus minimizing the registration burden.

Patients may benefit directly from such integration. In particular, tailoring standard health care infrastructure to systematically feed into research requires ongoing harmonization of clinical care routines, thus minimizing burden to the patient and making optimal use of the data that are gathered throughout the care process. Moreover, by implementing research protocols, both patient and research quality could benefit. Such harmonization, and the ongoing process of tinkering and reflection on what data to collect in what ways, facilitates collective learning and stimulates the wider adoption of clinical best practice. In this way, patient care stands to become enhanced by research processes themselves – not just by the outcomes of research (7).

The experiences of clinical biobanking infrastructure for research into neurodegenerative diseases within PSI provide a case in point (8,9). The Alzheimer Center of the VU Medical Center, a partner in PSI, holds a strict protocol for patients suspected from Alzheimer disease. During the standard diagnostic workup patients are seen by a medical neurologist, specialized nurses and a neuropsychologist. Team members collect visual and electronic read-outs of the brain (MRI, EEG), draw blood and conduct a lumbar puncture to collect cerebrospinal fluid (CSF). Processing and analysis of MRI images for research into prognostic markers and models for neurodegenerative disease will be automated in the near future, without radiologists having to manually assess and score these images. A standard set of neuropsychological tests is also part of the routine.

The establishment of these novel routines and infrastructures has led to rapid improvements in patient care throughout participating institutions, by stimulating inter-institutional comparison and learning processes for all kind of aspects of clinical procedures, by driving the uptake and diffusion of clinical best practice, as well as by facilitating ongoing comparison and improvement of clinical outcomes. A tangible outcome of such improved care is evidenced by the fact that the diagnostic protocol for PSI is still widely used in most UMCs by participating clinicians (7,8).

INTEGRATING CARE AND RESEARCH: ASPECTS TO CONSIDER

How might opportunities for learning through systematic integration of research and care be reinforced? A first point to consider pertains to the patients on which to focus. For a considerable number of patients, evidence-based standards and treatment options are hardly available (10). This involves particularly patients suffering from rare disorders as well as patients suffering from (multiple) complex diseases and/or diseases which require complex treatment. In many cases, people suffering from rare diseases remain undiagnosed for a long time and need to go through considerable trajectories to receive a proper diagnosis (11). For patients suffering from complex diseases, or from diseases requiring complex treatment, standard-level care will often also prove insufficient.

A particularly close integration of research and care is warranted to improve these patients' predicament. For such patients, receiving effective treatment or clarity on the underlying mechanisms involved in their disease is a puzzle, and providing professional care will often be a matter of trial and error. A full investigative picture of a clinical presentation will likely help patients to receive the best available healthcare. Moreover, these patients' unmet needs are relevant to improve biomedicine: their symptoms might help to raise hypotheses for new studies. By enrolling these patients in clinical trials and other clinical studies, the evidence base could be improved on. Such patients add to the variability and hence to the probability to detect meaningful differences. Furthermore, patients with extreme, contrasting clinical features (such as a very poor or very favourable response to therapy) are likely to yield novel insights into and understanding of basic underlying pathological and biological mechanisms involved in health and disease (12,13). Patients suffering from similar, less pronounced symptoms may also profit from these insights.

Second, focusing in particular on such patients will also involve attending to the institutional focus of academic medicine. Academic health care centres should ideally focus on patients who cannot be treated sufficiently in ordinary clinical care procedures. For these patients in particular, research and care should go together and be designed and organized for combining duties of research and care. Sufficient expertise in specialist centres is a crucial prerequisite in this regard, as is the concentration of care (10). In order to amass sufficient numbers of academic patients and to compare these against other patients suffering from comparable afflictions, such concentration of care and research capacities should also accommodate cross-institutional, national and ideally even transnational aggregation and exchange of data.

Third, integrating research and care also implies attention to clinical procedures and professional responsibilities in order to accommodate research routinely. This involves practical changes, such as adding research nurses permanently to the staff and accommodating research requirements into clinical processes. Moreover, it involves closer partnerships with other academic hospitals and stakeholders in order to be able to conduct cutting-edge research. The collaborations set up through the Parelsnoer Institute are an example of this. During the first visits at the clinical departments, patients are asked to participate and consent to the collection and use through PSI of their clinical and follow-up data, images, residual tissue, as well as

additional biomaterial of particular relevance to the understanding of their disease. As clinical care and clinical research are fully integrated in a natural and standardised way, patients do not have to make additional efforts, nor have to undergo extra burden while participating in research.

PSI provides but one way of pursuing such integration. Patient registries can also facilitate overviews and comparisons of standards of care (14). Moreover, prospective cohort studies such as the Prospective Dutch Colorectal Cancer cohort (PLCRC) may also serve as a model for a cohort infrastructure which can provide clinicians and researchers with baseline data and IT platforms which facilitate further studies and clinical trials (15). For all of these initiatives, maximizing the accessibility and use of such infrastructures by governing them according to FAIR principles of data stewardship is crucial (16,17).

Fourth, principles and practical requirements of research ethics will also need to be updated (18). The paradigm of participant protection stands at the heart of traditional research ethics. This paradigm is associated with risks of physical harm and the issue of therapeutic misconception, when patients unduly consider that research could have direct benefits for their individual predicament. The integration of research and care by data-driven raises different concerns. Risks of informational harm are more prominent in such situations, while research participation may now offer some promise for patients individually as well. Dealing with such concerns requires responsible integration of research and care instead of aiming for separation.

The principle of privacy and data protection by design is particularly important in this regard (19). In the PSI IT infrastructure, data protection was designed into the infrastructure by double encryption and deidentification of data and samples: first when periodically uploading data in encrypted fashion into a central database, and once more before making data and samples available to researchers.

Ethics and oversight systems for a learning health care system are another point for discussion. Such oversight could entail a focus on protecting risks across the board without relying on unwarranted assumptions about inherent differences in risk between research and care (20). The burden of integrating research into care for individual patient-participants should be minimized, with remaining risks and benefits regularly assessed through a combination of ethics review, governance and oversight (21). Emerging guidelines and practices in the area of biobanking also point towards relevant developments (22).

Fifth, patients' dual role as patients and research participants will also require more involvement and new forms of informed consent. Patient-participants should be adequately informed about the sense in which they may and may not stand to benefit about joining and being treated in a programmme for integrated research and care. This includes taking enough time and effort to inform, educate and discuss the kinds of care and research processes they will be and are participating in, enabling them to benefit from and keeping them up-to-date about current scientific state of the art and any relevant developments for them personally (23). Instead of project-specific, consent can be 'broad' by pertaining to research in a particular area or research programme. A crucial component of such broad consent is that it involves consent for governance; consent, that is, to a particular way of managing resources and deciding on proper

use (24,25). Informed consent provided for PSI, a template of which is available on the PSI website, provides an example of this. Novel interfaces which can facilitate online interaction, such as those linked to concepts of dynamic consent, are promising tools in this regard (26,27).

Sixth, efforts to ensure that research agendas in biomedical research cater to urgent medical needs, are also needed. The need for real-world relevance of research in countering problems of research waste also merits a more systematic approach to involvement, monitoring and data collection of patients (28). The experiences in the Parelsnoer Institute suggest that such infrastructures may at the same time provide a more efficient platform for translational research as well (7). Moreover, involvement of patient advocates and organisations could become a standard feature of the research agenda-setting process, protocol design and execution. Given the right circumstances – well-read up patient advocates, sufficient and well-thought out organizational support – patient and public engagement can help to improve the relevance and quality of research tremendously (29,30).

In sum, systematic integration of research and care offers a promising avenue for exceptional patients, provided that a number of conditions are met: data and IT infrastructures will require overhauls in order to facilitate secure, high-quality data integration between research and care; institutional focus is needed to bring patient populations and expertise together; ethical frameworks and approaches for integrating research and care responsibly require further elaboration; clinical procedures and professional responsibilities may need to be adapted in order to accommodate research requirements in clinical processes; and involvement of patients and other stakeholders in design and research priority setting is needed to further the goals of real-world and patient relevance.

CONCLUSION

Integrating research and care in academic medicine in a more systematic fashion offers a promising perspective to both current as well as future patients. In order to live up to these promises, research and care should be integrated more systematically in academic health science, with patients being included as research participants by default. Data and tissue infrastructures and facilities can provide a platform for doing so. At the same time, many issues remain to be settled in joint efforts of all involved, including clinicians, researchers, IT specialists, hospital boards, and patients. New ethical ways and means for protecting and respecting patient-participants in such a double role, such as through new forms of consent, more active attention to feedback of research findings, and more transparent governance arrangements, are also needed in this respect. In this way a deeper transformation is at stake as well: a change towards an environment in which patients fully take center stage in debate and action on the future of biomedicine.

AUTHOR CONTRIBUTIONS

The authors are or have been involved in the development of collaborative clinical biobanking initiatives in The Netherlands in various capacities: as policy advisor (MB),

as scientific director (PS), as manager and coordinator (TL, PM), as patient advocate and board member (CS), as ethics advisor and reviewer (ALB) and as managing director (GZ). The article is based on a review of the literature as well as on their collective experiences – both professional, managerial as well experiences as a patient. The article was inspired by discussions between GZ and MB, who led the drafting of this article. PS, TL, PM, ALB and CS contributed arguments and illustrations and provided feedback.

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5

ANCILLARY CARE OBLIGATIONS FOR SOCIAL MEDIA PLATFORMS

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The digital revolution brought us into the information age. The Internet and social media have rapidly entered our lives, homes, and also health care and biomedical research. As a result, traditional ways of launching and conducting human subject research are supplemented with novel digital strategies. Traditionally, participants are usually recruited for clinical research through a variety of mechanisms, for example, through referral by their treating physician and/or advertisements in hospitals, universities, or newspapers, or in advocacy group publications (1). Such methods are now frequently supplemented, and at times replaced, by online recruitment strategies using social media. Gelinas and colleagues offer useful ethical guidance for investigators and research ethics committees (institutional review boards, IRBs) faced with recruitment of research participants through social media (2). In doing so, they focus on the traditional parties involved with recruitment of participants for research: researchers, clinicians, and members of IRBs. However, in the digital age these make up only a part of the parties involved in research and participant recruitment. Moreover, social media are frequently more than just recruitment tools: They serve as "platforms" on and through which research is conducted and data are collected. Therefore, platforms themselves, and the companies and organizations operating them, also have ethical obligations relating to recruitment.

Here, we first argue that social media platforms themselves—and the companies and organizations running them—should have ancillary care obligations similar to researchers and research institutions. Second, we discuss the ethical implications for, among others, informed consent, the terms of agreement, and privacy policies.

ANCILLARY CARE OBLIGATIONS IN RESEARCH INVOLVING SOCIAL MEDIA

A wide array of care obligations exists in health care, not limited to only health care professionals. Also, medical researchers have moral obligations, among which are ancillary care obligations toward research participants (3). Ancillary care in this context means that participation in research involves at least a partial, even if tacit, entrustment of health to the researchers. The fact that a research project may not be therapeutic and is aimed at other goals, such as generating scientific knowledge, does not preclude other responsibilities toward participants (4). For example, in genomics research, the duty to offer research findings obtained by next generation sequencing (NGS), among which are whole exome sequencing and genome sequencing, is based in part on ancillary care obligations (4).

Historically, clinical research was conducted in the context of the doctor–patient relationship (1). However, all kinds of research will now continue to grow outside the traditional medical domain. For instance, Eric Topol expects that the smartphone will herald the "Gutenberg" of modern health care. Gutenberg's invention of the printing press emancipated people from dependency on the priestly classes, whereas the smartphone will emancipate people from their dependency on medical doctors, Topol argues (5). By means of their smartphone or tablet, people can get rapid test results,

receive a diagnosis without seeing a doctor, or participate in research without ever coming into a clinical care setting.

The rise of eHealth, here loosely defined as an umbrella term for the application of information and communication technology in health care, requires us to rethink research ethics. One major implication is that we should broaden bioethical thinking beyond the traditional doctor–patient or researcher–patient model to include nontraditional health care providers, companies not directly involved in health care, and different settings. Fiduciary relations, after all, are defined by whether one is entrusted with someone's interests such as their health or personal information, which is not necessarily restricted to the medical domain. Social media platforms are replete with companies offering health-related data applications and are increasingly used as online recruitment tools. Why then would social media and the companies and organizations operating them be excluded from ethical consideration? As the context for research increasingly shifts online, so should our considerations of the contextual norms relevant to research (6).

Gelinas and colleagues provide a valuable contribution to this shift. Still, they conceptualize social media primarily as a "tool" employed by researchers. However, social media are more than just tools serving as intermediaries in communication. Instead, these serve as platforms on and through which all kinds of data get generated, collected, and processed and that make up new social fabrics (7). It will therefore not always be possible to demarcate the use made of social media in recruitment from questions about research uses of social media more generally. In consequence, ethical obligations should also be extended to social media platforms' mode of operation, for at least three reasons. First, in order to live up to their ethical obligations, researchers making use of social media for recruitment of and communication with participants will become dependent on these platforms. Second, the very companies and organizations affiliated with and operating social media platforms (among which are Facebook, Google, and Apple) may also engage with and recruit participants for research. Third, conducting research may be an integral component of social media platforms and the data collected on and through these. These reasons require us to also consider the reasonable expectations that people making use of social media may have about research as part of engaging in social media activity. Moreover, these point toward the ancillary obligations of social media platforms themselves toward their users with respect to research. It therefore does not suffice to point out, as Gelinas and colleagues do, that possible side effects of research recruitment from online tracking are simply part and parcel of the "background risks associated with social media use," as addressed in platforms' "terms of use." Questions about moral obligations pertaining to research recruitment in social media are therefore closely intertwined with questions about moral obligations of social media platforms themselves.

BIOETHICS IN THE INFORMATION AGE

What moral obligations pertain to research recruitment considered in this broader sense? How might such obligations be fulfilled? A comprehensive answer to these questions is

beyond the scope of this response. Instead, we touch on the implications in three key areas: informed consent, terms of agreement, and privacy policies.

Many of the moral obligations of social media platforms and the actors operating on and through them would encompass informational obligations. Here we arrive at a difficulty. After all, it is rightly the traditional model of providing information and obtaining consent, that is, informed consent, that is challenged in Big Data decision making. This is clearly illustrated in consent policies for next generation sequencing (NGS) technologies, which are currently already offered offline and online as a service. NGS has the promise to personalize treatment for patients in many fields, but it may generate not only information relevant for the disease in question but also a wide variety of potential other findings. Most if not all patients will have difficulties making a reasonable selection out of the wide array of potential genetic findings. After all, the quantity, ambiguity, and significance of the genetic data generated by NGS will make any reasonable choice beforehand highly complex (7). We have therefore proposed to work with a default system, where specific sets of genetic information are prestructured in packages (8). Insights from behavioral economy and decision-making theory have shown the limits of ever-expanding choice, resulting in information overload rather than autonomous decision making. Offering patients the possibility to decide about any potential variant might result in what has been called the paradox of choice: "having no choice makes us unhappy, having some choice makes us happy, having too much choice makes us downright unhappy" (7,9). Similarly, people will have difficulties understanding the terms of agreement and privacy policy when recruited online via, for example, Facebook or Twitter. It is all too easy to press the "I agree" button while installing an app or using an online service. Terms of agreement, containing the privacy policy and other important conditions, currently are often lengthy and incomprehensible. Participants recruited through social media should be made as aware about what they are consenting to as participants recruited through more traditional channels. Moreover, recruitment in traditional research ethics requirements should meet all kinds of standards, such as adequate privacy protection, and advertisements should not be misleading or too touting (1). In addition, social media platforms arguably have additional responsibilities regarding, for example, data protection, internal ethics reviews, and oversight mechanisms.

In sum, as the context for research increasingly shifts online, so should bioethics shift along. This requires a broader analysis of the ethical dimensions of research participation on and through social media and the ethical obligations of the companies and organizations running them. Social media are more than just tools serving as intermediaries in communication. They are part of the social fabric of the world in which we live in the information age.

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A SOCIO-ETHICAL EXPLORATION OF THE RIGHT TO DATA PORTABILITY IN HEALTH RESEARCH

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ABSTRACT

The right to data portability has recently emerged as a significant addition to normative frameworks for data control, most prominently the European General Data Protection Regulation. Potentially, it could have individuals take up the role of data custodians, a role which could ultimately also change the ways in which control over data is organised and governed. However, the ramifications of data portability in health research remain to be explored. This article provides a brief analysis of the key ethical and social dimensions of data portability and qualifications, and discusses the ways in which data portability is likely to impact on health research and the opportunities, risks and uncertainties associated with this in a number of areas.

Data portability offers a number of opportunities to data subjects, research data stewardship, as well as participant-driven research initiatives and competitive health data platforms. At the same time, within the context of health data and health research, it could have disempowering effects as well. Data portability could be developed further in responsible ways, by strengthening safeguards to protect individuals against the associated risks of enhanced data access and exchange. Moreover, data portability could help bring recognition to the ways in which research participants, health researchers, health care providers and other data controllers are both co-producers as well as users of health data, thereby stimulating responsible data sharing and collaborative research.

INTRODUCTION

Access to and control of personal data in health research is a major topic of ethical and social concern. Drives to aggregate, recombine and share data on an unprecedented scale run into deep-running tensions with individuals' rights to privacy and data protection. The right to data portability (from here on refered to in short as data portability), introduced most prominently in the European General Data Protection Regulation (GDPR) and also being taken up in other areas of European and US law and policy (1), has recently emerged as a significant addition to normative frameworks for data control. Potentially, data portability could have individuals take up the role of 'data distribution hubs' (2); a role which could ultimately also change the ways in which control over data is organised and governed. Throughout the United Stated and Europe, initiatives are underway to implement the principle in personal health data and health care, in initiatives such as the US Blue Button initiative (3), the Dutch standard-setting initiative for personal health environments MedMij, and similar projects elsewhere such as the French Mes Données Ma Santé (4).

However, the ramifications of data portability in health research remain to be explored further. What effects will this novel right have on the role that data subjects play in health research? And what could be the wider impact of the emergence of data portability on the conduct and governance of health research and data stewardship? In order to contribute to a better understanding of the potential opened up by data portability, this article aims to analyse and evaluate the meaning and impact of data portability for health research from a socio-ethical perspective. First, we provide a brief analysis of the key ethical and social dimensions of data portability and qualifications. Second, we discuss the ways in which data portability is likely to impact on health research and the opportunities, risks and uncertainties associated with this in a number of areas: in relation to data subjects; health research and data stewardship, participant-driven research, and competition between data controllers.

DATA PORTABILITY: A SHORT ANALYSIS

Data portability emerged in the early 2000s as a technical term in relation to data transfer in general between online and cloud computing services. Google's Take Out service provides a familiar example of data portability in action, allowing Google users to download an archived copy of some of their personal data, such as search history or a copy of one's Gmail data. Data portability involves more than just copies of data though: data also needs to be useable using other software or platforms. Common data standards which allow for interoperability of services (such as the .eml format for mail and .ics format for agendas) are crucial prerequisites for this.

From 2009 onwards, data portability was introduced in European legal and policy discourse. Although the right turned out to be controversial during political negotiations over the GDPR, data portability eventually came out of the negotiations as a distinct right,

supplementing other individual rights such as the right to access, the right to be forgotten and the right to erasure.

In parallel, considerations related to regulating competition between online data-driven service providers and the ability for consumers to switch between them were also at play in other policy discussions (5). Data portability thereby became a concept at the intersection of a number of fields of law (6). The concept finds a normative underpinning both as an individual right and in part as a principle for data governance.

AN INDIVIDUAL RIGHT

Understood as an individual right, data portability is frequently considered as an extension of the right to access to one's personal data. The right to access is a well-established right linked to obligations of transparency and other individual control rights. Data portability arguably extends this right in two ways. First, data portability also provides data subjects with a positive right to re-use one's personal data, and a corresponding obligation on the part of controllers to facilitate re-use by adopting standard data formats. Second, the right can be exercised by data subjects to redistribute their personal data seamlessly to others, either by him- or herself or by putting in a request to do so with the data controller. In this way data portability also protects individuals against appropriation of their data by data controllers. Data portability thereby reflects underlying normative shifts in the area of data protection: active and positive rights to informational self-determination (i.e. rights providing data subjects with a capacity to actively shape their lives in and through control over their own data) receive more emphasis, in contrast to traditional understandings of rights to privacy in which individual rights are predominantly understood as negative rights and obligations protecting data subjects from particular forms of interference (2,7).

A PRINCIPLE OF GOVERNANCE

Data portability is also framed as a principle of personal data governance. Considered in this way, the principle links up to overarching policy objectives of stimulating access and the free flow of data between digital services in the European Commission Digital Single Market strategy as well as associated proposals for a new EU digital content directive (1). This dimension of data portability is associated with risks of so-called vendor or platform lock-in: services designed or operating in such a way so as to make switching to alternative service providers highly impractical. Data portability was also coined as a remedy against such dependencies, both to facilitate consumer freedom as well as a means to lower the barriers to competition between data services. Data portability is thereby as much about making data mobile – as in portable – as it is about transfering data from one party or controller to another – as in porting the data.

Considered as a remedy against vendor or platform lock-in, data portability turns personal data into a good which should be made more readily exchangeable between data controllers, particularly between those conducting similar activities. Personal data will

thereby become a more accessible and exchangeable good, which is in a sense less private, in part to foster competition. Data portability differs in this respect from classic rights to data protection and privacy as well: instead of protecting individual rights, data portability rights are also mobilised to shape socio-economic affairs.

QUALIFICATIONS

A number of qualifications are relevant in applying data portability and in determining exactly what data should be made portable. The codification of the right under the General Data Protection Regulation, and the ongoing legal debates over its scope of application, the kinds of data to be made portable, as well as the kinds of formats to be used in the process, are instructive in this regard (8).

First of all, the right to data portability only applies to data 'provided by' data subjects, not to all personal data. The Article 29 Working Party, the main European data protection advisory body in which data protection authorities of each EU Member State are represented, proposed a clarification by drawing a contrast between data '"provided" by the data subject by virtue of the use of the service or the device', and 'inferred and derived' data 'generated by a service provider' on the other. The argument for singling out a subset of personal data for portability rights seems to be that data controllers are co-producers of data as well, and thereby also partially entitled to some control and consideration of rights and interests over the personal data that they helped generate. However, the article 29 Working Party recommendations offer only limited clues as to how to balance these claims in a way which violates neither data subjects' rights nor commercial interests (9). The demarcation is further complicated by the fact that data is never simply provided by data subjects themselves, but always mediated by standards, tools, methods and techniques (10): from tests and probes performed by support staff and medical specialists (e.g. the administration of questionnaires), through lab tests ranging from run-of-the-mill cholesterol tests to highly advanced genetic sequencing, to data generated by (usually proprietary) wearable devices. Until a legal consensus emerges, considerable legal uncertainty will remain.

Second, the GDPR excludes 'controllers processing personal data in the exercise of their public duties' from the scope of application of data portability (GDPR, recital 68). A principled defence of this limited scope of application could be that data portability should be understood as a right applying only in private economic affairs, the exercise of which will often be overridden by considerations of public interest. Such a limitation would be similar to the research exemptions provided for processing personal data in public health registries, which are exempted in the GDPR from some requirements such as informed consent because of the the need to collect comprehensive population-level data as a prerequisite for insights into public health as well as the 'knowledge of great value' at the level of populations they help produce (recital 157). It could also be argued in more practical terms that data portability aims at safeguarding freedom of choice and diversity in providers in a way which would undermine the maintenance of some public services, or which at least make it so that data portability should not be prioritised in such cases.

Finally, particularly in a health context, data portability, like other individual rights, could be qualified by overriding professional obligations such as professional secrecy in a medical context, and by the fact that one person's personal data may also be relevant or even relates to other individuals. Genealogical and genetic data, relating as it does not just to persons individually but also to their family, is the most obvious case in point.

Underlying these legal and definitional struggles are normative and conceptual debates about the status of personal data: personal data is never just personal, since individual rights go hand in hand with claims and entitlements of other parties over that very same data by virtue of their interests and involvement in how and for what purposes data is generated, processed and used. This makes a socio-ethical exploration of potential concerns and opportunities all the more relevant. These numerous qualifications and uncertainties about the legal scope and meaning of data portability make it clear that the meaning of this new right still needs to be established through legal debate, strategic positioning and practical learning. It remains to be seen whether a 'minimalist' approach to data portability with limited scope of application and potential for use will prevail, or an 'empowering' approach to data portability in which the right can be applied widely so as to equip data subjects with more opportunities for control (6).

EXPLORING THE SOCIO-ETHICAL IMPACT OF DATA PORTABILITY IN HEALTH RESEARCH

How might data portability impact on data subjects and the conduct and governance of health research? This section explores the socio-ethical impact the principle may have in a number of key areas.

IMPACTS ON DATA SUBJECTS

Data portability could facilitate a move towards providing individuals with rights to acquire their personal data in interoperable and reusable form. This could make for an enhancement of existing individual access rights, particularly for research participants interested in exploring their personal data for themselves, such as in cases where participants can request with their raw genomic sequencing data. Moreover, research participants could play a role as individual data custodians as well. Guidance about how genomics data might be provided responsibly to individual participants is currently emerging (11). Participants share such data for various reasons: because they want to learn more about themselves, but also because they want to contribute to the advancement of medical research (12).

Whether data portability will apply to genomics research under the GDPR is as yet unclear: although participants actively provide DNA samples to research, genomic data is only generated after sample collection using sequencing technologies. Moreover, providing participants with their data raises questions over whether and to what extent providing data also entails an obligation to provide proper interpretation and counseling along with that data (11). The relationship between personal responsibilities and professional obligations

with respect to data control will need to be revisited once citizens and research participants become data custodians of their own. The setting in which such data is generated arguably makes a difference here as well: for research conducted in a health care setting involving patient-physician relationships as well arguably involve obligations to provide medical interpretation along with data; this may be less so in other settings in which research participation is detached from health care.

Furthermore, turning individuals into data custodians of their own also raises the level of personal responsibility involved (13). Public expectations about genomics research may not match with expert opinions about the current state of such research, with potentially inaccurate data of uncertain relevance (11). The question then is how individuals can be equiped to exercise this responsibility wisely and effectively. For instance, contrary to health professionals, patients and citizens do not operate under obligations of professional secrecy, and so cannot appeal to the same legal protections, and such obligations may not even fully apply in all jurisdictions to health researchers. Data portability may aggravate such issues. A right to personal patient secrecy, in analogy with professional secrecy obligations, could help counter this issue (14).

IMPACTS ON RESEARCH AND DATA STEWARDSHIP

Data portability could offer opportunities to research, by providing novel means for bringing more and more diverse data from individual participants together. For instance, data portability could help stimulate the uptake of FAIR data stewardship principles. The FAIR guiding principles for research data stewardship, with FAIR standing for Findability, Accessibility, Interoperability and Reusability, are currently emerging as a key way to implement and give substance to the vision of Open Science in European public research data stewardship (15). Implementing FAIR data stewardship could be considered a prerequisite for enacting data portability, since interoperable data standards and clear access and reuse policies are crucial for both. This is relevant among other situations to data portability for apps, wearables and other digital health devices, for instance to facilitate self-diagnosis and behavioural interventions. Data portability could even help facilitate independent evaluation of such devices without the express collaboration of their manufacturers, thereby short-cutting issues of data access similar to those in pharmaceutical research. This could even help address potential concerns about reliability and usefulness of self-monitoring devices (16).

Again, it is unclear whether these promises will actually be realised. Data portability as defined under the GDPR prescribes that data should be made available in 'commonly used' formats. This falls short of an obligation to invest in developing interoperable formats where they aren't available. Also, like with digital health, the FAIR principles raise ethical concerns of their own relating to data access, scientific and data quality and personal rights which remain to be addressed (17). Facilitating easier access to data from digital health devices for research purposes would make addressing concerns such as those related to data security, disclosure and consent more urgent as well (18).

IMPACTS ON PATIENT- AND PARTICIPANT-DRIVEN RESEARCH

Data portability also offers opportunities for democratising the governance and stewardship of data for health research. Participants could team up (and be teamed up) together to redistribute and control their data collectively in cooperative organisations distinct from those traditionally associated with health research, such as health care providers and health research institutions (19). Potentially, data portability could thereby drive new ways of citizen-led data science, for instance by facilitating patient organisations in mobilising their constituencies to participate and contribute data to health research (20). Patient organisations relating to rare diseases may be leading the way in this (21). Also, patients could pro-actively express their will to contribute to health research through data deposits and ask, for example, for moving data from specific studies to established and well-used research databases.

Whether the right can actively be used as a break-iron for mobilising participant data in this way depends on many factors. For instance, patient organisations will need to find ways to mobilise patient and participant constituencies effectively, all the while taking into account questions over the representativeness, interoperability and quality of data amassed. Moreover, regulatory frameworks may need to be adapted to participant-driven health research so as to facilitate responsible research practice (22). Data portability rights on their own are unlikely to tackle the barriers in these areas.

IMPACTS ON COMPETITION OVER PERSONAL DATA

Finally, by facilitating access to and exchange of data between data controllers, data portability could also stimulate competition among them. Data portability offers health data platforms novel opportunities to port data by enticing and seeking consent with participants, without having to deal with similar or competing providers directly. Such enhanced competition over data could also extend to commercial platforms facilitating health research such as PatientsLikeMe (23). Enhanced competition between platforms could in principle stimulate innovation and quality of service provision as platforms improve quality to gain competitive advantages and unsuccessful platforms close down. The benefits to health research might eventually 'trickle down'.

However, whether health research on the whole stands to benefit from such competition is uncertain at best. Stimulating competition in data stewardship for research purposes would seem to go against the collaborative ethos of open science (24). Community resources such as data repositories, genome databases and public health registries, often rely on shared access and use rules for their functioning and upkeep (25). Large commercial parties will be financially more capable of enticing individuals to port data to attractive commercial platforms, which would eventually be to the detriment of possibilities for public control over health data and research priorities, similar to the concerns over monopolisation of social media and search platforms (26). Finally, easier access to and exchange of data between providers also brings with it risks of enhanced privacy and security breaches (27).

CONCLUSION

Data portability is a promising novel concept in organising rights and responsibilities over personal health data. Through data portability, data subjects could take on a role in redistributing their personal data between controllers. Potentially, individuals' role in regulating and providing personal health data access could greatly increase, changing the ways in which control over data is organised and governed.

Data portability offers and stimulates a number of opportunities to data subjects, research data stewardship, as well as participant-driven research initiatives and competitive health data platforms. At the same time, data portability may create and aggravate a number of risks. The confidentiality and security of personal data could be undermined. And personal custodianship over one's own data also increases the level of individual responsibility involved, with individuals facing additional privacy and confidentiality risks. And although data portability could stimulate the uptake of FAIR research data stewardship principles and could open up avenues for cooperative data management, competition between data controllers could also undermine the possibilities for collaborative health research. Many of the promises and pitfalls associated with data portability are uncertain, as are the specific legal ramifications of the right as it has recently been codified under the GDPR. Within the context of health data and health research, data portability may not just be adopted through a 'minimalist' or 'empowering' approach: it could very well have disempowering effects as well.

That being said, there are several directions in which data portability could be developed further in responsible ways. First, given that data portability will stimulate the circulation of personal data, more appropriate legal and technical safeguards to protect individuals against such associated risks would seem to be in order. Moreover, efforts to equip and empower data subjects to exercise the rights in relevant ways should be stimulated, as should the development of strengthened protections against third party-induced abuse of data subjects' vulnerabilities when querying data subjects for personal data about themselves.

Second, given the collaborative nature of scientific research, the model of market-driven data competition from which the concept of data portability emerged seems too limited in this context. Data portability could be explored further as a stimulus to responsible data sharing, high-quality data stewardship and collaborative research. Instead of conceiving data portability primarily as a means of taking data elsewhere, it could also be mobilised as a way of opening up data and of bringing otherwise disparate data sets together. In this way, data portability could help bring recognition to the various ways in which research participants, health researchers, health care providers and other data controllers are both co-producers as well as users of health data in health research. Data portability could thereby be mobilised as a stimulus to set up new collective governance arrangements for data stewardship.

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DONORS AS PARTNERS: INVOLVING PATIENTS AND PUBLICS IN THE GOVERNANCE OF BIOBANKS AND REGISTRIES

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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. Multiple questions need to 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.

Participation in biobanks and biobank research is not an isolated topic. Linked issues include the pursuit of a positive relationship of biobanks with patients, donors and the public, and an emphasis on the ethical and societal issues 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 a participation strategy for itself. The starting point for a strategy is the idea that relevant publics (directly or indirectly) are involved or have a say in decisions on issues that are relevant to them. Deciding on such a strategy begins with an exploration of potential concerns 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.

WHAT ISSUES ARE RELEVANT TO THE BIOBANK, PATIENT REGISTRY OR BIOBANK RESEARCH?

Three themes are of interest here:

Research:

- Are research priorities related to the priorities 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?

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?

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?

ARE THE OPINIONS OF RELEVANT PUBLICS 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 important:

- 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.
- What opportunities are available to build on participation initiatives elsewhere in the research process? 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 publics. Recommendations for the various types of biobanks are therefore developed in the guideline:

- 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 public. 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 public, 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. More far-reaching forms are not necessarily better. The most appropriate form will vary per biobank and depend on several factors:

- What level of participation (in decision making, contribution of ideas, cooperation) is most appropriate? Should participation be structural or incidental?
- Which public should be involved? How can this group be best represented, given the required input and the availability of representatives?
- How can participation initiatives be integrated into general decision making in terms of timing and responsibility?
- 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:

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

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 need to consent to donation their tissue and data.

However, 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: by granting them 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 widely considered to be important. For instance, the 'Code Goed Gebruik', the Dutch code of conduct for responsible use of tissue, drawn up in collaboration with patient organizations for the ethical handling of biospecimens for scientific research, endorses it as well: 'Donors and/or patient organizations should be involved as much as possible in the management of and research with biospecimens' (1).

However, according to a survey of members of BBMRI-NL biobanks, participation is still limited in practice. Only 11 out of 73 respondents (from a total of 144 BBMRI-affiliated biobanks contacted) 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 in a neutral or even 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 show that these reservations are unnecessary. Participation is indeed substantively and strategically important for biobanks and biobank research. That is more than simply a claim. Many examples show that the involvement of donors in management is helpful for biobanks and registries. Biobanks should devote attention to participation. That being said, 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 (abridged) 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 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. The full guideline can be downloaded through BBMRI-NL.

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 appropriate 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 may aid the choice and development of the research goals facilitated by biobanks and patient registries. It may also aid choices related to the collection and management of biospecimens and data, the conditions under which donors participate and how biospecimens and data are used. In doing so, different

organizations and researchers will focus on different publics: 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, is seems obvious that end-users should be involved in the formulation of objectives and study design at an early stage (2).

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. Patient organizations have even argued for a right to innovation, the right to contribute to improving the outlook for patients in their particular field (3). Patient organizations are often a driver of research, for example by actively raising and distributing funds, by stimulating cooperation between researchers, or even by setting up their own biobanks (4).

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 (5,6). Biobanks can profit from the participation initiatives in research programs: examples include the involvement of patient organizations in research on rare diseases, and specifically the role of the Dutch CF Foundation in the Dutch CF registry.

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 financial supporters 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 (7).

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 (2). Patient experience can also assist in the operationalization of research, an example of which is patient input in research regarding appropriate outcome measures and effective, less invasive ways to collect biospecimens and data (8).

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 (9,10). 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 and the Dutch Cancer Registry (11).

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 enrollment. 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 regularly oppose researchers and patient organizations in these discussions (12–14). Donors often attach importance to matters other than those expected by many 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 (15,16).

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 (15–17). 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 may be less intrusive than a clinical trial, but far more enduring. Balancing the relationship between biobanks and donors is therefore an ongoing concern. Where the governance of clinical research focuses on control up front, the emphasis of biobanks is more focused on governance frameworks, the supply of regular updates to participants, and co-management – which should not detract from participants' individual opportunities for consent, however (1,18). Co-management of donors of blood supplies, of clients at care institutions, and of employees in companies already have a legal basis. Similar models can be advocated for biobanks.

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 personal expectations, needs and sensitivities that are involved in donation. 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 (19).

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 plans or informational activities developed by biobanks.

BIOBANKS AND PUBLIC SUPPORT

Biobanks ultimately depend on public support: not only in terms of 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 (12–14,20). 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 (21,22).

Compared with other sectors of society, trust in medical research and biobanks is relatively high, especially in the Netherlands (20,23,24). However, public support for biobanks cannot be taken for granted and many people are unfamiliar with biobanks and their activities, evinced by the discussions that have taken place in several countries regarding the use of blood spot cards for research (25). 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 (26). The participation of diverse publics plays an important role.

There are at least two 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 may help to address public and policy discussion of biobanks and allows biobanks to anticipate new concerns, challenges and sensitivities amongst the public (26).

Secondly, care and concern for public support and the interests of patients and donors can help biobanks obtain research funding and policy support. Participation can also create legitimacy for decision making and may thus offer strategic advantages during discussions with policymakers.

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 potential concerns of the various publics 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 factored into policies regarding the procurement and management of data and biospecimens more broadly. Speak to partners (clinicians, 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 need to 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 will always be topical for all organizations 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. Participation runs the risk of becoming meaningless if the space to contribute or influence decisions is lacking. 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 means 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 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 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 - 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 in 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 emphasise 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 often do not carry out research, they are usually associated with healthcare institutions; via this route, they 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.

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 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 (20,23,24,27). Efficiency, effectiveness and questions about what form of

participation best serves the interests of the relevant public are also relevant (28–30). The choice of a particular form of participation can best be tailored to the kind of result and appropriate form of influence of a particular public which is desired, 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 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 research with tangible results in the short term. They will therefore sometimes need to be convinced of the importance of intensive involvement in research 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.

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 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 can be found at UK Biobank, Mayo Clinic Biobank and the Wales Cancer Bank.

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 Dutch Code of Conduct for biobanking mentioned previously recommends, for example, that residual tissue biobanks send an annual report to the patient advisory council of their associated institution (1). 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 puts this form of participation into practice (11).

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. 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.

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 (31). 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 social-scientific projects in their own right (20,26), but there are also variants that are more accessible and easier to establish (5). Expertise in the field of social science research into the life sciences (ELSI) is widely available in the Netherlands. Several variations on focus groups played a role in the design of UK Biobank, BC BioLibrary and Mayo Clinic Biobank (32–34).

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.

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 (35). 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 (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 out to 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.

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 provides public accountability, and at the Mayo Clinic Biobank 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 imrpovements, 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 public at issue 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 participation initiatives and their outcomes are embedded in further 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 the full guideline. A general resource for background information on the theory and practice of participation is the site Participatiekompas.

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 provides an overview of the various forms of participation.

Form of participation	Suitable for	Level of participation	Variants	How hard to realize?	Points of attention
Involvement of patient organization in governance	Research and infrastructure in areas with organized patient community	Co-decision-making	Direct involvement or at some distance as advisor or supervisor	Fairly simple	Settling extent of involvement, expertise of patient organizations
Advisory council	Biobanks with strategic and practical issues w.r.t. the perspectives of donors or patients	Extensive advice	Patient and/ or Community Advisory Boards	Relatively extensive support needed	Long-term commitment of biobanks, clear mandate
Limited co-management	Particularly institutional biobanks and biobanks for residual use	Consultation, advice, co-decision making	Different kinds of patient or hospital councils	Relatively simple	Councils' background knowledge of biobanking and research
Patient knowledge	Clinical biobanks and biobanking research	Co-decision-making, advisory role	Research prioritization, collaboration over design and set-up, practical consultation	Varying	Training patient partners, willingness of researchers to engage in dialogue
Focus groups	Biobanks and research in need of systematic exploration of perspectives of donors and patients	Limited and extended advice	Simple group interviews, social-scientific research projects	Varying	Timing, budget, organization
Consultation rounds	In case of need for review or feedback on specific proposals	Limited advice	Small-scale forms (focus groups), large-scale surveys	Varying	Timing, budget, organization
Online engagement	Online forms of all the above	Limited and extended advice	See above	Varying	Timing, budget, organization

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 Goed Gebruik' goes into more detail on these aspects (1).

Online forms of communication such as local patient sites and communities (and the BBMRI-developed MyBiobank app) can also be used. Some biobanks and patient registries, one example being the Dutch Twin Register, have already implemented these approaches (36).

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.

ELSI RESEARCH

Many of the questions that are central to participation initiatives relate to the ethical and societal issues of biobanks and biobank research. These questions are the subject of so-called ELSI research (37). 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, ELSI research often acts as an extension of participation. Because medical ethicists and social scientists may 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.

ELSI 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 ELSI 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 the BBMRI.

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 will 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 indispensible 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 the BBMRI, 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 and EURORDIS 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.

BACKGROUND TO THE DRAFTING OF THE GUIDELINE

This guideline was prepared in the context of the BBMRI-Rainbow Project 6: Towards a joint strategy for the return of results and optimal communication with biobank donors, and more specifically from 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 (to 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, involving:

- 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 Pulmonary Fund (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. Those 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 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

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8

GENERAL DISCUSSION

INTRODUCTION

Health research infrastructures for personalized medicine aimed at the collection, curation, storage, management and distribution of personal data and tissue samples raise multiple ethical challenges. Focusing on clinical biobanking infrastructure, this thesis analyzed the emerging ethical challenges raised by health research infrastructures. The main aims to be addressed in the thesis were:

1. To identify and ethically evaluate efforts to improve data stewardship
2. To identify and ethically evaluate the ethical challenges and opportunities of integrating health research infrastructures into health care
3. To identify and ethically evaluate novel models and instruments for actively engaging participants through health research infrastructures

The following sections summarize the main findings for each chapter and will discuss general insights and ways forward for research ethics that can be derived from these.

THE ETHICS OF RESEARCH DATA STEWARDSHIP

MAIN FINDINGS

The FAIR guiding principles for research data stewardship discussed in chapter 2 look set to become a cornerstone of research in the life sciences. The FAIR principles, with FAIR standing for Findability, Accessibility, Interoperability, and Reusability, stress crucial preconditions for data sharing, urging researchers to take the possibility of subsequent data sharing and reuse into account from the outset. However, a number of conditions will need to be met in order to apply these principles responsibly. First of all, fair and impartial data sharing and reuse policies are needed to make data 'as open as possible, as closed as necessary'. Second, along with FAIR data and metadata standards, responsible data science will also require additional checks on research quality and integrity. Third, privacy and data protection should be taken on board 'by design', at every stage of the research cycle, hand in hand with efforts to help foster accountability, trust and participation in governance. Fourth, better models for valuing and providing credit for data sharing are needed.

Drawing on a case study of the Dutch Parelsnoer Institute, Chapter 3 discussed how new forms of ethics review for clinical biobanking have emerged. Over time, ethics review boards (ERBs) developed a basic regulatory approach to review biobanking initiatives analogous to the norms and procedures familiar from review of human subjects research. This approach requires review of collection protocols, governance arrangements and monitoring of actual use. In practice, however, considerable leeway remains in the manner in which clinical biobanking initiatives are governed. Chapter 4 argues that ethical oversight can help to assess risks for participants across the board. The principles of privacy and data protection

by design are particularly important for realizing these objectives.

Chapter 3 also discussed debates on reforming consent models and procedures. Informed consent is widely considered to require reform in the context of health research infrastructures. The challenge is to come up with forms of informed consent which respect participants' autonomy while also taking into account that tissue and data are supposed to contribute to research as a public good made in solidarity with others. For clinical biobanking, broad consent for research into a wide but circumscribed and ethically approved area of health research emerged as the de facto standard. Chapter 4 argued that broad consent is acceptable, conditional on governance measures that ensure that actual studies are in line with the original scope of consent and cater to urgent medical needs. Patient and public engagement, an aspect of governance discussed in detail in chapter 7, can contribute to achieving this.

The right to data portability discussed in chapter 6 provides participants with new rights to control and transfer their data in more usable forms, thereby offering opportunities to data subjects, FAIR research data stewardship and participant-driven research. Moreover, data portability could help circumvent issues of data access in commercial settings for research purposes and stimulate competition between different data controllers, including health research infrastructures in similar domains. At the same time, it is questionable whether data portability aimed at stimulating competition between controllers will always benefit collaborative health research. Moreover, data portability could aggravate concerns related to data security, disclosure and consent.

WAYS FORWARD

The facilitation of open-ended, distributed use of data for multiple research purposes is at the heart of many of the ethical challenges associated with data stewardship. Health research infrastructures violate the moral and legal principle of purpose limitation. This thesis provides arguments for reframing this principle for application in a data-driven research context without abandoning it altogether. A revised understanding of purpose limitation should take into account that health research infrastructures can serve multiple purposes which can change and only emerge specifically over time, without losing sight of the need to hold data stewardship practices to account. Part of the solution will reside in shifting regulatory and ethical focus to ex ante checks on data analysis and use (1). However, given that research infrastructure involve design choices and need to be governed with an eye towards long-term operation, differently aimed and timed measures are at stake as well. Three dimensions emerging from the studies in this thesis are important in the development of a life cycle of research data stewardship and infrastructures:

- Specification of purposes, through review of design choices, informed consent and rationales for integration of research and care;
- Demarcation of purposes, through appropriate safeguards for privacy, data protection and integration of research and care;
- Evaluation and adjustment of purposes, through participation and governance arrangements.

Further work in research ethics could focus on developing such a revised conception of purpose limitation, and use it to develop differential access regimes for various kinds of health research infrastructures.

A revised conception of purpose limitation is also relevant for the general direction of data stewardship for open science. The general discourse surrounding open science tends to equate openness with data sharing. The FAIR principles for data stewardship provide an important qualification to this. However, as discussed in chapter 2, these principles do not specify which regimes for data access and sharing should be considered legitimate. Taking the arguments in this thesis one step further, 'openness' could be reframed as a thick ideal involving interconnected practical, technical and scientific, as well as ethical, legal, political and economic considerations (2). This would entail a shift away from an ideal of openness as maximized data sharing towards a conception which explicitly takes societal and health needs and sustainability of infrastructures into account.

Ethical guidance is also needed to translate and update basic principles of privacy and data protection for the context of data-intensive health research infrastructure, especially against the legal backdrop of the European General Data Protection Regulation (GDPR). Scientific research can appeal to a number of exemptions under the GDPR, but a general justification for how privacy norms should be understood in the context of scientific (health) research seems absent from the regulation. For many basic legal concepts and principles such as data protection by design and default, data minimization and pseudonymization, guidance about how these should be understood and applied in the context of health research infrastructures could be developed further (3,4).

The commercialization of health research data is another important area for further ethics work (5). For health research infrastructures, the marketization of health data and the role played by big data and technology companies therein should be a topic of particular ethical concern. Ethics research could help devise principles and practical arrangements for governance and regulation aimed at facilitating private entrepreneurship while preventing concentration of control over health data. Companies such as Alphabet (Google Deep Mind and Verily), Amazon and Philips are trying to gain a foothold in health data for and through health research. Even if commercial research and public-private collaborations are common to health research, the concentration of control over health data and accompanying research infrastructures in the hands of a few major commercial players could lead to new digital divides and less research of public interest (6). As discussed in chapter 6, data portability rights could help counter such concentration of control, but these are probably not sufficient on their own. Terms of collaboration with private parties in the area of health research infrastructures should make sure that health data and the knowledge generated therefrom remains widely available for others to build on. Long-term sustainability and the safeguarding of public values of infrastructures are also important aspects to consider in this respect (7). Global human genomics research can perhaps serve as an example of how a global 'commons', made up of complex institutional arrangements for the ongoing provision,

curation and distribution of health research data, can help research and health care to thrive (8). It could also be interesting to compare the field of health research infrastructures with other infrastructural sectors where vital public interests and third party access are at stake, such as energy provision and telecommunications, and to see what lessons can be drawn for dealing with commercialization.

THE INTEGRATION OF RESEARCH AND CARE

MAIN FINDINGS

Chapter 3 showed how the integration of biobanking infrastructure into clinical care can raise tensions for existing modes of research ethics and governance in the area of clinical biobanking. Changes that were made to health care practice in order to accommodate research could only marginally be taken into account during ethics review. Professional responsibilities for reporting back secondary findings from research were unclear, particularly for findings of uncertain personal and clinical significance. Two approaches for managing such tensions could be discerned: one aimed at purification and the re-establishment of boundaries between research and care; the other aimed at hybridization, flexibly managing the traffic across the divide. Underlying these differences are divergent ideals of how research should contribute to the improvement of health care: either as a common good contributing to the well-being of anonymous others over the longer term, or as a good closely linked to the fate of current patient-participants as well.

Chapter 4 argued that the systematic integration of research and care in academic medicine offers opportunities to improve clinical care, particularly for 'exceptional' patients such as those suffering from rare diseases. In order to realize these opportunities, an health care and research environment in which patients more fully take center stage needs to be created. Research and care in academic health science should be integrated with patients being included as research participants by default. In order to do so responsibly, new ways and means for protecting and respecting patient-participants in their double role are also needed. Among other aspects, this should entail new forms of consent, more active attention to feedback of secondary findings from research, and more transparent governance arrangements.

Chapter 5 argued that professional responsibilities in health research should be extended beyond conventional research settings: ancillary care obligations in medical research should also apply to social media platforms involved in research recruitment. Social media are not just tools for communication: they help make up the social fabric of the information age. Ethical obligations related to recruitment of research participants should therefore be extended and adapted to online contexts. This will entail more scrutiny of the terms under which participants are recruited, new models of online consent, as well as close attention to the privacy policies of social media platforms.

WAYS FORWARD

Facilitating the integration of research and care need not and should not entail the dissolution of distinctions between both. Instead, this thesis has argued that health research infrastructures should aim at facilitating responsible integration of research and health care in ways which both protect and benefit current and future patients and participants. Further ethical reflection and clear guidance on how to achieve this is pertinent, not least since debates over personalized medicine and genetics foreshadow similar questions over the responsible integration of artificial intelligence and decision support systems in health care (9).

This thesis has focused on specific examples of how research and care can be integrated in clinical biobanking. Further guidance should take account of the diversity of ways in which such integration can be organized. For instance, the integration of research and care could be analyzed as a process, with pilot projects serving as learning exercises which can gradually be taken up within standard health care provision. The stepwise implementation of prenatal genetic carrier screening in The Netherlands, partly through research projects and partly through updates to national screening programmes, provide an example of such a process-oriented approach to integration (10,11). It could also be fruitful to conduct systematic comparisons between different areas of biomedicine and health, for instance, by comparing the case study of Parelsnoer Institute to other examples such as the integration of pragmatic randomized trials into routine general practictioner's care (12) and the efforts in the UK to combine individual genetic diagnosis and genetic screening with a nationwide biorepository for genomics research (13).

At the systems level, it would be worthwhile to elucidate the moral and conceptual ties between health research infrastructures for personalized medicine and learning health care systems. Personalized medicine ultimately centers on tailoring medical treatments, whereas learning health care systems focus on generating evidence for improving collective well-being. Still, learning health care systems involve similar ideas about integration of research and care, and the infrastructures required overlap considerably. The ethical considerations involved which need to take into account may be similar as well (14). Some ethicists have argued that the idea of personalized medicine is incompatible with 'We Medicine', as it foregrounds commercial interests in therapy development while over-emphasizing individual responsibility for managing health and disease (15). Others argue that personalized medicine carries the potential to stimulate solidarity and collective well-being (16). The question then remains how this potential can best be reached.

Chapters 3 and 4 argued that current regulatory frameworks for health research infrastructures lack standards which facilitate a proportionate weighting of risks and benefits involved (17). This is an important area for further work in ethics, law and policymaking as well. Normative frameworks in the context of learning healthcare systems may provide some of the groundwork (14). However, a number of points require further elaboration. For one, ethics frameworks for learning health care systems assume that patients should never incur any additional risks of physical harm. This

seems like a fair assumption from the perspective of clinical equipoise: it is probably not generally defensible to simply foreground research priorities at the expense of lowering standards of care (18). Yet personalized medicine research can also involve situations or afflictions in which such standards are lacking. In such cases, a contextual weighting of the additional risks and the short- and long-term research expectations could make more sense. Second, the issue of fairness in participant selection may need to be addressed further, not just in regard to the specific populations on which integration efforts should focus (a topic touched on in chapter 4), but also in regard to exclusive benefits that participants may get from their involvement, for instance in the form of extended feedback or genetic screening services. Clinical research ethics might serve as a source of inspiration for this issue (19).

CHANGING FORMS OF RESEARCH PARTICIPATION

MAIN FINDINGS

Chapter 2 argued that responsible application of the FAIR principles for research data stewardship will also require attention to the impact on participants, their rights and the risks they may face related to privacy, confidentiality and informational harm. Privacy and data protection by design should go hand in hand with governance frameworks which take participants' rights into account as well. Chapter 3 and chapter 4 showed that individual rights and collective solidarity both play a role in designing informed consent procedures for health research infrastructures. A model in which informed consent is reconceived as consent for governance can take both into account. Participants should also be provided with regular information about how their data has been used and be provided with opportunities to update consent preferences where feasible.

Chapter 6 showed that the right to data portability enables data subjects to take up the role of custodians over their own data. This offers new opportunities to data subjects, research data stewardship, and participant-driven research. At the same time, data subjects' increasing responsibility over their own data creates new risks for data confidentiality and security, risks which are carried by individuals themselves. Moreover, individuals could be drawn into the competition between data controllers, which could undermine the possibilities for collaborative health research. Data subjects need enhanced protections against personal vulnerabilities and support in shaping collaborative initiatives for personal data use.

The guideline presented in chapter 7 addressed how patients, participants and publics can become involved in the governance of biobanks and registries. The guideline is premised on the idea that participation in biobank research helps contribute to a robust embedding of research infrastructures in health care and society. Health research infrastructures are encouraged to develop a participation strategy that is responsive to the needs and concerns of patients, participants, and the general public. The guideline

provides direction about how biobanks can choose forms of participation that fit the needs and concerns of their participants and research efforts.

WAYS FORWARD

Health research infrastructures enable and rely on new forms of research participation. This thesis has analyzed the risks and opportunities these may bring, along with ways in which these can be dealt with responsibly. Multiple issues for further research and guidance remain. Despite much previous work, informed consent remains one of these. Arguably, the lack of consensus over the proper shape of consent also results from (too) large expectations of the ethical work that consent can carry. The ongoing uncertainty over the legal standards to which consent under the GDPR needs to live up is an issue in its own right (20). Experiments and guidance aimed at devising minimal models of consent are arguably at least as urgent in this respect as development of innovative models for dynamic consent (21,22).

Building on this, ethics research could be aimed at further developing the concept of consent for governance, for instance by explicating how consent for governance can incorporate norms such as transparancy and accountability towards participants over time (23). The idea of consent for governance also suggests that individual participation and engagement in governance should also be brought into a closer relationship with eachother (24–26). An analysis and evaluation of how this might be done could supplement the guidance on engagement in governance provided in chapter 7.

Individuals' capacities and rights to control their own data, such as through data portability (discussed in chapter 6) and personal feedback about secondary findings (touched on in chapters 3 and 5), are another theme for further work. Issues to address in this respect include participants' capacities to deal with additional responsibilities involved should be considered, along with ways to mitigate risks of individual liability. For instance, interdisciplinary research involving ethics, psychology and science and technology studies could explore how the skills and capacities of patients and citizens to interpret complex data and insights that can be derived from them can be enhanced and supported. The ongoing debate over making secondary findings from genetics research available to participants makes for a test case in how to deal with the effects of data-rich health risk information on the responsibilities for health and disease of both participants and professionals (27,28). As for mitigating risks of individual liability, confidentiality protections which were traditionally the domain of health care may need to be extended to encompass health research and data controlled by individual participants (29,30). One way of doing so could be to further elaborate and explore the concept of patient secrecy (31).

Finally, more guidance about public accountability for health research infrastructures is warranted. The FAIR principles guiding principles were coined to help improve research data stewardship. Potentially, however, the principles could also contribute to enhanced public accountability over how health research infrastructures function and how they are

used in practice. Advocates of public accountability in clinical trials emphasise the close relationship between public accountability and scientific quality and integrity (32,33). It would be worthwhile to explore what health research infrastructures could learn from these debates from an ethical perspective. Existing guidelines such as the Dutch code of conduct for biobanking and the Taipei Declaration oblige health research infrastructures to publicly account for their activities, but only large-scale biobanking initiatives with active outreach programmes do so in a meaningful way (34,35).

CONCLUSION

This thesis has argued that many keys to the ethics of 'Big Data' research reside in the responsible organization of health research infrastructures. Lacking prespecifiable research objectives of traditional hypothesis-driven research, norms for responsible research data stewardship can be specified. Sharp distinctions between research and care should make way for guidance about the responsible integration of both, with safeguards and controlled learning exercises to ensure that both current and future patients benefit from such arrangements. And new rights and roles for participants that are tailored to long-term, distributed and data-mediated forms of participation in health research infrastructures should be developed further, with an eye towards effective protections, a meaningful role for participants in governance, and public accountability. As this chapter has argued, each of these areas calls for further ethical attention.

Ethics parallel research can help to anticipate, identify and evaluate the ethical issues at stake, by making explicit the normative considerations in technoscientific developments and associated legal, regulatory and policy frameworks, and help guide the choices made in the process. This thesis has done so through a a series of studies combining case-based empirical investigation, conceptual analysis and normative evaluation. Employing a diverse repertoire of methods and collaborations with national health research infrastructure initiatives, the studies aimed to contribute to the so-called midstream development of health research infrastructures. Chapter 2, for instance, aimed to provide a normative dimension to ongoing debates on data stewardship in health research, and chapter 6 aimed at an early stage to contribute to the reflection on the novel right to data portability. Building on empirical studies, chapters 3 and 4 engaged with national biobanking initiative Parelsnoer Institute; earlier on, the studies also provided a basis for a joint contribution to the debate over regulation and ethics review of biobanking in The Netherlands (36). Finally, the guideline presented in chapter 7 contributed to the establishment of the BBMRI-NL Patient and Public Advisory Council. After nearly three years of service, this council is now regularly advising BBMRI-affiliated researchers and initiatives and will be integrated into the governance structure of the umbrella initiative Health-RI (37).

Shaping and governing health research infrastructures in an ethically responsible manner remains an ongoing manifold challenge. Many of the reforms will also involve national and international political action in order to implement effective regulatory

frameworks. The diversity of approaches taken in this thesis reflects the variety of ways in which ethics parallel research can help bring normative considerations to the fore. The impact of such research will usually be modest; this thesis is no exception. The choice to focus ethical analysis on issues closely associated with the organization of health research infrastructures themselves also has limits. For instance, a critical analysis of how the paradigm of personalized medicine transforms health research and whether alternative directions are ethically preferable fell beyond the scope of this thesis. Likewise, this thesis has not touched on national and cultural specificities of the co-production of health research infrastructures, normative challenges and their resolution (38,39). Still, modest contributions on a regular basis parallel to infrastructural developments such as those included in this thesis can help ensure that normative considerations are taken into account in the conduct, governance and regulation of health research and infrastructure. Now that patients and participants are increasingly contributing to an infrastructural ecosystem of health data for research purposes, it becomes more and more important to organize this ecosystem in a transparent and accountable manner, responsive to patients', citizens' and participants' needs. Research ethics has an important role to play in achieving this, in collaboration with health research, data stewardship, legal scholarship, social science and citizens, patients and participants.

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APPENDICES

SUMMARY

Large-scale data processing and analysis offers the promise of personalizing health and biomedicine. In order to realize this promise, growing numbers of patients and citizens are contributing data to health research. The infrastructures facilitating these processes raise multiple ethical challenges. These cannot be articulated and addressed properly through direct application of the principles and frameworks of clinical research ethics. Clinical research ethics assumes and reinforces a model of research with clear boundaries between individual research projects, and between research on the one hand and other societal domains such as the provision of health care on the other. Focusing on (clinical) biobanking, this thesis aims to identify and evaluate the emerging ethical challenges raised by health research infrastructures. Three themes will be addressed in particular: the ethics of research data stewardship (chapters 2 and 6), the integration of research and care (chapters 3 to 5), and changing forms of research participation (chapters 6 and 7).

The FAIR guiding principles for research data stewardship look set to become a cornerstone of research in the life sciences (chapter 2). The FAIR principles, with FAIR standing for Findability, Accessibility, Interoperability, and Reusability, stress crucial preconditions for data sharing, urging researchers to take the possibility of subsequent data sharing and reuse into account from the outset. However, a number of conditions will need to be met in order to apply these principles responsibly. First of all, fair and impartial data sharing and reuse policies are needed to make data 'as open as possible, as closed as necessary'. Second, along with FAIR data and metadata standards, responsible data science will also require additional checks on research quality and integrity. Third, privacy and data protection should be taken on board by design, at every stage of the research cycle, hand in hand with efforts to help foster accountability, trust and participation in governance. Fourth, better models for valuing and providing credit for data sharing are needed.

Drawing on a case study of the Dutch Parelsnoer Institute, Chapter 3 discusses how new forms of ethics review for clinical biobanking have emerged. Over time, ethics review boards (ERBs) developed a basic regulatory approach to review biobanking initiatives analogous to the norms and procedures familiar from review of human subjects research. This approach requires review of collection protocols, governance arrangements and monitoring of actual use. In practice, however, there is considerable leeway in the manner in which clinical biobanking initiatives are governed. Moreover, the integration of biobanking infrastructure into clinical care raises tensions for existing modes of research ethics and governance. Two approaches for managing such tensions can be discerned: one aimed at purification and the re-establishment of boundaries between research and care; the other aimed at hybridization, flexibly managing the traffic across the divide. Underlying these differences are divergent ideals of how research should contribute to the

improvement of health care: either as a common good contributing to the well-being of anonymous others over the longer term, or as a good closely linked to the fate of current patient-participants as well.

The systematic integration of research and care in academic medicine offers opportunities to improve clinical care, particularly for 'exceptional' patients such as those suffering from rare diseases (chapter 4). In order to realize these opportunities, an health care and research environment in which patients more fully take center stage needs to be created. Research and care in academic health science should be integrated with patients being included as research participants by default. In order to do so responsibly, new ways and means for protecting and respecting patient-participants in their double role are also needed. Among other aspects, this should entail new forms of consent, attention to feedback of secondary findings from research, and more transparent governance arrangements.

Professional responsibilities in health research should be extended beyond conventional research settings (Chapter 5): ancillary care obligations in medical research should also apply to social media platforms involved in research recruitment. Extending ethical obligations related to recruitment of research participants to online contexts will entail more scrutiny of the terms under which participants are recruited ,new models of online consent, as well as close attention to the privacy policies of social media platforms.

The right to data portability provides participants with new rights to control and transfer their data in more usable forms, thereby offering opportunities to data subjects, FAIR research data stewardship, and participant-driven research(chapter 6). Moreover, data portability could help circumvent issues of data access in commercial settings for research purposes and stimulate competition between health research infrastructures in similar domains. At the same time, it is questionable whether data portability aimed at stimulating such competition will benefit collaborative health research. Moreover, data portability could aggravate a number of concerns related to data security, disclosure and consent. Data subjects need enhanced protections against personal vulnerabilities and support in shaping collaborative initiatives for personal data use.

Guidance about how biobanks and registries can involve patients and the public in their governance can be found in 'donors as partners' (Chapter 7). The guideline is premised on the idea that participation in biobank research helps contribute to a robust embedding of research infrastructures in health care and society. Health research infrastructures are encouraged to develop a participation strategy that is responsive to the needs and concerns of patients, participants, and the general public. The guideline provides direction about how biobanks can choose forms of participation that fit the needs and concerns of their participants and research efforts.

A number of issues in the ethics of research data stewardship remain to be explored further. The principle of purpose limitation should be revised to take into account that health research infrastructures can serve multiple purposes which can change and only emerge specifically over time, without losing sight of the need to hold data stewardship

practices to account. This is also relevant for the general direction of data stewardship for open science. Instead of maximizing data sharing, a conception of openness which explicitly takes societal and health needs and sustainability of infrastructures into account is needed. Ethical guidance is also needed to translate and update basic principles of privacy and data protection for the context of data-intensive health research infrastructure, especially against the legal backdrop of the European General Data Protection Regulation (GDPR). Further ethics research could also help devise principles and arrangements for governance and regulation aimed at facilitating private entrepreneurship while preventing concentration of control over health data. Long-term sustainability and the safeguarding of public values of infrastructures are important aspects to consider in this respect.

Facilitating the integration of research and care need not and should not entail the dissolution of distinctions between both. Instead, health research infrastructures should aim at facilitating responsible integration of research and health care in ways which both protect and benefit current and future patients and participants. Further ethical guidance should take account of the diversity of ways in which such integration can be organized. At the systems level, it would be worthwhile to elucidate the moral and conceptual ties between health research infrastructures for personalized medicine and learning health care systems. Current regulatory frameworks will also require updating to facilitate a proportionate weighting of risks and benefits involved in such integration. Clinical research ethics might serve as a source of inspiration for dealing with issues such as equipoise and fairness in participant selection.

A number of issues for further research and guidance in relation to participation in health research infrastructures also remain. For one, minimal models of consent should be developed further. Building on this, the concept of consent for governance should be developed further, by explicating how transparancy and accountability over time can be incorporated and by evaluating how individual participation and engagement in governance should be brought into a closer relationship with one another. Interdisciplinary research involving ethics, psychology and science and technology studies could explore how the skills and capacities of patients and citizens to interpret complex data and insights that can be derived from them can be enhanced and supported. And ways of extending confidentiality protections beyond health care through norms of patient secrecy should be elaborated further. Finally, more guidance about public accountability for health research infrastructures is warranted.

Many keys to the ethics of 'Big Data' research reside in the responsible organization of health research infrastructures. Lacking prespecifiable research objectives of traditional hypothesis-driven research, norms for responsible research data stewardship can be specified. Sharp distinctions between research and care should make way for guidance about the responsible integration of both, with safeguards and controlled learning exercises to ensure that both current and future patients benefit from such arrangements. And new rights and roles for participants that are tailored to long-term, distributed and data-

mediated forms of participation in health research infrastructures should be developed further, with an eye towards effective protections, a meaningful role for participants in governance, and public accountability. Each of these areas calls for further ethical attention. Ethics parallel research can help to anticipate, identify and evaluate the ethical issues at stake, by making explicit the normative considerations in technoscientific developments and associated legal, regulatory and policy frameworks, and help guide the choices made in the process. The diversity of approaches taken in this thesis reflects the variety of ways in which ethics parallel research can help bring normative considerations to the fore. Now that patients and participants are increasingly contributing to an infrastructural ecosystem of health data for research purposes, it becomes more and more important to organize this ecosystem in a transparent and accountable manner, responsive to patients', citizens' and participants' needs. Research ethics has an important role to play in achieving this, in collaboration with health research, data stewardship, legal scholarship, social science and citizens, patients and participants.

SAMENVATTING

Grootschalige gegevensverwerking en -analyse is essentieel voor het realiseren van de beloften van precisiegeneeskunde en personalized medicine and health. Steeds meer patiënten en burgers dragen hiervoor gegevens bij aan gezondheidsonderzoek. De daarvoor benodigde infrastructuur brengt verschillende ethische uitdagingen met zich mee. De ethische principes en kaders van de klinische onderzoeksethiek zijn daarvoor deels ontoereikend. Klinische onderzoeksethiek gaat uit van onderzoek met duidelijk afgebakende grenzen tussen onderzoeksprojecten, en een helder onderscheid tussen onderzoek aan de ene kant en gezondheidszorg en andere activiteiten aan de andere. Dit proefschrift analyseert en evalueert de uitdagingen waar deze gezondheidsonderzoeksinfrastructuur voor staat. De nadruk ligt daarbij op een analyse van de uitdagingen zoals ze zich voordoen bij biobanken voor klinisch onderzoek. Drie thema's hebben daarbij bijzondere aandacht: de ethiek van research data stewardship (hoofdstukken 2 en 6), de integratie van onderzoek en gezondheidszorg (hoofdstukken 3, 4 en 5), en verandere vormen van participatie in onderzoek (hoofdstukken 6 en 7).

De FAIR-principes voor research data stewardship zijn inmiddels uitgegroeid tot één van de hoekstenen van gegevensbeheer in de levenswetenschappen (hoofdstuk 2). De FAIR-principes, waarbij FAIR staat voor vindbaarheid (findability), toegankelijkheid (accessibility), interoperabiliteit (interoperability) en herbruikbaarheid (reusability), vormen cruciale randvoorwaarden voor het zorgvuldig delen van gegevens. Ze vragen van onderzoekers om van voren af aan rekening te houden met toekomstig hergebruik en het breder delen van hun gegevens. Maar voor een verantwoorde toepassing is een aantal aanvullende voorwaarden van belang. Ten eerste is eerlijk en onafhankelijk toegangsbeleid van belang om gegevens 'zo open als mogelijk, zo gesloten als nodig' beschikbaar te stellen. Ten tweede zijn aanvullende maatregelen nodig voor de kwaliteit en integriteit van onderzoek en onderzoeksgegevens nodig, naast FAIR data- en metadatastandaarden. Ten derde horen privacy en gegevensbescherming meegenomen te worden in het ontwerp van onderzoek en de gehele verdere gegevensverwerking, samen met het stimuleren van participatie, vertrouwen en verantwoordingsmechanismen in beleid. En ten vierde zijn betere modellen voor het waarderen en belonen van het delen van onderzoeksgegevens nodig.

Aan de hand van een onderzoek naar het Parelsnoer Instituut wordt in hoofdstuk 3 besproken hoe nieuwe vormen van ethische toetsing van klinisch biobankonderzoek zijn ontstaan in Nederland. Medisch-ethische toetsingscomissies hebben gaandeweg een basale aanpak voor toetsing van biobanken ontwikkeld, naar analogie met de normen en procedures voor mensgebonden onderzoek met proefpersonen. Die aanpak legt de nadruk op het toetsen van verzamelingsprotocollen en beheersafspraken, met beperkt toezicht op het concrete gebruik van de aangelegde collecties. In de praktijk blijven de voorwaarden waaronder klinische biobanken opereren echter sterk uiteenlopen. Daarnaast

brengt de integratie van biobankinfrastructuur in de klinische gezondheidszorg een aantal spanningen met zich mee. Twee manieren om daarmee om te gaan lopen daarbij door elkaar: enerzijds een benadering gericht op zuivering en het opnieuw afbakenen van grenzen tussen onderzoek en zorg; anderzijds een benadering die gericht is op hybridisering en het flexibel omgaan met het grensverkeer tussen beide. Deze benaderingen hangen samen met verschillende idealen over hoe onderzoek bij kan dragen aan verbetering van de gezondheidszorg: als een publiek goed dat bijdraagt aan het welzijn van anderen op de lange duur, of als een goed dat sterk gelinkt blijft aan het lot van huidige patiënt-participanten.

De systematische integratie van onderzoek en gezondheidszorg in de academische geneeskunde biedt mogelijkheden voor verbetering van de klinische gezondheidszorg, in het bijzonder voor 'uitzonderlijke' patiënten zoals mensen met zeldzame ziekten (hoofdstuk 4). Om deze mogelijkheden te benutten is wel een omgeving nodig waarin patiënten nadrukkelijk centraal staan. Patiënten in universitair medische centra zouden daarbij standaard deel moeten kunnen nemen aan lopend onderzoek naar hun ziektebeelden, zeker aan observationeel onderzoek. Om dat verantwoord te kunnen doen zijn ook nieuwe manieren nodig om patiënt-participanten te beschermen en te respecteren in hun dubbele rol. Dat vraagt onder andere om nieuwe vormen van toestemming, aandacht voor terugkoppeling van nevenbevindingen en transparant beheer.

Professionele verantwoordelijkheden van gezondheidsonderzoekers zouden moeten worden uitgebreid tot buiten conventionele onderzoekssettings (hoofdstuk 5): verantwoordelijkheden voor ondersteunende zorg in medisch onderzoek zouden ook moeten gelden voor social media-platforms die gebruikt worden voor het werven van onderzoeksdeelnemers. Deze uitbreiding van de ethische verplichtingen rond het werven van deelnemers gaat onder andere gepaard met een kritische blik op recruteringsvoorwaarden, nieuwe modellen van online toestemming, en nauwe aandacht voor het privacybeleid.

Het recht op overdraagbaarheid van gegevens, beter bekend als het recht op data portability, geeft deelnemers nieuwe rechten om over hun gegevens te beschikken en deze over te laten dragen aan anderen in bruikbaardere vormen (hoofdstuk 6). Dat biedt kansen voor betrokkenen zelf, voor FAIR research data stewardship en voor het aanjagen van onderzoek door deelnemers zelf. Data portability kan daarnaast helpen bij het omzeilen van commerciële beperkingen aan de toegankelijkheid van gegevens en stimuleert mogelijk ook de concurrentie tussen onderzoeksinfrastructuren. Er zijn ook mogelijke nadelen. Zo is het de vraag of het aanjagen van concurrentie ten goede komt van samenwerking in gezondheidsonderzoek. Data portability kan ook bestaande zorgen over beveiliging en vertrouwelijkheid van gegevens en toestemming uitvergroten. Deelnemers hebben betere bescherming nodig bij de omgang met kwetsbare gegevens en ondersteuning bij het vormgeven van samenwerkingsinitiatieven met hun gegevens.

Hoofdstuk 7 geeft biobanken en patiëntenregistraties advies over hoe zij patiënten en publiek kunnen betrekken bij bestuur en beleid. Het richtsnoer 'de donor als partner' gaat

uit van het idee dat participatie in biobankonderzoek bijdraagt aan een stevige inbedding van gezondheidsonderzoeksinfrastructuur in de gezondheidszorg en samenleving. Infrastructuren worden aangemoedigd om daarvoor een strategie te ontwikkelen die recht doet aan de noden en wensen van patiënten, deelnemers en het algemene publiek. Het richtsnoer geeft inzicht in de keuzes van participatievormen die infrastructuren daarbij moeten maken.

Verschillende aspecten van de ethiek van research data stewardship vragen om nader onderzoek. Het uitgangspunt van doelbinding moet worden herzien om rekenschap te geven van het gegeven dat gezondheidsonderzoeksinfrastructuren meerdere onderzoeksdoelen dienen die vaak pas over langere tijd duidelijk worden, zonder daarbij het belang van het afleggen van verantwoording over beheer en gebruik uit het oog te verliezen. Dit is ook van belang voor de algemene richting van data stewardship voor open science. Het streven naar openheid moet niet begrepen worden als een streven naar zo laagdrempelig mogelijk delen van data, maar als een streven naar het duurzaam beschikbaar maken en houden van data in het belang van gezondheid, gezondheidszorg en maatschappij. Daarnaast zijn ethische richtlijnen nodig om de uitgangspunten van privacy en gegevensbescherming voor de context van data-intensief gezondheidsonderzoek, in het bijzonder tegen de achtergrond van de wettelijke kaders van de Algemene Verordening Gegevensbescherming. Ethisch onderzoek zou zich bovendien kunnen richten op het ontwikkelen van bestuurlijke en beleidsmatige modellen van onderzoeksinfrastructuur die zinvol commercieel gebruik combineren met voor goed onderzoek soms noodzakelijke concentratie van controle over gezondheidsdata. Borging van publieke waarden en duurzaamheid van infrastructuren zijn daarbij belangrijke overwegingen.

Infrastructuur voor de integratie van zorg en onderzoek hoeft niet te leiden tot het opheffen van de grenzen tussen beide. Gezondheidsonderzoeksinfrastructuren kunnen zich ook richten op verantwoorde integratie van zorg en onderzoek, op manieren die zowel huidige deelnemers als toekomstige patiënten beschermen én ten goede komen aan hun gezondheid en behandeling. Ethische richtlijnen zouden daarbij rekenschap moeten nemen van de uiteenlopende manieren waarop zulke integratie vorm kan krijgen. Op systeemniveau is het de moeite waard om de morele en conceptuele verbanden tussen gezondheidsonderzoeksinfrastructuur voor personalized medicine en het idee van een lerend zorgsysteem te verhelderen. Reguleringskaders vragen om herziening met het oog op het maken van een proportionele afweging van risico's en de met onderzoek te dienen belangen van deelnemers en andere huidige of toekomstige burgers en patiënten. Klinische onderzoeksethiek kan als inspiratiebron dienen bij vragen over equipoise en eerlijke selectie van deelnemers.

Een aantal kwesties rondom participatie in gezondheidsonderzoeksinfrastructuren vraagt om betere uitleg en nader onderzoek. Ten eerste zouden minimale toestemmingsvormen nader uitgewerkt moeten worden. Daarop voortbordurend kan het idee van toestemming voor beheer en beleid (consent for governance) verder uitgewerkt worden, onder andere door duidelijk te maken hoe doorlopende transparantie en verantwoording verwezenlijkt

kan worden, en het duidelijker verbinden van participatie van deelnemers in onderzoek enerzijds en het betrekken van hen bij beheer en beleid van hun gegevens anderzijds. De vaardigheden en competenties van burgers en patiënten om complexe gegevens en adviezen die daaruit worden afgeleid zouden moeten worden vergroot en ondersteund; interdisciplinair onderzoek met bijdragen van ethiek, psychologie en wetenschapsonderzoek zou daarbij kunnen helpen. Ook vraagt de vertrouwelijkheid van gezondheidsgegevens buiten de gezondheidszorg om aandacht, onder andere door nadere uitwerking van het idee van een patiëntgeheim. Ten slotte is meer ethische ondersteuning nodig voor publieke verantwoording van gezondheidsonderzoeksinfrastructuren.

De sleutel voor de ethiek van 'Big Data'-onderzoek ligt in meerdere opzichten bij de verantwoorde organisatie van infrastructuur. Normen voor verantwoorde research data stewardship vullen de normen voor de beoordeling van vooraf gedefinieerde onderzoeksdoelen en hypotheses aan. Een scherp onderscheid tussen gezondheidszorg en onderzoek kan plaats maken voor ondersteuning bij verantwoorde integratie van beide, met beschermingsmaatregelen en gecontroleerde experimenten waarin uitgezocht wordt hoe zowel huidige als toekomstige patiënten daarvan kunnen profiteren. En nieuwe rechten en rollen voor deelnemers kunnen verder worden ontwikkeld, toegesneden op participatie over langere periodes en vagere verbanden tussen deelnemers en onderzoekers en met oog op effectieve beschermingsmaatregelen, betekenisvolle bijdragen van deelnemers aan beheer en beleid, en publieke verantwoording. Elk van deze domeinen vraagt om nadere aandacht. Ethisch parallelonderzoek kan helpen om op zulke vragen te anticiperen en deze nader te identificeren en evalueren. Normatieve overwegingen in technowetenschappelijke ontwikkelingen en wettelijke, regulerings- en beleidskaders kunnen zo expliciet worden gemaakt, samen met de keuzes en afwegingen die daarbij een rol spelen. Ethisch parallelonderzoek kan dat op uiteenlopende manieren doen. De benaderingen in dit proefschrift vormt daarvan een beperkte afspiegeling. Patiënten en deelnemers dragen tegenwoordig continu bij aan een infrastructureel ecosysteem van gezondheidsgegevens voor onderzoek. Daarom wordt het steeds belangrijker om dat ecosysteem op een transparante manier te organiseren en daarover verantwoording af te leggen, op een manier die recht doet aan de noden en wensen van burgers, patiënten en deelnemers. Onderzoeksethiek speelt daarbij een belangrijke rol, samen met het gezondheidsonderzoek, data stewardship, juridisch en sociaal-wetenschappelijk onderzoek en burgers, patiënten en deelnemers zelf.

CURRICULUM VITAE

After a first year's degree (propedeuse) in mathematics at Utrecht University, Martin Boeckhout graduated in philosophy of science and science and technology studies at the University of Amsterdam (both cum laude). From 2005 until 2015, he taught various courses in science and technology studies at a number of interdisciplinary bachelor's and master's programmes. After a brief stint at the Dutch Scientific Council for Government Policy, where he contributed to the report on uncertain safety, Martin commenced his PhD research in 2008 with support from CSG: centre of society and the life sciences. From 2013 onwards, he worked for BBMRI-NL, first as postdoc based at Radboudumc on a guideline for patient engagement, afterwards as policy advisor on ethical, legal and societal issues (ELSI) and engagement. Among other things, he helped set up the BBMRI Patient and Public Advisory Council, contributed to national and European advocacy efforts over novel data protection legislation, contributed as policy advice as a member of the pan-European BBMRI-ERIC Common Service ELSI, and helped set up the Health RI ELSI Servicedesk. Since 2017 he works as senior policy advisor to the Netherlands Federation of University Medical Centres (NFU) on matters related to research regulation and data protection.

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