Small Samples, Big Questions

An Ethical Analysis of Consent in Pediatric Biobanking

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An Ethical Analysis of Consent in Pediatric Biobanking

Kleine samples, grote vragen

Een ethische analyse van het toestemmingsvereiste in kinderbiobanken

(met een samenvatting in het Nederlands)

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Noortje Allegonda Antonia Giesbertz

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CONTENTS

Chapter 1
General introduction

BIOBANKS

In 1996 the term 'biobank' was first used in the abstract of a PubMed publication.[1;2] In 2014 the number of publications in PubMed that use biobank in title or abstract was over 1700.[3] In 2008 the first journal was published that included biobanking in its title: 'Biopreservation and Biobanking'.[1;4] These developments illustrate that biobank is a relatively young term in biomedical publications, and, at the same time, show the rapid increase of its use. Although the term biobank is used in different ways,[1;5] a common definition, which is also adopted in this thesis, is 'the collection of human biological samples stored for biomedical-scientific research purposes, usually linked to phenotypic data'.[6;7] Although all biobanks store samples and data to conduct biomedical research, they can differ considerably in several ways. Biobanks can, for example, support or conduct different types of research, or store different types of material, such as blood, urine, tumor tissue. Also, participant's characteristics may differ; they may, for example, be healthy people or patients. Biobanks can furthermore have distinctive collaboration structures, such as partnerships with other institutes or commercial parties.[8;9]

Biobank research

The aim of biobanks is to facilitate research on biological samples, which can generate knowledge that may eventually be used to improve health care. Biobanks can both be used to support studies from independent researchers or research groups, as well as to initiate studies themselves. Although the term biobank is relatively young, research on biological material, also referred to as tissue research, is certainly not. Exploring the cellular basis of disease, for example, was already done by pathologists in the 19th century.[10;11] Still, in 2009 TIME Magazine presented biobanks as "one of the ten ideas changing the world right now",[12] and biobanking has become subject of ethical debate in the past decades. This raises the question what has changed in tissue research and what makes biobank research unique. A mixture of characteristics and developments needs to be taken into account. Typical for biobank research is that samples are usually stored for many years, while linkable to phenotypic data, and that the exact research questions are often not yet formulated at the time of sample inclusion.[9;13] Furthermore, developments in information and research technologies have triggered an increase of biobanking activities both in number and size.[14-16] It has become easier to process, store, link and share large amounts of data and the information that follows from data analysis. Likewise, more data and information is generated because of the developments in research technologies, especially in the fields of genetics and genomics. Genomics refers to "the study of the functions and interactions of all the genes in the genome, including their interactions with environmental factors", and "genetics is the study of single genes and their effects".[17] Completing the Human Genome Project in 2003, in which the entire human genome was mapped and sequenced for the first time, was one of the milestones in these fields.[18-20] Currently, DNA sequencing technologies are being further developed. An improvement in accuracy and speed, and a decrease in costs has been promised[21] and, in the meantime, also accomplished. This may lead to the introduction of these techniques as a common part of our health care.[22] Incorporating genomic information in health care fits the movement towards personalized medicine, which refers to managing a patient's health

by adapting treatment or preventive measures according to her molecular and clinical profile.[18;23] Besides genetics and genomics studies, biobank research can entail countless different types of studies; in principle every type of study that can be conducted on biological material is possible.

PEDIATRIC BIOBANKING

There is a special interest in the inclusion and use of biological samples from children.[24] At the same time, the inclusion and use of children's samples in and by biobanks, so called pediatric biobanking, give rise to specific ethical issues, which will be elaborated below.[25-28]

Pediatric research

Children form a special group within biomedical research. In order to respect autonomy and protect participants against harm, competent adults must be asked for their informed consent before they may be included in research.[29] Children, however, are often considered incompetent to make an autonomous decision on research participation, due to their immaturity,[30] and can therefore be referred to as a vulnerable population. Specific for children is that their incompetence is temporary and they are expected to grow up and become competent adults.[27] However, until they have matured, children are in need of special protection.[31;32] This protection took different shapes in the past decades. After the Second World War for example, the Nuremberg Code was formulated. The Code contains a set of ethical requirements and was used in the trials against doctors who performed atrocious experiments during the Second World War. In the Code it was put forward that a person must give her voluntary consent before she may be included in research.[33] Consequently, according to the Code, research with children was not allowed. A strict exclusion of children from research, however, leads to the situation that pediatric health care questions remain unanswered.[34] In order to improve pediatric health care, including children in research is necessary, since not all research questions can be answered through research with adults. First, some illnesses only occur in childhood. Second, diseases may occur both in adults and in children, but have a different manifestation in children. Third, reference values have to be collected in healthy children in order to diagnose diseases in childhood.[35]

Reasons for conducting pediatric biobank research

The three reasons to include children in biomedical research that are mentioned above, apply to pediatric biobanking as well. Consider, for example, pediatric oncology therapy research that studies pharmacogenetics.[36] Or think about research after childhood vaccination, which aims to provide new insight into immunological processes and the genetic basis for adverse reactions,[37] or asthma studies that measure immunoglobulin E (IgE) levels,[38;39] or bio-monitoring research in which the effects of different environmental exposures on children's health and development are studied,[40;41] for example through identification of biomarkers of environmental pollution.[40]

Another reason for including pediatric samples is to study a very rare condition for which it is difficult (or impossible) to obtain a sufficient number of samples within the adult population

exclusively.[42] In addition, research on pediatric biological samples can improve our understanding of the etiology of conditions that only occur during adulthood, but have their origin in childhood years. By studying children's samples, our understanding of the development of these conditions improves, which can provide leads for the development of treatment or preventative actions.[25;43] It should be noted, however, that this type of research might not be supported by some guidelines that require pediatric research to be group directed.[31] This means that the study should aim to benefit members of the group to which the participants belong.[35]

Risks and biobanking

Although there are good reasons to conduct pediatric biobank research, children's interests in the progress of (pediatric) health care, need to be balanced with an adequate protection of individual children who participate in research. Therefore, it is important to consider the risks for participants involved in biobanking.

Biobanking typically consists of three stages: (1) collection and inclusion of the sample, (2) storage of the sample and (3) usage of the sample (see Table 1). In biobanking, physical risks and harms are related to the first stage of biobanking; when the sample is taken. The level of risks and burdens depends highly on the type of sample and the way it is taken. A urine sample and a mouth swab, for example, are much less intrusive than a biopsy or blood withdrawal. Moreover, risks and burdens may differ between persons. Whereas one person would feel rather indifferent about a blood withdrawal, another can experience considerable discomfort. In the second and third stage of biobanking, generally there are no physical risks and burdens involved. However, so called informational risks and burdens can be associated with these phases. They involve risks and possible harms that may result from (inappropriate) release of information.[13;44] Especially information yielded from genetic/genomic research could harm or cause distress to a person.[26;45] Also, such information could be stigmatizing for groups when published or released otherwise.[45] The risks involved in biobank participation depend highly on the characteristics of the particular biobank. It matters, for example, whether a biobank shares its samples and data, or whether the samples are linked to other (health care) databases, or what the disclosure policy is on individual research results. The level of informational risk seems directly linked to the (confidentiality) governance of the biobank and the identifiability of the samples and data.

Table 1 Stages of biobanking

Stage I	Collection and inclusion of sample
Stage II	Storage of sample
Stage III	Usage of sample*

* When a sample is used (stage III), and there is leftover material, the sample can be restored (stage II)

CONSENT AND BIOBANKING

Whether a study that involves human participants has acceptable risk levels is usually assessed by a Research Ethics Committee (REC). In addition, a potential research participant is asked to personally consider the risks during the informed consent procedure.

As discussed earlier, in order to respect a participant's autonomy and protect her against harm, competent adults must provide informed consent before they may be included in research.[29] Essential elements of informed consent are: competence, disclosure (of information), understanding, voluntariness, and consent.[29] The feasibility of the traditional form of informed consent has been challenged in biobanking.[9] The exact research projects that will be conducted on the samples are often unknown at the time of inclusion, which complicates the estimation of possible consequences and risks for the participants. Hence, it is difficult to provide specific information to potential biobank participants at the start of their participation in the biobank. Several alternatives have been proposed, of which 'broad consent' is the most prominent. Broad consent refers to a consent procedure where general information about the governance of the biobank and expected research projects is provided, for example that the research goal is to generate biomedical knowledge related to chronic illnesses, but no specific information about the research question is given at the moment of enrollment.[46]

Apart from the difficulties in assigning an appropriate role for consent in biobanking in the adult context, the inclusion of pediatric samples gives rise to a set of specific questions with respect to consent related issues.[47;48]

Consent and pediatric biobanking

It has been suggested that in pediatric research informed consent is better understood as the combination of informed parental permission and if possible, the child's assent.[49;50] It is, however, not clear how these concepts should be interpreted and used in practice, both in general and in the biobanking context specifically.

Parental (or legal guardian) permission is considered essential to include a child into biomedical research. However, biobanks entail longitudinal research, in which the exact research projects are unknown. The question arises whether parents should be allowed to give permission for the enrollment of their child's tissue and data in a biobank,[27] and if so, whether parents should have the authority to give broad permission to all types of biobank activities.[51] In addition, this poses the question to what extent children themselves should be involved in the research discussion. The concepts assent and dissent have been articulated to involve children in a consent procedure.[28;48;52-57] Although parental permission is considered essential for including children in research, the roles of assent and dissent are less fixed. It remains, for example, unclear which reaction of the child should be considered dissent: should every refusal reaction of a child be respected, even when she does not understand what it is she refuses? Moreover, since biobank research can entail several procedures and studies, the question arises whether a child should be enabled to dissent to separate parts of a biobank's activities. In addition, considerable disagreement exists on the concept of assent, which has been referred to as 'the affirmative agreement of a child to participate in research'.[58] Moreover,

it is questioned what the attributed value of assent is.[59] Also it is unclear which children are capable of providing assent, and the age at which a child is considered mature enough to give assent for research varies per country.[60] Clearly, further reflection on the concepts of assent and dissent and the appropriate role and involvement of the child in pediatric biobank research is necessary. In addition, typical for children is that they are expected to grow into competent adults, and gain the ability (and right) to make autonomous decisions. Samples may still be stored and used by biobanks when children have become autonomous adults. The question arises whether children should be re-contacted when they reach maturity to obtain their consent for (or to give them the opportunity to withdraw from) the continued use of their samples?

AIMS AND SCOPE OF THIS THESIS

In view of the rapid developments in the field of pediatric biobanking, it is important to address the question of how consent should take shape in pediatric biobanks. In this thesis, 'consent in pediatric biobanking', refers to the discussed above concepts that relate to the child's and parental influence in the inclusion, storage and usage of the child's samples in a biobank. The main questions that are addressed in this thesis are:

I. What is the appropriate consent procedure for the inclusion of residual samples in biobanks?
II. What is the appropriate role for children in the consent procedure at the time of sample inclusion?
III. Should children be re-contacted when they reach maturity to obtain their consent for (or to give them the opportunity to withdraw from) the continued use of their samples?

SCTRUCTURE OF THIS THESIS

The first question, 'what is the appropriate consent procedure for the inclusion of residual samples in biobanks?', is addressed in **Chapter 2, 3** and **4**. Leftover human biological material provides a large potential source of samples for biobanks. Initially, the inclusion of residual tissue from children may seem less problematic than the inclusion of specifically obtained material, since no extra intervention is needed. However, a closer look reveals that the inclusion of residual tissue deserves ethical scrutiny as well. Precisely the use of leftover tissue gives rise to specific questions regarding consent. Whereas specifically for biobanks obtained material can only be accompanied with an opt-in procedure, where a person explicitly expresses consent, residual tissue can also be included with an opt-out procedure, where inaction is treated as a signal of consent. Considering the complexity of this issue, it is necessary to first address this issue in the adult context. In **Chapter 2** and **3** both procedures and their appropriateness for residual tissue research are discussed. In **Chapter 4** the line of reasoning that can be followed to determine whether an opt-in procedure is more appropriate than an opt-out procedure or vice versa, is illustrated with a case in which we discuss the inclusion of women in a breast implant registry.

Chapter 5, 6 and **7** focus on the second question: 'what is the appropriate role for children in the consent procedure at the time of sample inclusion?'. Since there is no consensus on the underlying grounds and interpretation of assent, we first clarify the concept of assent in **Chapter 5**. In addition, some starting points for the implementation of our concept of assent are provided. In **Chapter 6** we then analyze the current pediatric biobanking practice and consider how biobanks involve children in the consent procedure. This chapter is based on the case study, in which we studied four biobanks that include samples from children. In **Chapter 7** we provide further guidance on how biobanks can put assent in practice.

Once children's biological material is included in a biobank, it is likely that the samples are still stored when they reach maturity. In **Chapter 8** we discuss the third questions: 'should children be re-contacted when they reach maturity to obtain their consent for (or to give them the opportunity to withdraw from) the continued use of their samples?'.

Last, in **Chapter 9** the main results of this study will be discussed and reflected on. In addition, suggestions for future work will be put forward, and the attributed value of the case study will be considered. In addition, the conclusions of this study will be discussed in a broader perspective on research participation.

RESEARCH APPROACH

Practical ethics aims to make normative claims about a certain practice. These normative claims can be justified by presenting sufficient, consistent and coherent reasons for them.[61] In this thesis we use an integrated model to analyze the issues and evaluate the reasons presented. This integrated model has been referred to as 'reflective equilibrium' (RE).[61] In 1971 political philosopher John Rawls introduced the reflective equilibrium as an argumentative method for developing a theory of justice.[62;63] Others have adopted the concept of RE, particularly for addressing practical moral problems.[62] By matching various moral and non-moral ideas an equilibrium can be reached, which offers a coherentist account of justification.[62] RE can refer both to the process of argumentation and to the product. Ideally, all relevant elements will be involved in this process. However, since it is very unlikely that all factors are (or can be) known, and moreover, it will be virtually impossible for a person to work with all elements, one has to work with the factors that can be identified and are relevant for the specific purpose.[62] Searching for coherence between the widest set of moral and non-moral beliefs has been referred to as 'wide reflective equilibrium'.[61;62] The achieved equilibrium is not an endpoint, but a provisional fixed point. This indicates that the equilibrium can (and should) be challenged and altered when other relevant information, such as new facts or conceptions, are introduced.[62;63]

Reflective equilibrium and empirical ethics

Empirical ethics refers to the broad set of strategies that combine or integrate data from empirical studies and ethical analysis.[64;65] It considers empirical data and ethical analysis complementary to each other.[64;66] Especially in practical ethics, it seems invaluable to incorporate empirical data in an

ethical analysis when one wants to make well-informed and pro-active normative claims about a certain practice.[65-67] Empirical information can be considered one of the elements included in a wide-RE process. Depending on the purpose of the reasoning process and the issues at stake, the empirical data included in the process can be different in nature and can play several roles.[67] Since it is our aim to examine the appropriate role of consent in pediatric biobanking, we wanted to include empirical data about this practice in our analysis. Whereas empirical data can be used from existing, published empirical studies, data can also be generated specifically for ethical analysis. Considering the limited amount of empirical literature on consent and pediatric biobanking,[68] we conducted an empirical study on this subject ourselves.

Case study

The aim of our empirical study was to enrich our ethical analysis by scrutinizing the interpretation and use of consent in current pediatric biobanking practice. A case study can be used to investigate a phenomenon in depth within its real life context,[69] which made it particularly suitable for the aim of our study. Since there are several types of biobanks, the multiple-case design was selected, so that the influence of certain biobank characteristics on consent related issues could be compared. Data was collected from multiple sources from each biobank, such as websites, information leaflets, and informed consent forms. Furthermore, observations were made, for example, during informed consent conversations or during medical measurements. Also, interviews were conducted in order to supplement previously collected information and to provide context. Special attention was given to the inclusion of residual tissue, the involvement of children in the consent procedure and whether children were re-contacted when they reached maturity. Whereas only chapter 6 presents the results from the case study explicitly, with a focus on the child's role in the consent procedure, the obtained knowledge has been used implicitly throughout this thesis.

By including empirical data in our ethical analysis we aim to incorporate essential details of pediatric biobanking practice. Hereby we want to increase the chance that our conclusions will be relevant for, and applicable in practice.

Considering the importance of progress in pediatric health care and the role pediatric biobanking may play in this development, and at the same time, the importance of protecting and respecting the children involved, this thesis aims to morally enhance pediatric biobanking practice and contribute to a responsible development of (pediatric) biobanking.

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Chapter 2

Inclusion of residual tissue in biobanks: opt-in or opt-out?

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ABSTRACT

Residual samples are an important source of tissue for biobanks. They refer to leftover tissue that is obtained in the course of clinical care. Residual samples can be included through an opt-in method – that is, a person explicitly expresses consent to include residual tissue – or an opt-out method – that is, the tissue is stored unless a person explicitly refuses. At the moment there is a renewed interest in the appropriate method for the inclusion of residual samples in biobanks. The expansion of biobanks and rapid developments in biomedical research underscore the need to evaluate the proper procedure. In this article we revisit the arguments in favor and against opt-in and opt-out methods for residual tissue research. We conclude firstly that an opt-out method is only justifiable when certain conditions are met: (1) awareness has to be raised, (2) sufficient information has to be provided, and (3) a genuine possibility to object has to be offered. An opt-out procedure that fulfills these conditions can be called a 'thick' opt-out method. As a consequence, the dichotomy between opt-in and opt-out is less stark than usually suggested, as both methods require a certain amount of effort. Secondly, we conclude that because of the diversity of tissue and research, not every situation can be treated alike. There are at least four situations that require opt-in procedures: (1) research with higher risks or increased burdens, (2) the use of controversial or high-impact techniques, (3) research on sensitive tissue types, and (4) research involving vulnerable patients. We suggest that further interdisciplinary debate should answer the question when to opt-in or when to opt-out.

INTRODUCTION

A biobank can be defined as a collection of human biological samples stored for medical-scientific research purposes, usually linked to phenotypic data.[1;2] To collect material, biobanks have different strategies: they may collect tissue specifically for research purposes, but often contain residual samples as well. Residual samples refer to tissue that was taken in the course of clinical care and is leftover (e.g., a diagnostic biopsy or therapeutic removal of tissue). In many cases, the stored tissue will be most valuable for research when it remains linked to information about the person.[3-5] Therefore, the included samples will often be stored coded and consequently will not be anonymous—if complete anonymization would be possible at all.[6-8]

Regarding the inclusion of residual tissue, two predominant methods can be discerned: opting-in and opting-out. In an opt-in scheme, a person explicitly expresses his or her consent. Contrarily, in an opt-out scheme inaction is treated as a signal of consent.[9] A strong consensus exists that opting-in is the preferred method to include people in clinical research.[10] The same counts when tissue is collected specifically for research, since research is the only reason for taking the sample. However, at the moment, there is no consensus about the most appropriate procedure to include residual samples. Both opt-in and opt-out methods are practiced and advocated:[11] some even argue that there is no consent required at all.[12;13]

The expansion of biobanks and the rapid developments in biomedical research (e.g., the emergence of whole genome sequencing (WGS) and the increase of personal information that can be derived from research)[8] emphasize the need to rethink the appropriate way to include residual tissue in biobanks.[14;15] Therefore, we sought the key arguments in favor and against opt-in and opt-out methods for residual tissue research in the literature. The aim of the article is to present an overview of the arguments and to discuss them briefly. We focus on new residual tissue that is stored coded and will not review the subject of archival residual tissue – residual tissue that is already stored at this moment. We will conclude by offering some brief comments in order to take the current debate a step forward.

GLOSSARY

Biobank: a collection of human biological samples stored for medical-scientific research purposes, usually linked to phenotypic data

Opt-in procedure: a procedure where a person explicitly expresses his or her consent

Opt-out procedure: a procedure where inaction is treated as a signal of consent

Residual tissue: tissue that was taken in the course of clinical care and is leftover

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

Thin opt-out procedure: an opt-out procedure without the fulfillment of the three conditions

ARGUMENTS IN FAVOR OF AN OPT-OUT METHOD FOR THE INCLUSION OF RESIDUAL SAMPLES

Scientific advantage

Opt-out procedures for the inclusion of residual tissue in biobanks are associated with low refusal rates and therefore high participation rates.[16;17] In order to generate scientifically valid results, sufficient numbers of samples are needed. People who are indifferent or do not mind participating in research, but are not willing to make an effort to explicitly consent, will be enrolled in an opt-out procedure. Conversely, they will not be included in an opt-in procedure.

However, it has been noticed that an opt-out method could, in theory, have a negative effect on participation rates as well. If people dislike the idea that their consent is not explicitly sought, it is possible they opt-out of participation because of public distrust or because their 'gift' is taken for granted.[9]

Lower financial costs

An opt-out procedure is associated with lower costs[18;19] compared to an opt-in procedure – which is generally costlier due to extensive procedures and lower participation rates.[20;21] Money spent on the recruitment of participants cannot be used for other purposes. As a result the quality of the research may decrease or some projects may not be able to start at all.

However, whether an opt-out procedure indeed is considerably less costly depends on the way the formulated conditions are filled in. A very 'thin' opt-out procedure, without adequate information provision or genuine possibilities to object, will certainly be less expensive. But when more demanding conditions are formulated, an opt-out procedure requires certain amounts of efforts and thus money as well.[22]

Moral duty to participate

The aim of conducting biomedical research is to generate biomedical knowledge, which is a benefit as such[2;23;24] and may eventually also prevent serious harm.[25;26] Therefore, with an appeal to principles such as beneficence, solidarity, and reciprocity, participation in biomedical research can be considered a moral duty.[25;27-29] Solidarity calls for mutual support[30] and reciprocity appeals to a duty to contribute to the development of biomedical knowledge since we all benefit from it.[25;31] Although this duty would exist both with an opt-in and an opt-out procedure, it can nevertheless provide an argument for a less demanding procedure for the inclusion of residual tissue, like the opt-out procedure. After all, when there would be a moral duty to allow inclusion of residual tissue, it is reasonable to adopt a system where participation is the starting point or default position. Some even consider it an argument for not obtaining consent at all.[12;27]

However, several important objections have been made against this duty.[32;33] For example, there are many actions that would benefit others or could rescue them (e.g., donate money for food). Priority or a special status for participation in biomedical research, compared to other goals, has not been shown. Another objection that has been made is that people already contribute to biomedical research by paying taxes and paying for treatments; therefore, they would not have

a duty to participate based on reciprocity.[32;33] A complete overview of the extensive discussion on whether there is a moral duty to participate in biomedical research and if this duty would be strong enough is beyond the scope of this article. However, residual tissue research is considered to generate important biomedical knowledge and the association of the research with low risks and burdens would provide an additional argument for a moral duty.[31]

Low risks and burdens

Research on tissue does usually not entail the same risks as research on persons. Moreover, residual samples are taken in the course of clinical care; therefore, there are no additional physical burdens involved. Consequently, many have estimated the risks of biobank research as low or even absent.[3;5] However, the precise consequences of biobank research are sometimes difficult to predict[34] and the accompanying risks may be less clear than they appear to be.[35] Particularly, the information derived from samples can harm people.[36] There are psychological and/or social risks (e.g., genetic discrimination or stigmatization of groups, possible implications for family members, and consequences for employment or insurance possibilities).[37-40]

It follows that the risks involved in biobank research are tightly connected to the type of research that will be carried out on the sample, as there will be certain studies that are associated with higher risks or burdens. For example, when a researcher intends to conduct WGS, the risk of disturbing information is present. The risks are also tightly connected to the governance policy of the biobank (e.g., how the confidentiality and security measures are regulated). For example, a well-functioning Institutional Review Board (IRB), known in the European Union as a Research Ethics Committee (REC), can minimize the chance of (excessive) risks by assessing the research protocols and applying ways of risk management.[3;12]

Compatible with autonomy

Usually, a distinction is made between negative and positive autonomy. Negative autonomy is commonly understood as the right of a person to make personal decisions without undue influence or coercion from others.[41] Positive autonomy refers to the more 'thick' interpretation of autonomy and entails the ability to take control over one's life and to live according to one's values and beliefs. In a positive account, autonomy is associated with concepts like self-expression and self-determination.[41]

Within an opt-out procedure potential participants can be sufficiently informed and they can still make a personal choice whether they want to participate or not.[42;43] Therefore, an opt-out method could be an adequate and sufficient way to respect autonomy.[44] However, this again depends on the exact implementation of the procedure. Firstly, people should be made aware of inclusion of their residual tissue as the default position. Secondly, they should receive adequate information about this and have easy access to additional information. Furthermore, they should have an accessible way to object to participation and this should be adequately registered.[42;45;46] For example, it is difficult to maintain that negative autonomy is respected when residual tissue is included without people knowing this. Also, when people do not receive understandable information, they will not be able to judge whether participation corresponds with the idea(l)s they have and positive autonomy will

therefore not be fostered. It has been shown that, at present, there is (too) low awareness of people about the use of their residual tissue in research[47;48] and biobanks.[49]

Positive public attitude

In general, people seem to have a positive attitude towards the use of their residual tissue for biomedical research, as they consider it to be an important goal.[47;50-53] Some argue that because of this, an opt-out method is best suited for biobank research.[44]

However, a positive public attitude towards the use of residual tissue does not necessarily signify support for opt-out procedures. In addition, people themselves have expressed that although they emphasize participation, they expressed a preference for an opt-in procedure over an opt-out procedure.[54;55]

Also, there is considerable variation in the views of the public.[56] It has been suggested that in general patients have a more positive attitude towards biobank research than the general public.[57] More specific, it has been shown that cancer patients preferred a thick opt-out procedure over an opt-in.[58;59] In addition, surgical waste was regarded very differently compared to healthy tissue. There was less concern about how unhealthy tissue was used after removal.[48] Therefore, although a positive attitude may be shared by many, it cannot be generalized.[60] The opinion of the majority refers to democracy and should not be confused with autonomy.[61;62] When the majority approves inclusion of leftover tissue, this should not deprive others from their right to make an autonomous decision.[62]

ARGUMENTS IN FAVOR OF AN OPT-IN METHOD FOR RESIDUAL SAMPLES

Respect for negative autonomy

An opt-in procedure requires an act of consent from the individual before the proposed action will be carried out. Due to this requirement, respect for negative autonomy would be safeguarded. This will be of even greater importance when the participant can be considered the owner of the removed tissue – but who (if anyone) owns human tissue, once separated from the body, is an ongoing topic of debate.[51;63;64]

Even so, one of the main concerns with the opt-out method is the possibility of including samples from people without their knowledge and possibly against their wishes. Even when a participant is adequately protected against excessive risk, he or she can still be wronged when the decision about the inclusion of their residual tissue was taken from him or her.[5;65] It would be misleading not to actively inform people about inclusion as the default position, as it would be reasonable for people to assume that residual tissue will be discarded. In an opt-out method it is assumed that people are aware of their inclusion, understand the information, and will take action if they do not want to participate.[66] As there is no evidence that people are willing to participate, it has been stated that opt-out, in principle, can never be considered as actual consent.[67]

Fostering positive autonomy

To foster positive autonomy, non-interference is insufficient; one really needs to stimulate autonomous decision making. For example, when the research may generate relevant research results, mere non-interference is insufficient for adequate decision-making. Earlier we have defended a qualified disclosure policy, where different packages of individual research results are presented.[68] Opt-in will be a more suitable procedure to discuss such a policy.

Scientific citizenship

Scientific citizenship is in line with the fostering of positive autonomy. It refers to a societal ideal where citizens are well informed and well-equipped to make decisions concerning scientific research. The engagement of citizens would lead to better protection and promotion of their interests. Providing participants with the opportunity to reflect on their participation and to act on that can be a way to stimulate scientific citizenship.[69] It has been noted that there are different levels of citizen participation – ranging from manipulation to actual citizen control.[70] Although an opt-in procedure seems to be more suited to stimulate citizen control (which is perceived as the highest level of participation), an opt-in method does not necessarily safeguard citizen participation as such.

Protection of researcher

Consent is usually considered an instrument to protect the research participant and respect his or her autonomy. However, consent can also be viewed as a means to (legally) protect the researcher.[60;71] By obtaining consent from the participant, the responsibility of the acceptance of the entailed risks and burdens shifts (partly) from the researcher towards the participant. This may limit the liability of the researcher. Since only the opt-in procedure provides proof of consent, this method is more suited to protect the researcher.

Public trust

In order to conduct biomedical research public trust is indispensable. Public support is needed to facilitate research projects.[72] As noted before, distrust may result in high opt-out rates. Public distrust can be the result of people who are unaware of inclusion as the default position. Since people are not included without their explicit consent, an opt-in method is most likely to promote public trust. However, since within a thick opt-out procedure people are made aware of inclusion as the default position, public trust can be warranted as well.

Table 1 Arguments in favor opt-in and opt-out procedures

Arguments in favor of opt-out	Arguments in favor of opt-in
Scientific advantage – Opt-out procedures are associated with high participation rates	**Respect for negative autonomy** – Within an opt-in procedure, an act of consent from the individual before the proposed action will be carried out is required
Lower costs – Opt-out procedures are associated with lower costs	**Fostering positive autonomy** – An opt-in procedure is more suitable to stimulate autonomous decision making
Moral duty to participate – A moral duty to participate could provide an argument for a less strict consent procedure	**Scientific citizenship** – With an opt-in procedure, active and informed citizen participation is promoted since action is required, hence scientific citizenship is stimulated
Low risks and burdens – Biobank research with residual tissue is associated with no additional physical burdens or risks	**Protection of researcher** – Only the opt-in procedure provides proof of consent; therefore, this method is more suited to protect the researcher
Compatible with autonomy – Within a thick opt-out procedure potential participants can be sufficiently informed and they can still make a personal choice whether they want to participate or not	**Public trust** – Since people are not included without their explicit consent, an opt-in method may be more likely to promote public trust
Positive public attitude – Studies indicate a positive public attitude towards the use of residual tissue for scientific biomedical research	

CONCLUDING REMARKS

Taking stock of the arguments in favor and against opt-in and opt-out procedures for the inclusion of residual tissue in biobanks (see Table 1), we conclude that an opt-out procedure needs to fulfill certain conditions in order to be an appropriate method to include leftover material. Public trust and respect for negative autonomy can only be sufficiently protected and warranted within an opt-out procedure when (1) awareness is raised among people about inclusion of residual tissue as the default position, (2) adequate information is provided, and (3) a genuine possibility to object is presented and objections are adequately registered. In addition, although not a characteristic of the opt-out method, another condition that needs to be fulfilled is adequate governance of the biobank in order to protect participants (e.g., to ensure confidentiality). An IRB or equivalent committee should monitor the distribution of tissue by assessing research protocols. Adequate measures should be taken to fulfill these requirements. After all, an opt-out procedure should not result in the exploitation of people's ignorance. Patients need to be actively, preferably personally, informed about the opt-out procedure.[59] Merely putting posters or leaflets in a waiting room will be insufficient. In this information there should be a description of the governance of the biobank (e.g., general information about the type of research, the identifiability of the tissue, etc.). Empirical research is needed to evaluate the implemented opt-out method.

An opt-out procedure that does not satisfy these conditions can be called a 'thin' opt-out procedure and is clearly insufficient. An opt-out method that does fulfill the conditions can be classified as a 'thick' opt-out procedure. In practice, the dichotomy between a thick opt-out and an opt-in procedure may be less stark than usually suggested. To our best knowledge, no studies have examined the exact financial differences between a thick opt-out and an opt-in procedure, but we expect this difference to be relatively small. However, it is also reasonable to assume that an opt-out will involve less administrative burden. Moreover, even if they may not differ that much in practice, they do differ in the underlying moral message. Opt-out as the default position sends the moral message that allowing your residual tissue to be used for research is the right thing to do. In contrast, with an opt-in procedure this appears more like an extraordinary act.

Secondly, we conclude that the question is not whether in general an opt-in or opt-out procedure is most suitable for residual tissue, but in which specific cases one or the other is appropriate. Residual tissue is a collective term for a diversity of samples. In addition, a wide variety of research types can be conducted on them. Hence, the appropriate method to include the tissue is context-specific and it would be too simplistic to treat all situations alike. We suggest at least four situations that would require an opt-in procedure. Firstly, there are certain types of research that are associated with increased burdens or higher risks (e.g., increased psychological or social risks associated with genetic information from WGS). When the risks or burdens of the proposed research increase, an opt-out method is no longer sufficient. Secondly, in some studies controversial and/or high-impact techniques are involved (e.g., when an immortal cell line is derived or when chimaeras are created).[73] As these types of research are sensitive and difficult to explain adequately in the general research information, an opt-out procedure would be insufficient. Thirdly, when sensitive cells or tissues are used (e.g., gametes), a more extensive consent procedure would be appropriate.[74] Lastly, for certain groups of vulnerable patients an opt-in method is required (e.g., psychiatric patients). For this group, the competency to understand the presented information needs to be evaluated before tissue can be included.[75] It should be the role of an independent IRB to determine when an opt-in procedure is required. Although a comprehensive overview of the situations that require an opt-in procedure has not been given, we submit that the type of tissue and research affect the appropriate consent procedure. Further discussion is needed to formulate the amount of risks and burdens, the nature of the techniques, the types of tissue, and the groups of vulnerable patients that would require an opt-in procedure. As the appropriate method is context-specific, the role of an opt-out procedure can differ between institutions and can change over time when developments in research alter the biomedical field. For instance, when a biobank intends to facilitate WGS for all samples, an opt-out method will be unfeasible. However, although the use of WGS is increasing, at the moment straightforward research still plays an important role in the scientific landscape and it seems reasonable to assume that this will continue to exist in the near future.

A third comment can be made about a consequence of the inclusion of residual tissue with a thick opt-out method. The drawback of this proposal is that researchers will have to re-contact participants when they want to conduct certain types of research (e.g., WGS, immortal cell lines) to ask additional consent. As there can be years between the inclusion of a residual sample and the actual research that will be conducted on them, it may be difficult to approach people. However,

the distress that is caused to people by re-contacting them will probably decrease in a thick opt-out procedure as they will be aware of the inclusion of their residual tissue and the possibility that they will be contacted for specific research. In addition, introducing an opt-in procedure for all residual tissue research will not solve the dilemma of re-consent. Even within a broad opt-in consent procedure, it is impossible to discuss all the research possibilities that can be conducted on a sample. Previously described situations (i.e., high risks and controversial techniques) will therefore require a specific opt-in procedure as well. Hence, re-consent will also be necessary when an opt-in consent procedure is adopted for the inclusion of all residual tissue.[8] Moreover, introducing an opt-in procedure for all residual tissue research is at least at this moment overly restrictive and likely to hamper basic biomedical research unnecessarily.

In summary, an opt-out procedure is only appropriate when certain conditions are fulfilled; hence, we propose a thick opt-out method. The appropriateness of a thick opt-out method or an opt-in method is context specific. Further interdisciplinary debate is needed to determine when to opt-in or opt-out.

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Chapter 3

A thick opt-out is often sufficient

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INTRODUCTION

Consent bias, which refers to a form of selection bias that is caused by the refusal of consent by particular groups, is an often-heard argument against stringent consent procedures. In their article, Rothstein and Shober (2013) argue that the degree and consequences of consent bias are usually overstated.[1] Though they recognize that some concern is justified, particularly in the context of large-scale database studies, they emphasize the importance of obtaining informed consent for ethically sound research. Rothstein and Shober argue that abandoning informed consent is too high a price to pay for scientific advantages, but they at the same time are open to alterations of the informed consent procedure in order to reduce the researcher's burden and improve efficiency. They make some suggestions for alterations, by suggesting the use of DVDs and introducing the possibility of consenting to minimal participation. Here we elaborate on their proposal to alter the informed consent procedure by, first, putting forward the distinction between the 'content' and the 'process' of an informed consent procedure. This is illustrated by means of biobanking research. Second, we argue that implementing a so-called 'thick' opt-out consent mechanism fits a tiered consent procedure and may both mitigate consent bias and be often sufficient for the inclusion of residual tissue in biobanks.

INFORMED CONSENT: CONTENT AND PROCESS

Two essential aspects of an informed consent procedure are the 'content' and the 'process' of obtaining consent.[2] Regarding the content of informed consent within the biobank context, there is discussion about the type and extensiveness of information that can and should be given to potential research participants. Traditionally a valid informed consent should include specific information about the aim, nature, risks, and burdens of a specific study. However, it is characteristic for biobanking that at the time of collection it is often unknown what future research will be conducted on the biobank samples. Therefore, 'broad' consent has been proposed as an alternative way to obtain informed consent at the moment of inclusion.[3] Adjusting the content of the informed consent procedure can also help to correct for consent bias. Rothstein and Shober propose, for example, to allow consent for minimal participation. This must enable researchers to collect basic information about people who do not want to participate fully and help them to correct for possible bias.

The process of the informed consent procedure refers to how consent is obtained. Rothstein and Shober refer to this when they cite the DVD intervention that resulted in higher participation rates. Regarding the process of informed consent, in the context of biobanks an often-debated subject is the inclusion of residual tissue, that is, tissue that is leftover after clinical care. Two consent methods can be discerned for the inclusion of residual tissue: 'opting in' and 'opting out'. In an opt-in scheme, a research participant explicitly expresses his or her consent. Contrarily, in an opt-out scheme, inaction is treated as a signal of consent. Although opt-out is mentioned briefly by Rothstein and Shober, it is not elaborated on, while opt-out procedures have been associated with lower selection bias[4]

and opt-in methods with a high selection bias.[5-7] This illustrates that also the process of an informed consent procedure can be used to influence consent bias. Moreover, opt-out is not only beneficial for research but can correspond with ethically sound research as well, as we next argue.

A THICK OPT-OUT IS OFTEN SUFFICIENT FOR RESIDUAL TISSUE RESEARCH

Earlier we reviewed the key-arguments in favor of and against opt-in and opt-out procedures for biobanks.[8] In brief, the main arguments in favor of an opt-out method are the scientific advantages, as we expect a higher participation rate and a lower selection bias. In addition, also lower financial costs are anticipated. Moreover, biobank research is a public good, of importance for the advancement of health care. As in residual tissue research the physical risks and burdens seem low, since the material is already collected, and people have benefited from the health care system themselves, one could state a moral duty to allow inclusion of tissue, grounded in such principles as solidarity, beneficence, and reciprocity. Although they consider discussing such a duty to be beyond the scope of their article, Rothstein and Shober seem to sympathize with such a duty when they write that individuals ought to consent to the inclusion of their health care information in research. Although the presence of this duty would be independent of an opt-in or opt-out procedure, accepting such a duty would justify the implementation of participation as the default position.

The arguments in favor of an opt-in procedure are associated with respect for autonomy and public trust. However, when certain conditions are fulfilled, public trust and respect for autonomy can be safeguarded within an opt-out procedure as well. We refer to this as 'thick' opt-out and describe the following conditions: (1) awareness of the opt-out procedure has to be raised, (2) sufficient information about the procedure has to be provided, and (3) a genuine possibility of objecting has to be offered. When these conditions are fulfilled, the dichotomy between an opt-out and an opt-in procedure may be less stark. The difference in participation rates (and consent bias) would only consist of people who are indifferent about participation. In contrast with a thin opt-out procedure, also people would be included who are opposed to participation but were, for example, unaware of the possibility to opt out. The data that Rothstein and Shober put forward suggest no difference in participation rates between opt-in and opt-out procedures for residual tissue. However, more empirical research is necessary to underscore this. In addition, also other practical differences, such as lower financial costs, should be examined. Although a thick opt-out may be justifiable for residual tissue research, we also concluded in our previous paper that there is no one-size-fits-all.

Although thick opt-out is appropriate for basic research, we think that certain situations require an opt-in as the moral duty to participate would decrease or the thick opt-out conditions cannot be fulfilled. Further discussion is required to identify these situations, but we suggested at least these four: (1) research with higher risks or increased burdens, (2) the use of controversial or high-impact techniques, (3) research on sensitive tissue types, and (4) research involving certain vulnerable patients. Biobank research is a process with different stages: (1) inclusion, (2) storage, and (3) usage of the material. It is important to note that the situations that require an opt-in can occur at different

moments in the biobank process. For example, before including tissue from psychiatric patients, their competency to consent needs to be evaluated; hence, an opt-in would be more appropriate at the time of including a sample. Another example would be when tissue is included through an opt-out procedure but researchers want to use it to produce an immortal cell line. Additional opt-in is required then at the time of sample usage.

THICK OPT-OUT CONSENT FOR MINIMAL PARTICIPATION

Rothstein and Shober stress the need for organized consent processes in biobanks and refer to offering potential participants a variety of options to consent to, as opposed to offering one total package. They suggest that tiered consent will provide the possibility of balancing the needs of researchers and respect participants as well. We agree that a tiered consent process can be beneficial for both researcher and participant. An additional advantage of a tiered consent procedure is that other matters can be dealt within packages or categories as well, for example, returning of individual research results in genetic research.[9;10] However, Rothstein and Shoben's proposal to allow consent for minimal participation seems to refer only to the content of the informed consent process. Our proposal of thick opt-out also refers to the process of obtaining informed consent for minimal or basic participation. By combining the considerations about the content and the process, a more complete evaluation of the informed consent procedure is possible.

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Chapter 4

Consent for medical device registries

Commentary on Schofield, B. (2013) The role of consent and individual autonomy in the PIP breast implant scandal

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ABSTRACT

The clinical introduction of medical devices often occurs with relatively little oversight, regulation and (long-term) follow-up. Some recent controversies underscore the weaknesses of the current regime, such as the complications surrounding the metal-on-metal hip implants and the scandal surrounding the global breast implant scare of silicone implants made by France's Poly Implant Prothese (PIP) Company. The absence of national registries hampered the collection of reliable information on the risks and harms of the PIP breast implants. To warrant long-term safety, a case can be made for mandatory post-marketing surveillance by means of the establishment of compulsory registries. In this edition of Public Health Ethics, Schofield calls for debate on how such a registry system should be initiated and maintained and how it would relate to the ethical requirement of consent. Here we use breast implant registries as a case to discuss whether and when a so-called 'thick' opt-out would be an appropriate method to include people in medical device registries. We conclude that a thick opt-out procedure for medical device registries is only justifiable in cases where inclusion does not involve burdens (or very low), when it does not involve a sensitive subject and when the data are stored anonymously (or at least not directly linked to the medical record). Otherwise, inclusion should be sought by means of an opt-in.

INTRODUCTION

Unlike pharmaceuticals, the clinical introduction of medical devices often occurs with relatively little oversight and regulation. Novel medical devices are usually evaluated for efficacy in a group of patients too small to identify uncommon complications.[1] Safety, efficacy and long-term effects are insufficiently known.[1;2] Some recent controversies underscore the weaknesses of the current regulatory regime, such as the scandal surrounding the global breast implant scare of silicone implants made by France's Poly Implant Prothese (PIP) Company and the complications surrounding the metal-on-metal hip implants.[3] Responsible innovation in medical devices can be enhanced in at least two ways: by preventing inadequately tested devices coming on the market and by taking measures to enhance post-marketing surveillance, for example by means of compulsory registry systems. In this edition of Public Health Ethics, Schofield (2013) describes how the absence of national registries hampered the collection of reliable information on the risks and harms of the PIP breast implants.[4] This issue will only increase in relevance now the amount of medical devices is growing and a novel class of medical devices is emerging that combine (degradable and non-degradable) devices with for example biomaterials and cells. To warrant long-term safety, a case can be made for mandatory post-marketing surveillance by means of the establishment of compulsory registries. Schofield's call for debate on whether and how such registries should be initiated and maintained and, particularly, how a compulsory registry system would relate to the ethical requirement of consent is therefore timely and important. She suggests that an opt-out procedure for the inclusion of women in a breast implant registry might be considered as an alternative for informed consent as we know from clinical research. Here, we use breast implant registries as a case to discuss whether and when a so-called 'thick' opt- out would be an appropriate method to include people in medical device registries.

TWO PROCEDURES TO OBTAIN CONSENT: OPT-IN AND OPT-OUT

There are two ways in which consent can be obtained: opt-in and opt-out. In an opt-in procedure, a person explicitly expresses her consent. In an opt-out method, inaction is treated as a signal of consent. Earlier, we reviewed the arguments in favor and against opt-in and opt-out procedures.[5] The most important argument in favor of an opt-in is respect for autonomy. Often, a distinction is made between negative and positive autonomy.[6] Negative autonomy refers to a person's right to make decisions without undue interference. Positive autonomy refers to a more 'thick' understanding of autonomy.[7] It entails the ability to take control of one's life and to live according to one's values and beliefs. This understanding of autonomy is more associated with concepts such as authenticity, self-expression and self-governance. To show respect for people's autonomy in some contexts does not only include noninterference but may also entail fostering people's capacities for autonomy.[8] An opt-in procedure requires explicit consent from the individual before her data can be included, which ensures that people are aware that their data are included in the registry; hence, negative

autonomy would be safeguarded. In addition, opt-in appears more appropriate to foster positive autonomy. Asking for explicit consent will provide an opportunity to discuss the situation, emphasize the importance of registries for public health and stimulate autonomous decision-making. Another argument in favor of an opt-in procedure is the maintenance of public trust in biomedical research. When women would note that they are included in a breast implant registry without their awareness, it could result in their distrust in the health care system. An important argument in favor of an opt-out procedure is the association with higher participation rates compared with an opt-in method. To conduct scientifically valid research, a sufficient number of research participants are required. In case of the PIP breast implant scandal, too few women were included in the central breast implant registry to make valid calculations of the incidence and prevalence of conditions.[4] In addition, there is a risk of consent bias, i.e. a form of selection bias that is caused by the refusal of consent. Decreasing consent bias is another important argument in favor of opt-out. Even those who argue that the degree and consequences of consent bias are usually overstated admit that concern is justified in the context of large-scale databases.[9] When the central breast implant registry would have deployed an opt-out procedure, one could have expected higher participation rates and a lower selection bias, which clearly would have had scientific and public health advantages. Moreover, an opt-out is probably also associated with lower financial costs, although we expect this difference to be small.[5] Also, a more principled argument in favor of an opt-out procedure exists: the moral duty to participate in (public health) research, grounded in principles such as solidarity, beneficence and reciprocity.[10] This prima facie moral duty becomes stronger when it involves a non-invasive procedure with small risks and burdens but high public health benefits. Although this duty exists irrespectively of the consent procedure, it provides an argument in favor of an opt-out procedure, as it would send the moral message that participation is the ordinary thing to do (and not a supererogatory act).

THICK OPT-OUT FOR MEDICAL DEVICE REGISTRIES?

Clearly, an opt-out procedure would be more attractive from a scientific and public health perspective but less attractive for safeguarding autonomy and public trust. Earlier, we have argued that an opt-out procedure can be compatible with autonomy and the maintenance of public trust as long as the opt-out procedure fulfills three essential conditions:[5] (1) awareness needs to be raised among people about participation in research as the default position, (2) adequate information needs to be provided, and (3) a genuine possibility to object needs to be presented and objections must be registered adequately. We referred to such an opt-out method as a 'thick' opt-out procedure. Schofield seems to refer to this thick account of an opt-out procedure, as she points out that women should be made aware of the option to opt-out.[4] Would such a thick opt-out be ethically acceptable? In case of a breast implant registry, it may be possible to fulfill the required conditions of a thick opt-out procedure. Patients could, for example, be informed about the inclusion in the registry as the default position both on a general level, e.g. brochure, posters, website and a personal level, e.g. by explicit information by their surgeon. However, even when the

conditions can be fulfilled, the question remains whether it is justifiable to deviate from an opt-in. After all, inclusion in breast implant registries is not without burdens. First, it concerns access to and storage of personal information. The registry would only be valuable when there would be long-term follow-up of the participants. This could be done either by an active follow-up (e.g. survey) or by linking the registry to the participant's medical record. Either way it can be classified as a potential invasion of people's privacy, requiring explicit consent. Second, it is conceivable that women experience their breast implants as a sensitive subject – they might feel ashamed. Third, in the unfortunate case of a woman developing a condition that requires further investigation, e.g. additional questions or physical examination, one should have the possibility to re-contact people to obtain further information. This also works the other way around: women can be warned in case of adverse events with breast implants in other women. Clearly, the establishment of registries would allow the collection of reliable data on adverse events and monitoring of long-term safety and efficacy, which are essential for women who undergo breast implant surgery. Medical devices are complex assemblies of multiple components, making it impossible to design an implantable device without any risks or harms.[11] As Ardaugh et al. (2013) rightly noticed after the metal-on-metal hip implant disaster: "implanted body parts cannot be recalled as easy as defective auto parts".[3] These are all reasons to prevent inadequately tested devices coming on the market and improve the implementation of systems for monitoring safety after a medical device is on the market. We nevertheless warn to be cautious with the inclusion of people in medical device registries for the sake of public health without their explicit consent. Autonomy can on the one hand not always be given priority in public health, where other values such as protection of the health of the group are central, but not all breaches to autonomy can on the other hand be justified because there is a public interest at stake.[12] Although the importance of an adequate breast implant registry seems undisputed, we think this does not necessarily justify an opt-out procedure because of the burdens involved, the sensitivity of the subject and the linkage to medical records or the obtainment of additional health information. We think a thick opt-out procedure for medical device registries might be suitable in cases where inclusion does not involve burdens (or low), when it does not involve a sensitive subject and when the data are stored anonymously (or at least not directly linked to the medical record). An opt-out is suitable when public health benefits are large and potential intrusion on privacy is low. Otherwise, inclusion should be sought by means of an opt-in. In all cases, hospitals, clinics and physicians involved should make as much efforts as possible to provide a well-informed option to enter medical device registries and to discuss with people the importance of registries for public health. We hope people themselves will subsequently feel it as their moral duty to contribute to these important kinds of research.

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Chapter 5

Clarifying assent in pediatric research

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ABSTRACT

Assent is a relatively young term in research ethics, but became an often mentioned ethical requirement in current pediatric research guidelines. Also, the European Society of Human Genetics considers assent an important condition for the inclusion of children in biobanks. However, although many emphasize the importance of assent, few explain how they understand the concept and few have elaborated on the underlying grounds. In this paper, we will discuss the different underlying ethical principles of assent. In the first category, assent appears to be derived from informed consent. This understanding is grounded in respect for autonomy and protection against harm. We conclude that this interpretation of assent is not of added value as a majority of children cannot be considered competent to make autonomous decisions. In addition, other safeguards are more appropriate to protect children against harm. The grounds from the second category can be classified as engagement grounds. These grounds do justice to the specifics of childhood and are of added value. Furthermore, we argue that it follows that both the content and the process of assent should be adjusted to the individual child. This can be referred to as personalized assent. Personalized assent is an appeal to the moral responsibility and integrity of the researcher.

INTRODUCTION

The inclusion of children in biobank research is considered important for the advancement of pediatric health care.[1-5] A biobank can be defined as a collection of human biological samples stored for medical-scientific research purposes, usually linked to phenotypic data in one way or another.[6-8] Hence, the primary goal of biobanks is to facilitate research, not to provide medical care. The inclusion of children in biobanks brings forward specific ethical issues. Notably, at the moment of inclusion, children are not able (and legally not allowed) to give consent and they are considered a vulnerable research population. In order to provide children with adequate protection against harm, appropriate safeguard measures are needed.

In current guidelines, assent is an often mentioned ethical requirement for the inclusion of children in biomedical research.[9-11] Also, the European Society of Human Genetics (ESHG) considers assent an important condition for the inclusion of a child's material in biobanks, as they put forward in a recent policy statement.[12] With regard to the different types of pediatric biobanks, the prevailing view is that assent should be obtained when possible.[3;13-19] However, though many emphasize the importance of assent, few explain how they understand the concept and few have elaborated on the underlying grounds of assent and its role in pediatric biobanks.[20] This is not surprising as no consensus exists about how assent should be interpreted and implemented in biomedical research.[21-28] The importance of conducting ethically sound pediatric biobank research[29] and the rapid developments in this field stress the need to scrutinize the concept of assent in pediatric biobank research.[14;18] Here, we will provide a conceptual analysis of assent, discuss the different underlying ethical principles and its, in our opinion, most tenable interpretation in pediatric research. In addition, we will consider how it should be implemented in biomedical research.

INTERPRETATION OF ASSENT: POTENTIAL UNDERLYING GROUNDS

Assent is a relatively young term in research ethics. Although it already appeared in a report by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1977,[27;30] it was only introduced in the 5th version of the Declaration of Helsinki in 2000 (the statement of the World Medical Association of ethical principles for medical research with human participants).[9;31]

In the past years, different underlying grounds for the attainment of assent have been put forward in the literature. They can broadly be divided into two categories. The grounds in the first category appear to be derived from informed consent. Assent is interpreted and used here by analogy of informed consent, as a kind of copy or imitation. By contrast, the second category of grounds allocate assent with a specific task and present it as a concept distinct from informed consent.

Category I – derived from informed consent

The grounds of the first category are similar to underlying reasons for obtaining informed consent, particularly 'respect for autonomy' and 'protection of the research participant'.[32]

Concerning the first ground, 'respect for autonomy', it needs to be taken into account that a person must have the capacity to make autonomous decisions before she is thought of as an autonomous person. Children are deemed to have insufficient decision-making capacities and are therefore, in general, not regarded as autonomous persons. As their cognitive development is incomplete, they are considered to lack an adequate understanding of the research proposal. In addition, they seem more vulnerable to the influences of their surroundings (e.g., parents), and the voluntariness of their decisions is at least questionable.[33] However, typical for children is that this incapability is temporary, as their capacity to make autonomous decisions develops as they grow older.

When grounding assent in 'respect for autonomy', assent can only be reserved for those children who are capable of making autonomous decisions about research participation. Children will need to reach a certain threshold before they can be asked to assent. The setting of this threshold is a subject of discussion. It is unclear what a child should understand in order to make an autonomous decision about research participation and also when a child reaches this level.[34] For instance, it has been suggested that children should be capable of understanding the risks, benefits and the procedure,[35] or that they should be capable of understanding altruism.[36]

A second ground for assent that has been put forward in the literature is the 'protection rationale'.[20] It is in line with the reasoning behind informed consent and refers to the capacity of a person to protect herself against harm by having control over what happens to her. In research with children, the protective function of informed consent is usually considered to be warranted by the requirement of parental permission, combined with more strict regulations about acceptable risks, the supervision of research ethics committees (REC) and the responsibility of clinicians/researchers.[37-39] As proxies could misjudge the impact or distress of a study on a child, there remains a role for the child to protect herself as well. However, this role rather takes the shape of 'dissent'[36;40] instead of assent, and is linked to the widely supported view that the dissent (or distress) of a child should always be respected, at least when the research does not offer potential benefits directly to the child.[9;39-41] Although respect for dissent is generally accepted, there is a lack of clarity about dissent as well, particularly regarding the question when opposition counts as valid dissent.[42] It has been argued that not every sign of dissent should be treated this way, but that first the reason behind the dissent needs to be uncovered.[36] For example, when the objection of the child has nothing to do with distress for the study but she rather wants to play in the playground, this should not be interpreted as dissent.[43;44] In addition, it is not clear how the silence of a child should be interpreted. Some define dissent as opposition or silence,[45] while others refer to it as the absence of assent.[46] We will return to the interpretation of the silence of the child later.

Although in reality instructions for assent are often derived from informed consent,[20;26] many have objected against grounding assent in the underlying reasons similar to informed consent.[20;23;33;39;47-50] When one would ground assent in respect for autonomy, it is one of the two: either children are considered incapable of autonomous decision-making and then it does not make sense to use a concept that requires autonomy, or a child can be considered competent to make autonomous

decisions and then it would be untenable not to grant the child the same level of control as an adult, at least from an ethical perspective. In that case, the informed consent procedure could be expanded to apply to competent children as well.[51] Protection against harm, the second ground, seems to be safeguarded mainly in other ways than assent: parental permission, more strict regulations about acceptable risks, the supervision of RECs, the responsibility of clinicians/researchers and respect for dissent. To conclude, assent derived from informed consent does not seem to have a real added value.

Category II – engagement grounds

Other grounds that have been put forward for assent lead to a more distinct role for assent. The first ground in this category, respect for the child and its developing autonomy,[23;24;33;39] has also been referred to as the 'development' rationale.[20] Supporters of this view generally argue that the principle of respect for a person requires that children are empowered to participate in decision-making to the extent of their capacity. As, in general, a child's capacities will develop as it grows older, its role in the decision-making process should increase as well.

A second, closely related, ground is the promotion of or the support for the development of the child. Assent in this way should be understood as a tool or a means to educate. In this case the obtainment of assent contributes to the child's upbringing and moral education. It has been suggested that through assent, different lessons can be passed on during participation in biomedical research, such as fostering autonomy, teaching altruism and supporting self-confidence.[20;30;33;48;50;52]

The third ground in this category considers assent as a support for communication between the researcher and the child.[20] An assent requirement most likely incites the researcher to provide research information to the child.[52] As a result, the child's trust towards the researcher may be promoted, which in turn can lead to a better researcher-child relationship.[46] This is especially important when the researcher is also the treating physician.

As these grounds from the second category do justice to the specifics of childhood, they are more appealing and have more added value. Assent understood in this way focuses on the involvement or engagement of the child in the decision-making process and has been referred to as the 'development' rationale.[20]

IMPLEMENTATION OF ASSENT: ITS POTENTIAL CONTENT AND PROCESS

Thus, we concluded that assent should be understood from an engagement point of view. The aim is a child's involvement in the decision-making process. The next step is to determine how assent should be designed in order to reach this goal. Two important elements of assent are the content, that is, which information will be discussed, and the process, that is, how the information will be discussed and which reaction will be considered assent.[33;39]

Concerning the content of assent, there are different levels of information that a researcher can present to a child, ranging from basic information to a content that resembles the information that would be presented to a competent adult.[24] When the goal is to engage the child in the decision-

making process, it follows that the amount of information should be adjusted to the developmental level of the child. It is therefore important to realize that the content of assent should be considered dynamic, not fixed. This may mean that the information provided can range from, for example, the procedure of blood drawing to concepts referring to altruism or returning individual research results.[53;54] An estimation of the appropriate amount and type of information should be made before the assent procedure takes place, for example, preparing of written information pamphlets for children. However, during the assent procedure it should be assessed whether the information was appropriate for the individual child. It may, for instance, be necessary to explain the information in an easier way to some children, while others would like to have extra information.[55]

In the process of the obtainment of assent, the manner of information disclosure and the reaction of the child are of great importance. First, it has been the subject of discussion whether research information should be communicated in written and/or verbally.[35] As disclosing information in both ways increases understanding of the child,[35] it is preferable to use both methods in such a way that they supplement each other.[56] Obviously, this should also be adjusted to the child and written information should only be provided when the child is able to read. In addition, other techniques can be used as well, for example, pictures to clarify the verbal information, but additional studies should be performed to optimize understanding.[57]

Second, it is important to decide which reaction of the child is sufficient for assent. Two themes of importance here are, the interpretation of silence and whether or not a signature is required. As discussed, it is unclear how silence should be interpreted. When we address this question in the light of assent founded in engagement grounds, it seems convincing that silence should not be considered sufficient for assent, except when it is paired with a non-verbal reaction such as nodding. When the goal is to truly engage children, it would be inconsistent to treat 'no-reaction' as assent. Second, the requirement of a signature has been the subject of discussion. It has been recommended that a signature should be obtained when the child is able to provide it.[41] No clear motivation was provided by the authors so we can only speculate, but this requirement could have been set in order to motivate the researcher to include the child in the decision-making process or because it is a clear and explicit requisite. However, it is also stated that a signature should not be the focus of an assent procedure.[24] A requirement for a signature could make the assent procedure more rigid and could disturb the relational aspect.[46] In addition, when a signature would be a requisite, there is a risk of focusing too much on merely the signature as it can be a form to protect the researcher against legal claims. Therefore, we think a signature should not be a strict requirement for assent procedures.

IMPLICATION: PERSONALIZED ASSENT

Both elements, the content and the process of assent, need to be adjusted according to the child's capabilities and the study at hand in order to accomplish optimal engagement. This implies that there is no 'one-size-fits-all' assent procedure for all children in research.[34] Different elements should therefore be assessed in order to determine the child's capacity to assent. When the development

of children is considered to evolve in stages,[58] age can easily be used to categorize children into groups, as is also the case at the moment. Assent can be adjusted in accordance to the expected development, for example, to offer information for the different age categories. Although this approach has a practical advantage, it can be criticized as well. Linking a child's capacity solely to age would not do justice to the individual differences between (the development of) children.[39] Factors such as individual circumstances, life experiences, emotional and psychological maturity, intellectual capabilities and the child's family have all been put forward as elements that should be taken into account in the assent procedure.[15;25;33;45;47;59;60] We therefore arrive at a more individualized or case-by-case approach.[15;55;59] This can be referred to as personalized assent. A similar line of reasoning can be found in the Gillick competency judgment, insofar as they both assess the maturity and competency of the child. The concept of the Gillick-competent child refers to a child below the age of 16 who is considered mature enough to be legally allowed to give consent to a clinical procedure.[61] It has been proposed that the concept of Gillick competency can be applied to pediatric research as well.[62]

For personalized assent an (inter)active structure of assent is required – the content and the process needs to be adjustable to the individual child and assent should be thought of as an ongoing process instead of a single act. In addition, personalized assent possibly effects the issues of re-contact and re-consent. However, the exact implications are complex and beyond the scope of this paper.

The requirement of a personalized assent gives rise to a dilemma. As the potential level of engagement will be different in each case, fixed end-points are difficult to determine. Instead, accepting a child's right to personalized assent implies a researcher's duty to commit herself to involve a child in the decision-making process as much as possible. We are aware that the demandingness of this duty is difficult to determine. It raises the question which efforts are reasonable to expect from researchers to engage a child in the decision-making process. As the assent procedure should be adjusted to the child's capabilities and the study at hand, it is difficult to formulate a general answer to this question. It would be more appropriate to address this issue by discussing specific research areas and cases.

CONCLUSION

Although many consider assent an important ethical requirement for the inclusion of children in biobanks, as is recently shown by the ESHG, few explain how they define and interpret assent. In this paper, it is argued that assent should be understood from engagement grounds in order to do justice to the characteristics of childhood. It follows that both the content and the process of assent should be adjusted to the individual child and study, which can be referred to as personalized assent. Although fixed end-points are appealing from a practical perspective, it is difficult to provide these with assent interpreted from an engagement point of view. Further discussion is needed to provide a concrete filling in of the duty to seek personalized assent in pediatric biobanking. Nevertheless, at this point, we make an old-fashioned appeal to the moral integrity and responsibility of the researcher with this contemporary interpretation of assent.

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Chapter 6

Consent procedures in pediatric biobanks

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ABSTRACT

Objective To show how four pediatric biobanks designed their consent policy and the child's role in the consent procedure and discuss lessons learned from practice.

Study design An international multiple-case study is conducted with four biobanks with different characteristics: (1) LifeLines (2) Prevention and Incidence of Asthma and Mite Allergy (PIAMA) (3) Young-HUNT-3 and (4) Oxford Radcliffe Biobank contribution to the Children's Cancer and Leukaemia Group tissue bank (ORB/CCLG). Data is collected from multiple sources in each biobank.

Results Four themes linked to the child's role in the consent procedure emerge from the multiple-case study: (1) motives to involve the child (2) informing the child (3) the role of dissent, assent and consent and (4) voluntariness of children to participate.

Conclusions Biobank characteristics influence the biobank's motives to include children in the consent procedure. Moreover, the motives to involve children influence the implementation of the consent procedure, and the extent to which children are able to make voluntary decisions as part of the consent process. Regulation is an important motive for including children in the consent procedure. However, actual realization of rules depends on their operationalization. Biobanks that seek follow-up efforts from children have a strong incentive to involve children in the consent procedure in order to promote research interests, in contrast to 'one-off effort' biobanks. Respect for the child should be the leading motive. Understanding which underlying motives play a role in different biobanks is valuable when designing pediatric biobank governance that is aimed at appropriate involvement of children.

INTRODUCTION

A biobank can be defined as a collection of human biological material, stored for biomedical scientific research purposes, and is usually linked to phenotypic data.[1;2] Pediatric biobanks are considered important for improving (children's) health care.[3-8] However, the inclusion of children in biomedical research in general, and pediatric biobanks in particular, gives rise to specific ethical dilemmas.[9-11] Children form a special group within biomedical research. They are usually considered incompetent to make an autonomous decision on research participation due to their immaturity.[12] Generally parents (or legally authorized guardians) must give permission before children may be included. Ethical and legal guidelines indicate that children should be involved in the consent procedure as well.[13-15] The Code of Federal Regulations, for example, states that adequate provisions must be made for soliciting assent from children.[14] The WMA declaration of Helsinki, does not mention children specifically, but states that when the research subject, who is incapable of giving informed consent, is able to give assent it should be sought, and that dissent should be respected.[13] The few biobanking guidelines that refer specifically to pediatric biobanks frequently allocate a certain role for the child in the consent procedure as well.[1;16;17] Furthermore, several empirical studies about biobank participation show that generally children want to be involved in the decision-making procedure about the inclusion of their material in the biobank.[18-20] It is, however, unclear how to allocate an appropriate role for children for the inclusion of their samples in biobanks. Knowledge of current practice will be helpful in addressing this issue. At the moment, little is known on the child's role in consent in pediatric biobanking practice, only that children's opinions are indeed frequently (planned to be) sought,[6;21] and that there is a considerable variability in consent forms[22] and that forms can be confusing.[23] However, to our knowledge, there are no studies that analyzed consent procedures and the child's role in depth.

We conducted a multiple-case study on the child's role in the consent procedures of four biobanks that include pediatric samples. Our study aims to provide insight into normative decisions and practical solutions biobanks develop in the pediatric context. This valuable information can be used to determine and assign an appropriate role for children in the consent procedure in pediatric biobanking. Moreover, considering the variety of types of biobanks, it is useful to examine whether biobank characteristics influence how to allocate an appropriate role for children, and if so, what this influence is.

METHODS

The case study method enables investigating a phenomenon in depth.[24] We studied the whole range of aspects that are part of the consent procedure, ranging from information provision to the consideration of the child's opinion.

Case selection

Four biobanks with diverse characteristics are included: (1) LifeLines, a population cohort from the Netherlands[25] (2) Prevention and Incidence of Asthma and Mite Allergy (PIAMA), a birth cohort study from the Netherlands[26] (3) Young-HUNT3, the adolescent part of the third wave of the population based Health Study of Nord-Trøndelag, Norway; the HUNT study[27] and (4) the Oxford Radcliffe Biobank contribution to the Children's Cancer and Leukaemia Group tissue bank, in this paper referred to as ORB/CCLG, a residual pediatric oncology tissue bank in the United Kingdom.

Data collection

After receiving permission from the biobank officials/management, data was collected from multiple sources in each biobank. Data was collected from November 2012 until August 2013. The biobank features and (consent) policies were outlined by studying textual sources such as websites, information leaflets, and informed consent forms. Furthermore, observations were made, e.g. during informed consent conversations or during medical measurements. Also, interviews were conducted in order to supplement previous collected information and to provide context. For each biobank, six to ten people were interviewed (three interviews were conducted over the phone). Respondents were purposively sampled and approached in cooperation with biobank officials. An information letter regarding the case study and the interview was provided to potential participants. The information letters were formulated specifically for biobank staff, parents and children respectively. Our main focus was interviewing people with knowledge of (the construction of) the child protocol, the consent/assent procedure and people with practical experience in the field. However, other stakeholders were included as well when possible, e.g. participating children and parents. Except for one child and one research nurse, all persons approached consented to participation. A total of 29 people were interviewed (see Table 1).

Data analysis

The aim of this multiple-case study is to provide insight into normative decisions and practical solutions for consent related issues in the pediatric context. In addition, it wants to examine whether biobank characteristics influence how to allocate an appropriate role for children in the consent procedure. In order to reach this goal, first each biobank, its characteristics and consent procedure were described (see Tables 2 and 3). Next, two analytic techniques were used: pattern matching and explanation building.[28] Pattern matching involves comparison of the empirically based pattern with a predictive one. In this study, we expected that biobanks would show similarities and differences in their consent procedures and how they involved children in this procedure. In addition, the explanation building technique was used. The goal of this technique is to explain a phenomenon, i.e. describe how or why something happened.[28] In this study we want to explain the similarities and differences between the consent procedures of the biobanks. For this, NG coded all the data in NVivo 10 by labeling units of texts that were relevant to our research aim.[29] ALB read the coded data and checked the codes for consistency. The codes were adjusted through discussion within the whole research group and by constant comparison across the cases and different data sources. When consensus was reached, themes were developed. Each theme was analyzed both within a

single case and across cases. By analyzing the themes across cases, we aimed to gain insight in the influence of biobank characteristics on the child's role in the consent procedure. The results of the case description are presented in Tables 2 and 3, the themes that form the in depth analysis of this study, are presented in the results section.

Ethical approval

The project was evaluated in the Netherlands by the Research Ethics Committee (REC) of the University Medical Center Utrecht. In addition, the inclusion of Young-HUNT3 was assessed by the REC Central Norway. Both RECs exempted the project from further ethical scrutiny. The inclusion from ORB/CCLG was evaluated by the Inter Divisional Research Ethics Committee from the University of Oxford and ethical approval was obtained.

Table 1 Interview respondents' characteristics

	n = 29
Biobank official	11
Research nurse/assistant	6
Researcher	3
Parent	3
Child	6

RESULTS

Four themes linked to a child's role in the consent procedure in pediatric biobanking emerged from the data.

Theme 1: Motives to involve the child

Three types of motives for biobanks to involve the child in the consent procedure can be recognized in the cases. Firstly, the wish to adhere to regulation that is aimed at the involvement of children in the decision-making procedure functions as a motive to involve children in all cases. In all three countries national law requires involvement of children, though they differ in their exact requirements.[30-33] Sometimes regulation is primarily aimed at clinical research and therefore not always considered appropriate for (longitudinal) biobank research. Other institutions, for example RECs, regularly offer guidance or instruct biobanks on the implementation of legal requirements in practice. Moreover, it is articulated that rules cannot be comprehensive and that the actual involvement of the child depends highly on how people act in practice.

Table 2 Case characteristics

	LifeLines	PIAMA	Young-HUNT 3	ORB/CCLG
Country	Netherlands	Netherlands	Norway	United Kingdom
Type	A three-generation population based cohort study	Birth cohort study	Cross sectional survey, with possibility for follow-up	Tissue bank with residual tumor samples
Participants	Aim is to include 165,000 participants, of which 15,000 children 0-18 years. Official number will follow in 2014. Children included between 2010 – 2013.	Baseline consists of 3963 children born in 1996 - 1997	8677 adolescents (13-19 years) included in 2006-2008	Patients from the John Radcliffe hospital with a suspected diagnosis of a pediatric type solid cancer. The cooperation started in 2009. Estimation: 10-30 patients/year provide consent.
Research protocol	Questionnaire parent, questionnaire children ≥ 13 years, clinical tests children ≥ 8 years. Follow up every 5 years.	Part 1: Research aimed at mite allergy and asthma. Children followed up to 8 years with questionnaires for parents and clinical tests in sub-groups at 1, 4, 8. Residual blood from the newborn screening was used. Part 2: Extension of follow-up to 16 years. Research goal broadened to chronic diseases. Clinical tests (at 11/12 years and 15/16 years) and questionnaires parents and children.	Questionnaires, clinical tests and short interview at school. Phase 2 studies in subgroups: physical fitness, acne, sight or social anxiety	Residual tissue (from a diagnostic or therapeutic sampling procedure) is stored in the tissue bank. Blood sample taken during routine blood tests
Biological material	Blood and urine samples	Blood samples, nasal epithelial cells, DNA swabs	Buccal swabs	Tumor tissue and blood samples
Inclusion	Through parents who participate in LifeLines	Through pregnant women	Through schools	Through hospital staff

Table 3 Description of consent procedures

LifeLines	Parents participating in LifeLines receive an invitation for their child to participate. After parental agreement, the family receives a letter, an information folder for parents and an informed consent form that must be signed by at least one parent. A children's information brochure is added for children ≥ 8 years. An informed consent form for the child is added for children ≥ 12 years. By returning the signed informed consent form(s) to Lifelines, parents receive a questionnaire and/or an invitation for screening of the child on location.
PIAMA	For the first part of the PIAMA project, pregnant women must provide written consent for the inclusion of their child. Both parents must provide written consent for clinical tests at 1, 4 and 8 years old. Parents need to provide additional written consents for, amongst other things, the use of residual blood from the newborn screening (for an IgE measurement) and additional measurements in former blood samples (glucose, HbA1c, cholesterol). For the second part of the PIAMA project, families receive, when the children are 11/12 years, an invitation letter, information material (both for parents and children), a consent form for the parents and a separate form for children ≥ 12 years. The signed consent form(s) must be returned to PIAMA. When the children are 15/16 years, families receive two invitation letters (one addressed to the parent and one to the child), combined information material for parents and child, a combined consent form that needs to be signed by the parents and child. One parent may sign at home; the other parent and the child must sign at location after an informed consent conversation.
Young-HUNT3	HUNT provides information to the schools/teachers and the school board must give permission for participation of the school in HUNT. Subsequently, the teachers inform the students in the class and hand out the information brochure for the children to take home and to discuss it with their parents. Consent must be signed by at least one of the parents and returned to the school. The child needs to sign a consent form at the time of the questionnaire (in the class). Before and after the clinical tests, the nurse asks whether the children have questions. If children want to participate, but the parents do not give consent, the children may participate in the questionnaire/tests, however, in that case the data will not be saved.
ORB/CCLG	First a consultant or research nurse gives a verbal explanation to patients and parents. Thereafter written information is handed out (both for the child and the parents). Later patient and parents must sign the consent forms. It depends on the child's capacities and wishes whether the child and/or the parents must sign an assent/consent form.

"You have to be convinced that this is something the child wants. But, that's also up to the people who work with the children. Rules cannot be all-embracing." Interview 27

Secondly, involvement of the child is considered to have a positive effect on her participation in the research. Particularly, biobanks that solicit a contribution from their participants at a later stage put forward that it would have a positive effect on continuous participation.

"We prefer that they come back in the future for follow-up measurements rather than they quit right now, cause then we would have nothing. So if the child doesn't want a venipuncture, we don't do it." Interview 26

Thirdly, the motive of respecting the child as a person, in influencing how to involve children in decision making can be recognized in all cases. Biobank staff considers it self-evident to involve children in the consent procedure, as it is the child's material that is included in the biobank.

"We don't want to take advantage of children. We don't want them to do something that they don't want to do." Interview 10

Moreover, respondents from the biobank that includes residual tissue from pediatric oncology patients indicate that involving children can contribute to an overall feeling of trust in the hospital and feeling of control.

Theme 2: Informing the child

Three cases have written information for children at the time of their inclusion. The birth cohort study provides written information at a later stage. The information usually covers research procedures and basic information on the storage of data and/or samples. A difference in information content is whether it is clearly mentioned that children can withdraw their data and/or material at a later stage, which is possible in all four biobanks.

Biobank staff from all cases considers verbal information an important method to inform children (and their parents). Some put forward that written information is actually supportive for verbal explanation.

"From my experience of consenting, a lot of your work is done via conversation. And so, if you have a brief document like that, people can quickly read it and will generate their own questions on the back of that." Interview 5

Although not all biobank protocols specifically require personal verbal explanation by biobank employees, in all four cases oral clarification or description of the biobank was given. However, our observations show there is variety in the content and the amount of effort biobank employees put into informing children personally. Moreover, in several biobanks a leading role was assigned to the parents. Although the parental role is considered important for informing children, respondents also

noted that in practice children are regularly poorly informed by the parents and that it is left to the biobank employees to correct this. Furthermore, the timing of verbal explanation differs between the biobanks: first time personal contact with biobanks employees is scheduled before, during or after the child and/or parent sign the consent form.

Theme 3: The role of dissent, assent and consent

Dissent, assent and consent are linked to a child's expression of her opinion. These three concepts played a role at the time of the child's inclusion in three cases. In the birth cohort study, the concepts become apparent at a later stage. In line with established international norms, all biobanks mention in written sources that if a child does not want to participate, this should be respected, which refers to dissent.

> *"During the medical examination the participant can stop participating at any given moment."* Project proposal approved by REC

However, it is not always clear how a child's dissent is respected in practice (see theme 4). In contrast, sometimes children's refusal is given considerable weight and can even influence biobank policy. In three cases, children's refusal to blood withdrawal, or possible refusal, had an effect on research protocols. Since children could refuse participation altogether, blood samples were made an optional part of biobank participation or left out.

> *"We noticed that people were inclined to refuse participation because of the blood sample. Since there are a lot of other tests that are of interest to use, we said that if the child does not want to participate in one or more parts of the study, this could be indicated and then we would discuss whether the child wants to participate in the other tests."* Interview 18

Besides a child's refusal, all cases pay attention to (the need to obtain) a child's agreement or permission, which is usually referred to as assent and consent. The actual implementation of assent and consent differs between biobanks. An important reason for this diversity is the variation between national laws and the instructions of formal organizations like RECs. Prominent differences are the use of age limits and/or individual competency assessments. The Human Tissue Act in the United Kingdom states that appropriate consent should be obtained from children for the use of tissue in research.[31] This means obtaining consent from the child when he is competent to deal with that issue. It is commonly assumed that the principle of 'Gillick competence' can be applied here, whereby children with sufficient maturity to make a decision can give consent on their own behalf.[34-36] When a young person is believed to be competent, consent from those with parental responsibility is not legally necessary for use of biological samples in research. However, in practice, the involvement of parents in decision-making will probably be required by most RECs.[34;35] In contrast, it is required by Dutch law that children ≥ 12 years provide written consent.[30] The Norwegian law also mentions age limits, though it also specifically states that as the child grows older and more mature, increasing importance should be attached to her opinion.[32;33]

Theme 4: Voluntariness of children to participate

Children participate in biobanks for different reasons. There seems to be a continuum from pressure/coercion, complying with parental wishes, echoing parents and having personal altruistic feelings. It appears that both researchers and parents can put pressure on the child to participate in the biobank.

> *"I have seen that some parents, when their children start crying with the blood withdrawal, say 'just do it.'."* Interview 13

> *"She [the research nurse] said 'Let's see if I can talk him into it'.… But I thought if she pushes him, and he really doesn't want to, I would stop her."* Interview 22

The next step on the scale is compliance of the child with their parents' wishes. It is difficult to make a clear distinction between pressure and compliance, but compliance may indicate that the children are at least not against participation. Also, some children stated that they participate to help other children. However, several respondents questioned whether these are the children's own words or their parents'.

DISCUSSION

The results show that all four cases involve children in the consent procedure. The exact implementation (theme 2 and 3) is affected by biobank motives to involve children in the consent procedure (theme 1). In turn, the exact implementation of the role for children influences the extent to which children are able to make voluntary decisions as part of the consent process (theme 4). Thus the motives to involve children appear to be leading for biobanks when they consider the role for children in the consent procedure. The following remarks can be made about the effect and interplay of the three motives achieved in this case study.

For all cases the wish to adhere to 'regulation' is an important motive to involve children in the consent procedure. Although regulation applied to all cases, the actual involvement of children varied because rules and regulation content differs, such as the differences in the use of age limits (see theme 3). However, not all variation can be explained by the variety of rules. How people act in practice depends on the interpretation of rules,[37] which may (at least partly) be influenced by underlying motives. This case study shows that two other motives to involve children in the consent procedure, 'research interests' and 'respect for the child', are of importance here.

Several cases in this study emphasize a child's freedom to refuse blood withdrawal, since it may otherwise result in the refusal of the child's continuous participation in the biobank altogether. Hence, this is a clear 'research interests' motive to involve children in the consent procedure. This finding resonates with the widely held view that in general biobank interests run parallel with those of the participants. Since continuous participation is essential for the success of biobank research, biobank governance is often committed to gaining and maintaining trust of the participants and

related issues such as privacy and consent.[38-41] The 'research interests' motive to involve children is clear for biobanks which seek follow-up efforts from children.[19]

All cases emphasize 'respect for the child' as a motive, which refers to the intrinsic motivation to involve children in the consent procedure. Thus for the biobanks that solicit follow-up efforts from children, both 'research interests' and 'respect for the child' are underlying motives to involve the child in the consent procedure. When the actual involvement of the child is considered, the two motives go hand in hand. However, this is true up to a certain point. There is a difference between involving children out of research interests or out of respect for children. For example, although it is theoretically possible for children to withdraw their (not used) biological samples in all cases, this is not always communicated clearly. From a research interests perspective this may be rational, whereas from a respect for the child point of view this would be inappropriate.

Furthermore, biobanks that seek only a one-off effort from children do not have a clear research motive to involve children in the consent procedure, such as the residual tissue biobank in this case study. In this particular case, multiple respondents articulate a strong motivation to include the children in the consent procedure, since they want to generate a feeling of trust and control for the children. Especially, since the children in this biobank are part of a very vulnerable group in a hospital. However, as we only studied one 'one-off effort' biobank, it may be possible that there are biobanks that do not have, or only to a minimal extent, respect for the child as an underlying motive to involve children. Since there is no underlying research motive for these biobanks either, the role for children in the consent procedure may come under pressure.

Good pediatric biobanking principles

In our opinion, the motive of respecting the child as a person should be the main motive when the role for children in the consent procedure is considered. This would, for example, mean that a child's right to withdraw must always be clearly articulated. The motive of respecting the child is connected to treating the child as an individual, recognizing the child's rights to be involved in matters that affect her, and to express her personal views, as articulated by the United Nations Convention on the Rights of the Child.[42] Earlier we have argued that involving children in accordance with their capabilities and wishes does justice to the characteristics of childhood.[43] Regulation offers guidance and protection of the child's right to be involved and is therefore of great importance. The European Society of Human Genetics (ESHG), for example, recently stated in their principles for good practice in pediatric biobanking that children should be informed and that assent should be obtained and dissent should be respected.[17] However, at the moment, there is no consistent legal framework for biobanking in Europe.[44] In addition, even when such a framework is developed, regulation alone cannot guarantee appropriate involvement of the child,[37] as is also shown in this case study. Therefore, we add that when biobanks take children seriously as persons, these principles should be operationalized from a 'respect for the child' point of view in all layers of the biobank organization.

Our study has some limitations. Although biobanks with different characteristics are included, not all potential characteristics are represented. In addition, a limited number of observations are made of consent procedures, as they did not always take place at the time of the study. Furthermore, part of the study concerns historical research and interview respondents may have altered recollections

of the situation. However, by combining different types of sources we aimed to achieve as complete an image of pediatric biobanks as possible. Since the focus of this paper is the inclusion of children, the issue of re-contacting the child at maturity to obtain her consent (or give the opportunity to withdraw) was not discussed. This important topic, however, should be addressed in future work.

Concluding remarks

Regulation is important to protect a child's right to be involved in the consent procedure. The actual involvement of the child however, depends on the underlying motives. For 'one-off effort' biobanks there is no clear research motive to involve children. It is essential for these biobanks to implement governance mechanisms that emphasize the importance of respect for the child. For 'follow-up effort' biobanks, the promotion of research interests is a strong incentive to involve children in the consent procedure. Although for these biobanks research interests go hand in hand with the child's interests, this is only to a certain extent and respect for the child should be the main motive.

In sum, different biobank models lead to a different involvement of children in the consent procedure. This is a valuable insight when designing pediatric biobank governance. Involving children in the consent procedure does not only respect the children, it also contributes to the sustainable development of biobanks in general.

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Chapter 7

Personalized assent for pediatric biobanks

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ABSTRACT

Pediatric biobanking is considered important for generating biomedical knowledge and improving (pediatric) health care. However, the inclusion of children's samples in biobanks involves specific ethical issues. One of the main concerns is how to appropriately engage children in the consent procedure. We suggest that children should be involved through a personalized assent procedure. This means that both the content and the process of assent are adjusted to the individual child. In this paper we provide guidance on how to implement personalized assent in pediatric biobanks. In this perspective, we consider which information about the biobank should be discussed and how to offer this information. A key point is to offer information in a layered form. Particularly for biobanks, the characteristic three phases of inclusion, storage and use of samples, provide a natural arrangement of the information layers. In addition, we discuss topics such as the role of the researcher and parent(s) and how to assess a child's wish and capacities to assent.

Furthermore, we argue that the assent procedure itself is formative. Investing in the procedure should be a requirement for pediatric biobank research. Although personalized assent will require certain efforts, the pediatric (biobank) community must be aware of its importance. The investment and trust earned can result in ongoing engagement, important longitudinal information, and stability in/for the research infrastructure, as well as increased knowledge among its participants about research activity. Implementing personalized assent will both respect the child and support biobank research.

INTRODUCTION

Many biobanks, collections of human biological samples stored for medical-scientific research purposes, include biological samples from children.[1-3] Samples can be specifically obtained for biobanks, or may be left over after clinical care.[4] Pediatric biobanking is considered important for generating biomedical knowledge and improving (pediatric) health care.[5-10] However, biobanks give rise to ethical issues, such as appropriate forms of consent, questions about confidentiality and appropriate governance.[11;12] Since children are not considered competent (and legally not allowed) to provide informed consent,[13] pediatric biobanks involve additional specific ethical issues.[14-18]
Generally, parents (or legal guardians) must give permission for the inclusion of their children in biomedical research. Over the last decades, there has been a move towards recognition of a child's right to be involved in matters that affect him or her and to express personal views.[19] This right is also recognized in biomedical research guidelines, specifically in the requirement to seek a child's 'assent'. In general, guidelines state that when a child is capable to provide assent for participation in biomedical research it should be sought. It is considered a necessary, though insufficient condition for the inclusion of children in research.[20-22] This view has also been articulated in the context of pediatric biobank research.[18;23-26] Earlier we, and others, have argued that assent should be understood from an engagement point of view in order to do justice to the characteristics of childhood.[27-31] To fully acknowledge the differences between children, the assent procedure needs to be adjusted to the individual child. We referred to this as personalized assent.[27] While this approach does justice to the individual child, it at the same time creates a dilemma. Accepting a child's right to personalized assent implies a moral duty of the researcher to make his or her best effort to engage the child. However, this is a positive duty and, without accurate demarcation, a positive duty can be limitless. It is necessary to determine which efforts are reasonable to ask from researchers. Without further articulation, personalized assent is at risk of becoming an empty concept.

In this paper we will therefore discuss what it means to engage a child, provide guidance on how to put personalized assent into pediatric biobanking practice and reflect on personalized assent.

CONTENT OF ASSENT

The content of the assent procedure refers to the information that is discussed with the child. Since assent must be understood from an engagement point of view, children need to be involved in accordance with their capacities and wishes. It follows that the content of the assent procedure is directly linked to the individual child's capacities and wishes, and therefore varies.[27] For some children it may only be possible to discuss that a blood sample will be taken and that he or she can say no. For more mature children, the detail of information may be similar to informed consent procedures for adults.[30;31] Eventually, the child may decide whether he or she wants to participate in the study as he or she understands it.[32]

Which information should be discussed first?

There are several empirical studies on children's understanding of research information and competence to assent/consent.[33] However, it is problematic to combine and generalize the results of empirical assent studies, because of the context specific factors that may have influenced the results.[33;34] In this paper we are particularly interested in children's understanding of and desire for information on biobank research and will therefore focus on this type of studies. Studies on the perception of healthy children found a considerable variation in their understanding of the biobank study rationale.[35-37] It was therefore deemed more appropriate to focus on practical procedures, like a venipuncture.[35] It seems plausible to focus on concrete information first, since this matches the general insight that children develop the ability for concrete reasoning before the ability to reason about more abstract concepts.[38;39] Moreover, information about what the child's experience will be in the study seems most relevant for the child. It follows that generally the first phase of biobank research will be easier to understand and should therefore be the starting point in informing children. The information related to the second and the third stage of biobank research should be offered to children who are competent to understand this and moreover, want to receive more information.[30]

PROCESS OF ASSENT

In order to determine the appropriate content of the assent procedure for an individual child, the assent 'process' is of great importance.

Structure to offer information

Certain models of obtaining consent can be useful for and translated into assent. Layered consent entails different layers of information.[40] The first layer is offered to all potential participants and contains the information that is indispensable for informed consent.[40] In case of personalized assent for biobanks, the first layer of information would contain basic information about the first phase of biobank research.

Another model of consent that is useful for personalized assent in biobanks is staged consent.[40] Staged consent emphasizes that informed consent is an ongoing process and that it takes time for people to understand what they are asked to consent to and decide whether they want to participate.[40] One way to offer children time to consider participation is by sending printed information and letting children discuss the study with their parents. Thereafter, if the child and parents decide that the child can participate, an assent/consent conversation can take place. Such an approach was taken in the most recent wave of the PIAMA[41] cohort.[42] Staged assent is particularly suitable for biobanks, since one of the characteristics is the longitudinal character of their research. When children grow older and expand their capacities, they can be asked for their assent (or consent) again. This particularly refers to the issue of re-contact once the child reaches maturity to obtain consent for continuous use of samples.[23;43] This complex issue needs further elaboration, but is beyond the scope of this paper.

An additional model that may be helpful is tiered consent, which refers to offering the participant a menu of options.[40;44] In the context of personalized assent this could be done by offering the child a possibility to assent or dissent to parts of the research, for example a blood withdrawal.

How to offer information?

Another aspect of the way to offer information is the choice of means or material used to inform children. Several means and methods have been suggested to support the transfer of information, such as pictures, games and DVDs (see Textbox 1). Making use of different styles, techniques and technical innovation, can be useful. However, additional research is required to determine the appropriate role for different techniques. Optimal engagement of the child should be the main goal.

Currently, information technology (IT) interfaces as part of participant-centered initiatives (PCI) are being developed in adult biobanks.[45;46] These developments can also be used in pediatric biobanking and can play a crucial role in maintaining the relation between the biobank and child (and future adult participant). Interfaces can be used to communicate with children over time and help to address an issue like re-contact. In addition, the quality of biobank research can be improved by investing in ongoing contact with the participating children. Participants are a valuable source for qualitative, experiential, and longitudinal information. An interface can be used to obtain such data.[45]

Textbox 1

Previously, we discussed that combining the classic methods of written information and verbal explanation increases the child's understanding.[27;47] and that these methods should be used in such a way as to supplement each other.[27;48] We also suggested the use of other techniques, e.g. pictures. However, merely adding pictures to written information does not seem to increase understanding and additional research is required to optimize communication techniques.[49]

One way to improve information provision is the use of stories and/or characters that children are familiar with. This can be helpful in explaining even difficult subjects. Harry Potter or the X-men, for example, can be used to explain genetics and hereditability.[50] Another suggestion is to shape the assent procedure as an activity.[51;52] This way children truly become part of the research discussion and it seems a promising method to engage them in a way that appeals to them. Examples are creating a storyboard and playing word games as a way to discuss research.[51]

Technical innovations can also be used, particularly since present-day children have grown up with multimedia. Biobanks already make use of computer games to perform measurements. LifeLines, for example, uses a fireman videogame during the lung function measurement. Although one study showed an increased comprehension of study procedures and risks among children who received multimedia information,[53] a review on the improvement of understanding of informed consent elements for adults concluded that multimedia interventions often fail.[54] Moreover, one small study showed that generally children preferred written information sent to them individually, instead of being informed through websites or email.[55] Hence, more research is needed on how to use technological innovations and multimedia effectively. When using multimedia, at least two points need to be considered. First, multimedia can be implemented in a passive form, for example showing a DVD, and/or an active form, for example a computer game. Second, multimedia should not be considered a substitute for interaction between researcher and child.[52]

The role for adults in the assent procedure

Obviously, there must be a contact moment between the child and someone who can assess the child´s capacities and wishes to personalize the assent procedure. Typically, there is a triangular relationship between the child, the parent(s) and the researcher.[56]

The researcher is an obvious candidate to seek assent from the child. The researcher is the one who wants to study the child (or the biological material) and is probably most knowledgeable about the research. However, one of the main dilemmas of assigning the role to obtain personalized assent to the researcher is his or her personal interest in including the child in the study. It may be appealing not to invest much effort in informing the child and elaborating on the child's opinion. Selecting research staff who is aware of their responsibility to respect the child and have a sense for working with children is therefore indispensable. In addition, training the persons who will obtain assent is very important. They should know what the aim of assent is, how to offer information to children, how to assess their capacities and wishes and how to act on it.[48;57]

Parents know their child and may have particular insights into interpreting verbal and non-verbal signals. Therefore, they can have an important part in the assent procedure. They can advise or assist in explaining (parts of) the study. In addition, parents may also play an important role in protecting their child's right to dissent and/or assent if a researcher does not take his or her responsibility.[42] However, it must not be overlooked that parents can also disrespect their child's dissent[35;42;58] and can be opposed to their child's right to assent or consent.[59;60] Therefore, it is important that researchers retain the assent procedure as part of their professional responsibility.

The assessment itself

The next question is how a researcher (or research staff) can assess the individual child in order to personalize assent. The first thing that obviously needs to be considered is whether communication with the child is possible. When communication is possible, first the basic research information should be offered. Hereafter, the researcher needs to find out what the child understands, what the child wants to know and what the child can and wants to decide.[61] Factors that are considered to influence these matters for example are, psychological state, anxiety, level and types of (research) experience, health status, maturity, culture, religion, familial and societal context and complexity of the research.[33;34;61-66] During a personal conversation the researcher should attempt to find out what the child understands by asking to explain their understanding of the study in their own words.[62] In addition, researchers need to listen and respond to the concerns and questions of the child. The aim of this conversation is for researchers to ascertain what information is valuable to this particular child and to try to fit the information to the child's needs.[61] Some may say that it is difficult for researchers to assess children. However, this does not mean that it should not be strived for.[62;67] Moreover, some consider assessing a child's capacities not as difficult as it may seem.[68]

Subjectivity of the assessment

A dilemma with the above approach is that it relies heavily on the researcher's capacities and efforts to optimize the assent procedure. If a researcher fails to invest in the assent procedure sufficiently, there is a risk of not involving the child at all, or at least not enough. As discussed, this

risk originates from the researcher's interests in including the child (or his or her biological material) in the research. Researchers are interested in the research that will be possible with the material of children and want to include the child's sample. Therefore, they may not be fully commited to optimizing the assent procedure. This may be particularly the case where researchers view assent as an 'extra' and parental consent as the only legal or ethical requirement. Furthermore, presumptions of the researcher about the incapacities of children may lead to failure to include children in the research discussion.[69] Introducing a 'presumption of competence' for children as a starting point in the research discussion about biobank participation, has been suggested as a way to ensure that children are taken seriously.[70] Further studies of such an approach and the attitudes of the persons who seek assent will be valuable. In addition, well validated tools to assess a child's capacities to assent/consent can be helpful to objectify the assessment outcome.[71;72] However, since the aim of assent is to engage with children, we think there remains a central role for the researcher in the assent procedure.

The reaction of the child

It is reasonably straightforward that an affirmative agreement of the child constitutes assent and that a clear objection refers to dissent. How should we consider the grey area between a clear dissent and an affirmative agreement? It is quite possible that children stay silent when their parents have given permission for participation and they feel intimidated.[32;73] Although children are aware of the possibility to dissent, they find it difficult to say no in reality.[36;37] Furthermore, when children do not give a clear answer about whether they want to participate, it is questionable whether they have understood the research information.[51] Thus, especially when children keep silent, extreme caution must be exercised before proceeding with the study.

DISCUSSION

Having described the practical considerations for the implementation of personalized assent (see Table 1), several comments can be made.

First, the question arises whether assent is a strict requirement in pediatric research. The assent procedure is itself formative; appropriate engagement adds to the integrity of the research relationship and its meaning for both researcher and child. Only when it is absolutely impossible to follow the assent procedure, the duty of the personalized assent procedure may be waived by a research ethics committee (REC) beforehand, for example in research with newborns. Otherwise a researcher must make the effort to seek assent in practice. Whether an affirmative answer of the child is required, however, is more complicated. It is possible that during the assent procedure, it becomes clear that the child does not have the capacities or desire to be involved in the decision-making procedure.[30;74] Since we conclude that not all children can and/or want to give assent after going through the assent procedure, it would be strange to impose an affirmative agreement of the child as a strict requirement on researchers. Therefore, we argue that provided that other safeguards are in place, i.e. the requirement of parental permission, strict regulations about acceptable risks,

supervision of a REC, the responsibility of researchers to respect their participants and respect for dissent,[27] a child may be included in a study without his or her affirmative agreement. However, this caveat should not be used as a way to circumvent the general duty to make the effort to seek assent. In addition, when there is no affirmative agreement of the child, the onus of proof is on the researcher to show that he or she did honor the personalized assent procedure and that it is justified to continue the research. Note that when the research population consists of children who are quite mature and/or the proposed study is reasonably straightforward, it will be more difficult to prove that it is justified to continue with the study without an affirmative agreement.

Second, investing in a personalized assent procedure can serve two goals. An appropriate involvement of the child shows respect for the child as a person. It is the moral (and professional) responsibility of the researcher to put effort into the engagement of the child in the research discussion and personalized assent.[27] It is interesting to see that children themselves also articulate some sort of duty on the part of the biobank researcher to involve them in the research discussion based on reciprocity: when they participate, researchers have a responsibility to treat them with respect.[55] It is important for researchers to be aware of this expectation and trust: it is another reason to take seriously their responsibility to engage children. Next to respect for the child, an appropriate involvement of the child in the research discussion also contributes to the quality and success of the research.[42;55] It may lead to a general trust in the biobank and children who are well informed and intrinsically motivated to participate, will probably provide more accurate information and are likely to participate longer.[34;42;55;75;76] This is especially important for biobanks, since they generally conduct longitudinal research and often want to collect phenotypic information on a regular basis. Children may stop providing information or even withdraw their samples if they cannot identify with the biobank.

Third, in the introduction we described that the duty to involve children in the research discussion is a positive duty and needs further demarcation. The amount of effort required to invest in the child must be reasonable.[44] There will be practical limits to this responsibility, for example the development of interactive games may be too expensive for small biobanks. Moreover, the efforts required must be proportionate to the study, hence, to the characteristics of the biobank. For example, taking a one-time saliva sample for a few measurements differs considerably from monthly blood withdrawal and providing information by filling in several questionnaires. There is also a difference between biobanks that want to conduct simple tests, like a hemoglobin measurement, compared to biobanks that want to use DNA sequencing methods. In general it can be stated that the greater the burdens and/or higher the risks, the greater the effort that must be put into the assent procedure.

Fourth, in line with the former remark, ethics governance can play both a formative and controlling role. RECs can explain what the underlying aim of assent is and advise on how to put it into practice. In addition, they can request a thorough assent policy as part of a research or biobank proposal in order to create a system of checks and balances.[24] This policy must clearly describe the entire assent procedure, including data on the persons who will be obtaining assent and which information materials will be used. The proposal should also discuss the course of action when the child does not give an affirmative reaction. A local REC can check whether the proposed assent policy is appropriate and proportionate for that particular biobank.

Table 1 Points to consider

Information material
– Use empirical studies of children's understanding and wishes about research discussions as a basis for the information material.
– Make use of tools that appeal to children: for example, make use of pictures, IT applications or design games. Try to activate the child.
Assent procedure
– Staged form: ensure longer period and invest in ongoing relationship
– Layered form: different layers of information. 1st layer concrete and basic information, usually about the sample removal (first stage of biobank process).
– Tiered form: offer a menu of options
– Build in a contact moment to personalize the assent procedure
Role of biobank
– Design personalized assent policy
– Make information material available
– Appoint appropriate staff to obtain assent and offer them training
– Monitor personalized assent in practice and adjust if necessary
Role of person seeking assent (generally biobank staff, research nurse or researcher)
– Personalize the assent procedure:
– Assess child and his/her personal capacities, situation and wishes. Part of the child's situation assessment is to determine the influence and role of parents.
– Explain and discuss biobank research according to the child's capacities and wishes
– Ask for the child's opinion
– Make notes about the assent procedure. Especially when a child does not give an affirmative agreement
Role REC
– Take a formative role and advice biobanks and researcher on how (and why) to implement personalized assent
– Check the assent procedure in biobank research proposal: the assent procedure must be clear in advance and part of the protocol.
– Supervise the implementation of the assent procedure in practice.

Fifth, a criticism of the account of personalized assent is that it would be impractical and/or not enforceable.[77;78] As discussed previously, we are aware that personalized assent is an appeal to a researcher's integrity and that it is difficult to provide fixed end points.[27;79] The assent procedure must be flexible enough to adapt to different (biobank) studies and the different situations of individual children, for example, their difference in maturation, diversity in family dynamics or culture.[30;34;80] Researchers must be reminded of their professional responsibility and moral duty to engage children and strive for empowerment of the individual child.[62] Since biobank employees reported a natural desire to engage children in the consent procedure out of respect for the child,[42] we are confident that an appropriate awareness can be achieved. However, making this duty explicit and increasing awareness of researchers and biobank employees is needed.

Last, we want to remark that consent procedures can benefit from working from the engagement point of view as well. Although informed consent nowadays gained an important legal function, our

view emphasizes the ethical origins of consent. People differ in informational interests and in the ways they want to be informed.[81] Viewing consent more from an engagement point of view may add to honoring these differences.

Concluding remarks

Personalized assent is aimed at engaging children in accordance to their personal capacities and desires. The assent procedure can be designed in order to support the goal of engaging children. A key point is to offer information in a layered form. Particularly for biobanks, the characteristic three phases (i.e. inclusion, storage and use of samples) provide a natural arrangement of the information layers. Since issues related to the first phase are usually most concrete and relevant for the child, it is sensible to start with these subjects. Topics linked to the other two stages could be added according to the child's desires and capacities.

Investing in the assent procedure as such should be a requirement for pediatric research and (biobank) researchers must invest in the assent procedure. However, since some children do not have the capacity or desire to be involved in the research discussion, an affirmative agreement of the child cannot be a strict requirement. It is important to note that researchers should still strive for such an agreement, and that the onus of proof is on the researcher to justify continuing research without an affirmative agreement of the child.

Although personalized assent will require certain efforts, the pediatric (biobank) community must be aware of its mutual importance. The investment and trust earned, if maintained, can result in ongoing engagement, important longitudinal information, and stability in/for the research infrastructure, as well as increased knowledge among its participants about research activity. Implementing personalized assent will both respect the child and support biobank research.

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Chapter 8

When children become adults: should biobanks re-contact?

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Submitted

ABSTRACT

The inclusion of children's samples in biobanks is invaluable for conducting biomedical (genetic) research and the development of pediatric health care. Children's samples, however, are usually included with parental permission and the question arises whether children should be re-contacted at maturity to obtain their permission for the continued use of their samples. We argue in favor of re-contact and conclude that biobanks need to have a clear re-contact strategy. We discuss four policies, ranging from an opt-out policy (participants can withdraw their samples, but the biobank does not re-contact the participant) to a strict opt-in (samples will be destroyed when participants do not give their consent). We conclude that a thick opt-out policy should be the default, meaning that participants are re-contacted by the biobank and given the opportunity to withdraw. We emphasize the importance of actually reaching the participants. Our proposal balances the interests of participants, biobanks and society, and hereby contributes to morally sound pediatric biobank research.

INTRODUCTION

At the moment, there are many collections of human biological samples stored for medical-scientific research purposes that include samples from children.[1] These pediatric biobanks facilitate research, which is considered important for improving (pediatric) health care by generating biomedical knowledge.[2;3] However, pediatric biobank research gives rise to specific ethical issues. At the time of inclusion, many children cannot, or are legally not allowed to, consent for themselves and typically parental permission is required. Samples may still be stored and used by biobanks when children become autonomous adults. The question arises whether children should be re-contacted to obtain their own consent, or give the opportunity to withdraw their samples, when they reach adulthood. Often this is referred to as re-consent.[4-6] This term, however, is a misnomer, since the child has not consented in the first place. We will therefore use the terms re-contact and consent.

Although some guidelines indicate that children should be re-contacted,[7-9] re-contact has been scarcely implemented in pediatric biobank practice.[3;10-12] This is not surprising since there is limited literature available that analyses re-contact in depth,[4-6;13] and there is disagreement on whether and how to put re-contact into practice.[14] Given the fact that biobanks already include pediatric samples and in light of the rapid developments in biobank research, it is important to address this issue now. In this paper we will discuss whether children should be re-contacted when they reach adulthood, and if so, which policy should be followed by biobanks.

ARGUMENTS IN FAVOR OF RE-CONTACT

Respect for autonomy and privacy

A first argument to re-contact a child is respect for her – then developed – autonomy. Respect for autonomy in a research setting refers to the right of a person to only participate in a study with her authorization and to enable a potential research participant to decide whether participating is in accordance with her own values and believes. Although the parental permission requirement may protect children against harm, parents cannot exercise their child's autonomy. Autonomy can after all only be exercised by a person herself. Hence, a parental decision made on behalf of a child, is not the same as a decision taken by an adult for herself.[13;15-18] One could argue that autonomy can be considered less relevant in biobank research. After all, tissue research differs from research involving participants themselves, especially when samples are anonymized. However, the vast majority of biobanks will store samples coded, since they will be most valuable for research when linked to information about the person.[19] Also, it can be questioned whether complete anonymization of biological material and datasets would be possible at all.[20] Since there is still an identifiable link between participants and their material, and study projects may infringe on a participant's personal values, we consider it important that they have a say in its use.

In line with respect for autonomy is the right to privacy. Privacy in research has been referred to as the right of the participant to decide on how much information about herself is shared with

researchers.[21] Obviously, participants should then be aware of their sample and data inclusion in the first place.

By re-contacting and informing the participants, they will be given the opportunity to decide whether they want to be part of this biobank.[5;6;10]

Engagement and scientific citizenship

Another argument to re-contact is that it will actively involve the participant in research. It acknowledges that translational research cannot be conducted without the involvement of individuals willing to act as research participant. This can also be a way to educate her about biobank research and the role she has.[22] This argument is linked to a broader ideal of scientific citizenship, here understood as the ideal of active citizens who are well informed and enabled to make decisions about scientific research.[22-24]

Re-contact may be beneficial for biobanks

In case one considers the scope of parental permission as limited, re-contacting may be beneficial for biobanks by enhancing research possibilities. It has been argued that there should be a certain restriction on the use of pediatric samples when they are included with parental permission only. According to some, publicizing full genomes[4] or sharing samples and/or data by population biobanks[25] should only take place based on a participant's personal consent. Although, at the moment, there is no consensus on the limits on the use of pediatric samples,[25-29] when restrictions are accepted, re-contacting the child will provide the opportunity for biobanks to expand their research possibilities.

Re-contact enables a disclosure policy

Biobank research may yield results that can be of interest for participants on a personal level. Particularly the return of individual genetic research results in the context of next generation sequencing (NGS) of DNA has been discussed extensively in the literature.[22;30] Grounded in a child's right to an open future, a child should decide if and which type of genetic information is given once she reaches maturity.[31;32] Although it is not an argument for 're-contact on continued research', re-contacting will enable the participant to decide on the return of individual genetic information.

ARGUMENTS AGAINST RE-CONTACT

Re-contact hampers biobank research

Re-contacting all participants can hamper research in several ways. First it will cost time and requires a logistic and financial investment, especially when there is no follow-up contact planned for the study itself.[5] Re-contact may not even be feasible, for example when a participant has moved or passed away.

It is undeniable that re-contacting participants will cost biobanks certain efforts or that in some cases it will be impossible to reach someone. If we conclude that children should be re-contacted,

the question is which efforts are reasonable to require from biobanks. This issue will be addressed later.

Second, research can be hampered when participants refuse the continued research on their data and tissue. This may impair research quality since the number of available samples decreases. However, a decrease of samples as an effect of the refusal for continued participation does not seem a valid reason against re-contact. After all, this is the reason why re-contact is implemented in the first place: so people can decide whether they want to continue participation. Moreover, two studies that used hypothetical scenarios to investigate the willingness of adults to provide consent for the continued use of their pediatric samples, concluded that a majority of their respondents would support continued research.[19;33]

Burdensome for participants

Another argument against re-contact is that the participant may find it intrusive to be re-contacted for something that happened many years ago. Particularly, when her material was obtained during an intense period of his or her life, for example when she had cancer in childhood, being re-contacted about this period may cause emotional distress.

This could however be the other way around as well: cancer survivors may be very eager to contribute to research. In addition, many biobanks, for example population biobanks, will include material from healthy persons for whom the burden may be minimal. In addition, informing parents and participants about the re-contact policy might ease the burden.

A DUTY TO RE-CONTACT

Above we argued that respect for autonomy and protection of privacy provide a ground for re-contacting children at maturity. We consider the promotion of scientific citizenship to be a favorable side-effect. In addition, re-contact enables a qualified disclosure policy, which is relevant for certain biobanks. We also discussed that re-contact may be beneficial for biobanks by enhancing research possibilities. One of the undeniable negative effects of re-contacting is that it will generate financial costs for biobanks and requires organizational efforts, which may hamper research. Although we think that this does not outweigh respect for autonomy and privacy rights, we do think it should be taken into account in re-contact policies. How to appropriately balance interests of participants and biobanks?

THE APPROPRIATE RE-CONTACT POLICY

We consider four potential re-contact policies for biobanks ranging from an opt-out policy to a strict opt-in (Table 1).

At one end of the spectrum is an opt-out (policy I): re-contact is not initiated by the biobank, but children can withdraw their samples and/or data. This policy would require the least amount

of efforts from biobanks, but the participant's autonomy is hardly respected and protection of a participant's privacy is difficult. After all, how can someone exercise the right to withdraw when she is not aware of her inclusion in a biobank? It could be reasoned that parents, instead of the biobank, should inform their child about the biobank and the possibility to withdraw. Although involving the parents should certainly be encouraged, we think that the responsibility to inform the participant cannot be transferred to the parents (completely). The biobank uses samples of an individual who is now capable to decide for herself and has therefore responsibilities towards that person. We conclude that the first policy does not protect the participant's interests sufficiently and is hard to defend for biobank research in general. Only in exceptional situations, for example, where the expected value of the research is very high and re-contact is not feasible, this policy could be appropriate.

On the other end of the spectrum is a strict opt-in (policy IV): children are re-contacted and asked for consent; if they cannot be located or do not answer, the samples and data will be destroyed. This policy may jeopardize the biobank's interests, since research could be hampered considerably. Not only will the material from individuals who are against participation be destroyed, the samples from persons who are indifferent to participation and do not want to put an effort into consenting will be excluded as well. We consider such a strict opt-in procedure disproportionate in many cases of biobank research. At least for the types of tissue research that can be referred to as ordinary and unlikely to infringe on personal values of the participant.[34] There are no physical burdens and risks associated with research on previously collected samples. Combined with the main goal of biobank research, which is generating biomedical knowledge and ultimately improving medical care, a strict opt-in procedure would be too stringent. In addition, a proxy has already provided permission for the inclusion and use of the samples, and the child might have been involved in this decision as well through personalized assent. Some value might be attributed to this. Moreover, based on the principles of solidarity and beneficence, there might even be a moral duty to permit the continued used of samples, though further ethical reflection is required on whether there is a duty to allow continued participation and what this duty entails.

In addition, it should not be overlooked that there may still be certain risks involved in biobank research such as psychological and social risks linked to information that can be generated, stored and used by biobanks.[17;24] These risks will be higher depending on the type of biobank, for instance, biobanks that generate much genetic data or study a small population with specific characteristics. Although we consider the fourth policy too strict for most biobank research, this policy may be appropriate when the risks are deemed higher. Also when biobank practices are more likely to infringe on personal values, for example the creation of chimeras or when commercial interests are involved, we conclude that policy four should be adopted.

For straightforward biobank research, then, a thick opt-out (policy II) or best effort opt-in (policy III) seems most suitable. In both policies, the use of samples from people who cannot be reached will be continued. In either policy, it is necessary to discuss which efforts biobanks should put into re-contacting a participant. A thick opt-out procedure, in the context of residual tissue, refers to an opt-out method with three conditions: (1) awareness has to be raised, (2) sufficient information has to be provided, and (3) a genuine possibility to object has to be offered and this objection has to be

administered in such a way that it will be implemented.[24] In the context of pediatric biobanking and re-contact, an important question is whether biobanks should ensure that the participants are truly re-contacted, which concerns both policy two and three. Incorporating such assurance provides a better insight in whether contact has been actually made or whether extra measures are required. Especially when there is no personal contact between the biobank and participants, we think a verification of notifying, such as a recorded delivery or a read receipt is appropriate. The difference, then, between a 'thick opt-out' and a 'best effort opt-in' is very small. Both approaches require similar amounts of effort from the researchers to contact the participant. The distinction is that in one policy the participant is asked to refrain from acting to continue participation, in the other she is asked to explicitly consent. However, in both policies the usage of the samples and data of participants who do not act will be continued. Therefore we consider the third policy not of added value compared to a thick opt-out policy.

Table 1 Re-contact policies for biobanks

Policy I	Opt-out: re-contact is not initiated by the biobank, but children can withdraw their samples and/or data.
Policy II	Thick opt-out: children are re-contacted once they reach maturity and given the opportunity to withdraw. If children do not withdraw, the samples and/or data may still be used in accordance with the earlier obtained parental permission.
Policy III	Best effort opt-in: children are re-contacted and asked for consent. If children cannot be located or do not answer, the samples and data may still be used in accordance with the earlier obtained parental permission.
Policy IV	Strict opt-in: children are re-contacted and asked for consent. If children cannot be located or do not answer, the samples and data will be destroyed.

CONCLUSION

Pediatric biobanks need to have clear policies on re-contact. Within the policy the parent(s) and child should, at the time of sample inclusion, be adequately informed about the re-contact policy for continued research.[6] We conclude that a thick opt-out procedure should be the default. Our proposal balances the interests of participants, biobanks and society, and hereby contributes to morally sound pediatric biobank research.

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Chapter 9
General discussion

INTRODUCTION

Whereas research on biological samples already exists for many years, the technological developments in biomedical research and information technology gave rise to the development and expansion of biobanks in size and number. Biobank research is considered important to generate biomedical knowledge. Also, research on children's biological material may yield valuable information, which can be important for the development of (pediatric) health care. The inclusion, storage and use of children's samples in biobanks, however, give rise to specific ethical issues. Children form a special group within biomedical research. They are usually considered incompetent to make an autonomous decision on research participation, due to their immaturity. Therefore, it is important to scrutinize how consent should take shape in pediatric biobanking. The main questions that are addressed in this thesis are:

I. What is the appropriate consent procedure for the inclusion of residual samples in biobanks?
II. What is the appropriate role for children in the consent procedure at the time of sample inclusion?
III. Should children be re-contacted when they reach maturity to obtain their consent for (or to give them the opportunity to withdraw from) the continued use of their samples?

Below, I will discuss the main conclusions of this thesis per question, reflect on them and identify issues for future research. Next, I will shortly consider the attributed value of the case study for this thesis. Last, the conclusions of this study will be discussed in a broader perspective on research participation.

THE APPROPRIATE CONSENT PROCEDURE FOR THE INCLUSION OF RESIDUAL SAMPLES IN BIOBANKS

At the onset of this thesis, it became clear that although leftover tissue is used for biomedical research for many years, there was no consensus on the appropriate consent procedure. Chapter 3 made the distinction between the 'content', i.e. which information is discussed, and the 'process', i.e. how consent is obtained, of a consent procedure. The classic view on both the content and process of consent are challenged in biobanking. Traditionally, the content of a consent procedure contains specific information about the proposed study and the associated risks. The consequences of biobank research are, however, difficult to estimate because the exact research projects that will be conducted on the samples are often unknown at the time of sample inclusion. Furthermore, the inclusion of residual samples brings forward questions about the process of consent. It is beyond discussion that opting-in is the preferred method to include people in clinical research, i.e. a person explicitly expresses his or her consent.[1] However, for residual tissue an opt-out procedure may be appropriate as well, in which inaction is treated as a signal of consent. Chapter 2 presents the arguments in favor and against an opt-in and opt-out procedure. Scientific advantages and lower financial costs are important arguments in favor of an opt-out procedure. Arguments in favor of an

opt-in procedure are associated with respect for autonomy and public trust. However, in chapter 2 and 3 we argue that respect for autonomy and public trust can be safeguarded within an opt-out procedure as well, provided that certain conditions are fulfilled.

The conditions of a thick opt-out procedure

In order to respect the participant's autonomy and safeguard public trust within an opt-out procedure, the following conditions need to be fulfilled: (1) awareness is raised among people about inclusion of residual tissue as the default position, (2) adequate information is provided, and (3) a genuine possibility to object is presented and objections are adequately registered. An opt-out procedure that fulfills these conditions is referred to as a thick opt-out.[1;2]

Since this thesis aims to relate its theoretical conclusions to practice, it is important to consider whether these formulated conditions of a thick opt-out procedure are feasible. Therefore, it is valuable to consider biobanks that aim to fulfill the formulated conditions of a thick opt-out procedure and study their achievements. A biobank that adopted an opt-out procedure and studied the awareness of their public of the possibility to opt-out is the BioVU, the Vanderbilt DNA Databank.[3] This biobank is composed of leftover blood samples from patients from the Vanderbilt University Medical Center, combined with de-identified medical record information. Information on BioVU and an opt-out checkbox were included on the consent for treatment form. In addition, posters and leaflets in clinical areas and advertisements in local publications were used to notify the patients.[4] An interview study showed that awareness of the possible use of leftover blood for research among adult patients fluctuated, with as highest level of awareness 50%.[4] The researchers put forward that it is unclear what the appropriate goal for awareness should be. Particularly, because participants who have completed a traditional informed consent procedure, are not always aware of their engagement in research as well.[4;5] Nevertheless, they also conclude that at the moment the opt-out procedure of BioVU is not optimal, and they are working to improve their informing procedure.[4]

At least two lessons can be learned from the BioVU case. First, the results of this awareness study support the claim in chapter 2 that patients need to be actively, preferably personally, informed about the opt-out procedure.[1] Second, the BioVU biobank shows the importance of continuous evaluation of the results and effectiveness of consent procedures.

Opt-in versus a thick opt-out

When the conditions for a thick opt-out procedure are fulfilled, the dichotomy between an opt-in and an opt-out procedure is less stark.[1] The difference in participation rates between an opt-in and a thick opt-out would consist only of the people who are indifferent to participation.[2] Empirical studies should be conducted to scrutinize the exact variability in participation rates, consent bias and financial and/or organizational burdens.

Nevertheless, there is a difference in the underlying moral message, which is discussed in chapter 2 and 3. Whereas with a thick opt-out procedure people are expected to contribute, this is less clear with an opt-in procedure. With an opt-in procedure, allowing inclusion of one's residual tissue seems more a supererogatory act. Supererogatory acts refer to actions that are considered morally good, but are more than people are required to do.[6] The moral message that allowing inclusion is

the ordinary thing to do can be supported by a moral duty to permit the use of leftover tissue for research, discussed in chapter 2 and 3. This duty can be rooted in the wider debate on a moral duty to participate in scientific research, which will be discussed later.

Although this thesis supports a general duty to allow the use of leftover tissue, which will be discussed in more detail further on, this duty would not be equally strong in all leftover tissue situations. Chapter 2 and 3 discuss that there is no one-size-fits all consent procedure for all residual samples and research. Residual tissue is a collective term for a diversity of samples. In addition, a wide variety of research types can be conducted on them.[1] The question arises for which specific cases an opt-in or a thick opt-out is appropriate. Chapter 2 and 3 suggest four situations that require an opt-in: (1) research with higher risks or increased burdens, (2) the use of controversial or high-impact techniques, (3) research on sensitive tissue types and (4) certain groups of vulnerable patients, for whom the competency to understand the presented information needs to be evaluated before tissue can be included.[1,2] As discussed in chapter 2, further discussion is needed to formulate the amount of risks and burdens, the nature of the techniques, the types of tissue, and the groups of vulnerable patients that would require an opt-in procedure. In other words, the following questions need further research: when can a research activity no longer be considered basic or straightforward biobanking research, and therefore require an opt-in, and for which groups of patients does an opt-out insufficiently protect their interests? The answers to these questions will, at least partly, be based on a proportionality assessment, as is also shown in chapter 4 with the case of including women in a breast implant registry. This underscores that the appropriate consent method is context-specific and may change over time, and should therefore remain subject of continuous interdisciplinary debate.

Residual tissue from children

A further question that needs to be addressed, is whether a thick opt-out procedure is justifiable (and feasible) for the inclusion and use of residual samples from children by biobanks. Several issues are of importance here. First, the choice between an opt-in and an opt-out procedure concerns the informed consent procedure for the participant herself in a competent adult context. Since children are generally considered incompetent to provide consent, the choice of 'consent' procedure rather concerns parental permission and the child's assent or dissent. The question arises whether an opt-out procedure for parental permission would sufficiently safeguard the children's interest in the form of protection, and whether an opt-out procedure could assign the appropriate role for children. Second, the moral message of an opt-out procedure is that allowing inclusion is the normal thing to do. This message was grounded in the moral duty to permit the use of residual tissue and grounded in the principles beneficence, solidarity and reciprocity, which will be discussed in more detail below. Here it is important to question whether these principles, and a duty to permit the use of residual tissue based on them, can be equally used in a pediatric context. It has been argued that it seems incorrect to speak of a duty to participate in research for children, when children are incapable of making an autonomous decision about participating.[7] In contrast, others argue that with the exception of very young infants, children are moral agents and share the moral obligation to participate in biomedical research with competent adults.[8] However, the same author states that

we should be cautious about enrolling those who cannot consent.[8] Others propose a model of limited solidarity for children in genetic biobank research.[9] The solidarity principle for children would be limited by certain conditions; such as adherence to the minimal risk standard and a minimization of burdens.[9] These are mere three examples of viewpoints relevant for addressing the question whether a moral message should be adopted that children ought to participate in a residual tissue biobank. Further research needs to scrutinize how beneficence, solidarity and reciprocity should be understood and weighed in a pediatric context and what the consequences are for the inclusion of residual tissue from children. Third, a significant factor may be that particularly samples from children can be considered an extreme waste to leave unused. Specific collection of biological samples for research purposes may unnecessary burden children when leftover samples are stored and can be made available. Although this issue is also relevant within an adult context, minimization of risk and burden is a central issue in pediatric research specifically, because of children's limited capacities to understand the research procedure and to make autonomous decisions.[9]

Opt-in does not automatically resolve all issues

Chapter 2 discusses one of the drawbacks of including residual material with a thick opt-out procedure: researchers will have to re-contact people and ask for additional consent when they want to conduct studies that require an opt-in procedure. This dilemma, however, will not be completely resolved by introducing an opt-in procedure. Even within a broad opt-in consent procedure, it is impossible to discuss all potential research possibilities that can be conducted on a sample. Previously described situations, e.g. involvement of high risks and/or controversial techniques, will therefore require a specific opt-in procedure as well; hence, researchers will have to contact the participants as well. An example of a study for which an opt-in is necessary that is discussed in chapter 2 is the use of NGS, or more precisely whole genome or whole exome analysis. In NGS the order of base pairs that form the exome or genome are determined.[10] The raw sequence data can be interpreted by using an exome or genome analysis.[10] When large parts of the exome or genome sequence are analyzed, it brings forward extensive genetic data of the research participant.[11] This information can be associated with increased difficulty to keep individuals unidentified,[12] the option or duty to return individual research results and increased psychological or social risks, which justifies an opt-in procedure.

Although an opt-in procedure can be considered a more strict method than an opt-out, it should be noted that similar to a thin opt-out procedure, an opt-in procedure can be poorly implemented. It will highly depend on the efforts of the biobank and/or researcher, whether the potential participant truly is aware and understands what she is consenting to. A criticism on the account of contemporary informed consent procedures is that they have become a mere formality, where participants are given extensive information and asked to sign a form.[13] This corresponds mainly with the legal side of informed consent that protects the researcher and functions as a release of liability.[14] In order to meet the moral goals of informed consent,[14] I would like to stress that irrespectively of an opt-in or opt-out method, attention needs to be given to the actual procedure.

THE APPROPRIATE ROLE FOR CHILDREN IN THE CONSENT PROCEDURE AT THE TIME OF SAMPLE INCLUSION

Over the last decades, there has been a move towards recognition of a child's right to be involved in matters that affect him or her and to express personal views.[15;16] This right is also acknowledged in biomedical research guidelines, specifically in the requirements to seek a child's assent and respect her dissent.[17-20]

Assent

Since there is no consensus on the underlying grounds and interpretation of assent, we first clarify the concept of assent. Two categories of underlying grounds for assent in the literature are discussed in chapter 5. The grounds in the first category, respect for autonomy and protection against harm, seem to be derived from informed consent. Assent understood from these grounds is not of added value. When one would ground assent in respect for autonomy, it is one of the two: either children are considered incapable of autonomous decision-making and then it does not make sense to use a concept that requires autonomy, or a child can be considered competent to make autonomous decisions and then it would be untenable not to grant the child the same level of control as an adult, at least from an ethical perspective. Protection against harm is safeguarded mainly in other ways than assent: parental permission, more strict regulations about acceptable risks, the supervision of RECs, the responsibility of clinicians/researchers and respect for dissent.[17] In contrast, the grounds from the second category, respect for developing autonomy, promotion/support for development and support for communication between child and research, are of added value. They can be classified as engagement grounds and assent understood from this perspective does justice to the specifics of childhood.[17]

Personalized assent

Since children differ considerably in their capacities and wishes on being involved in a research discussion, and studies (biobanks) may differ in their complexity, assent needs a case-by-case approach. Both the 'content' and the 'process' need to be adjusted to the individual child, which is referred to as personalized assent in chapter 5. Three models of obtaining consent that can be translated into assent are described in chapter 7. First, a layered model, in which the first layer contains basic information about the first phase of biobank research, is examined. Particularly for biobanks, the characteristic three phases of inclusion, storage and use of samples, provide a natural arrangement of the information layers. Second, a staged model emphasizes that assent is an ongoing process. Staged assent is particularly suitable for biobanks, since one of the characteristics is the longitudinal character of biobank research. When children grow older and expand their capacities, they can be asked for their assent (or consent) again. This refers to the issue of re-contact once the child reaches maturity to obtain consent for continuous use of sample, which is addressed in chapter 8. Third, a tiered model offers children the possibility to assent (or dissent) to a selection of options.[15]

Assent as a requirement

Chapter 7 discusses that making an effort in seeking assent should be a requirement for pediatric research, and should only be waived when absolutely irrelevant or unfeasible. The affirmative agreement of a child, however, is not a strict requirement, since not all children can and/or want to give assent after going through the assent procedure. Therefore, I would define the assent requirement as 'engaging the child in the research discussion in accordance with his or her capacities and wishes'.[21] This definition emphasizes that the level of information that needs to be discussed and understood by the child is not fixed.

However, some propose that assent can be (part of) a justification for allowing a minor increase over minimal risk in research without the prospect of direct benefit,[22;23] which would make an affirmative answer from the child a strict requirement. The authors provide two factors that they together consider sufficient to allow a minor increase over minimal risk and/or burden: the assent of the child and the value of the study.[22;23] Here I focus on the first factor, the assent of the child. The following line of argument is provided: research without the prospect of direct benefit for participants is problematic with children because they are at risk of being used merely as means when they have a purely passive role. In order to protect incompetent research subjects, a minimal risk and burden requirement was established.[23] However, when children can provide assent, their role is not purely passive.[22] Consequently, the acceptable levels of risks and burdens can be a bit more permissive.[23] It is important that the child is generally capable of understanding the study, the risks and burdens involved and should be capable of making her own decision based on this knowledge.[23] Assent is in this case referred to as "a positive agreement of those subjects who can be involved in the decision-making process in a truly meaningful way".[23]

I think, however, that this an example of conflating assent with consent, which denotes the first category of underlying grounds for assent mentioned in chapter 5. Whether assent can play a role in justifying higher risks is highly doubtful and needs further scrutiny.

Dissent

As discussed in chapter 5, there is a lack of clarity about dissent.[17;24] It has been put forward that not each sign of distress or objection should be treated as dissent and that the reason behind a sign of dissent is of importance here.[25] For example, when a child objects to participating in research because she rather plays outside, this should not be considered dissent.[26;27]

The concept of dissent needs further clarification in (biobanking) practice. Furthermore, it becomes clear from the case study, presented in chapter 6 that both parents and researchers can pressure the child into participation, which means that a child's dissent may not be respected (or recognized). In addition, chapter 7 discusses that even when children were aware of the possibility of dissent, they find it very difficult to refuse to research participation in reality.[15;28;29] Therefore, extreme caution that must be exercised before proceeding with a study when a child keeps silent is stressed in chapter 7.[15] In sum, when a child's right to dissent is taken seriously, both conceptual clarification and practical guidance for biobanks aimed at enabling children to exercise their right to dissent, need to be further developed.

RE-CONTACT AND CONSENT

An important question in pediatric biobank research is whether children should be re-contacted when they reach maturity to obtain their consent for (or to give them the opportunity to withdraw from) the continued use of their samples. In chapter 8 'respect for autonomy' and 'protection of privacy' are put forward as grounds for re-contacting children at maturity, and the promotion of scientific citizenship is considered a favorable side-effect. In addition re-contact enables a qualified disclosure policy for the return of individual research results, which is relevant for certain biobanks.[30] Chapter 8 also puts forward that re-contact may be beneficial for biobanks by enhancing research possibilities, in case one considers the scope of parental permission as limited. One of the undeniable negative effects of re-contacting is that it will generate financial costs for biobanks and requires organizational efforts, which may hamper research. Although costs and efforts are not considered overridden arguments against re-contact, it should be taken into account when the appropriate policy is formulated.

Four re-contact policies are discussed in chapter 8, ranging from an opt-out policy (participants can withdraw their samples, but the biobank does not re-contact the participant) to a strict opt-in (samples will be destroyed when participants do not give their consent). It is concluded that a thick opt-out policy should be the default, meaning that participants are re-contacted by the biobank and given the opportunity to withdraw. This policy is appropriate for all types of tissue research that can be referred to as ordinary and unlikely to infringe on personal values of the participant.[31]

The discussions on residual tissue in chapter 2 and 3, and on re-contact in chapter 8 show a strong resemblance. In both situations an argument is made for a thick opt-out procedure, based on respect for the participant's autonomy, public trust, the public benefits of biobank research and the low risks and burdens for the participants. In case of residual tissue, an argument in favor of a moral duty to allow inclusion based on reciprocity, solidarity and beneficence is referred to. Whereas reciprocity would be less applicable in the discussion on re-contact, since participants have not explicitly accepted the benefits of health care, solidarity and beneficence would still apply. These principles might be sufficient ground for a moral duty to permit the continued used of samples; however, further ethical reflection is required on this matter.

Parental permission

The discussion on re-contact refers to the temporal dimension of parental permission on a child's participation in biobanks. Next to the temporal dimension, there is a content related dimension of parental permission.[32] It can be questioned whether parents may authorize the inclusion of their child's sample in every type of biobank and to all sorts of research projects. As discussed in chapter 8, according to some, publicizing full genomes[32] or sharing samples and/or data by population biobanks[33] should only take place based on a participant's personal consent. Restricting research on pediatric samples has been grounded in a child's right to an open future,[32] which refers to a child's right to make her own decisions in the future, once she is capable of doing so.[34] This corresponds with a parental duty to promote their child to develop into a competent autonomous being and leave as many options as reasonably possible open for their child.[35]

At the moment, there is no consensus on the limits on the use of pediatric samples.[33;36-39] It will be valuable to further study this issue, and to scrutinize whether, and if so, which role, the argument of a child's right to an open future may fulfill here.

THE CASE STUDY

The goal of including empirical data in the ethical analysis was to incorporate essential details of the pediatric biobanking practice, hereby increasing the change that the conclusions will be relevant for, and applicable in practice. The aim of the case study in this thesis was to enrich our ethical analysis by scrutinizing the interpretation and use of consent in current pediatric biobanking practice. Four biobanks with different characteristics were included and data was collected from multiple sources in each biobank. Special attention was given to the inclusion of residual tissue, the role that was assigned to children in the consent procedure and whether children were re-contacted when they reached maturity. Whereas only chapter 6 presents the results from the case study explicitly, with a focus on the child's role in the consent procedure, the obtained knowledge has been used implicitly throughout this thesis.

Since the case study approach is uncommon within the field of ethics, I will reflect on its attributed value for this thesis by giving an example that illustrates how a better understanding of the current practice was gained. Moreover, it shows how a theoretical concept (personalized assent) could be linked to practice.

A criticism on the account of personalized assent is that it would be impractical and/or not enforceable.[15;40;41] As discussed in chapter 5 and 7, we are aware that personalized assent is an appeal to a researcher's integrity and that it is difficult to provide fixed end points.[15;17] The assent procedure must be flexible enough to adapt to different (biobank) studies and the different situations of individual children. By conducting the case study, different underlying motives for involving children in the research discussion in current pediatric biobank practice were recognized. This provided valuable information on the feasibility of personalized assent. Based on the case study, regulation was recognized as an important motive for all biobanks to involve children in the consent procedure. Although regulation applied to all cases, the actual involvement of children varied because rules and regulation differed in content. However, not all variation could be explained by the variety of rules. How people act in practice depends on the interpretation of rules,[42] which may be influenced by underlying motives. This case study shows that two other motives to involve children in the consent procedure are of importance here: 'research interests' and 'respect for the child'.[43] All cases emphasize 'respect for the child' as a motive, which refers to the intrinsic motivation to involve children in the consent procedure. This corresponds with the appeal personalized assent makes to the biobank's staff and researchers' integrity.

Nevertheless, an additional incentive to include children in the consent procedure is the research interests for 'follow-up effort' biobanks. By involving children in the consent procedure, they may be inclined towards continuing their participation, which is very important for biobanks that solicit further data collection in the future. Although for these biobanks research interests go

hand in hand with the child's interests, this is only to a certain extent. There is a difference between involving children out of research interests or out of respect for children. Moreover, for 'one-off effort' biobanks there is no clear research motive to involve children in the research discussion. Therefore, it is important that although there may be an intrinsic motivation to involve children, biobanks and researchers are reminded of their professional responsibility and moral duty to engage children. By analyzing the underlying motives for involving the child in the consent procedure it becomes clear that making an appeal to the moral integrity of researchers and biobanks may be fruitful, and at the same time shows that regulation and guidance should support this appeal.

A BROADER PERSPECTIVE ON RESEARCH PARTICIPATION

The past few decades the prevailing view in research ethics seems that human participants should be protected from risks, burdens and exploitation.[44] Although this is indeed an important role for research ethics, at the same time, it is important to serve society's interests. Particularly in the context of biobanks, a trend towards a more participatory approach grounded in reciprocity and solidarity approach has been emphasized.[45] Although, in this thesis, a participatory approached can be recognized as well, this approach is primarily grounded in taking people seriously as participants, e.g. by informing them properly. Therefore, an appeal is made to biobanks and researchers to treat participants as partners. When people are treated seriously as participants, a moral appeal may be made to them to contribute to biomedical research. Below I will first discuss a moral appeal to people to participate in biomedical research; next, I will elaborate on treating research participants as partners.

A moral appeal to research participation

Is there a moral duty to participate in research?

Earlier I referred to the wider debate on a moral duty to participate in scientific research. The debate on this duty will be briefly discussed here. Although, in general, participation in biomedical scientific research is considered a supererogatory act, some have argued in favor of a moral duty to participate in such research.[8;46;47] Several arguments have been put forward, in which the duty is particularly linked to research directed towards the prevention of serious harm or providing considerable benefit for mankind.[8] First, the duty to participate in biomedical research is grounded in the rule or duty of rescue. A duty of rescue refers to our obligation neither to cause nor fail to prevent harm, hereby taking into account the balance of risk and burden to ourselves and benefit to others.[8;46] It is reasoned that since serious biomedical research is necessary to help the sick, it is a moral obligation to participate in such research.[8] Others have challenged the duty of rescue as an argument in favor of a moral duty to participate in biomedical research.[48-50] It is reasoned that a rule of rescue can be overly demanding. There are many actions that can prevent harm from happening and no special status to participate in biomedical research has been shown.[48] Other rescue actions may even prevail over participation in biomedical research, for instance, helping a currently living hungry person by feeding her, instead of someone in the future with the development of biomedical knowledge.[49] In

addition, it is questioned whether research can actually be classified as rescue because it does not save people from imminent danger.[50]

A second argument in favor of a duty to participate in research has been grounded in fairness and a duty of reciprocity.[8;46] It has been argued that since a person accepts the benefits of biomedical research, there is an obligation to contribute to it. Not participating in research while profiting from the benefits of health care, has been referred to as 'free riding'.[8;46] Several objections have been made against this argument as well. It is, for example, questioned whether people truly 'free ride' when they do not participate in research, since they can also contribute to scientific research in other ways, for example paying for their treatment.[49;50] Moreover, since people cannot choose ***not*** to use the advantages of biomedical knowledge, because they are simply incorporated in our everyday life, it is difficult to establish a duty based on the acceptance of these benefits.[48] In addition, some objected that since a person benefits from past biomedical research and can only contribute to current research, she can never repay the person who participated in the past.[48] It was concluded that although we (probably) all benefit from research and will so in the future, it does not follow that everyone has the duty to participate.[50]

A duty to allow inclusion of residual tissue in biobanks

Although the debate on a general duty to research participation remains unsettled, in this thesis a specific case is made in favor of a duty to permit the inclusion of residual tissue in biobanks in chapter 2 and 3. Here I will elaborate on this duty by considering the counterarguments against a general duty to participate, which are presented above. First, it was argued that the rule of rescue is overly demanding and that other actions would prevail over participation in biomedical research. This counterargument refers to the limited resources one has or that can be called upon to rescue (or benefit) others. However, in case of residual tissue research, it hardly costs a person anything to allow inclusion and it does not conflict with other rescue actions. The sample is already taken, and, provided that adequate governance policies are in place, the informational risks and burdens are low. Allowing the use of residual tissue would then be reasonable (or proportionate) to ask from people. The second counterargument, research does not save people from imminent danger and can therefore not be classified as rescue, seems to apply to residual tissue research as well. Although research is aimed at improving health care, it remains to be seen what the exact implications for health care are of a particular (residual tissue) study. Also, the objection that people are not actually free riders, since they contribute to research in other ways, seems to be valid in case of residual tissue research. Next it was stated that it is difficult to establish a duty based upon the acceptance of the benefits derived from biomedical knowledge when such benefits can hardly be denied. However, in case of residual tissue research, there is clearly an active acceptance of the health care services; otherwise there would be no residual tissue in the first place. Last, I discussed the objection that people can never repay the people who have provided them with the benefits of biomedical knowledge by participating, since these will be persons from the past and their current efforts will most likely benefit people from the future. However, instead of situating a duty of reciprocity towards the individual who have earlier participated in the trials, the scope can be widened and one could aim a reciprocal action towards society at large. And although it may not be clear what such a

reciprocal action should entail, considering the low risks and burdens, it seems at least appropriate to allow the use of residual tissue.

In sum, since approving the inclusion of residual tissue involves low (or no) risks and burdens, has the potential to improve health care, and a person has actively accepted the benefits of health care, I think there is a case in favor of a duty to allow inclusion of residual tissue, based on the principles of beneficence, solidarity and reciprocity.

Against a legal duty

Although there seems to be a case in favor of a moral duty to allow inclusion of residual tissue, it does not follow that this should be a legal duty. An important principle, at least in a liberal democratic society, is respect for autonomy. It can be debated whether a moral duty to allow inclusion should override the principle of respect for autonomy. Some argue that self-determination on the use of your own tissue is in practice limited, since we lose bodily material every day, such as cells from our skin or by urine excretion. We are generally not concerned about this material either and thus self-determination should not be the overriding principle.[51] However, this comparison misses the point. Although it is true that our self-determination on the use of our bodily material is limited in practice, we expect those skin cells and urine not be used by anyone for a research project. If they were, we might be more concerned. Others argued that autonomy is not an overriding principle since residual tissue research has minimal risks and is of interest to us all. Because we limit our freedom in different ways in order to strive for common goals in our society, for example by traffic rules or compulsory education,[52] this should also be the case for residual tissue. However, even when there are common goals for which we limit our freedom, these are exceptions in need of considerable justification. Residual tissue concerns bodily samples, which are linked to a person, and respect for autonomy should not be set aside easily. In line with respect for autonomy, here, is respect for privacy, which in in research has been referred to as the right of the participant to decide on how much information about herself is shared with researchers.[31;53] Some people may feel very uncomfortable when their samples are used in research or may have personal (religious) believes that do not match the research practices proposed. Thus although I support a moral duty to allow inclusion, I think this should be balanced with respect for autonomy, and a thick opt-out, which is also argued for in chapter 2 and 3, would be most appropriate.

Positive attitude towards research participation

Although a general duty for participation in research is still subject of debate, in this thesis, a positive attitude towards research participation is adopted in the specific situations of residual tissue research and the continued use of pediatric samples. Perhaps a more fruitful approach to address the question 'whether there is a moral duty to research participation', would be to consider the circumstances of participation in a particular type of research, hereby recognizing the great variety in research. Referring to the proportionality part of the rule of rescue, a duty to participate in low risk and burden research, such as residual tissue research, seems much easier to support than participating in a clinical trial in which a new drug is tested and participants run the risk of severe side-effects.

Research participants as partners

Besides an appeal to people to participate in (residual) biobanks, this thesis propagates that a biobank should invest in its participants and put effort into engaging them. Particularly the concept of personalized assent, which is discussed in chapter 5 and 7, is grounded in the importance of engaging participants (children). However, also the thick opt-out procedure recommended for residual tissue and for the re-contact policy, is aimed at taking participants seriously by providing them with sufficient information and the opportunity to decide for themselves.

Encouraging a framework in which participants are engaged in research corresponds with the ideal of scientific citizenship described in chapter 2.[1;13;30] Scientific citizenship is referred to as the societal ideal where citizens are well informed and well-equipped to make decisions about research participation, which would lead to better protection and promotion of their own interests.[1;13] This ideal has been particularly linked to biobanks, both in this thesis and by others.[13;30] The longitudinal character of biobank research and the unknown future studies at the time of sample inclusion, have provided a strong incentive to challenge traditional thinking in research ethics. Instead of a one-time agreement at the start of a research project, it is argued that the continuous approach of an authorization model, with an opt-out clause, is more appropriate. Such a model provides individuals with the opportunity to check whether 'what they consented to' is actually happening and vice versa.[13] This model could promote more informed, active and critical participants by creating the conditions for citizens to reflect on their participation in the biobanks.[13] This ideal is linked to a liberal view that citizens are not passively subjected to policies, but that they are provided with the opportunity to act and co-shape, though they are not necessarily required to do so.[13]

Dynamic consent

From chapter 5, 6 and 7 it becomes clear that both the child's interests and research interests can be promoted by engaging a child in the consent procedure. The promotion of both the participant's and biobank's interests by engaging participants has been articulated in biobank research earlier, of which the proposal of dynamic consent is a good example. Dynamic consent has been thought of as a personalized, digital communication interface that gives the participants a central place in decision making.[54] It enables participants to give multiple consents to the use of their sample and information.[12;54] The interface is a way to connect biobank and participant.[54] This model can be considered particularly suitable for longitudinal and progressing character of biobanks and thus fits the authorization model discussed earlier. While dynamic consent may require certain efforts in the form of time and resource investments, it, at the same time, may yield valuable sources in the form of future recruitment and further data collection.[12] Such a dynamic interface, with the primary goal of keeping participants informed and aware, without forcing them to interact, fits well to the ideal of scientific citizenship.[13]

Science education

The objective of scientific citizenship, to promote well informed or educated citizens who can make personal decisions about research participation, can be promoted through education.[13] One of the cases presented in chapter 6 that invests in schools, is Young-HUNT3. This case included their

young participants, after approval by the local regulatory research authorities, through schools. Although ethical evaluation on, for example, voluntariness and including children through schools, may be valuable, I want to focus on a different aspect here. Young-HUNT3 made a specific effort to educate and inform children at schools about the biobank. They, for example, provided tours at the HUNT complex for classes of schoolchildren, and presented about their biobank and research at schools. Young-HUNT3 staff articulated both a need to respect their participants and give them something in return for their participation, as well as a need to sustain a relationship in order to conduct follow-up measurements with their participants. Besides an investment of biobanks and researchers in their participants to promote this development, an investment in science education by the government may be helpful as well.[13] Education about research may contribute to awareness and public engagement in this field.

Children as partners

The investment of Young-HUNT3 in their child participants is an example of investing in children as individuals. It underscores the recognition of children's rights to be involved in matters that affect them, as has been put forward by the United Nations in the Convention on the Rights of the Child.[16] It seems to support the viewpoint that not only competent adults should be considered partners in research, but children as well, which is also emphasized in this thesis. As one of the respondents in the case study stated: "it starts with the children".

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Chapter 10

Summary

Samenvatting

Dankwoord

List of publications

Curriculum Vitae

Summary

Biobanks are collections of human biological samples that are usually linked to phenotypic data and stored for biomedical-scientific research purposes. Whereas research on biological samples already exists for many years, the technological developments in biomedical research and information technology gave rise to the development and expansion of biobanks in size and number. Although all biobanks store samples and data to conduct biomedical research, they can differ considerably in numerous ways. Several biobanks include, store and use children's samples. So called pediatric biobanking is considered important to improve (pediatric) health care. At the same time, the inclusion and use of children's samples in biobanks give rise to specific ethical issues. Whereas competent adults need to provide informed consent before they may be included in research, children are often considered incompetent to make an autonomous decision on research participation. This poses questions about the appropriate way to include children in biomedical research. In addition, these questions become more complex in biobanking, since biobanking entails longitudinal research, in which the exact research projects are often unknown at the time of sample inclusion, and moreover, children may mature during the time of biobank research. Questions on how consent should take shape in pediatric biobanking need to be scrutinized. The three main questions that are addressed in this thesis are: (1) what is the appropriate consent procedure for the inclusion of residual samples in biobanks? (2) What is the appropriate role for children in the consent procedure at the time of sample inclusion? And, (3) should children be re-contacted when they reach maturity to obtain their consent for (or to give them the opportunity to withdraw from) the continued use of their samples? By addressing these questions, this thesis aims to morally enhance pediatric biobanking practice and contribute to a responsible development of (pediatric) biobanking.

Biobank material can be collected in different manners. Residual tissue refers to human biological samples that are leftover after clinical care. This is an important source for biobanks. In **Chapter 2** the two predominant procedures for the inclusion of residual tissue are discussed: opt-in, a person explicitly expresses consent to allow inclusion of their residual samples, and opt-out, tissue is stored unless the person objects. The expected scientific advantages, lower costs and a moral duty to participate in biomedical research are arguments in favor of an opt-out procedure. Certain conditions, however, need to be fulfilled in an opt-out procedure in order to respect the participant's autonomy and safeguard public trust: (1) awareness must be raised among people about inclusion of residual tissue as the default position, (2) adequate information needs to be provided, and (3) a genuine possibility to object must be presented and objections adequately registered. This is referred to as a 'thick opt-out' procedure. The practical differences between a thick opt-out and an opt-in may be small. Nevertheless there is a difference in the underlying moral message. Whereas with a thick opt-out procedure people are expected to contribute, this is less clear with an opt-in procedure. Considering the diversity of residual tissue and research, we conclude that further interdisciplinary debate is necessary to determine when to opt-in or when to opt-out.

Chapter 3 further elaborates on the inclusion of residual tissue. Consent bias, which refers to a form of selection bias that is caused by the refusal of consent by particular groups, is an often-heard argument against stringent consent procedures. In this chapter we discuss that both the 'content'

and 'process' of a consent procedure can be altered to reduce the researcher's burden and improve efficiency. The 'content' of a consent procedure refers to the type and amount of information that is discussed, and the 'process' refers to how consent is obtained. The distinction between an opt-in and opt-out method refers to the process of a consent procedure, and is important since an opt-out procedure has been associated with lower selection bias. Furthermore, the three stages of biobank research are discussed: (1) inclusion, (2) storage, and (3) usage of biological material. All stages should be considered when selecting an opt-in or opt-out procedure. It is possible that although an opt-out was appropriate at the time of inclusion, an additional opt-in is required when the samples are for example used to produce an immortal cell line.

In **Chapter 4** the use of an opt-in method is weighed against the introduction of a thick opt-out procedure in a specific situation. The clinical introduction of medical devices often occurs with relatively little oversight, regulation and (longterm) follow-up. The scandal surrounding the global breast implant scare of silicone implants made by France's Poly Implant Prothese (PIP) Company underscores the weakness of the current regime. The absence of national registries hampered the collection of reliable information on the risks and harms of the PIP breast implants. Although an opt-out procedure would be more attractive from a scientific and public health perspective, a thick opt-out is not justifiable considering the potential invasion of people's privacy, the sensitive subject it concerns and the possible follow-up investigations, that can be associated with inclusion in breast implant registries. Although registries are important for monitoring safety after a medical device is on the market, we warn to be cautious with the inclusion of people in medical device registries for the sake of public health without their explicit consent.

In **Chapter 5** 'assent' is scrutinized. Different underlying grounds for the attainment of assent are addressed, which can be divided into two categories. The grounds in the first category appear to be derived from informed consent. This understanding is grounded in respect for autonomy and protection against harm. It, however, appears that assent understood from these grounds is not of added value compared to consent and other ways to protect a child against harm. By contrast, the grounds of the second category allocate assent with a specific task and present assent as a concept distinct from informed consent. Three grounds are discussed: respect for the child's developing autonomy, the promotion of or the support for the development of the child and support for communication. The three grounds are closely related and can be classified as engagement grounds. Based on these grounds, assent should be understood from an engagement point of view. The aim of the assent procedure is to involve the child in the research discussion as much as possible. For this, both the content and the process of the assent procedure need to be adjusted according to the child's capabilities and wishes. This is referred to as personalized assent.

Chapter 6 presents the results from the multiple-case study on the child's role in the consent procedures of biobanks that include samples from children. Four biobanks with diverse characteristics were included from the Netherlands, Norway and the United Kingdom. The case study shows that the extent to which children are able to make voluntary decisions as part of the consent procedure, depends on the information provided to the child and the role given to dissent, assent and consent; which in turn is influenced by the motives of biobanks to involve children in the consent procedure. Regulation is an important motive for all biobanks. However, actual realization of rules depends on

how people act in practice. This case study shows that two other motives to involve children in the consent procedure are of importance here: 'respect for the child' and 'research interests'. For 'follow-up effort' biobanks, research interests go hand in hand with the child's interests, though this is only to a certain extent. For 'one-off effort' biobanks there is no clear research motive to involve children. It is essential that biobanks implement governance mechanisms that emphasize the importance of respect for the child.

In **Chapter 7** practical guidance is provided on personalized assent for pediatric biobanking. Both the content and the process of an assent procedure are considered. The content of the information should be adjusted to the individual needs and capacities of the child. This means that basic information should be discussed first and if possible substituted with additional data on the study. The typical three stages of biobanking (inclusion, storage and use of samples) provide a natural ordering of information. Issues related to the first phase of biobank research are often reasonably straightforward, whereas more abstract, long-term issues are linked to the storage and use of samples. Next, the process of assent is discussed. Here, three models of obtaining consent are translated into assent and topics such as the role of the researcher and parent(s) are addressed. Furthermore it is argued that an investment from the researcher or biobank in the assent procedure is a requirement for including children. By contrast, since not all children can and/or want to give assent after going through the assent procedure, it would be strange to impose an affirmative agreement of the child as a strict requirement on researchers. It is important to stress that investing in a personalized assent procedure both show respect for the child and may contribute to the quality and success of the research.

In **Chapter 8** it is discussed whether children should be re-contacted at maturity to obtain their consent for (or to give them the opportunity to withdraw from) the continued use of their samples and data. It is argued that respect for autonomy and protection of privacy provide arguments for re-contact. Although costs and efforts are not considered overridden arguments against re-contact, they should be taken into account when the appropriate policy is formulated. Four policies are discussed. At one end of the spectrum is an opt-out (policy I): re-contact is not initiated by the biobank, but children can withdraw their samples and/or data. On the other end of the spectrum is a strict opt-in (policy IV): children are re-contacted and asked for consent; if they cannot be located or do not answer, the samples and data will be destroyed. These two policies are considered either inadequate or too stringent. For straightforward biobank research, then, a thick opt-out (policy II) or best effort opt in (policy III) seem most suitable. It is concluded that since in both policies the samples and data of participants who do not act will be used continuously, a best-effort opt-in is not of added value. Therefore, a thick opt-out policy should be the default, meaning that participants are re-contacted by the biobank at maturity and given the opportunity to withdraw.

In **Chapter 9** the conclusions of this thesis are discussed and reflected on per main question. Limitations and issues for future research are identified. In addition, the attributed value of the case study is considered. Last, it is put forward that in this thesis a positive attitude towards biomedical research participation, also referred to as a participatory approach, can be recognized. At the same time, it is propagated that a biobank should invest in its participants and should put effort in engaging them. Treating participants as partners is important when one wants to make an appeal to

people to participate in biomedical research and corresponds with the ideal of scientific citizenship. In addition, it is emphasized that children should be considered partners in biomedical research as well.

Samenvatting

Een biobank is een verzameling van menselijk lichaamsmateriaal dat, meestal in combinatie met fenotypische informatie, wordt opgeslagen voor medisch-wetenschappelijk onderzoek. Al vele jaren wordt er wetenschappelijk onderzoek gedaan waarbij gebruik gemaakt wordt van lichaamsmateriaal. Technologische vooruitgang, onder andere op het gebied van informatietechnologie, heeft de ontwikkeling en groei van zogenaamde biobanken gestimuleerd. Alle biobanken verzamelen en gebruiken biologisch materiaal en bijbehorende data voor onderzoek. Toch kunnen ze onderling op verschillende vlakken sterk van elkaar verschillen. Een aantal biobanken verzamelt en gebruikt weefsel van kinderen. Deze zogenaamde kinderbiobanken kunnen belangrijk zijn voor de verbetering van de gezondheidszorg, zowel voor kinderen als voor volwassenen. Tegelijkertijd brengen het includeren en gebruiken van materiaal van kinderen ook specifieke ethische vragen met zich mee. Terwijl competente volwassenen geïnformeerde toestemming moeten geven voordat zij geïncludeerd mogen worden in onderzoek, zijn kinderen vaak nog niet in staat om een autonome keuze te maken over deelname aan onderzoek. Dit werpt vragen op over de juiste wijze om kinderen te includeren in biomedisch onderzoek. Deze vragen worden gecompliceerder in de biobankcontext; het betreft hier longitudinaal onderzoek, waarbij de uiteindelijke onderzoeksprojecten op het moment van weefselafname nog onduidelijk zijn, en bovendien worden de kinderen volwassen gedurende de loop van de biobankstudies. Vragen met betrekking tot het gebruik en de vormgeving van het toestemmingsvereiste door kinderbiobanken moeten dan ook onderzocht worden. De drie hoofdvragen die in dit proefschrift aan bod komen zijn: (1) wat is de geschikte toestemmingsprocedure voor het includeren van restmateriaal in biobanken? (2) Wat is de geschikte rol voor kinderen tijdens de toestemmingsprocedure op het moment van afname en inclusie van lichaamsmateriaal? En, (3) moeten kinderen gehercontacteerd worden wanneer ze volwassen zijn, om hun toestemming te vragen voor (of om ze de kans te geven bezwaar te maken tegen) het gebruik van hun lichaamsmateriaal? Door deze vraagstukken te bespreken, hoopt dit proefschrift een moreel verantwoorde ontwikkeling van kinderbiobanken te stimuleren.

Biobankmateriaal kan op verschillende manieren verzameld worden. Restmateriaal, dat wil zeggen weefsel dat over is na klinische zorg, is een belangrijke bron van weefsel voor biobanken. In **Hoofdstuk 2** wordt besproken of voor de inclusie van restmateriaal een geen-bezwaarregeling, restmateriaal wordt geïncludeerd tenzij iemand bezwaar maakt, voldoende is, of dat er expliciete toestemming nodig is, waarbij materiaal alleen wordt geïncludeerd wanneer iemand hier explicitiet toestemming voor geeft. De verwachte wetenschappelijke voordelen, lagere kosten en een morele plicht tot deelname aan biomedisch wetenschappelijk onderzoek vormen argumenten voor een geen-bezwaarprocedure. Wil een geen-bezwaarsysteem echter ook passend zijn voor het respecteren van de autonomie van een proefpersoon en publiek vertrouwen waarborgen, zal de procedure aan bepaalde voorwaarden moeten voldoen: (1) mensen moeten op de hoogte worden gebracht van de mogelijkheid tot het maken van bezwaar tegen het gebruik van hun restmateriaal, (2) er moet voldoende informatie gegeven worden, en (3) er moet een werkelijke mogelijkheid geboden worden tot het maken van bezwaar en geuit bezwaar moet geregistreerd

worden. Een dergelijke geen-bezwaarprocedure kan een aangekleed geen-bezwaarsysteem genoemd worden. De verschillen tussen een aangekleed geen-bezwaarsysteem en een explicitiete toestemmingsprocedure kunnen klein zijn. Desalnietemin is er een verschil in de onderliggende morele boodschap. In tegenstelling tot bij een expliciete toestemmingsprocedure, lijkt bij een aangekleed geen-bezwaarsysteem de boodschap te zijn dat mensen het gebruik van hun restmateriaal toe horen te staan. Gezien de grote diversiteit aan typen restmateriaal en studies, concluderen we dat er nader bepaald zal moeten worden wanneer er expliciete toestemming nodig is en wanneer een geen-bezwaarsysteem afdoende is.

Hoofdstuk 3 gaat verder in op de inclusie van restmateriaal. Consent bias is een argument tegen al te strikte toestemmingsprocedures voor de inclusie van deelnemers in onderzoek. Consent bias is een vorm van selectiebias, waarbij er een systemische vertekening is van de onderzoeksresultaten doordat bepaalde groepen geen toestemming geven voor onderzoek. In dit hoofdstuk wordt er besproken dat zowel de inhoud als het proces van een toestemmingsprocedure aangepast kunnen worden, zodat de onderzoeker minder belast wordt en de inclusie efficiëntier verloopt. De inhoud van een toestemmingsprocedure verwijst naar het type en de hoeveelheid informatie die wordt besproken, en het proces verwijst naar de manier waarop toestemming wordt gevraagd en verkregen. Het onderscheid tussen een geen-bezwaarmethode en expliciete toestemmingsprocedure heeft betrekking op het proces, en is van belang omdat een geen-bezwaarprocedure geassocieerd wordt met een lagere selectiebias. De drie fases van biobankonderzoek (inclusie, opslag en gebruik van materiaal) worden besproken aangezien ze alledrie van belang zijn voor het kiezen van een geen-bezwaarmethode of expliciete toestemmingsprocedure. Het is mogelijk dat op het moment van weefselafname een geen-bezwaarmethode geschikt is, maar dat uiteindelijk toch expliciete toestemming nodig is, bijvoorbeeld wanneer een onderzoeker het materiaal wil gebruiken voor het kweken van een onsterfelijke cellijn.

In **Hoofdstuk 4** wordt de invoering van een expliciete toestemmingsprocedure vergeleken met de invoering van een geen-bezwaarsysteem in een specifieke situatie. Medische apparatuur en hulpmiddelen worden vaak met weinig toezicht, voorschriften en langdurige follow-up geïntroduceerd in de kliniek. Het schandaal rondom de siliconen borstimplantaten van de Franse firma Poly Implant Prothese (PIP) laat de kwetsbaarheid van het huidige systeem zien. Door de afwezigheid van nationale registratie, werd er geen betrouwbare informatie over de risico's en schade van de PIP-borstimplantaten verzameld. Een geen-bezwaarprocedure lijkt aantrekkelijk vanuit een wetenschappelijk oogpunt en volksgezondheidsperspectief. Echter, we beargumenteren dat een aangekleed geen-bezwaar niet gepast zou zijn vanwege de belasting die gepaard kan gaan met opname in een borstimplantaatregister; in de vorm van een mogelijke inbreuk op privacy, het onderwerp dat mogelijk gevoelig ligt en de eventuele follow-up onderzoeken. Ondanks het belang van registratie voor het monitoren van de veiligheid van medische apparatuur of hulpmiddelen, is er voorzichtigheid geboden voordat mensen zonder hun expliciete toestemming in een register worden opgenomen.

In **Hoofdstuk 5** wordt het concept 'instemming' onderzocht. De redenen om instemming te vragen kunnen in twee categorieën worden verdeeld. Tot de eerste categorie behoren de redenen die afgeleid lijken te zijn van geïnformeerde toestemming. Instemming is in dit geval gericht op het respecteren van de autonomie van de deelnemer en haar bescherming. Het blijkt echter dat wanneer instemming op basis van deze redenen geïnterpreteerd wordt, het niet van toegevoegde waarde is ten opzichte van toestemming en andere vormen van bescherming voor kinderen. Dit in tegenstelling tot interpretatie op basis van de onderliggende redenen uit de tweede categorie; hierbij dient het vragen van instemming duidelijk een ander doel dan geïnformeerde toestemming. Er worden drie onderliggende redenen gepresenteerd: respect voor de ontwikkelende autonomie van het kind, het stimuleren van de ontwikkeling van het kind en ondersteuning van communicatie. De drie redenen zijn nauw met elkaar verbonden en leiden er allen toe dat het kind zoveel mogelijk betrokken zal moeten worden in de toetsemmingsprocedure. Hiertoe zullen zowel de inhoud als het proces van de instemmingsprocedure aangepast moeten worden aan een individueel kind. Dit wordt gepersonaliseerde instemming genoemd.

Hoofdstuk 6 geeft de resultaten weer van de meervoudige casestudie naar de rol van kinderen in de toestemmingsprocedure van biobanken. Vier verschillende typen biobanken die samples van kinderen includeren uit Nederland, Noorwegen en het Verenigd Koninkrijk werden geïncludeerd in de casestudie. Op basis van de casestudie wordt geconcludeerd dat de mate waarin het kind in staat is om een vrijwillige keuze te maken in de toestemmingsprocedure afhankelijk is van de informatie die gegeven wordt en de rol die aan verzet, instemming en toestemming toegekend wordt; dit wordt weer beïnvloed door de motieven van biobanken om kinderen in de toestemmingsprocedure te betrekken. Regelgeving is een belangrijk motief voor alle biobanken. Echter, de uitwerking van regels hangt af van de invulling die mensen er in de praktijk aan geven. Deze casestudie laat zien dat twee andere motieven om kinderen in de toestemmingsprocedure te betrekken, onderzoeksbelangen en respect voor het kind, hier een rol spelen. Voor follow-up-biobanken gaan de onderzoeksbelangen tot op zekere hoogte samen met de belangen van het kind. Daarentegen is er voor biobanken die slechts een éénmalige inspanning van het kind verlangen, geen duidelijk onderzoeksmotief om kinderen te betrekken in de toestemmingsprocedure. We benadrukken dat het van belang is dat biobanken een beleid hebben waarin respect voor het kind uitgedragen wordt.

In **Hoofdstuk 7** wordt invulling gegeven aan gepersonaliseerde instemming voor kinderbiobanken. Hiertoe worden zowel de inhoud als het proces van de instemmingsprocedure besproken. De inhoud van de informatie zal aangepast moeten worden aan de individuele behoeften en capaciteiten van het kind. Dit betekent dat basale informatie eerst zou moeten worden aangeboden en indien mogelijk worden uitgebreid met aanvullende informatie over de kinderbiobankstudies. De typische drie fases van biobankonderzoek (inclusie, opslag en gebruik van materiaal) vormen een natuurlijke scheiding van informatie. De aan afname en inclusie gerelateerde zaken zijn vaak redelijk concreet, terwijl de meer abstractere concepten voornamelijk gelieerd zijn aan de opslag en het gebruik van het materiaal. Verder wordt de vormgeving van het instemmingsproces besproken. Hier worden onder meer verschillende modellen van toestemmingsprocedures vertaald naar instemming en

wordt de rol voor ouders en onderzoekers besproken. Verder wordt er beargumenteerd dat een investering van onderzoekers of de biobank in het verkrijgen van instemming een vereiste is voor het includeren van kinderen in onderzoek. Dit in tegenstelling tot een werkelijke instemming van kinderen; aangezien niet alle kinderen instemming kunnen of willen geven, zou het vreemd zijn om dit verplicht te stellen. Het wordt benadrukt dat een investering in een gepersonaliseerde instemmingsprocedure zowel respect voor het kind toont als de kwaliteit van onderzoek ten goede kan komen.

In **Hoofdstuk 8** wordt besproken of kinderen gehercontacteerd moeten worden wanneer ze volwassen zijn om hun toestemming te vragen voor (of om ze de kans te geven bezwaar te maken tegen) het gebruik van hun lichaamsmateriaal en data. Respect voor autonomie en het waarborgen van privacy vormen argumenten voor hercontacteren. Hoewel kosten en lasten niet gezien worden als doorslaggevende argumenten tegen het hercontacteren van kinderen, moeten ze wel worden meegenomen in de keuze voor de uiteindelijke invoering van een hercontacteer-strategie. Er worden vier strategieën besproken. Aan het ene uiteinde van het spectrum bevindt zich de geen-bezwaarmethode (beleid I): biobanken nemen hierbij niet actief contact op met de inmiddels volwassen deelnemers, maar deelnemers kunnen wel hun data en weefsel terugtrekken. Aan de andere kant bevindt zich een strikte expliciete toestemmingsprocedure (beleid IV): kinderen worden op volwassen leeftijd gehercontacteerd en zij moeten hun expliciete toestemming geven; wordt dit niet verkregen, dan moeten weefsel en data vernietigd worden. Deze twee vormen worden danwel ontoereikend, danwel te restrictief bevonden. De twee methodes die dan overblijven zijn een aangekleed geen-bezwaarsysteem (beleid II) en een expliciet toestemmingssysteem op basis van een inspanningsverpliching (beleid III). Echter, aangezien bij beide methodes het weefsel en de data van een deelnemer gebruikt zullen blijven worden wanneer een deelnemer niks laat horen, is beleid III niet van toegevoegde waarde. Dit betekent dat een aangekleed geen-bezwaarsysteem het uitgangspunt moet zijn. Dit betekent dat biobanken deelnemers moeten hercontacteren wanneer zij volwassen worden en dat deelnemers de kans moeten krijgen om zich terug te trekken uit de biobank.

In **Hoofdstuk 9** worden de conclusies besproken en bediscussieerd per hoofdvraag. Er wordt gekeken naar beperkingen en vragen voor toekomstig onderzoek worden geformuleerd. Daarnaast wordt de toegevoegde waarde van de casestudie bespoken. Ten slotte wordt er besproken dat dit proefschrift een positieve houding heeft ten opzichte van deelname aan biomedisch onderzoek. Tegelijkertijd wordt er een investering van biobanken in haar deelnemers gevraagd en wordt er een inspanning van biobanken verlangd om de deelnemers te betrekken. Deelnemers als partners benaderen is van belang wanneer je een beroep wilt doen op mensen om deel te nemen aan biomedisch onderzoek en correspondeert met het ideaal van *scientifc citizenship*. Ten slotte wordt er benadrukt dat ook kinderen als partners benaderd moeten worden.

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List of publications

Giesbertz NAA, Bredenoord AL, van Delden JJM. When children become adults – should biobanks re-contact? ***Submitted***

Giesbertz NAA, Bredenoord AL, van Delden JJM. Personalized assent for pediatric biobanks. *Submitted*

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Curriculum vitae

Noor Giesbertz was born on December 1, 1983 in Nijmegen, the Netherlands. In 2002 she graduated from secondary school 'het Dominicus College' in Nijmegen. In 2003 she started her medical training at the University Medical Center Utrecht. She completed her scientific internship at the Medical Ethics department of the Julius Center, University Medical Center of Utrecht. From 2007 until 2008 she obtained the minor 'religion in the modern world' at the University of Utrecht and a certificate for the subject 'philosophical ethics'. After receiving her medical degree in 2010, she worked at the emergency department of the Jeroen Bosch hospital in 's Herthogenbosch, the Netherlands. In May 2011 she started the research presented in this thesis at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (supervised by prof. dr. J.J.M. van Delden and dr. A.L. Bredenoord). During her PhD she taught ethics at the medical school and obtained a teaching certificate. In addition, she organized the journal club of the Medical Humanities department and followed several courses on ethics. She had the opportunity to present and discuss her work during an academic visit of the HeLEX centre (Centre for Health, Law and Emerging Technologies) and ETHOX centre (multidisciplinary bioethics research centre) at the University of Oxford. As of October 2014 she works at the medical genetics department of the Erasmus MC, Rotterdam, the Netherlands.