A network of exchange

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Chapter 1

Introduction

Introduction

Preface

> *"I think it was really good because my parents let me decide, they didn't see it as their decision. They realized that I was mature enough and it was my life I was playing with and that I should be able to make that decision. I mean, parents as well as doctors have to understand that when a child gets a serious illness, they're not children anymore. They're almost adults in the way they think and the way they do things."* (Mohini, 12 years old, diagnosed with acute lymphoblastic leukemia at the age of 9)

This is how it all started: an intriguing quote from Mohini, a girl only 12 years old, explaining how important it is to listen closely to children who are invited to participate in medical research. I came across this quote on the Health Talk website (healthtalk.org), on a video showing how shared experiences promote understanding about what it is like to live with a health condition. The website, led by the Dipex Charity in the United Kingdom (UK) based in Oxford University's Department of Primary Health Care, contains the stories collected by academic researchers of people whom they interviewed in their own homes.[1] One section is on the experiences of young people taking part in medical research. It provides insight into how they felt and what their thoughts were at the time they were invited to participate in medical research, why and how they decided to participate, or not, and how they coped with feelings like hope and insecurity.[2]

Mohini's story and those of other children touched me. It made me realize how unique children's voices are. Moreover, I realized how important this type of research is to further improve child healthcare. It also made me wonder how children in the Netherlands are involved in decisions about their participating in research. When is a child mature enough to make such a decision? Is this only related to age or should other experiences also be considered? What kind of support do children need and how can we improve their overall experiences? All these questions led to the research presented in this thesis. Our aim is to give children who participate in research a voice and to empower them, while at the same time adding to scientific knowledge and to develop my own skills as a qualitative researcher.

Children's rights

On 20 November 1989, the United Nations General Assembly adopted the Convention on the Rights of the Child (CRC). Hereby the human rights of children, defined as all persons until 18 years of age, were formally recognized in international law.[3] It is hard to believe that this happened only 30 years ago. Fortunately, much has changed since then and the CRC has become the most widely ratified human rights treaty in history.[4] This thesis in not about children's rights, nevertheless, my sense of justice was a major drive in designing and conducting this research.

> *"States Parties recognize the right of the child to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health. States Parties shall strive to ensure that no child is deprived of his or her right of access to such health care services."* (Article 24.1, CRC)

The CRC states that children have the right to the highest possible health care.[3] There is a lack of knowledge about safety and efficacy of many treatments given to children. Some medicines, for example, are used off-label. This means that the medicines are not tested for children in a specific patient group or not tested in children at all.[5–7] Children differ from adults in their physiological, developmental, psychological, and pharmacological characteristics. In addition, some diseases are unique to children and cannot be studied in adults.[8–10] Thus making pediatric research all the more important.

> *"States Parties shall protect the child against all other forms of exploitation prejudicial to any aspects of the child's welfare."* (Article 36, CRC)

The CRC states that children should be protected against everything that may result in exploitation.[3] Off-label use of medicines is considered to do greater potential harm to children compared to well-designed clinical research.[11] Nevertheless, health professionals sometimes feel reluctant to recruit children for medical research because of their supposed vulnerability.[12–14] Parents too have reported being cautious about enrolling their children in research for fear of the anxiety it might provoke.[15]

> *"States Parties shall assure to the child who is capable of forming his or her own views the right to express those views freely in all matters affecting the child,*

> *the views of the child being given due weight in accordance with the age and maturity of the child."* (Article 12.1, CRC)

The Convention states that children have the right to express their views on all matters that concern them and that they should be listened to.[3] To this end, one could argue that children should also have a voice in medical research. This thesis fleshes out children's real-life stories to reveal the impact that their rights could have if only we were to listen to them closely and start collaborating with them.

Regulation in pediatric research

Fundamental to the balance of children's right to participate and to obtain the highest possible healthcare on the one hand and to be protected on the other hand are the basic principles of biomedical research. These principles are respect for persons and their autonomy, beneficence and non-maleficence, and justice. As a result of the violation of these principles in the past many national and international regulations were developed to provide ethical guidance for doctors and researchers performing studies on human beings.[16–24]

Respect for persons and their autonomy leads to the requirement of informed consent, which can be defined as:

> *"a subject's free and voluntary expression of his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate or, in case of minors and of incapacitated subjects, an authorization or agreement from their legally designated representative to include them in the study"*[19]

During childhood autonomy is considered to develop alongside maturity. Young children are considered incapable of making decisions concerning themselves. As they grow older, they first make decisions in collaboration with their parents until they are considered mature enough to make decisions independently. Children are therefore seen as a vulnerable group insufficiently competent to give their informed consent and who depend on others to make decisions on their behalf.[25,26] As a result, stricter rules apply for involving them in research. The role of research ethics committees (RECs) is to investigate whether research proposals comply with the requirements. Children may only be involved in research that will potentially promote the health of the group they represent and only if the

research cannot be carried out in another group that is considered fully capable of providing informed consent.[16]

Children depend on their parents or legal representatives to give consent on their behalves. Children should be informed about all important aspects of the research. If possible, assent or co-consent must be obtained from the child in addition to the parents' consent and dissent should be respected.[16] Assent is a child's affirmative, non-legal agreement to participate in research, whereas co-consent refers to the child giving legal permission to participate in research that is equal to their parents' permission. National or local law determines at what age children are asked to give their assent or when they can formally give informed consent.[24,27] According to the Dutch Medical Research Involving Human Subjects Act,[21] children between the age of 12 and 16 are asked to give their co-consent in addition to parental consent. When children are 16 years or older, children's consent alone suffices, provided they are capable of reasonable consideration of their interests in the matter. Previously, this age limit was 18, but in March 2017, on the recommendation of the Doek Committee, it moved from the view that 'a child [is] merely seen as object of care and protection, towards the view that a child is also a subject with his or her own opinions and feelings.[28–31] The age is now identical to the age at which children are considered capable of making decisions about their medical treatments.[32] In the UK, informed consent requirements depend on the type of study and the country in the UK where the study is conducted. In most cases, young people over 16 are considered capable of giving informed consent themselves without parental consent.[33] In the United States of America, informed consent is required from parents if children have not yet reached the legal age to give consent themselves. Legal age depends on State and local law.[24] In most of California, for example, children can give consent when they are 18 years of age. Assent is sought from children from the age of 7 onward when parents give formal consent.[34]

Beneficence and non-maleficence refer to maximizing benefits and minimizing harm and avoiding unnecessary burden. Justice implies that there should be no inequality between sharing the burden and the risk of harm and the benefit for research.[26] Because children are considered vulnerable, research may only cause minimal risk and minimal burden.[16] Potential risks and burdens such as blood taking potentially have a greater impact on children compared to adults.[35] Impact is related to factors such as discomfort, inconvenience, pain, fear of harm, separation from parents or unfamiliar surroundings, and to the effects on their growing and developing bodies.[23]

Pediatric research in practice

The regulations we described above provide guidance when involving children in research, but when we consider the practical issues concerning the participation of children in research, several questions remain. Below, we consider some of the main questions and point out gaps in our knowledge that we aim to address in this thesis.

Children's decision-making

Implementing the legal requirements of assent and consent is difficult because of the on-going debate about the extent to which children can be involved in decision-making. This seems to not only relate to age. Instead, collaborative decision-making between parents and children dependents on several factors relating to the individual child, parents or family, situational aspects such as consequences of the decision, and the extent to which children experience the symptoms of their diseases.[36–41] Children and their parents do not always agree on the child's preferred level of involvement and children sometimes wish to be involved more in decision-making than their parents allow them to be.[38,42] Many studies have investigated why parents enroll their children in medical research. Mostly these include hope for improvement of their child's health, helping other children, or contributing to science.[15,43–45] Yet, little is known about how children perceive research opportunities and why they decide to participate, or not.[46] Studies that analyzed children's reasons for participation were predominantly quantitative and often focused on particular diseases or types of research.[42,47] Quantitative research provides invaluable insights but is limited by the use of predefined categories that are explored mainly in terms of frequencies. A qualitative approach is needed to provide in-depth knowledge on how to improve collaborative decision-making of children. To achieve in-depth knowledge children with a broad range of health conditions and who participate in different types of medical research should be included. This will ultimately improve recruitment of children for medical research.

Role of the doctor in children's decision-making

In addition to the role of the parents, doctors also often play a role in the decision-making process regarding children's participation in research. Children are in a dependent relationship with their doctor who might invite them for research.[39] It is clear that coercive consent as a result of a dependent relationship should always be avoided. In theory the dependent relationship of children and parents with their doctors does not need to compromise a voluntary decision.[48] Yet, in

practice parents and children could still feel that their dependent relationship compromises a voluntary decision. Grady and colleagues found that about 25% of the young people included in their study reported pressure to enroll, not only from parents or relatives but also from doctors and research teams.[49] On the contrary, a qualitative study in pediatric oncology showed that parents and adolescents valued the involvement of the treating physician in their decision-making and support from the oncologists was suggested to improve voluntariness of informed consent.[50] Yet, in another qualitative oncology study , most of the young people perceived the doctors' involvement as supportive, while others felt pressured to participate.[38] More in-depth knowledge is needed to find out how children perceive their relationships with the doctors in general pediatrics, not only in giving consent but also while they participate in research. A good child-doctor relationship might help to improve recruitment and the overall experiences of children who participate in research.[46,51]

Children's perception of vulnerability

We pointed out that children are considered vulnerable because they have a diminished decision-making capacity. In addition, they have a greater risk of being harmed and burdened by research. Therefore, they are highly protected by law. There is debate about the acceptable level of risks and burdens in pediatric research and how this relates to age and levels of maturity.[52–55] Little scientific knowledge is available on how children themselves experience risks and burdens in research.[56] This makes it difficult to provide adequate protection. Besides, focusing only on how to overcome risks and burdens could obscure the balance with potential benefits. Research-related benefits mostly relate to health benefits but may also contribute to patients' quality of life.[35] Benefits of research could therefore help children to feel more comfortable about their diseases. Traditional guidelines provide safeguards in relation to the age group children belong to. When focusing only on group characteristics that render children vulnerable, researchers and RECs might lose sight of other potentially harmful features. Such features might be aspects of the study itself, the institutional environment, social or economic context, or prior personal experiences, and these may change over time.[57] This may result in underprotecting those children who are more vulnerable on account of negative influences from such circumstances. Children who are less influenced by such circumstances may be overprotected. Therefore, they may be unnecessarily excluded from taking part in research. Several attempts have been made to re-conceptualize vulnerability in a way that does justice to potential participants, both in terms of protecting them and enabling them to participate.[57–63] The recent guidelines issued by the Council for International

Organizations of Medical Sciences (CIOMS) suggest that children's vulnerability should be viewed more individually by recognizing potential differences between and among age groups including differences in contextualization based on Luna's approach.[18,64] Luna's approach could help to sufficiently protect children according to their needs. At the same time, it could help to prevent children from being overly protected and it could enable them to participate as much as possible according to their wishes. We need in depth-knowledge on children's own perception of their vulnerability to adequately protect and support them during medical research.

Children as co-researchers

In the previous paragraphs we called upon the need for more knowledge on children's self-reported experiences of their participation in research. Yet, where we aim to attune research to children's individual needs and wishes, we need to look beyond participation towards true involvement. Only if children are involved as collaborators can we do justice to their voices and tailor research to what is important to them. This refers to 'patient and public involvement' (PPI). INVOLVE is one of the originators of PPI and is based in the UK. It was established in 1996 and supported by the National Institute for Health Research. To be involved in research should be clearly distinguished from taking part in research and from being engaged in research. Nevertheless, in the literature participation, involvement, and engagement are often erroneously used as synonyms. *Participation* refers to people who take part in a study that may include testing a new medicine or completing a questionnaire. *Involvement* implies that patients and members of the public, such as potential patients or caregivers, are actively involved in setting up and organizing research projects. When children are asked to take place in a research advisory group to help identify research priorities or to develop and improve the readability of patient information leaflets are cases in point. *Engagement* refers to creating awareness about research by providing and disseminating information and knowledge with the public, for example through social media. Although engagement and participation clearly differ from involvement, the three can overlap and strengthen each other.[65]

Several benefits of PPI have been reported including that research shall be directed more towards the needs and wishes of its end-users and that this will increase their self-esteem.[66,67] Nevertheless, PPI in pediatric research is not yet common practice. Problems relate to lack of funding and time and other challenges such as gatekeeping or power imbalances and training on how and to what extent children should be involved.[67–75] Besides, it is difficult to measure

the impact of PPI in terms of research output.[76,77] Therefore, we need descriptive evidence on how children could be involved in research and how they experience being involved as co-researchers.

Aim of this thesis

We aimed to explore and evaluate children's self-reported experiences to increase in-depth knowledge about their point of view on participating in medical research. In addition, we aimed to explore the feasibility of involving children as co-researchers in our analysis of these reported experiences. In so doing, we aspire to do justice to the voice of children in research. Based on our findings we shall formulate recommendations for improving pediatric research to better meet the needs and wishes of children.

Research questions

Following from the above aims we formulated the research questions below:

- Why do children participate in medical research? (Chapter 2)
- What value do children attach to the relationship with their doctors while taking part in medical research? (Chapter 3)
- How do children experience vulnerability while participating in medical research? (Chapter 4)
- Is it feasible to involve children as co-researchers in the analysis of qualitative research? (Chapter 5)

Methodological approach

Most medical studies use quantitative research methods. By contrast, the study presented in this thesis uses qualitative methods. Over the years, qualitative research has become increasingly common in medical sciences and is a valuable complement to quantitative studies.[78,79] Qualitative research is designed to gain detailed insight into underlying reasons and beliefs, to understand why, how, and what it is that influences a given process. It aims at developing concepts or theory rather than at verification, as is the case in quantitative research. Qualitative data analysis is interpretive rather than statistical and is presented in narrative style. Thus, qualitative research can provide knowledge that cannot be captured in quantitative research.[80–85] Quantitative designs could, for example, aim to provide answers in terms of frequencies or to verifying answers. In our research we looked for in-depth knowledge in as wide a range as possible to capture

different perspectives rather than findings that are generalizable to the average person in one group.

A frequently-used way of data collection in qualitative studies is to conduct interviews with participants in their usual surroundings.[86] The data we present in this thesis were collected by means of semi-structured interviews with children in their own home. The children's own stories formed the basis for developing hypotheses and concepts. Recruitment of the participants aimed at maximum variation sampling. Rather than aiming for numerical representativeness, this method seeks to include as wide a range as possible of participants belonging to a specific group, both in terms of (illness) experiences and socio-demographic variables.[87,88] Data collection aimed for saturation, meaning that collection continued until a reliable sense of exhaustion and a variety of themes were captured in the data.[84,86,89]

The interviews were transcribed verbatim by a professional company, coded by using Atlas.ti software and thematically analyzed following a grounded theory approach. In this approach, theory is derived from the data and systematically collected and analyzed in an iterative process during which data collection and analysis take place in parallel.[90,91] We chose the constructivist grounded theory approach, as introduced by Kathy Charmaz, which views reality s as being interpretative and relative to social situations and the interactions of the individuals involved, which includes participants and researchers.[92–94] Multiple datasets were developed, (re)used, and combined to analyze children's experiences of participating in medical research. We performed an amplified analysis for the purpose of enlarging our dataset to explore the child-doctor relationship and the vulnerability of children who participated in medical research in more detail.[95]

Interview study in the United Kingdom

The data presented on the Health Talk website was based on scientific research collected mostly by the Health Experience Research Group (HERG) at Oxford University's Nuffield Department of Primary Care Health Sciences in the UK. The young people who were interviewed were between 10 and 23 years of age. They had all been invited to participate in medical research, some as patients, others as healthy volunteers. The interviews were transcribed verbatim. Although the data were analyzed provisionally and placed on the Health Talk website[2] the interviews had not been subjected to thorough scientific analysis. We undertook

to perform such an analysis of the interview data and report the outcomes in Chapters 2, 3, and 4.

Interview study in the Netherlands

We set up a Dutch interview study according to the methodology developed by HERG that had also been used to collect the UK data. We drew up a topic guide based on the UK dataset that we consulted while performing the interviews. The main topics included reasons for participating or not, the information supplied, and considerations that influenced decision-making including feeling obliged to take part to help their doctor, experiences during participation, involvement of doctors and parents, and children's recommendations on how to improve their experience. Notes were taken after the interview to record any noteworthy statements or contextual aspects that could be useful in the early stage of analysis and to inform about changes necessary to the topic guide. Altogether, we interviewed 23 children between the age of 9 and 18 years old. The age limits were based on research by Hein and colleagues who showed that the minimum age for competent decision-making lies around nine years, with an optimal cutoff age of 10.4 years old.[96] The upper limit of 18 years was chosen because at the onset of the research for this thesis 18 was the age at which young people could decide for themselves whether they would participate or not. Participants included children who had been asked to participate in medical research and who had either consented or had declined to take part. Children who were participating in a study were eligible for an interview if at least 75% of the study had been completed to make sure they could reflect on their experiences. If the study they had participated in had already ended, they could be interviewed up to a year afterwards. The studies described in Chapters 3 and 4 are based on these data, combined with the dataset from the UK in an amplified analysis. The Dutch data were also used for the study presented in Chapter 5.

Children as co-researchers

In qualitative research one should be cautious about interpretation bias in the data analysis. Qualitative research has a subjective component that makes reflexivity an important aspect.[80] Qualitative researchers should adopt a self-critical stance regarding the influence of their own values and biases that stem from their cultural, political, and social background.[82] Children might interpret the voices of their peers differently and they might emphasize different aspects compared to adults, because children have different life experiences and social situations. Therefore, we asked children to help us analyze the Dutch interview data to strengthen our analysis. Given the lack of descriptive literature on how

to involve children in the analysis stage of research, we did some pioneering. The result was a two-phase method. This method aimed at limiting preselection of data by adults by asking children to help identify themes from the original data before we explored these themes in more detail. It also addressed issues related to time investment. The first phase consisted of one-on-one sessions, while the second phase entailed group meetings. We report on this method and evaluate the process of involvement in Chapter 5.

Outline of this thesis

Chapter 2 provides an overview of young people's experiences of taking part in clinical trials in the UK. We explored the reasons of children and young adults to participate in clinical trials, as well as the lessons they learned from taking part and any recommendations they had for researchers.

> *"I thought about it for a couple of days and then I decided that I wanted to do it. And I wanted to do this trial because it was the first trial that I'd ever done including, for diabetes. And to me, I felt like because I didn't have a good time to begin with doing it, I wanted to help other people. And if this was one way that I could help them in the future, I wanted to do that. …And I also thought that if I did the trial, I might feel better about myself and better about having this illness, kind of disease kind of thing."* (Girl, 15 years old)

Chapter 3 provides insight into the child-doctor relationships in pediatric research in the Netherlands and the UK.

> *"Well, I was in touch with my doctor for a couple of weeks before diagnosis. So yes, I did see [the doctor] as a confidant, someone who knows what he was talking about. So, when he asked me that question, it didn't feel strange at all to me. I actually experienced it as pleasant. If two strangers stood at my bedside, asking if I wanted to participate in research, that would maybe, um, be a little bit more confusing. So, I thought…. Um, it was kind of nice that he asked me."* (Boy, 17 years old)

> *"I think that is just normal, like… I think it is kind of, like yes, you can give something back. Yes, I don't know exactly how to say it, but I think it is just super cool that you can say thank you in this way, but that you can really give it back. And that you see like yes, this is me. And yes, the doctor would say that is cool too."* (Boy, 13 years old)

Chapter 4 explores how children perceive what makes them feel safe and supported while they participate in medical research.

> *"That [researchers] will look at them. That instead of 'a research project is performed on number 104', it will really be oriented towards that person. Look, let's say that person finds it a bit scary, then you should spend more time on this child, like that. So, I just hope that this will be implemented because of the advice I gave, I think that is important."* (Girl, 16 years old)

Chapter 5 reports on our two-phase method for involving children in the analysis of qualitative interviews. In addition, we reflect on the process from the perspectives of adult and child researchers alike.

> *"I thought it could be fun and I had never done such a thing before, and I like to help people, and perhaps I want to become a doctor in the future so I thought it would be fantastic!"* (Girl, 11 years old)

> *"It actually felt a bit like I was a researcher myself"* (Girl, 11 years old)

Chapter 6 is a general discussion in which we provide an overview of important findings in the context of existing literature, we consider strengths and limitations of the research presented in this thesis, and we point out implications for clinical research practice and for future research.

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"I thought about it for a couple of days and then I decided that I wanted to do it. And I wanted to do this trial because it was the first trial that I'd ever done including, for diabetes. And to me, I felt like because I didn't have a good time to begin with doing it, I wanted to help other people. And if this was one way that I could help them in the future, I wanted to do that. …And I also thought that if I did the trial, I might feel better about myself and better about having this illness, kind of disease kind of thing."