Hearing the Voices of the Children:

the views of children participating in clinical research

Mira Staphorst

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de ervaringen van kinderen in wetenschappelijk onderzoek

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In liefdevolle herinnering aan mijn moeder

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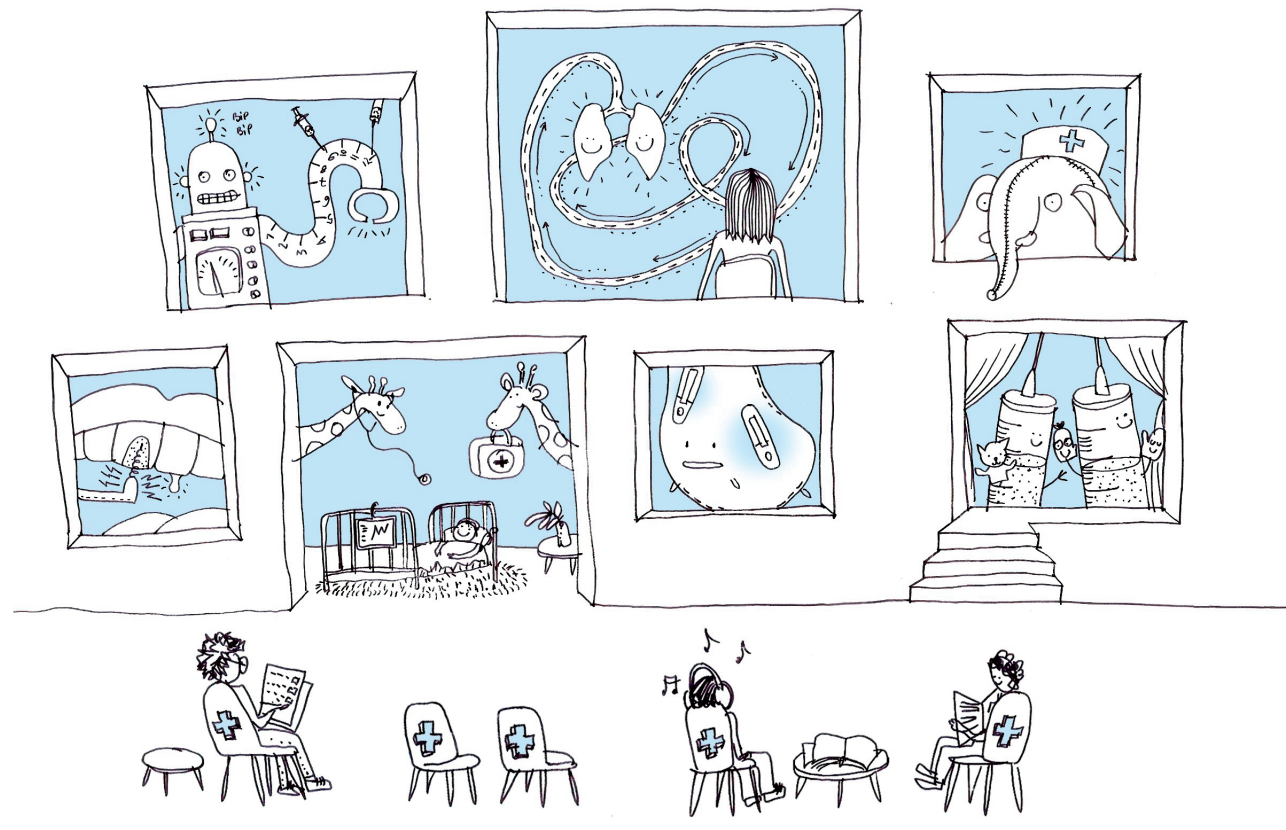
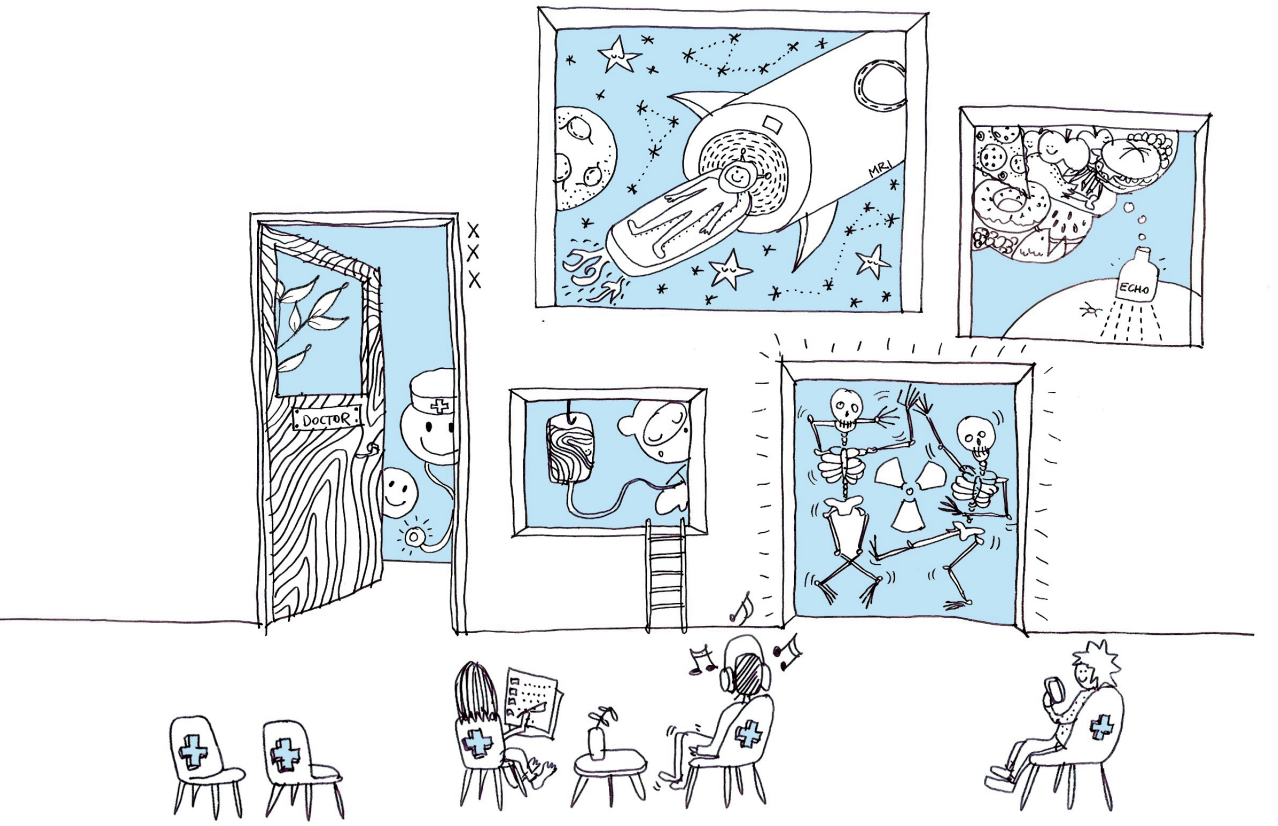


CHAPTER 1.

GENERAL INTRODUCTION



NEED FOR PEDIATRIC RESEARCH

In clinical research with children (i.e. pediatric research), there is a tension between what is needed for the development of evidence-based drugs and treatments for children and what is ethically acceptable concerning the involvement of children in research, given that children are legally considered to be unable to give informed consent. While children are viewed as being vulnerable and in need of protection against risky and discomforting research procedures, withholding them from participation in clinical research might be considered unethical and it impedes them from getting access to the benefits of clinical research. Research shows that approximately 65% of the medicines pediatricians prescribed to children are unregistered or off-label,[1] which may pose children to an increased risk of an under- or overdose of medication. Without the participation of children and adolescents in clinical research, it cannot be adequately demonstrated that (new) medicines and treatments are safe and effective for them. Also observational research is needed to establish reference values in children (e.g. anatomy, metabolism) and to evaluate the outcomes and (long-term) effectiveness of health care in everyday life. More pediatric research is therefore urgently needed.[1, 2]

RISK AND DISCOMFORT IN PEDIATRIC RESEARCH

An important part of the ethical discussions in pediatric research is about risk and discomfort of the research procedures involved. Guidelines, laws and regulations regarding pediatric research participation restrict the participation from children in clinical research when it involves considerable discomfort and/or risk. In general in therapeutic research,[a] risk and discomfort are accepted as long as the benefits for the participant outweigh these. In non-therapeutic research,[b] risk and discomfort should be minimal, although some guidelines and regulations allow a minor increase over minimal discomfort in certain situations.[3, 4] (Note: in 2016 a new European regulation has been passed for clinical trials. An important improvement is that risk and discomfort should be minimal compared to the standard treatment of the child.[5] To be further elaborated on in Chapter 8 'General Discussion').

a Research with potential medical benefits for the participants

b Research without direct medical benefits for the participants

EVALUATION OF RISK AND DISCOMFORT IN CLINICAL RESEARCH

Clinical studies have to be reviewed whether they are designed in accordance with regulations and ethics guidelines. Ethics committees[c] evaluate the ethical aspects of clinical research. One of their responsibilities is to review the balance between discomfort and risk of clinical research on the one hand, and its benefits for the participant or study population on the other hand. During the informed consent process, a second evaluation takes place in which the children and their legal caretakers evaluate - in consultation with the researcher/pediatrician - whether discomfort and risk are acceptable for this individual child.

EMPIRICAL DATA

A review by Hunfeld and Passchier revealed that empirical research on discomfort of children in clinical research is limited.[6] Although different ethics reports recommend defining and monitoring children's discomfort during research procedures,[2, 7] there are only a few small studies published about the self-reported discomfort of children in research.[8-10] Ethics committees therefore have limited empirical evidence to guide their decision-making on what is an acceptable level of discomfort. They have to rely on their own subjective assumptions, experiences and observations, and those of other persons (e.g. pediatricians, pediatric nurses, ethicists). Literature shows that pediatric healthcare professionals and parents likely overestimate children's discomfort in medical settings, although in some cases the opposite occurs.[11-13] If discomfort in pediatric research is overestimated, it can lead to the rejection of studies because of expected discomfort for the children, while in fact the children may think it is acceptable, and vice versa. It is therefore crucial to take children´s own perspectives into account when evaluating discomfort of research. Moreover, it is reflected in article 12 of the United Nations Convention on the Rights of the Child that children deserve to give their opinions in matters that concern them.[14]

The need to have empirical data about the experiences of children in clinical research is seen, for instance, by the development of the Reactions to Research Participation Questionnaire for Children (RRPQ-C)[15] and the Pediatric Research Participation Questionnaire (PRPQ).[16] These questionnaires give insight in the perceived benefits and barriers to pediatric research participation. However, they give limited insight into discomfort and do not address children's experiences during the individual research procedures of a study. Since ethics committees often evaluate discomfort of the separate research

c In the Netherlands, ethics committees are referred to as Medical Ethics Committees (METCs), in the United Kingdom as Research Ethics Committees (RECs) and in the United States as Institutional Review Boards (IRBs).

procedures (in addition to the study as a whole),[17, 18] the so-called component-analysis approach,[19] it is important to have information on discomfort of individual research procedures, as such information can be generalized across different research studies with similar procedures. So far, there are no instruments to obtain this information.

AIMS AND OUTLINE OF THIS THESIS

In this thesis, we support evidence-based decision-making on discomfort in pediatric research by providing information on children's self-reported discomfort. These data are an important first step in providing benchmarks for discomfort of various research procedures in pediatric research. In the absence of an instrument that specifically measures discomfort, we developed a short instrument to measure generic forms of discomfort applicable to all kinds of pediatric research procedures.

Apart from being helpful to ethics committees, information on children's self-reported discomfort helps pediatric researchers to get more insight into the experience of their studies reported by children in terms of discomfort. It can also help to provide new participants with evidence-based information on discomfort based on the reports of children who underwent the same procedures in previous research. Moreover, with this information, children and their parents will be better informed when making a decision for participating in research.

While the focus of this thesis is on discomfort, positive experiences and benefits are addressed as well. We did not plan to incorporate these on the first hand, but we noticed during our interview study that children were eager to talk about positive experiences and benefits. We think that adding these experiences to this thesis give a more balanced picture of the overall experiences of children in research.

The main research questions of the thesis were:

1. What is the degree of discomfort of common medical research procedures?
2. Do children experience clinically relevant stress symptoms due to common medical research procedures in the long-term?
3. Do age, anxiety-proneness, gender, medical condition and previous experiences with the procedures influence discomfort?
4. Are there differences in discomfort of the same medical procedures that are conducted for research purposes versus clinical care?
5. What are children's suggestions to reduce the discomfort of research procedures?

In **Chapter 2** the protocol of our research project is described.

Although pain, distress and anxiety are often labeled as discomfort, a clear description of what constitutes discomfort remains unclear. **Chapter 3** gives insight into what can be considered as discomfort in clinical research according to the children involved.

Chapter 4 presents the construction of a generic, practical and short instrument to measure children's self-reported discomfort during medical research procedures in a quantitative way: the Child's Discomfort during Research Procedures Questionnaire (CDRPQ).

In **Chapter 5** children's self-reported discomfort during common medical research procedures is presented from a quantitative point of view. It is explored whether age, anxiety-proneness, gender, medical condition and previous experiences with the procedures influence discomfort. Additionally, it was exploratively studied whether there are differences between discomfort in medical procedures that are conducted for research purposes and for routine clinical care (i.e. purpose of the procedure). This chapter also addresses the children's suggestions for reducing discomfort.

In **Chapter 6** the psychological risk of clinical research for children is addressed, which is operationalized as clinically relevant stress symptoms. We looked at stress symptoms one month and one year after undergoing research procedures.

Chapter 7a and 7b address the positive experiences children report in clinical research, and discuss which of these positive experiences could justifiably be seen as benefits taken into account into the risk-benefit analysis.

Chapter 8 constitutes a general discussion on the main findings of the studies presented in this thesis. It also gives recommendations for practice and future research.

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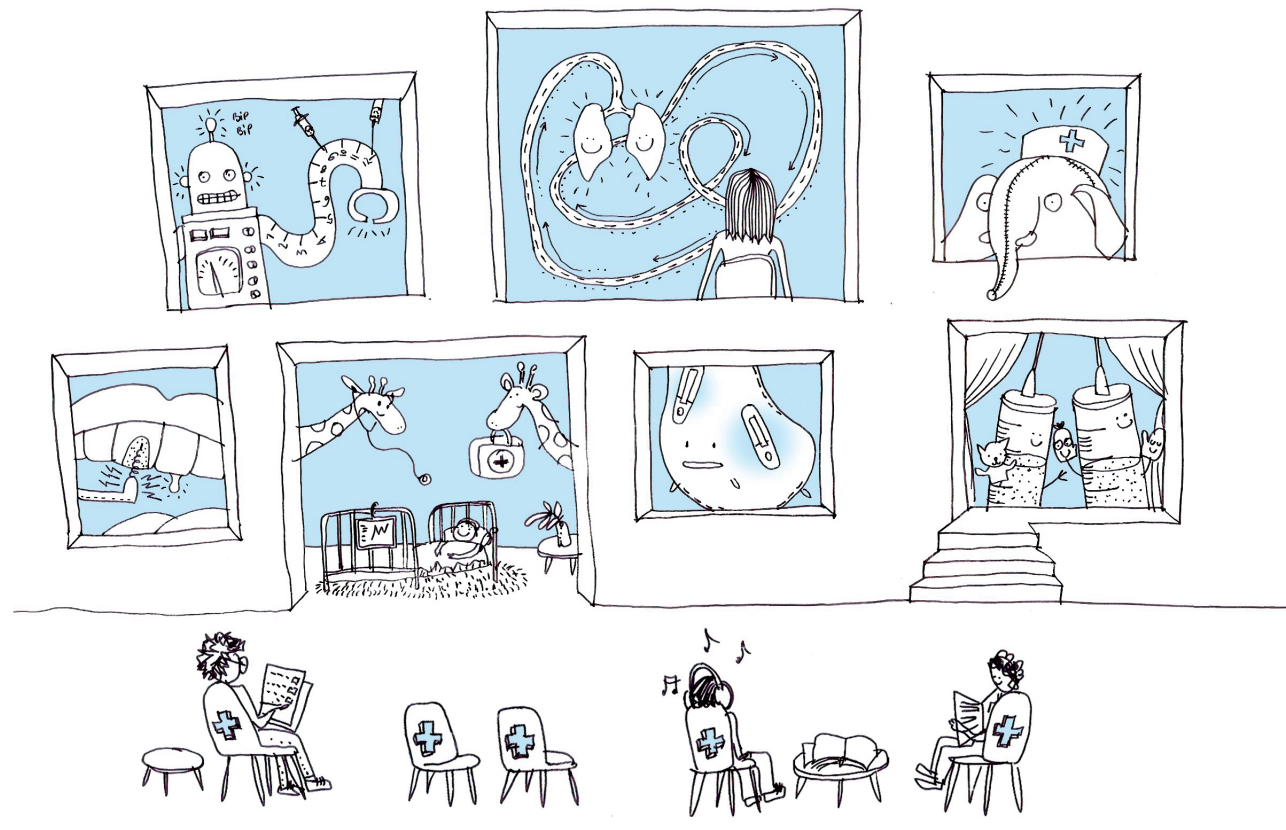

CHAPTER 2.

Hearing the voices of children: self-reported information on children's experiences during research procedures: a study protocol

MS Staphorst, JAM Hunfeld, R Timman, J Passchier, JB van Goudoever

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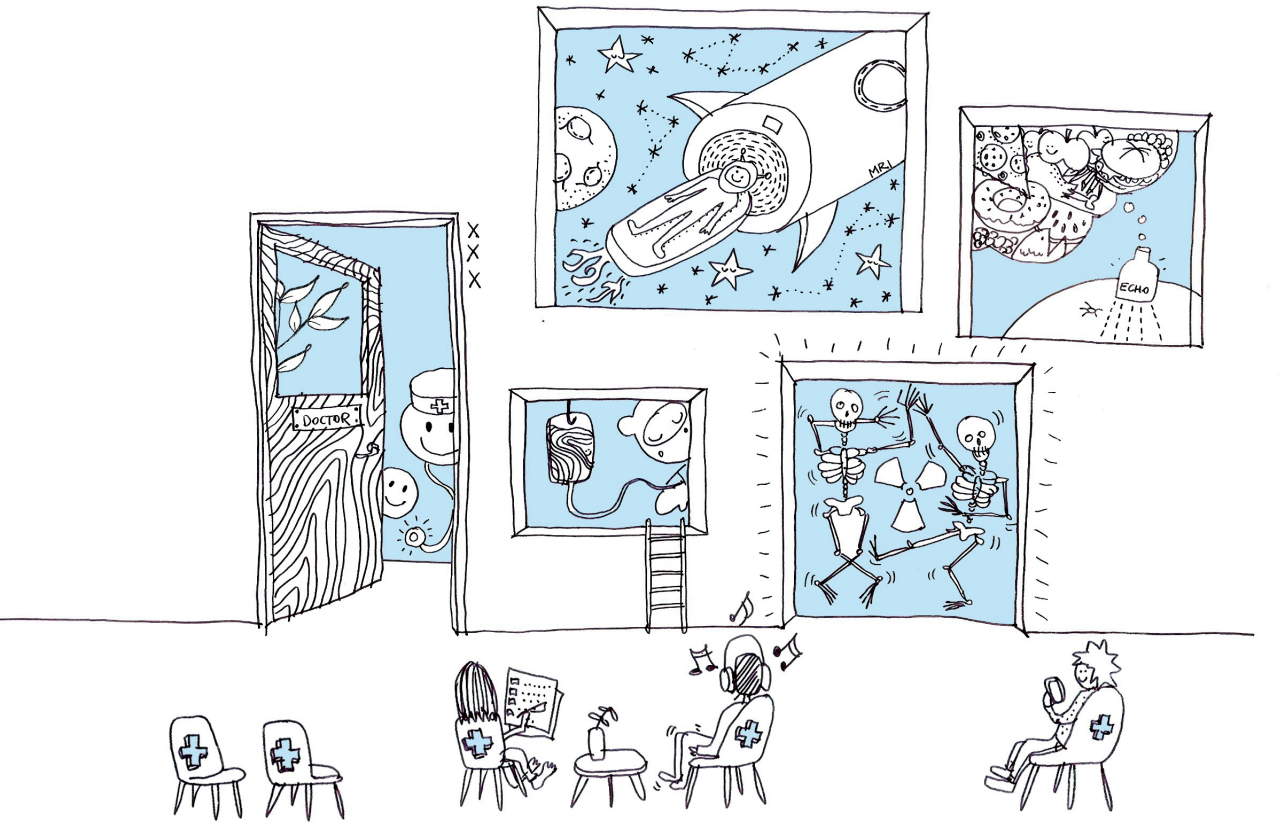

ABSTRACT

Introduction. In paediatric research, there is a tension between what you can ask from a child and what is needed for the development of evidence-based treatments. To find an optimal balance in conducting clinical research and protecting the child, it is necessary to have empirical data on children's experiences. Until now, there are scarce empirical data on the experiences from the perspective of the child. In this manuscript, we describe the protocol of a two-phase study measuring children's self-reported experiences during research procedures.

Methods and analysis. In the first phase of our study, we aim to interview approximately 40 children (6–18 years) about their self-reported experiences during research procedures. In the second phase, we will develop a questionnaire to measure children's experiences during research procedures in a quantitative way. We will use the interview outcomes for the development of this questionnaire. Next, we will measure the experiences of children during seven research procedures with this questionnaire. A one-month follow-up is conducted to investigate the emotional impact of the research procedures on the children. Children will be recruited from different research studies in three academic children's hospitals in the Netherlands.

Ethics and dissemination. The ethics committee of the VU University medical center evaluated both studies and indicated that there was no risk/discomfort associated, stating that both phases are exempt from getting approval under the Dutch Law. Dissemination of results will occur by conference presentations and peer-reviewed publications. The findings of our project can help Institutional Review Boards and paediatric researchers when evaluating the discomforts of research procedures described in study protocols or when designing a study. Information on experiences of children involved in previous studies may also help children and parents in future research with their decision-making about participation in clinical research, or parts thereof.

INTRODUCTION

In paediatric research, there is a tension between what is needed for the development of evidence-based drugs and treatments for children and what is ethically acceptable concerning the involvement of children in research, given that they are (legally) unable to give informed consent. For instance, there are scarce data about the dosage and effect of medicines for children, which amount to 65% of all prescribed drugs. More paediatric research is therefore needed.[1] While children are rightly considered to be vulnerable and in need of protection against risky and burdensome research procedures, withholding children from participation in clinical research might be considered unethical as well; children deserve to get access to the benefits of clinical research.

Institutional Review Boards

The balance between the burdens and risks of clinical research and its benefits for the child plays an important role in the decision-making of Institutional Review Boards (IRBs). Since little is known about children's self-reported experiences of discomfort in clinical research,[2] IRBs have limited empirical evidence to guide their decision-making, which is why they often rely on observations and assumptions of other persons (e.g. paediatricians, paediatric nurses, ethicists). Literature shows, however, that paediatric nurses, paediatricians, psychologists and parents are likely to overestimate,[3, 4] or underestimate,[4, 5] children's discomfort in medical settings. It is therefore crucial to also take children's own perspectives into account when evaluating discomfort of research procedures. This argument is also reflected by an advisory council of the Dutch government, Committee Doek, that proposed that one of the conditions for clinical research in children is to define and permanently monitor children's discomforts during research procedures.[6]

The measurement of children's experiences in paediatric research

Hunfeld & Passchier reviewed the literature on discomfort of paediatric research a few years ago.[7] They concluded: "Several limitations of the present body of knowledge on the burden of child participants in medical research can be mentioned. So far no systematic research has been conducted covering and comparing the amount and different aspects of perceived burden and risks in children, like regular hospital visits, the time needed to undergo the medical procedure or the unpleasantness of particular procedures". In addition, they mentioned that there is scarce information on the experiences of research procedures based on the perspectives of the children themselves.

The need to have empirical data about the experiences of children in clinical research on an international level is seen, for instance, by the development of two questionnaires about this topic: the Reactions to Research Participation Questionnaire for Children (RRPQ-C)[8] and the Pediatric Research Participation Questionnaire (PRPQ).[9] The PRPQ

concerns perceived benefits and barriers to paediatric clinical trials participation. The RRPQ-C concerns children's experiences with research studies in general. Since research studies vary in the procedures involved and often involve a combination of procedures, the outcomes of these questionnaires are difficult to generalise. It is therefore important to have additional information about the experiences of the individual research procedures as well as an instrument to measure this.

Current study

In this manuscript, we describe the protocols of a two-phase study: an interview study and a questionnaire study. The primary aim of this project is to get insight into the self-reported experiences of children when undergoing research procedures, in particular in relation to discomfort, and the emotional impact of the procedure for the child. Secondary aims are to get insight into children's suggestions to reduce possible discomforts of research procedures and whether there are differences in experiences between subgroups of children (age, anxiety-proneness and health condition).

Since there is limited information about this topic, the first phase of our project is a qualitative study to explore the experiences of children in clinical research in particular related to discomfort. We will use the outcomes of the interviews (i.e. the different experiences of the children) for the development of a questionnaire to measure children's experiences in a quantitative way. In the second phase, we will use this questionnaire to measure children's experiences during research procedures in order to get insight into the percentages of children who experience certain discomforts and to what extent.

Research questions

Primary research questions

1. What are children's experiences during (common) research procedures, and do these differ between different procedures?
2. What is the emotional impact of research procedures for children after 1 month?

Secondary research questions

1. Are there differences in experiences and emotional impact of research procedures between (a) healthy children and children with a chronic condition, (b) young (<12 years) and older children (≥12 years) and (c) between anxiety-prone versus not anxiety-prone children?
2. Are there differences in experiences between medical procedures that are conducted for research purposes or routine clinical care?
3. What are children's suggestions to decrease discomfort related to research procedures?

METHODS AND ANALYSIS - INTERVIEW STUDY

Design

In the first phase of our study, we will interview a group of children who participate in clinical research studies to explore their experiences during research procedures and their suggestions to reduce potential discomfort caused by the procedures. The primary outcomes of this interview study are the different discomforting aspects during research procedures that children experience. These aspects will be categorised into themes. Secondary outcomes are children's positive experiences and their suggestions to reduce discomfort.

In addition, for the development of the questionnaire in the second phase of our project, children will answer some written questions about their experiences with the research procedures. We will ask children to fill in each question on three different response options and will ask them which of these options they prefer. The reason why we will investigate this is because there is discussion about what the most suitable response option is for children. We will use the response option that is most often preferred by the children for the questionnaire in the second phase of our project.

Population

The focus of the interviews is to explore the experiences of a diverse group of children. We will purposefully select a wide range of children (ages and medical conditions) undergoing various types of clinical research procedures to ensure a wide range of experiences, influences and attitudes. In qualitative research, this is called a maximum variation sample.[10] This method is designed to represent a wide range of experiences, rather than aiming at numerical representativeness. We will interview children from 6 years of age because the literature shows that children aged 6 years and older are cognitively capable and have language capacities to accurately verbalise their experiences.[11] We aim to include approximately 40 children, or until saturation is reached. In qualitative research, this is the point when additional interviews do not provide new information.[12] The point of saturation will determined by the interviewer (MSS) in consultation with other members of the project group (JAMH and JP). Children are eligible to be interviewed if they meet the following criteria: (1) aged between 6 and 18 years, (2) fluent in Dutch, (3) no current psychological treatment for pain or anxiety disorders, (4) no severe psychosocial problems (such as anxiety disorders and depression), (5) accompanied by at least one parent or caretaker and (6) able to express themselves verbally. These inclusion criteria will be determined by asking the parent(s) of the children and/or by consulting the child's medical record.

The children will be recruited from research studies at three academic hospitals in the Netherlands: Sophia children's hospital (Erasmus University Medical Center) in Rotterdam, the department of Paediatrics of the VU Medical Center in Amsterdam and

Emma children's hospital (Academic Medical Center) in Amsterdam. We aim to include children from four different paediatric departments: gastroenterology, pulmonology, nephrology and oncology, to cover a large variety of research procedures and to include children from a broad range of diseases. We will also include healthy children who participate in research studies at these departments.

Procedure

The children and their parents will be approached by the researchers of the studies we will cooperate with. If interested, parents and children will receive an information letter, which will be adapted for children (6–11 years) and adolescents (12–18 years). Parents and children will also have an opportunity to ask the interviewer questions about the interview in a face-to-face conversation, which will probably take place on the day of the child's research visit. After agreement, written parent consent and child assent (children ≥12 years) will be obtained. Children younger than 12 years have to verbally agree to participate. The interviews will be conducted by the PhD student of the project (MS, a health psychologist) who will receive specific training in interview skills by experts in the field of medical and paediatric psychology. Children will receive a gift card (€7.50) for being interviewed. Interviews will be conducted in a private room at the hospital, directly after the child's participation in a research study. Parents are allowed to be in the room during the interview but will be asked not to intervene as the focus is on the child's perspective. During the interviews, parents will fill in some questions about the child's demographics and medical history. After the interview, children will fill in some written questions about their experiences with the research procedures.

Instruments

Demographics

We will collect demographics by asking the parent of the child to fill in some questions about the child's gender, date of birth, ethnicity, educational level, paediatric disease and medical history. If the parent does not know this information, we will collect the data from the child's medical record.

Interview

The interviews about children's experiences in clinical research will be semi-structured and will focus on the discomforts the child experienced in relation to research procedures. Children will also be asked about positive experiences and suggestions to decrease possible discomfort. The interview questions are based on the literature, a review about the discomfort of children in clinical research,[7] and input from several paediatricians, psychologists and paediatric nurses. The interview will contain questions about

children's experiences during participation, in particular related to discomfort, future research participation, preparation for the study and suggestions to reduce discomforts.

Written questions

To find out the most preferred response option, children will fill in five questions about their experiences with the research procedures. These questions will be based on input from the project group and the literature. We will ask the children to fill in each question on three response options: a 5-point Likert scale, a 100 mm coloured visual analogue scale (VAS) and a simple 100 mm VAS. Children will be asked which of the three response options they prefer.

Analyses

Interview

The interviews will be audio-recorded and transcribed verbatim. The transcripts will be analysed using 'thematic analysis' in QSR NVivo 10 to identify themes related to children's experiences and their suggestions to reduce discomforts.[13] Thematic analysis is a method to interpret the findings of qualitative research, in which the transcripts will first be coded using open coding. The codes obtained during open coding will then be divided into categories covering all relevant information. Finally, the categories will merged into main themes. Two researchers (PhD student and supervisor) will independently analyze the interviews to ensure interrater-agreement on the relevance of the themes derived from the interviews. In case of disagreement, the researchers will discuss until consensus about the themes is reached.

Written questions

We will investigate which response option is most frequently preferred by the children.

METHODS AND ANALYSIS - QUESTIONNAIRE STUDY

Design

In the second phase of our study, we will first develop a questionnaire based on the information gathered in the interview study (i.e. the themes/categories on children's experiences during research procedures) as well as in expert meetings with different healthcare professionals involved in paediatric research (paediatricians, paediatric nurses, ethicists, psychologists, pedagogics and parents). This draft questionnaire will be pretested in a sample of 25 children. The final questionnaire will be used to measure children's experiences during several research procedures. At two time points, we will ask children to fill in questionnaires: directly after undergoing a research procedure and 1 month later.

The primary outcomes of this questionnaire study are children's experiences, in particular related to discomfort, during research procedures and the emotional impact of the research procedures on them. Secondary outcomes will be their suggestions to reduce discomfort, and possible factors that influence children's experiences.

Population

Since this study is a first step in systematically investigating children's experiences during research procedures, we cannot say beforehand how many children are needed to be included. We plan to include a sample of 50 children for each research procedure. We think this number will be reasonable given the duration of our study, and the availability of children undergoing the research procedures at the different locations during the inclusion period of our study. Recruitment is based on the same criteria as previously mentioned for the interview study, except that the lower age limit will be 8 years instead of six because we will use two questionnaires that are suitable for children aged eight and older. Again, we aim to recruit children from the same three academic children's hospitals in the Netherlands.

In addition, 50 healthy children (8–18 years) will be included to measure their experiences after a check-up visit at the dentist. With this group of children, we aim to measure the experiences of a common medical procedure in a child's 'daily life'. We will compare this outcome with the experiences during the other research procedures.

Procedure

Parents and children will be recruited in the same way as for the interview study. Directly after undergoing the research procedure, the child will complete the *'What do you think of …?'*-questionnaire, which is the questionnaire we will develop to measure children's experiences during a research procedure. Children also fill in the '*Zelfbeoordelings Vragenlijst voor Kinderen*' (ZBV-K) to measure anxiety-proneness. After 1 month, the child receives an email with the link to fill in the two questionnaires online: the *'What do you think of …?'*-questionnaire again to investigate whether the moment of measuring may influence children's answers and the Child Revised Impact of Event Scale (CRIES-13) for the assessment of the emotional impact of the clinical research procedure. After having completed all questionnaires, children will be sent a gift card (€7.50) to their home as a token of appreciation for their participation in our study. To send the gift card to the children, it is necessary to ask for their addresses. We will delete this information directly after sending the gift card.

Instruments

Discomfort - 'What do you think of …?'-questionnaire.

Children's experiences during research procedures, in particular related to discomfort will be measured using the questionnaire we developed ('*What do you think of …?*'-questionnaire). This questionnaire will contain questions about: (1) experiences during a clinical research procedure, both positive and negative experiences; (2) the most burdensome part of the research study in which the child participates; (3) whether the child would undergo the research procedure again in the future; (4) the child's experiences with the same medical procedure in routine clinical care and (5) an open question to ask children about suggestions for decreasing discomfort of the research

procedures. The specific questions of the '*What do you think of …?*'-questionnaire will be based on the topics on children's experiences from the interviews and on input from professionals during the expert meetings. The method of answering the questions is based on the children's preferences for response options on the written questions in the first phase of the study (i.e. five-point Likert scale, 100 mm coloured VAS or 100 mm simple VAS).

Emotional impact - Child's Revised Impact of Event Scale (CRIES-13)

The emotional (traumatic) impact of the research procedures will be measured by the Dutch version of the Child's Revised Impact of Event Scale (CRIES-13).[14] The CRIES-13 is a child self-report scale about the frequency of event-related (traumatic) distress (in our study, we measure the distress caused by the research procedures). The questionnaire consists of 13 items which are divided into three subscales: avoidance, intrusion or re-experiencing and arousal. Children have to rate each question on a 4-point Likert scale, with the following categories: 0='not at all', 1='rarely', 3='sometimes', 5='often'. The CRIES-13 demonstrates satisfactory to good psychometric characteristics.[15] It has good internal consistency for the total scale (Cronbach's $\alpha = 0.80$) and satisfactory internal consistency for the three subscales: intrusions or re-experiencing (Cronbach's $\alpha = 0.70$), avoidance (Cronbach's $\alpha = 0.73$), and arousal (Cronbach's $\alpha = 0.60$), for example, when a child has a total score of 30 or above on the CRIES-13, this child is considered to have clinically elevated stress response symptoms.[16]

Anxiety-proneness - Zelfbeoordelings Vragenlijst voor Kinderen (ZBV-K)

Anxiety-proneness of the children will be measured by the *Zelfbeoordelings Vragenlijst voor Kinderen* (ZBV–K).[17] The ZBV-K is a Dutch translation of the State–Trait Anxiety Inventory for Children (STAI-C)[18] and consists of two scales: state and trait anxiety. Each scale consists of 20 items. For this study, the trait scale was used, which addresses the frequency and intensity of general anxious symptoms. The child was instructed to rate the frequency with which he or she experiences anxiety symptoms in general (i.e.

anxiety-prone) on a three-point Likert scale (e.g. 'I worry about school'), with the following categories: 1='almost never', 2='sometimes', 3='often'. Individuals scoring high on this scale tend to interpret situations as more threatening than do individuals with lower scores. The trait scale demonstrates good internal consistency in a Dutch norm population (Cronbach's $\alpha > 0.80$).[17] The total ZBV-K score for trait-anxiety ranges between 20 and 60. Test–retest reliability for both children and adolescents has been found to be acceptable (Dutch norm population: $r > 0.65$).[17] Since the manual of the ZBV-K does not mention a clinical cut-off score, based on previous studies with the ZBV-K, we consider children as anxiety-prone when they have a total score of at least 38 on the ZBV-K.

The ZBV-K is used for children between 8 and 15 years old. However, it has been suggested that the child version of ZBV (ZBV-K) may be more useful for adolescent populations than the adult version (ZBV), given that even older adolescents may have difficulty understanding some of the vocabulary in the adult version.[19] Kirisci et al. studied whether the ZBV-K was also reliable an valid for adolescents (12-18 years old) and indicated that the ZBV-K was applicable to this age-group.[20] We therefore decided to also use the ZBV-K for children between 16-18 years old.

Demographics

Demographics that we will collect include the child's age, gender, health status, ethnicity, previous experiences with the medical procedure. Since we will include children from different hospitals, the research procedures may not be conducted in an identical way between those hospitals. Therefore we will also collect data about how the child is prepared for the study, who performed the procedure (e.g. paediatrician, lab worker, PhD student), the duration of the procedure, and whether the child had local anaesthetics. This information will be asked from the parents, from the researchers of the studies and/or derived from the child's medical record.

Research procedures

We will measure children's experiences during several research procedures: echoscopy, faeces testing, MRI-scan, pulmonary function test, buccal swab, skin prick test (allergy test), and venepuncture. The research procedures are selected based on an expert meeting with paediatricians, paediatric nurses, ethicists, psychologists, pedagogics and parents, and on which research procedures are conducted during the timeframe of our study at the departments of the three hospitals we cooperate with.

Analyses

Primary outcomes

Discomfort

Depending on the response option (VAS or Likert scale) of the questionnaire, parametric or non-parametric tests will be used. The mean respectively median scores of the individual questions on the *'What do you think of…?'*-questionnaire will be calculated. Differences in outcomes between baseline and one-month follow-up on the '*What do you think of…?'*-questionnaire will be tested with paired t-tests respectively Wilcoxon matched-pairs tests. Differences in experiences on the different research procedures will be tested by one-way between groups ANOVAs respectively Kruskal-Wallis tests. For each research procedure, the percentage will be calculated of children willing to undergo a similar procedure again in the future.

Emotional impact

We will measure the percentage of children who have elevated stress symptoms caused by the research procedure after one month (i.e. total CRIES-13 score of 30 or more). We will also study whether there is a relation between emotional impact and the type of research procedure by one-way between groups ANOVAs.

Secondary outcomes

Suggestions

Suggestions for reducing discomforts of the research procedures will be coded into categories, and frequencies on each category will be measured.

Influencing factors on children's experiences and emotional impact

Depending on the response option (VAS or Likert scale) of the '*What do you think of… ?'*-questionnaire, parametric (independent-samples t-test) or non-parametric (Mann-Whitney U test) tests will be used. Possible differences between anxiety-prone children (children with a score of 38 or higher on the ZBV-K trait scale) and non-anxious children (children who score of 37 or lower on the ZBV-K trait scale) on their experiences will be tested. The same tests will be used to study the differences between young children (<12 years) and older children (≥ 12 years), and between healthy children and children with a chronic condition.

To measure if there are differences on emotional impact between 1) anxiety-prone versus non-anxiety-prone children, 2) young children (<12 years) versus older children (≥ 12 years), and 3) healthy children versus children with a chronic condition, we will perform independent-samples t-tests.

ETHICS AND DISSEMINATION

The IRB of the VU Medical Center in Amsterdam (The Netherlands) evaluated both studies described in this manuscript and indicated that there was no risk or discomfort associated with the interview study (2012/279) nor the questionnaire study (2014/010), stating that both phases are exempt from getting approval under the Dutch Law.

Dissemination of results will occur by conference presentations and peer-reviewed publications. No identifying participant information will be made available. Only investigators will have access to the raw data of the studies. The outcomes on children's discomfort during research procedures will be available for IRBs and paediatric researchers in an online database. These outcomes will not include identifying participant information.

DISCUSSION

In this manuscript, we describe the protocol of a two-phase study to measure children's experiences during research procedures. The findings of this study give insight into children's experiences during some common research procedures, the emotional impact of these procedures and suggestions to reduce discomforts of research procedures, as seen from the perspective of children themselves. This study also explores whether age, health condition and/or anxiety-proneness influence children's experiences. Finally, this study provides an instrument to measure children's self-reported experiences of research procedures.

We will provide the findings of this study on a website which will be accessible for parents, children, IRBs, researchers and others who are interested. The findings of our project can help IRBs and paediatric researchers when evaluating the discomforts of research procedures or when designing a study. Information on experiences of children involved in previous studies may also help children and parents in future research with their decision-making concerning participation in clinical research, or parts thereof.

Limitations

A limitation of our study is that we cannot acquire a complete overview of the experiences of all research procedures, subgroups of children, and all factors influencing their experiences given the limited time and funding.

Future research

A future aim is to use our questionnaire to obtain empirical data from other research procedures than the ones we investigated in our study. This requires the development of a network in which physicians, researchers, IRBs, parents and children are involved. We are currently working on the development of this network.

Next to age, medical condition and anxiety-proneness, other variables may have an impact on children's experiences, such as the interaction of the child, parent and researcher during research procedures. Since children's age, health condition and anxiety-proneness are important factors for IRBs to take into account when evaluating the discomfort in paediatric study protocols, we decided to focus on these three factors.

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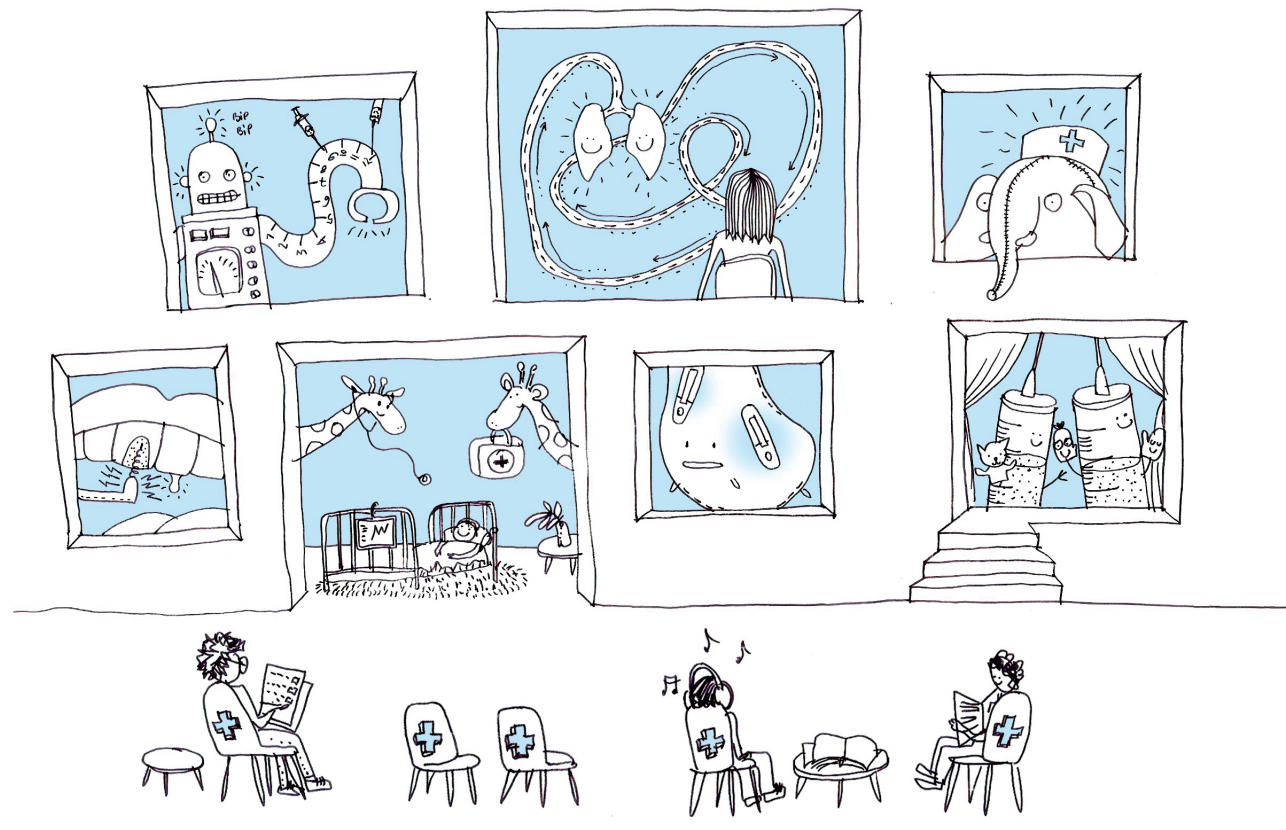

CHAPTER 3.

Children's self reported discomforts as participants in clinical research

MS Staphorst, JAM Hunfeld, S van de Vathorst, J Passchier, JB van Goudoever on behalf of the BURDEN-group

BURDEN-group
WMC van Aalderen, N Adriaens, MA Benninga, F Beukers, S Hashimoto, L Hulshof, NW de Jong, A Kindermann, SM Mugie, CM Nusman, L de Ridder, JPM van der Valk, I de Vreede, A van Wassenaer

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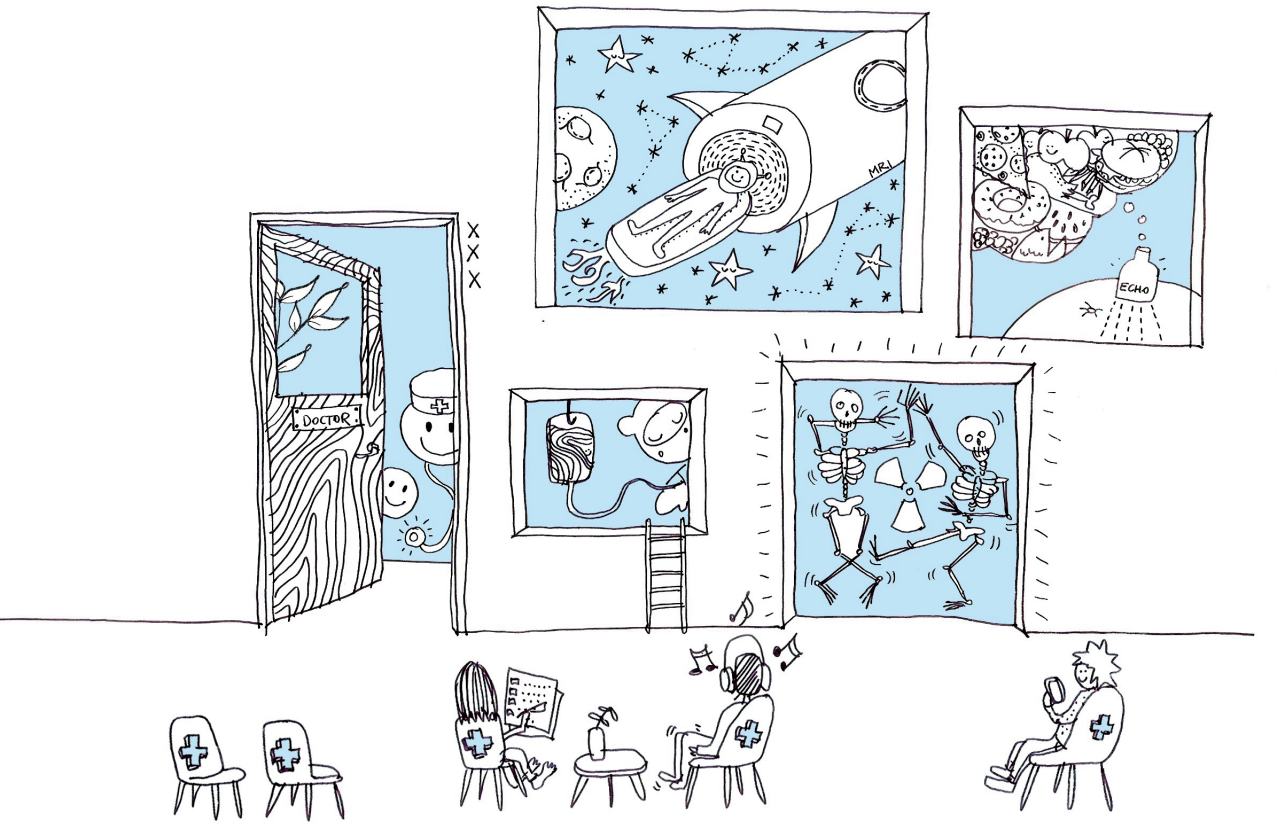

ABSTRACT

Introduction. There is little empirical evidence on children's subjective experiences of discomfort during clinical research procedures. Therefore, Institutional Review Boards have limited empirical information to guide their decision-making on discomforts for children in clinical research. To get more insight into what children's discomforts are during clinical research procedures, we interviewed a group of children on this topic and also asked for suggestions to reduce possible discomforts.

Materials and methods. Forty-six children (aged 6-18) participating in clinical research studies (including needle-related procedures, food provocation tests, MRI scans, pulmonary function tests, questionnaires) were interviewed about their experiences during the research procedures. Thematic analysis was used to analyze the interviews.

Results. The discomforts of the interviewed children could be divided into two main groups: physical and mental discomforts. The majority experienced physical discomforts during the research procedures: pain, shortness of breath, nausea, itchiness, and feeling hungry, which were often caused by needle procedures, some pulmonary procedures, and food provocation tests. Mental discomforts included anxiousness because of anticipated pain and not knowing what to expect from a research procedure, boredom and tiredness during lengthy research procedures and waiting, and embarrassment during Tanner staging. Children's suggestions to reduce the discomforts of the research procedures were providing distraction (e.g. watching a movie or listening to music), providing age-appropriate information and shortening the duration of lengthy procedures.

Discussion. Our study shows that children can experience various discomforts during research procedures, and it provides information about how these discomforts can be reduced according to them. Further research is needed with larger samples to study the number of children that experience these mentioned discomforts during research procedures in a quantitative way.

INTRODUCTION

Clinical research in children

Pediatric research is necessary to develop safe and effective treatments for children. However, children are vulnerable and need to be protected against high levels of risk and burden in clinical research. It is an ethical and legal requirement for pediatric research that the risks and burdens of research participation are proportionate to the expected benefits of participation.[1] It is the responsibility of Institutional Review Boards (IRBs) to weigh these burdens and risks to establish whether they are acceptable. To be able to properly conduct this responsibility, research on the possible discomforts of research procedures is required, which involves knowing the perspectives of the participating children. For an overview of the terminology used in this article, we refer to Table 1.

Table 1. Terminology

Term	Description
Medical research	The over-arching term for all types of medical research, which can be divided into primary research and secondary research. Primary research includes basic research, clinical research (experimental and observational research) and epidemiological research. Secondary research includes meta-analyses and systematic reviews.[2]
Clinical research procedures	Medical procedures that are used for clinical research purposes.
Therapeutic research	Therapeutic research is clinical research that is likely to directly benefit the participant.
Non-therapeutic research	Non-therapeutic research is clinical research that is not likely to directly benefit the participant but may benefit future patients.
Discomfort:	Something that causes one to feel uncomfortable.[3]

Children's experiences in clinical research

Since little is known about children's subjective experiences of discomfort during clinical research procedures,[4, 5] IRBs have limited empirical information to guide their decision-making, which is why they often have to rely on the observations and assumptions of others. Literature shows, however, that pediatric nurses, pediatricians, psychologists and parents are likely to overestimate[6, 7] or sometimes underestimate[7, 8] children's discomfort in medical settings. It is therefore crucial to also take children´s *own* perspectives into account when evaluating the discomforts of clinical research procedures. This position is reflected in Article 12.1 of the Convention on the Rights of the Child [9] *"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"* as well as Article 3.2.a of the EU Clinical Trials Directive (2001/20/EC).[10]

Empirical data on children's experiences in clinical research

The experiences of children who participated in research were studied in few studies. In two of these studies, children were asked about the worst (and best) parts of the study they participated in. Most frequently mentioned were blood work and needles because of pain or unpleasantness.[4, 11] In another study children were asked to rate their level of comfort in relation to IV insertion, Tanner stage assessment, blood draws and staying overnight in the hospital after their participation in a research study.[12] The results indicated low levels of discomfort, although Tanner staging and IV insertion were perceived as more discomforting than the other procedures. Some other studies in trauma-focused research investigated children's experiences by using the Reactions to Research Participation Questionnaire for Children (RRPQ-C),[13] which includes three questions on children's discomforts: feeling bored during the study, feeling upset or sad during the study, and feeling sorry for having taken part in the study. Studies that used this questionnaire for investigating the discomforts of trauma-focused research showed that the majority of the children was not bored, upset/sad or felt sorry about participating in these research studies.[14-16] There is also some literature on the (expected) discomforts that children mention in hypothetical research situations.[e.g. 17, 18] In these studies discomforts mentioned by the children were concerns and worries (e.g. about the safety of the procedures or uncertainty that comes with test results), and pain.

Prior literature gives us some insight into discomforts children experience during clinical research procedures. Limitations are that these studies focused on the experiences of a homogenous group of children (e.g. only children with asthma or children from a limited age-range) during a small number of research procedures, or did not distinguish between different kinds of discomforts. In addition, the experiences of children in hypothetical situations may not be totally generalizable to the actual experience of children because children undergoing a painful procedure often *expect* to experience higher levels of discomfort than they actually experienced.[19, 20]

Purpose of this study

To get a more complete picture of children's discomforts during clinical research procedures as described in their own words, we interviewed a diverse group of children about the discomforts they experience during a wide range of clinical research procedures. In addition, we asked the children for their views on reducing discomfort of the research procedures, which as far as we know has not been done in prior research.

MATERIALS AND METHODS

Subjects

Children (6-18 years) who participated in clinical research studies at two academic pediatric hospitals in the Netherlands (Sophia Children's Hospital in Rotterdam and Emma Children's Hospital in Amsterdam) were interviewed between November 2012 and June 2013. We purposefully selected a wide range of children (ages and medical conditions) undergoing various types of clinical research procedures to ensure a wide range of experiences, influences and attitudes. In qualitative research, this is called a maximum variation sample.[21] This method is designed to represent a wide range of experiences, rather than to aim for numerical representativeness. The age of six was chosen as lower age limit because literature shows that children from six years onwards are cognitively capable and have language capacities to accurately verbalize their experiences.[22]

Children were enrolled in one of the outpatient pediatric studies described in Table 2. The children we interviewed all participated in clinical research studies: in either experimental or observational/follow-up studies. We enrolled children until saturation was reached. In qualitative research, this is the point when additional interviews do not provide new information.[23] The point of saturation was determined by the interviewer (MS) in consultation with other members of the project group (JH and JP).

Exclusion criteria were 1) children with mental health issues (such as anxiety disorders and depression) to avoid information being biased by their mental condition, 2) children who underwent research procedures that are used for both clinical and research purposes (e.g. the child´s blood is taken for medical check-up, and some extra tubes are taken for research purposes) because this would make it difficult for the children to distinguish between procedural aspects for research purposes and those for routine clinical care, and 3) children who are not being able to orally express themselves. No children however were excluded for these reasons.

Procedure

The researchers of the cooperating studies informed parents and children about our interview. Parents and children also received an information letter, which was adapted for children (6-11 years) and adolescents (12-18 years). Parents and children had an opportunity to ask questions about the interview in a face-to-face conversation with the interviewer, which was prior to the start of the study on the day of the child's research visit. Once parents and children agreed to participate, written parent consent and child assent (children ≥ 12 years) were obtained. Children younger than twelve years verbally agreed to participate. All children received a gift card (€7.50) for being interviewed.

Interviews were conducted in a private room at the hospital, directly after the children's participation in the research studies by the first author (MS), who has a degree in health psychology and was trained in interviewing children. The interviews were

audio recorded and field notes on the circumstances of the interview (e.g. about being disturbed during the interview) were taken by the interviewer. Parents were kindly requested not to intervene in the interview as the focus was on the child's perspective. During the interview, parents completed a brief survey about the child's demographics and medical history.

Table 2. Description of the research studies children participated in

Study type	Study aim	Non-therapeutic/ Therapeutic study	Health condition
Experimental study randomized controlled trial (RCT)	To study the efficacy of an intervention for the prevention of Cystic Fibrosis exacerbations	Therapeutic	Cystic Fibrosis
Observational study	To study the development of severe asthma	Non-therapeutic	Mild and severe asthma
Observational study	To study the development of Inflammatory Bowel Disease	Non-therapeutic	Inflammatory Bowel Disease
Observational	Follow-up study to investigate the effects of an intervention on atopic dermatitis	Non-therapeutic	Healthy children
Experimental study: double-blind placebo-controlled trial	To improve the diagnostic methods for cashew allergy	Therapeutic	Cashew allergy
Observational study	To get normative standards of the synovial membrane (soft tissue between the articular capsule (joint capsule) and the joint cavity of synovial joints)	Non-therapeutic	Inflammatory Bowel Disease (children were used as a control group)
Observational follow-up study	To investigate the cognitive and physical development of children whose mothers participated in a RCT for severe preeclampsia.	Non-therapeutic	Healthy children

Instruments

The interviews were semi-structured. The content of the questions was based on input from pediatricians, pediatric nurses and child psychologists as well as literature.[4, 11] We also consulted literature on interviewing children about their experiences to make the questions age-appropriate.[24, 25] We started the interviews by asking about the children's general experiences with the research studies, and how they felt before and afterwards. Then questions were asked about discomfort experienced during the specific clinical research procedures. In line with previous studies,[4, 11] we also asked about the children's worst experiences. Previous research had shown that children who are not given (age-) appropriate information during medical care, are more anxious and consequently experience more distress.[26-29] Therefore we asked the children how they had been prepared and whether this was sufficient for them. In line with a previous study by Wagner et

al., we asked the children whether they would participate in the study again.[11] We also asked the children who did not want to participate again, what their concerns were. Finally, we asked questions about their suggestions to reduce the discomforts of the clinical research procedures. The interview schedule can be found in Appendix A.

Table 3. Description of the participating children

Age		**Years**
Range		6.3-17.8
Mean		11.9
Standard deviation		3.8
Gender		**Number of children**
Boy		24
Girl		22
Ethnic origin		**Number of children**
Dutch		38
Moroccan		3
Surinamese		2
Dutch/Surinamese		1
Dutch/Hindustani		1
Dutch/Nigerian		1
Health condition		**Number of children**
Chronic condition	Cashew allergy	7
	Crohn's disease or ulcerative colitis	11
	Cystic fibrosis	9
	Mild asthma	4
	Severe asthma	3
Healthy	Mothers had suffered from preeclampsia	7
	Atopic dermatitis (AD) as infant	5
Number of visits of the research study		**Number of children**
One visit		23
Two visits		14
More than 2 visits		9
Previous research experience (participated in another research study before)		**Number of children**
Yes		38
No		8

Data analysis

Audiotaped interviews and field notes were transcribed verbatim. After initial transcription by trained 3rd year psychology students, the transcript was checked for accuracy by

Table 4. Clinical research procedures performed on the children

Clinical research procedures	Number of children	Age (years)	Health condition of the children undergoing this procedure	Number of children with previous experience with this procedure
Barostat device (air-filled bag inserted into rectum)	1	16	IBD	0/1
Blood pressure	28	6-18	Asthma, cashew allergy, CF, Children whose mothers suffered from preeclampsia	28/28
Body box pulmonary function test	7	6-16	Asthma	7/7
Buccal swab	4	7-18	IBD	4/4
Cashew provocation test (i.e. eating muffins with cashew allergens)	7	6-13	Cashew allergy	4/7
Cognitive capacity	7	12-13	Children whose mothers suffered from preeclampsia	7/7
Concentration/focus skills tests	7	12-13	Children whose mothers suffered from preeclampsia	7/7
Electronic nose test	7	6-16	Asthma	7/7
Exhaled breath condensate test	9	6-18	CF	9/9
Forced oscillation technique (a method to measure respiratory mechanics)	7	6-16	Asthma	0/7
Height, weight	46	6-18	All children	46/46
Intra venous procedures	9	6-18	Cashew allergy, IBD	5/9
MRI	8	6-18	IBD	2/8
Nasal brushing	7	6-16	Asthma	0/7
NO testing	7	6-16	Asthma	0/7
Pubertal development examination (Tanner staging)	7	12-13	Children whose mothers suffered from preeclampsia	0/7
Questionnaires (health status, medical history and/or quality of life)	46	6-18	All children	46/46
Regular pulmonary function test	21	6-18	Asthma, CF, AD as infant	21/21
Skin prick test	14	6-18	Asthma, cashew allergy	7/14
Sputum induction	5	11-16	Asthma	5/5
Throat swab test	7	6-16	Asthma	7/7
Urine examination	7	6-16	Asthma	7/7
Venipuncture (with EMLA©)	26 (3)	6-18 (6-8)	Asthma, AD as infant, IBD (Asthma, AD as infant, IBD)	26/26
Waist and head circumference	7	12-13	Children whose mothers suffered from preeclampsia	7/7

AD: Atopic Dermatitis; CF: Cystic Fibrosis; IBD: Inflammatory Bowel Disease (Crohn's disease or ulcerative colitis)

MS. Data were analyzed (NVivo 10.0) by MS using 'thematic analysis' to identify themes related to the discomforts and suggestions of the children.[30] First, the transcripts were coded using open coding. The codes obtained during open coding were divided into categories covering all relevant information. Finally, the categories were merged into main themes. The second author (JH) independently analyzed 25% of the interviews to ensure agreement on the relevance of the themes. In case of disagreement, we discussed until we reached consensus. Citations from the children are used to illustrate the themes.

Ethical approval

The ethical committee of the VU Medical Center in Amsterdam (The Netherlands) evaluated this study and indicated that there was no risk or discomfort associated with the interview, stating that this study was therefore exempt from obtaining approval under the Dutch law.

RESULTS

Subjects

Children were recruited from seven different research studies (Table 2). Children with chronic conditions and healthy children were both included. We considered the children with cystic fibrosis (CF), Inflammatory Bowel Disease (IBD) and severe asthma as children with severe chronic conditions. Children with cashew allergy and mild asthma were considered as children with a mild chronic condition. One group of healthy children participated in a study because they had atopic dermatitis as an infant. The other group of healthy children participated in an observational follow-up study because their mothers suffered from severe preeclampsia during pregnancy. These two groups of children were considered to be healthy now. The characteristics of the children included are shown in Table 3. A more detailed description of each child can be found in Appendix B. The majority had previous experiences with the procedures (Table 4) and with participating in research (85%) (Table 3). The parent(s) of the children were present during 85% of the interviews (N=39). The interviews ranged from 9.04 to 43.59 minutes (M=23.46 minutes).

In total, forty-eight children and their parents were approached to participate. The parents of two children declined to participate: one because the parents thought the interview would take too much of their time and a second because the parents thought the interview would be too burdensome for their child. They wanted to minimize the exposure of their child with CF to disease related events. The remaining 46 children appeared to be a sufficient number to reach saturation.

Clinical research procedures

The clinical research procedures that were performed on the children were 24 different research procedures, which included both invasive (such as needle-related procedures, provocation tests) and non-invasive procedures (such as pulmonary function tests, taking medical history, questionnaires). The research procedures are listed in Table 4.

Children's discomforts related to clinical research procedures

We identified two main themes related to discomfort: physical discomfort and mental discomfort. These themes are elaborated on below.

Physical discomfort

The majority of the children experienced several physical discomforts. The ones mentioned most often were pain, nausea, shortness of breath, itchiness and feeling hungry.

Five of the 35 children who had an intravenous procedure, venipuncture or skin prick test (aged 7, 8, 15, 16, 17) indicated that the needle-related procedure was the worst part of the study because of the pain it caused (Note: some children had different needle procedures, and therefore the total of children who had a needle procedure is not equal to the numbers of the children undergoing a needle procedure in Table 4.). Three healthy children (aged 6 and 7), for whom venipuncture was part of the study, refused this procedure because of previous painful venipuncture experiences (Note: these children are not included in the 35 children undergoing needle procedures that are described in Table 4.). The forced oscillation technique and exhaled breath condensate test were also mentioned by almost all children as painful because of the uncomfortable mouthpiece and nose clip, and shortness of breath: *"You get a nose clip and you cannot swallow and you almost have no air and your mouth is on some sort of piece and you get a dry throat"* ***(boy #23, aged 11****)*. For six out of 16 children these tests were considered the worst part of the study because of the pain and shortness of breath it caused. The sputum induction test was also painful for the children because they had difficulty coughing up secretions from their lungs, which caused pain because of a sore throat.

About half of the children who had to fast before the study (ca. 25% of all children) experienced this as discomfort, which was primarily related to feeling hungry *"I did not like that [not being allowed to eat], because I was really starving. When I feel hungry, I just want to eat"* ***(girl #17, aged 6).*** Two children with severe asthma felt short of breath because they were not allowed to use their medication on the morning of the study. For six children, fasting before the study was the worst part of the study because of these discomforts.

Other physical discomforts were related to allergic reactions when children underwent a cashew provocation test or skin prick test which resulted in an itchy tongue,

nausea, shortness of breath and/or irritated airways: *"It was itchy, and it tickled"* ***(boy #25, aged 11)***.

Mental discomfort

Mental discomfort included anxiousness, tiredness, feeling bored, and embarrassed. Some of the healthy children and children with a mild chronic condition were somewhat anxious because they did not know what to expect from the procedures, the hospital environment and researchers: *"The first time I was a little scared, because I did not know the people [i.e. researchers], now [that I know them] it is more pleasant"* ***(girl #14, aged 7).*** Most children felt only anxious during the first time they underwent a procedure *"For me it is quite normal [the MRI], I know how it works. The first time I was a little bit scared but now I'm used to it." (****boy #13, aged 15).*** On the other hand, some children reported that they felt anxious because of previous negative experiences, which were mainly related to needle-procedures: *"The previous time I got a needle just above my elbow. It was quite painful, so this time I did not look forward to it. It actually did not hurt this time but I was a little anxious."* ***(girl #24, aged 12).***

Boredom was also mentioned because of the length of the research procedures (such as lying in an MRI scanner for up to 60 minutes, the cashew provocation test that took approximately four to five hours, the cognitive capacity tests) or because of a lack of distraction during the research procedures or while waiting. *"I think it [the study] took too long"****(girl #22, aged 8).*** Children also became tired and bored after having undergone various consecutive research procedures for several hours. Having to go to the hospital instead of going to play with friends or going to school and travel time were other discomforting aspects, mentioned by the children with chronic conditions. For eight children who mentioned boredom as causing discomfort, it was the most burdensome part of the study *"You're sitting there for 10 minutes and it [exhaled breath condensation test] is really boring" (girl#34, aged 9)*.

Most of the children undergoing Tanner staging felt somewhat embarrassed that a researcher was to examine their developing bodies: *"I was a little embarrassed when she was looking if I already started puberty"* ***(boy #44, aged 12)***.

Willingness to participate in the study again

About two-thirds of the children (N=28) indicated that they would, participate in the same research study again; five children did not know and thirteen would not. The reasons of children who did not want to participate again were boredom because of the duration of the procedures (N=3) (mentioned by children who did the cashew provocation test) and (travel) time (N=4) (mentioned by children with CF and IBD): *"I don't want to do it [participate] again because I don't want to travel so far"* ***(boy #8, aged 6****)*. The other children, who were all children with a severe chronic condition, did not want

to participate again because the research procedures caused pain (N=4) or because of disappointment in the planning of the research visits (N=2) (i.e. the researcher said that these children could combine the research visits with their regular medical check-ups at the hospital. In practice, this was not always possible).

Children's suggestions to reduce discomfort

About half of the children gave suggestions to reduce discomfort. Some children recommended to reduce the duration of both waiting and the lengthy procedures because these caused boredom and tiredness: *"I would make the procedures shorter and make it a bit more of a game" (**boy #16, aged 11)***, or recommended to provide distraction to make the procedures less discomforting and/or boring: *"I did not like some of the procedures. During these, you need to have a distraction, so you can think of something else and you are not thinking 'this does not feel pleasant'" (**girl #31, aged 16).*** Suggestions for distraction were watching movies, making the procedure more like a game or listening to music. While most hospitals do have special playrooms for children, these rooms are predominantly designed for younger children; older children mentioned that: *"The waiting room looks like fun, but for a twelve year old there is actually not much you can do, unless you bring something yourself" (**boy #32, aged 12)***.

Children with a severe chronic condition mentioned that it would be convenient if the study's test results could also be used for their regular check-up. They would then not have to go to the hospital twice and it would cause less physical and mental discomfort. In addition, they would prefer the study visits to be scheduled at a convenient time (after school or during a regular visit to the hospital), because they did not like missing school, whereas most of the healthy children did not mind going to hospital as they did not mind missing school.

Several children mentioned that the (written) information provided about the study should be made more 'age-appropriate' as it was often too difficult to understand, or did not include enough information on aspects they were interested in, such as whether an MRI is painful or what the liquid that the child has to drink before the MRI tastes like. The children believed that receiving better information would make them feel less anxious.

Some children said they would have liked to get a small gift as a token of appreciation (e.g. a gift card for the movies) for their participation in the research study. Younger children indicated that they would like to get a sticker or diploma, which would make them feel proud of having undergone a research procedure, particularly if it was painful.

DISCUSSION

Discomfort during research procedures from the child's perspective

In addition to the discomforts reported in prior research, we also found that children's discomforts during research procedures can be nausea, shortness of breath, itchiness, feeling hungry, feeling embarrassed and bored. On the other hand, concerns and worries about the safety of the procedures and/or uncertainty that comes with test results, found in previous research,[17, 18] were not mentioned by the children we interviewed. The children we interviewed primarily participated in non-therapeutic studies and therefore the results of the research procedures may not have an important influence on their health, which may be an explanation why concerns and worries were not mentioned.

Differences in discomfort

Age

Having included children from a wide age-range, we explored whether there might be age-differences in their experiences. Some of the younger (healthy) children refused venipuncture, but no further salient age differences were found. In most literature on children's experiences during medical care, however, younger children display more distress and report more pain than older ones,[e.g. 7, 31, 32] which may be because older children usually have more experience with a certain procedure. In general, children with more experience with a medical procedure report less discomfort than children who are less experienced.[33, 34]

Medical condition

The healthy children seemed to mention fewer physically discomforting aspects than the children with a chronic condition. This is not surprising, as the healthy children we interviewed did not undergo physically invasive procedures (except for venipuncture). The healthy children often mentioned feeling anxious and bored (i.e. mental discomfort) as discomfort. This is probably because these children are often unfamiliar with a hospital environment, and may therefore feel anxious about not knowing what to expect. They are also not used to spending a day or half a day in a hospital, which can make them feel bored. For children with a chronic condition the fact that they had to go to the hospital was in itself discomforting because they said they would have preferred to do other things such as go to school or go and see friends. This was usually not an issue for the healthy children.

Another difference we noticed was that all of the healthy children would participate again in the research studies, while the children who did not, were all children with a chronic condition. Most of them did not want to participate because of logistic inconveniences, such as travel time and poor planning of the research visits. Previous studies state that logistics are important factors that both parents and children consider when

making a decision for participating in a (hypothetical) study.[e.g. 35, 36] It is valuable to know that although the logistical aspects were not a factor for the parents and children we interviewed for refusing to participate in the clinical research studies, the children who did not want to participate in similar research often mentioned logistics as a reason. This indicates that children may not be able to completely foresee what discomfort/inconvenience the logistics of participating in a study will cause, or they may not be informed well enough about the discomforts related to logistics during the informed consent procedure.

Suggestions to reduce discomfort

Most of children's suggestions for reducing discomfort of the clinical research procedures should be easy to implement in many pediatric studies, such as providing distraction during lengthy procedures or while waiting, by showing a movie or making research procedures more like a game. Distraction has proven to be effective in reducing discomfort during medical procedures in children of all ages,[e.g. 37] and it is also cost-effective because of the relatively low start-up and maintenance costs.[38]

We think it is also feasible to provide more age-appropriate information to the children during assent and during the research study. Many studies show that age-appropriate information helps to reduce anxiousness,[27, 28, 39] because children will be more prepared what will happen during the study. Researchers could do this by using the format of an information letter and assent form designed by Ford et al.[40] This material was designed in consultation with a group of children and provides the information about participating in research children are interested to know about, and leaves out all information not relevant according to them. Researchers can easily adapt this letter to their own study. To make the information about the study more appealing to children, researchers might think of other ways of informing children about their study. For instance, in a recent study a comic strip was used to support children's understanding of participating in research. Children enjoyed reading the material and liked it that the information was provided as a comic story format instead of plain text.[41] When children like the way the information is presented, it may help to increase their understanding of what the study will be like.

In addition, it should be within reach of the researcher to give children a small gift, a sticker, or a diploma after the study. Giving children a small gift does not necessarily reduce discomfort, but it helps to give children the feeling that their participation is valued, especially children who do not directly benefit from the research study (i.e. non-therapeutic research).

On the other hand, some of the children's suggestions may be harder or even impossible to implement, for instance, coordinating research visits with regular check-ups at the hospital. Although it is understandable from the perspective of the children with a

chronic condition, rooms are limited in hospitals and researchers have to adapt to the availability. Also, the children's pediatricians are not always the same ones who perform the clinical research procedures, which makes it difficult to schedule research visits and regular visits consecutively. A possible solution could be for researchers and children's health care staff to consult the hospital's or department's administration office before the start of the study to see if there are possibilities to combine research with regular visits.

Since each research study involves different research procedures, children's suggestions to reduce discomforts may differ across different studies. It is therefore important that all researchers ask children for suggestions to reduce discomfort during their studies. For instance, researchers could ask children in the pilot phase of the study about suggestions for reducing discomfort and incorporate the feasible ones at a later stage of the study.

Limitations

Although we interviewed a diverse group of children undergoing a wide range of clinical research procedures, a limitation of our study is that we did not interview children who underwent severe invasive research procedures, such as bone marrow aspirations or biopsies. These procedures may be conducted in studies with children with acute life threatening conditions. The discomforts experienced by these children may include aspects not identified in this study.

Recommendations

Additional research is needed for severe invasive research procedures, so as to identify possible other discomforts. Furthermore, we suggest that mental discomforts should be given more attention in the evaluation of discomfort in pediatric study protocols, which is in accordance with a previous study that children may be more focused on the immediate psychological discomforts than physical discomforts and risks.[42]

This qualitative study gives a broad view on children's discomforts during clinical research procedures, but does not provide numeric representativeness. Therefore, a next step is a quantitative study of the self-reported discomforts of children during clinical research procedures to get an insight into the number of children that experience these discomforts and the degrees of discomfort experienced by the children. Larger sample sizes make it also possible to investigate whether there are differences in discomfort between subgroups (e.g. healthy versus chronically ill children, younger versus older children, research procedures for therapeutic purposes versus non-therapeutic research procedures).

Kassam-Adams and Newman previously recommended systematically monitoring children's experiences in research studies.[13] We support their recommendation, and

suggest to take this a step further, and also ask children about discomforts during the specific research procedures of the studies. If children's personal experiences during clinical research procedures are systematically monitored, IRBs and pediatric researchers have empirical information to guide them when evaluating the discomforts of the research procedures described in study protocols or when designing a study. Information on experiences of children involved in previous studies may also help children and parents in future research with their decision-making concerning participation in clinical research, or parts thereof. Additionally, if children are systematically asked for their suggestions for improvements, research procedures in future studies can be conducted with minimized discomfort.

Conclusion

Our study provides further insight into what discomforts children can experience during clinical research procedures, and it provides unique information on how discomforts of research procedures could be reduced according to the children involved. It is important that IRBs and pediatric researchers take into account that discomfort for children during research procedures includes various physical discomforts (e.g. pain, shortness of breath, feeling hungry, itchiness) and mental discomforts (e.g. feeling anxious, bored and embarrassed).

Research is needed to investigate children's possible discomforts in a greater number of research procedures and during more invasive procedures. IRBs can benefit from this knowledge when evaluating the discomfort of research procedures in study protocols. Information on the discomforts of children involved in previous studies, may also help children and parents in future research with their decision-making concerning participation in clinical research.

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APPENDIX A. INTERVIEW SCHEDULE

General experiences

How did you feel about the study in general?
How did you feel before the study?
How did you feel afterwards?
Can you describe your experiences during the study?
Can you describe your experiences during *procedure X*?

Experiences related to discomfort

Can you describe any discomfort you experienced in the study?
Is there any part of the study that you did not like? Which part? Why?
Can you describe any discomfort you experienced because of *procedure X*?

Worst experiences

What was/were the most burdensome/discomforting part(s) of the study? Which part? Why?

Preparation

Who prepared you for the study?
What information did you get about the study? Was this information sufficient?
Did you know what to expect of the study?

Suggestions to reduce discomfort

Can you think of anything that would have made the study easier for you? If so, could you tell me about it?
Can you think of anything that will make *procedure X* less discomforting for you? If so, could you tell me about it?
Can you think of anything that will make *procedure X* more comfortable for you? If so, could you tell me about it?

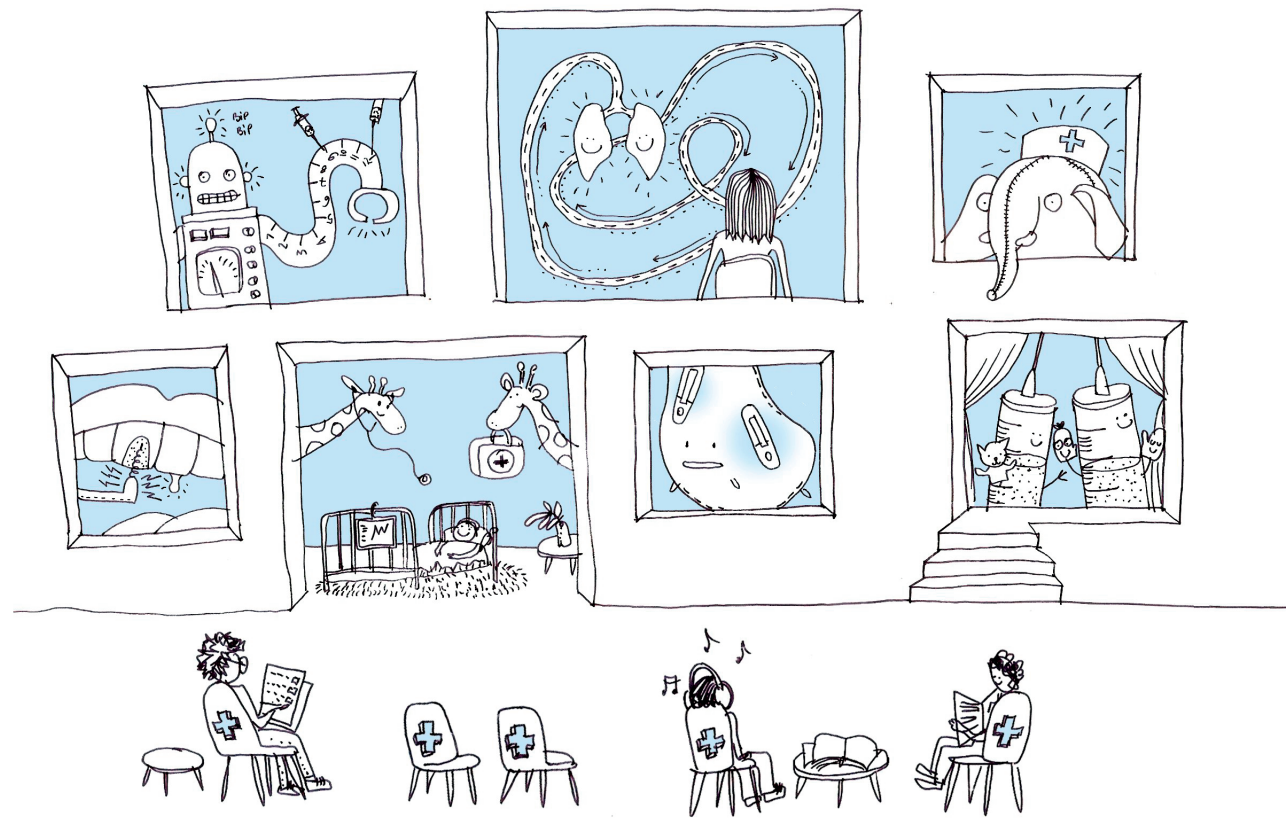
Future research

Would you participate in this research study again? Why (not)?

APPENDIX B. DESCRIPTION OF THE INCLUDED CHILDREN

ID	Gender	Age in years	Health condition	(non) therapeutic study
1.	Girl	7	IBD	Non-therapeutic
2.	Boy	6	Healthy	Non-therapeutic
3.	Girl	6	Healthy	Non-therapeutic
4.	Boy	17	IBD	Non-therapeutic
5.	Boy	8	IBD	Non-therapeutic
6.	Boy	6	Healthy	Non-therapeutic
7.	Boy	17	IBD	Non-therapeutic
8.	Boy	6	Healthy	Non-therapeutic
9.	Girl	11	Asthma	Non-therapeutic
10.	Girl	11	CF	Therapeutic
11.	Boy	9	CF	Therapeutic
12.	Boy	14	IBD	Non-therapeutic
13.	Boy	15	IBD	Non-therapeutic
14.	Girl	7	Cashew allergy	Therapeutic
15.	Boy	6	Cashew allergy	Therapeutic
16.	Girl	17	IBD	Non-therapeutic
17.	Girl	6	Cashew allergy	Therapeutic
18.	Boy	8	Cashew allergy	Therapeutic
19.	Boy	6	Asthma	Non-therapeutic
20.	Boy	15	CF	Therapeutic
21.	Boy	17	CF	Therapeutic
22.	Girl	8	Asthma	Non-therapeutic
23.	Boy	11	CF	Therapeutic
24.	Girl	12	Cashew allergy	Therapeutic
25.	Boy	11	Cashew allergy	Therapeutic
26.	Boy	11	CF	Therapeutic
27.	Girl	11	IBD	Non-therapeutic
28.	Girl	13	Cashew allergy	Therapeutic
29.	Girl	16	IBD	Non-therapeutic
30.	Boy	13	CF	Therapeutic
31.	Girl	16	Asthma	Non-therapeutic
32.	Boy	13	Healthy	Non-therapeutic
33.	Girl	12	Healthy	Non-therapeutic
34.	Girl	9	CF	Therapeutic
35.	Boy	17	IBD	Non-therapeutic
36.	Boy	12	Healthy	Non-therapeutic

37.	Girl	6	Healthy	Non-therapeutic
38.	Girl	12	Healthy	Non-therapeutic
39.	Boy	15	Healthy	Non-therapeutic
40.	Girl	15	IBD	Non-therapeutic
41.	Girl	12	Healthy	Non-therapeutic
42.	Boy	6	CF	Therapeutic
43.	Girl	12	Asthma	Non-therapeutic
44.	Boy	12	Healthy	Non-therapeutic
45.	Girl	16	Asthma	Non-therapeutic
46.	Boy	16	Asthma	Non-therapeutic

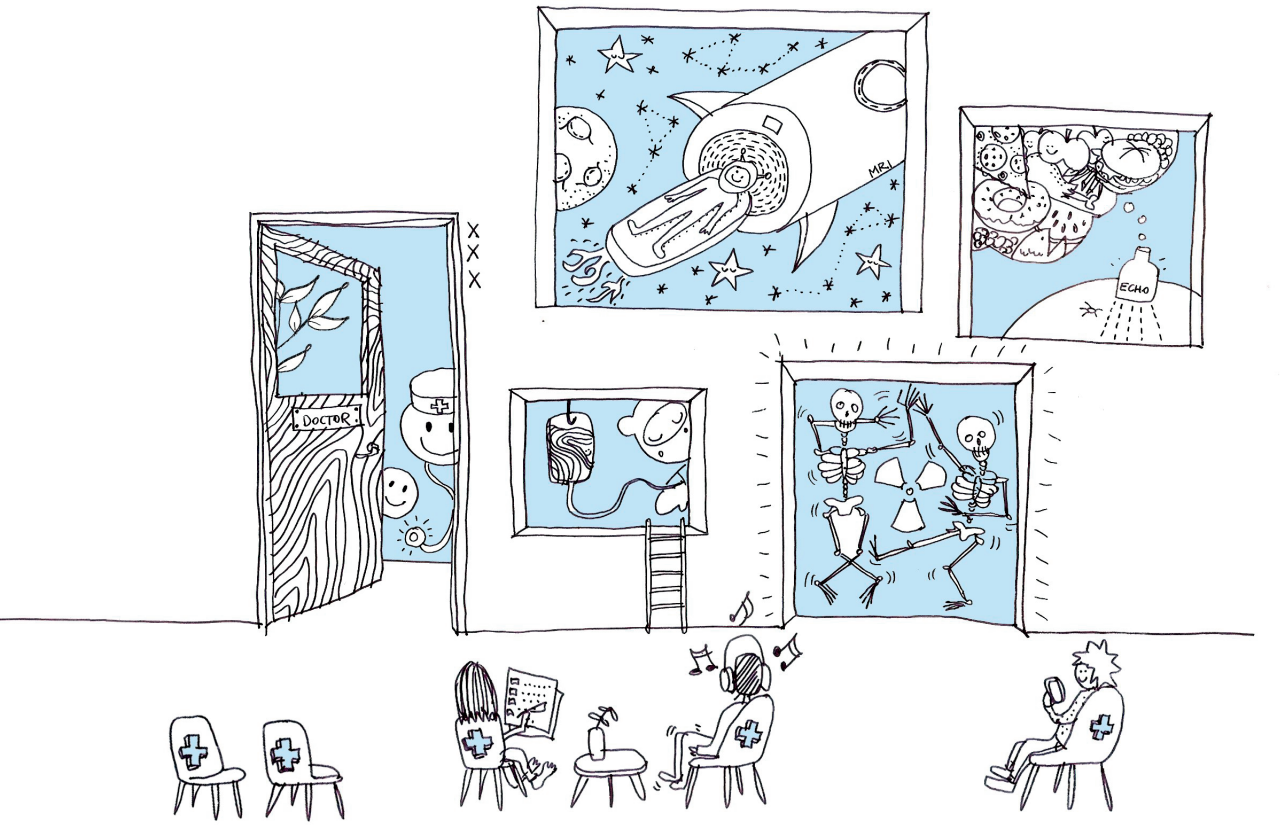


CHAPTER 4.

The development of the 'Children's Discomfort during Research Procedures Questionnaire' (CDRPQ)

MS Staphorst, R Timman, J Passchier, JJV Busschbach,
JB van Goudoever, JAM Hunfeld

Submitted



ABSTRACT

Background. There is a need for data on children's self-reported discomfort in clinical research, making the evaluations of discomfort by ethics committees evidence-based. Because there is no appropriate instrument to measure children's discomfort, we aimed to develop a generic, short and child-friendly instrument: Children's Discomfort during Research Procedures Questionnaire (CDRPQ).

Methods. This article describes the six steps of the development of the CDRPQ. First, we updated a literature search on children's self-reported discomfort in clinical research to get insight in what words are used to measure discomfort (step 1). Subsequently, we interviewed 46 children (6-18 years) participating in research to get insight into important forms of discomfort for children (step 2), and asked them about their preferred response option for measuring discomfort (step 3). Next, we consulted nine paediatric experts from various backgrounds for input on the content and feasibility of the CDRPQ (step 4). Based on input from these previous steps, we developed a draft version of the CDRPQ, which we discussed with the experts. The CDRPQ was then pretested in 25 children to ensure face-validity from the child's perspective and feasibility (step 5). Finally, validity, reliability and internal consistency were tested based on the scores of 418 children (step 6).

Results. The search update revealed several words used for measuring discomfort in research (e.g. 'worries', 'unpleasantness'). The interviews gave insight into important forms of discomfort for children in research (e.g. 'pain', 'boredom'). Children preferred a 5-point Likert scale as response option for the CDRPQ. The experts recommended a short, digital instrument involving different forms of discomfort, and measuring discomfort of individual research procedures. Pretesting of the CDRPQ resulted in a few layout changes, and feedback from the children confirmed the feasibility of the CDRPQ. Convergent validity and test-retest reliability were acceptable. Internal consistency based on item-rest correlations and Cronbach's alpha were low, as expected.

Conclusions. The CDRPQ is a generic, practical and psychometrically sound instrument for measuring children's discomfort during research procedures. It contributes to make the evaluation of discomfort in paediatric research evidence-based. Therefore, we recommend including the CDRPQ as standard component of paediatric research studies.

BACKGROUND

Institutional Review Boards (IRBs) estimate children's discomfort in research but have little information on children's self-reported discomfort during the research procedures to guide their decision-making.[1] They therefore often have to rely on their own expertise and experience in paediatric care, which can give a biased view as literature shows that adults often perceive children's discomfort in medical settings higher than the children themselves.[2-4] In addition, a study by Shah et al. shows that among IRB chairs there is little consensus on the level of discomfort of research procedures.[5] It is therefore important to take children´s own perspectives into account when evaluating discomfort of research procedures to make this evaluation evidence-based. This argument is reflected in different reports, stating that it is necessary to define and permanently monitor children's discomforts during research procedures.[6, 7] Moreover, it is reflected in Article 12 of the United Nations Convention on the Rights of the Child that children deserve to give their opinion in matters that concern them.[8]

The need to have self-reported data about the experiences of children in clinical research is seen, for instance, by the development of the Reactions to Research Participation Questionnaire for Children (RRPQ-C)[9] and the Pediatric Research Participation Questionnaire (PRPQ).[10] Although these questionnaires give a general view of paediatric research participation (e.g. trust in the research team), they give limited insight into discomfort, and do not address children's experiences during the individual research procedures of a study. Since it is preferable that IRBs evaluate discomfort of the individual research procedures within a study,[11, 12] the so-called component-analysis approach,[13] it is important to have information on the discomfort of individual research procedures as well. Such information can be generalized across different research studies with similar procedures to estimate the level of discomfort that might be expected for children in future research with a given procedure.

In the absence of an appropriate instrument, we aimed to develop a questionnaire measuring children's self-reported discomfort during research procedures. We aimed for a generic questionnaire that measures forms of discomfort relevant for all kinds of medical research procedures to enable comparisons between different research procedures, omitting aspects that are too specific (e.g. 'feeling out of breath' is only relevant for certain research procedures). We also aimed to use a very limited number of questions, as the questionnaire should be short and easy to complete, and we did not want our questionnaire to be an extra burden for research participation. This paper describes the step-by-step development of the questionnaire: the Children's Discomfort during Research Procedures Questionnaire (CDRPQ).

METHODS

Step 1. Literature search

To gain insight into children's discomfort in clinical research, two of the authors (JH and JP) first reviewed the state of knowledge regarding children's discomfort or risk of children and adolescents who participate in research.[1] They searched literature from onset to December 2010. Inclusion criteria were: published in a peer-reviewed journal, empirical studies that addressed children's self-reported experiences in clinical research, and written in English. Studies on parental burden, burden of illness, economic burden, non-empirical studies, and studies on the willingness to participate in medical research were excluded. They found eight articles concerning discomfort or risk. They concluded that studies on children's self-reported discomfort in clinical research are scarce.

For the development of the CDRPQ we specifically looked at the words that these studies used to get insight into discomfort. We also carried out an update and extension of this search (Appendix A), for which PubMed, PsycINFO, Web-of-Science, Cochrane central, Medline and Embase were searched from onset to December 2012.

Step 2. Interview study

To incorporate the perspective of the children for item-generation, we conducted a qualitative study in 46 children (aged 6-18, M=11.9, SD=3.8) participating in different kinds of research studies (experimental, observational or follow-up studies) at two paediatric academic hospitals. The aim of these interviews was to get insight into important forms of discomfort for children during research procedures, and what words they use to describe discomfort. A majority of these children (74%) was considered ill (asthma, cystic fibrosis, cashew allergy, Inflammatory Bowel Syndrome) and an approximately even number of boys and girls was enrolled. Twenty-four different research procedures were performed on the children, which included both invasive (such as needle-related procedures, provocation tests) and non-invasive procedures (such as pulmonary function tests, taking medical history, questionnaires). Children were interviewed directly after the study visit. The interview schedule is provided in Appendix B.

Audiotaped interviews were transcribed verbatim and imported into NVivo 10.0 software.[14] To ensure anonymity, all identifying information was removed from the transcripts. Data were analysed using 'thematic analysis', which was chosen to categorise important themes related to discomfort.[15] The first author analysed the interviews and a supervising researcher independently analysed 25% of the interviews. Disagreements were discussed until consensus was reached.

Step 3. Children's preferred response option

The aim of this step was to measure the type of response option children prefer for our questionnaire measuring discomfort, because literature is inconclusive about the 'best'

response option for children to report their experiences in medical situations.[16-21] After the interview, children were asked to answer five written questions about their experiences with the research procedures. Forty-one of the 46 children (89%) of the previous step completed all five questions. These questions were based on input from literature, paediatricians, paediatric nurses and psychologists. Each question had three different types of response options: a 5-point Likert scale, a coloured numeric 100mm visual analogue scale (VAS) (ranging from green 'no discomfort' to red 'extreme discomfort'), and a simple 100mm black line VAS. Children were asked to fill in all three response options for the five questions and at the end we asked them which option they preferred. We calculated Spearman correlations for the three different response options of each question to detect a possible discrepancy. We intentionally did not include a 'faces' scale because the reliability is often poor in older children,[22] and we preferred to have a response option for children of all ages, without it coming across as being childish. Frequencies were used to determine children's preference for a response option. We also determined whether there were preferences for a specific response option related to age differences by using a one-way ANOVA.

Step 4. Consulting an expert panel

In order to develop a questionnaire that met the needs of paediatric healthcare professionals, we consulted an expert panel involving nine paediatric healthcare professionals from different backgrounds and disciplines: three paediatricians (one of which held a PhD in research ethics concerning paediatric research participation); one paediatric research nurse; one paediatric research coordinator at an academic hospital, who was also a member of an IRB; a chairman of a parent association for children with Duchenne muscular dystrophy; two psychologists, and a pedagogic. The aim of this phase was to incorporate the perspective of paediatric experts for item-generation and to discuss the practical implementation of the instrument. We presented the information that we had gathered from the literature, the interview study, the preference for a response option, and discussed about the content and layout of the questionnaire. The information gained from the previous steps and the input from the experts was used to develop a draft questionnaire of the CDRPQ. We then presented this draft questionnaire to the experts for additional review.

Step 5. Pretesting the CDRPQ

The draft version of the CDRPQ was pretested on 25 children in clinical research to ensure feasibility and face-validity from the child's perspective. The children were asked to comment on relevance and comprehensiveness of the items, whether they understood the questions, whether using the questionnaire on an iPad-mini led to practical issues, and whether the time needed to complete the CDRPQ was acceptable.

Step 6. Psychometrics of the CDRPQ

The final step of the development of the CDRPQ was testing its psychometrics, using the scores of 418 children (8-18 years, M=10.9 ± 2.1): 307 children in clinical research, 61 in routine clinical care (ultrasound imaging, MRI scans, pulmonary function test) and 50 children during dental check-ups. The latter two groups were included because of a research question for another study, but we also used them for validation purposes of the CDRPQ. The minimum age for the child's participation in this study was eight years, because the questionnaire we used for measuring convergent validity is only suitable for children aged eight and older (Children's version of the Impact of Event Scale,[23] and because some of the children aged six or seven (step 3) had difficulties with answering the written questions. An approximate equal percentage of boys and girls participated. About 75% of the children were healthy (i.e. they did not have a known disease). All children completed the CDRPQ directly after undergoing the procedure.

Validity (convergent)

Event-related (traumatic) distress

For other research purposes, the Children's version of the Impact of Event Scale (CRIES-13) was used:[23] a self-report scale that measures the frequency of event-related (traumatic) distress. This gave us the possibility to compare the scores of the CDRPQ with those of the CRIES-13 as an indication of the convergent validity of the CDRPQ. The CRIES-13 consists of 13 items, which are divided into three subscales: avoidance (four questions, e.g. 'Did you try not to talk about it?'), intrusion/re-experiencing (four questions, e.g. 'Did pictures about it pop into your mind?'), and arousal (five questions, e.g. 'Did you get easily irritable?'). Children have to rate each question on a 4-point Likert scale, with the following weights and categories: 0 = 'not at all', 1 = 'rarely', 3 = 'sometimes', 5 = 'often'. When a child has a total score of 30 or above on the CRIES-13, this child is considered to have clinically elevated stress response symptoms.[24] The CRIES-13 demonstrates satisfactory to good psychometric characteristics,[25] and has good internal consistency for the total score (Cronbach's $\alpha = 0.80$). To measure the convergent validity of the CDRPQ, we calculated a Spearman correlation between the average discomfort score of the CDRPQ, which is based on the different forms of discomfort, and the total score of the CRIES-13.

Parents' ratings

We asked parents to rate their child's annoyance during the procedures in order to measure convergent validity. We compared the children's scores on annoyance (one of the questions of the CDRPQ) with their parents' ratings of annoyance by calculating the weighted kappa between these ratings.[26, 27] The reason for choosing 'annoyance' is

that it reflects a general discomfort rather than a specific, and because we focused on children's self-report rather than proxy reports.

Internal consistency

To evaluate the internal consistency of the CDRPQ, we calculated Spearman correlations between each of the forms of discomfort (e.g. nervousness) and the discomfort score averaged across the other forms of discomfort while correcting for self-correlation (i.e. item-rest correlations). As discomfort was shown to be a multidimensional construct (Step 2), it was expected that these correlations would be modest, as well as the Cronbach's alpha which was calculated too.

Test-retest reliability

We measured discomfort of the procedures twice: directly after undergoing the procedure and after one month. Test-retest reliability of the CDRPQ was calculated with Spearman correlations of different forms of discomfort and the average discomfort score directly after the procedure and after one month. Additionally, to test the stability in level of discomfort over time, we analysed a possible difference between the two measurement moments with Wilcoxon's signed rank tests.

RESULTS

A diagram of the different steps of the questionnaire development is presented in Figure 1.

Step 1. Literature search

For the initial search 413 abstracts were identified of which eight were included that were focused on discomfort or risk. For item-generation of the CDRPQ, we identified 'discomfort', '(un)comfortable', 'scared', 'worries' and '(un)pleasantness' as possible items based on the included articles. The extension and update of the search from onset until December 2012 revealed 2780 potential articles, but did not reveal new original empirical studies on children's self-reported discomfort related to medical research procedures in addition to the initial search.

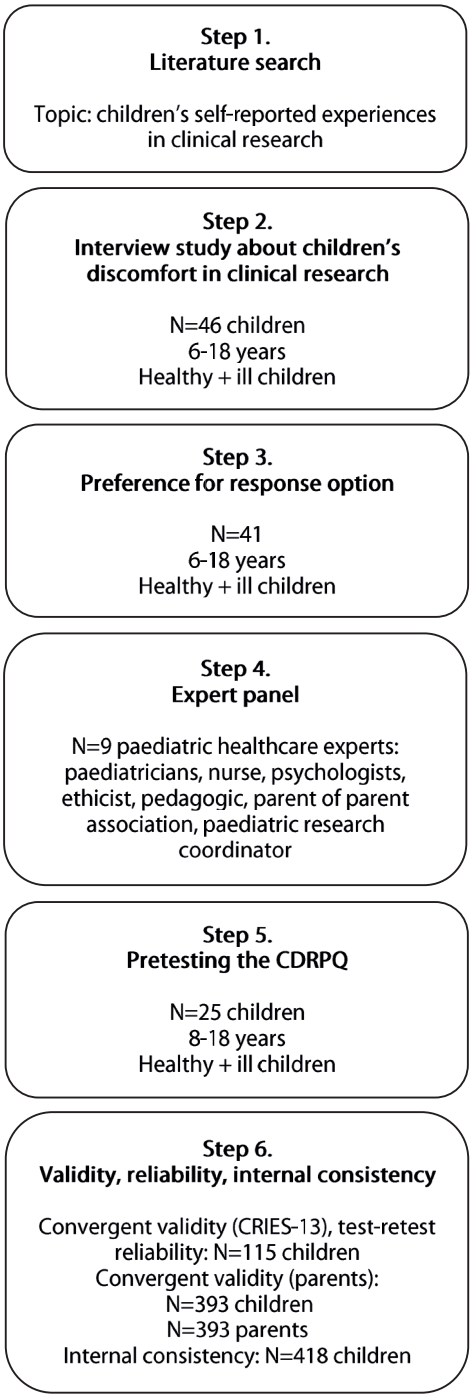


Figure 1. Scheme of the different steps of the development of the CDRPQ

Step 2. Interview study

The majority of the children experienced various forms of discomfort. Forms of discomfort that were frequently mentioned included feeling tired, having pain, feeling nervous/anxious because of anticipated pain or not knowing what to expect from the research study, shortness of breath, nausea, itchiness, and feeling hungry, feeling frightened, feeling bored because of the duration and/or waiting, and feeling ashamed. These various forms of discomfort suggest that discomfort is a multidimensional construct. The extensive description of the results of the interview study is published elsewhere.[28]

Half of the children, in particular the younger ones, did not know the meaning of 'discomfort' or 'burden' or did not know how to describe the word. The most frequently mentioned description by the children who did understand the word said discomfort means 'annoying'.

Step 3. Children's preferred response option

For each of the five questions, the three different response options (Likert scale, coloured numeric VAS, simple VAS) were strongly correlated (rho=0.76-0.99, $p < 0.01$). Twenty-one children (51%) preferred the 5-point Likert scale, followed by 14 children (34%) preferring a coloured numeric 100mm VAS (Table 1). Two children (aged six and eight) spontaneously said they would have preferred a faces scale. There were no age-related differences for the preferred response option ($p = 0.21$).

Table 1. Preference for response option

	Number of children	Percentage
5-point Likert scale	21	51.2%
Coloured 100mm VAS	14	34.1%
Plain 100mm VAS	2	4.9%
No preference	2	4.9%
5-point Likert scale or coloured 100mm VAS	1	2.4%
Coloured 100mm VAS or plain 100mm VAS	1	2.4%
Total	41	100.0%

Step 4. Consulting an expert panel

During the expert panel meeting, the paediatric healthcare professionals gave practical suggestions for the development of the questionnaire. The most important suggestions are presented in Table 2.

In consultation with the experts we included the most frequently mentioned and relevant forms of discomfort, mentioned in Step 2, into the CDRPQ: 'feeling nervous', 'feeling annoyed', 'having pain', 'feeling frightened', 'feeling bored', and 'feeling tired'.

Table 2. Suggestions of the expert panel about the questionnaire

Suggestions
1.The questionnaire should be administered **digitally** to make it more appealing to children and easier to distribute data to other researchers.
2.The questionnaire should be **short**, because children and parents are already loaded with questionnaires in research, e.g. about their health status. Questionnaires themselves are often perceived as a burden. They also indicated that the questionnaire should be short, so it does not interfere with their research studies.
3.**Parents** should also be asked to rate their child's discomfort to study whether their ratings are similar.
4.The discomfort of **individual research procedures** should be measured because IRBs often evaluate the discomfort of the various research procedures of a study separately (i.e. component analysis approach).
5.Children do not like to fill in questionnaires that focus only on negative experiences. They should therefore also be asked about **positive experiences** (i.e. whether children liked the research procedures).
6.As children are the subjects who undergo the procedures, they probably have good ideas how to improve these. Therefore, children should be asked about **improvements**, which is useful for researchers to design the study to minimize discomfort
7.It is helpful to know whether children would undergo the research procedure in the **future** to get an impression of the child's discomfort.

'Annoyed' was included because children frequently mentioned it as a synonym for discomfort, and moreover it represents a generic form of discomfort.

Although feeling ashamed/embarrassed, shortness of breath, nausea, itchiness, and feeling hungry are important forms of discomfort that were frequently mentioned by children as well, we decided not to include these as items, as these are only relevant for certain research procedures. In consultation with the experts, we did not use the forms of discomfort we found during literature search because the children did not mention these once during the interview study.

In addition to the questions about discomfort, we added three questions to the CDRPQ: 1) a question about 'having fun' because the experts mentioned that the CDRPQ should not only focus on negative experiences, 2) a question about suggestions on how to reduce discomfort related to the research procedure which can help researchers to improve their studies, and 3) a question whether children would undergo the research procedure in the future. We used Qualtrics© software to design a digital version of the CDRPQ, which we used on an iPad-mini tablet.

Based on the previous steps and the consultation with the expert panel, we developed a draft version of the CDRPQ in which we incorporated their suggestions. We discussed this draft version with the experts until we reached consensus on the content and the phrasing of the questions.

Step 5. Pretesting the CDRPQ

Children during pretesting found it easy to complete the CDRPQ and reported that they experienced no discomfort or burden because of the CDRPQ. Instead, many said they liked filling in the CDRPQ. They understood the questions, most considered the

questions were relevant for getting insight into their experiences during the research procedures, and said that they preferred an online questionnaire to a paper one, just as the expert panel had expected. However, the Internet connection failed sometimes (in three children), in which case the CDRPQ was administered on paper. Some children considered the question about 'liking the research procedure' irrelevant. They said that if they did not like the research procedure, it did not mean that they experienced the procedure as discomforting, and vice versa. The children said that they did not mind that the questions were primarily about negative experiences. Furthermore, the children provided some recommendations to improve the layout of the questionnaire (i.e. larger font, fewer questions on one page).

Step 6. Psychometrics of the CDRPQ

Validity (convergent)

We observed a moderate Spearman correlation ($r = 0.43$; $p < 0.001$) between the average score on the CDRPQ and the total score of the CRIES-13. The weighted kappa between the rating of the parents and children on the child's annoyance was 0.41, which is considered moderate.[29]

Internal consistency

Spearman correlations reflecting the contribution of the individual forms of discomfort on the average discomfort score are presented in Table 3. All the correlations were statistically significant ($p < 0.05$), but were low, implying that discomfort is determined by diverse non-overlapping aspects. This was also illustrated by a low Cronbach's alpha (0.547).

Test-retest reliability

The test-retest reliability of the items of the CDRPQ, directly after the procedure and after one month, was high (Table 3). The retest scores did not differ significantly from the baseline scores for any of the items.

The final version of the CDRPQ is presented in Appendix C (Note: the CDRPQ was developed in Dutch and then translated to English for this manuscript). We removed two questions from the final version, namely: 'Did you like undergoing procedure X?' and 'Would you undergo research procedure X again in the future?'. The first question was removed because, like the pretest, a considerable number of children regarded this question as irrelevant; they said they did not mind the CDRPQ focusing on negative experiences. The latter question was removed because on further consideration, it did not give additional insight into the child's discomfort over and above the other questions.

Table 3. Item-correlation with average discomfort score, test-retest correlations, differences in measurement moment

	Item-rest correlation with average score N=418	p-value	Test-retest correlation N=115	p-value[1)]	Wilcoxon's Z N=115	p-value
Nervousness	0.202	<0.001	0.665	<0.001	-0.011	0.991
Annoyed	0.401	<0.001	0.586	<0.001	-0.461	0.645
Pain	0.262	<0.001	0.725	<0.001	-0.600	0.549
Frightened	0.275	<0.001	0.525	<0.001	-0.209	0.835
Bored	0.163	0.001	0.440	<0.001	-1.213	0.222
Tired	0.248	<0.001	0.510	<0.001	-1.673	0.225
Average discomfort score	n/a	n/a	0.710	<0.001	-1.146	0.252

[1)] p-values are one-sided

DISCUSSION

This article describes the development of the CDRPQ, which was designed to measure discomfort of common medical research procedures in children (8-18 years) in order to make the evaluation of discomfort in clinical research evidence-based. Since there is no 'gold standard' for measuring discomfort of research procedures (e.g. by self-report, by proxy, or by physiological measures such as cortisol levels), we focused on self-report because children's self-reports are an important source of information that cannot be ignored and because we do not have much information on discomfort from children's perspectives.

In general, we found that the CDRPQ is a reliable and valid questionnaire to measure generic discomfort related to medical research procedures, and can be easily completed by children between the ages of 8 to 18. The children themselves indicated that they liked completing the CDRPQ and did not experience it as being burdensome.

The moment of measurement (directly after the procedures versus after one month) did not significantly influence children's answers, as there were no significant differences in discomfort between these measurement moments in our sample. This suggests that it is not necessary to complete the CDRPQ directly after the procedure. Children can complete it at a more convenient moment, for instance at home, which may be less burdensome for them.

Although the CDRPQ was developed to measure discomfort in clinical research, the questionnaire could be used for measuring discomfort in clinical care as well. The reason why we focused on research is because there are strict guidelines for the level of discomfort, while these do not exist in clinical care. Although there are several instruments measuring children's negative experiences in medical situations in clinical care,[30-40] limitations of these instruments are that these primarily focus on the measurement of

pain or distress. The interviews with the children showed that discomfort is an umbrella term that also represents other forms of discomfort than pain and anxiety. Measuring a variety of forms therefore provides a more thorough measure of the child's discomfort in clinical research.

Strengths and limitations

A strength of the CDRPQ is that the content is based on literature, and input from children and paediatric healthcare professionals. It gives a good overview of discomfort experienced by children during research procedures in a short time. The CDRPQ is a generic questionnaire that makes it possible to compare the discomfort caused by different research procedures. The CDRPQ helps to identify discomfort from a procedures-related approach rather than a study-related approach, and therefore provides crucial complement to existing instruments measuring children's experiences in research, such as the RRPQ-C and PRPQ. Furthermore, the CDRPQ not only focuses on discomfort, but also on suggestions by children to reduce discomfort. This provides paediatric researchers with practical information to minimize discomfort of their studies, which is also a requirement of various ethical codes and regulations on paediatric research participation.[41, 42]

We administered the CDRPQ online, which has several advantages compared to paper-and-pencil questionnaires in terms of completeness of data (i.e. it can remind users that they skipped a question), less proneness to social desirability answering, and higher-cost effectiveness.[43] In addition, the outcomes of an online questionnaire can be easily stored online, which can make it easy for children, parents, IRBs, and paediatric researchers to have access to this information.

The CDRPQ is limited in a way that for some procedures certain important forms of discomfort are not measured, which may give an incomplete view of the overall discomfort. For instance, for children during Tanner staging, embarrassment may be an important for of discomfort. It is time-consuming to measure all forms of discomfort for all kinds of research procedures, which is why we decided to develop a generic questionnaire, suitable to compare discomfort of different research procedures and between different groups of children.

The validation of the CDRPQ is limited. For instance, measuring convergent validity between parents' and children's scores was only based on one of the questions of the CDRPQ. Another limitation is the way 'test-retest reliability' is measured, which was based on retrospective recall. The situation during the retest is not equal to the first test, as time has passed since the research took place. A 'real' test-reliability would imply that the child would have to undergo the research procedure and the measurement of discomfort a second time, which is obviously unethical solely for the development of a questionnaire. However, assuming it has an equal effect on all children, the Spearman

correlation we used is considered adequate for this purpose, as it reflects the order of the responses, not the level.

Future research

We are the first to validate the CDRPQ in Dutch children. Additional validation of the CDRPQ is needed, as is validation in other languages. It would be helpful to measure convergent validity based on all questions of the CDRPQ, reported by parents, researchers and children. Furthermore, future research is needed to investigate whether the CDRPQ can also be used in younger children (< 8 years).

Future directions

The CDRPQ can help to establish the level of discomfort of research procedures (i.e. 'minimal', 'minor increase over minimal', and 'more than minimal'). As there is no clear description when a research procedure involves minimal discomfort, Westra et al. propose that "empirical data, expert opinions and/or the procedural characteristics suggest that at most a quarter of the persons (25%) concerned will experience considerable discomfort".[44] Considerable discomfort could be conceptualized as children who reported "very" or "extremely" discomfort on the average score of the CDRPQ. Although it can be questioned whether 25% is a fair cut-off level, it gives IRBs and paediatric researchers guidance for the evaluation of discomfort and make it evidence-based.

In order to collect information on children's discomfort during research procedures, it would be helpful if paediatric researchers include the CDRPQ as a standard component to their studies, and IRBs explicitly recommend paediatric researchers to do this. The information ideally would be published online (anonymously), so that the whole field of paediatric research can benefit from this information.

CONCLUSIONS

The CDRPQ is a generic, short and practical instrument for measuring children's discomfort during research procedures. It contributes to make the evaluation of discomfort in paediatric research evidence-based. We recommend including the CDRPQ as a standard component of paediatric research studies to measure children's discomfort.

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APPENDIX A. SEARCH STRING TO SEARCH FOR LITERATURE RELATING TO CHILDREN'S EXPERIENCES IN RESEARCH

EMBASE

((annoy* OR anxiet* OR bored* OR emotion* OR fear* OR feeling* OR frustrat* OR helpless* OR irritat* OR mood* OR pleasure* OR regret* OR shame OR sorrow* OR coping OR cope OR coped OR stress* OR distress* OR burden OR perception* OR perceive* OR experience* OR comfort* OR discomfort*) NEAR/6 (procedure* OR technique* OR research* OR imaging* OR mri OR anesthe* OR anaesthe* OR intubat* OR surger* OR surgic* OR cannulat* OR infus* OR inject* OR 'drug administration' OR 'x ray' OR dialys* OR invasive OR noninvasive)):ab,ti AND (child/exp OR newborn/exp OR 'child behavior'/de OR 'child psychology'/de OR 'child hospitalization'/de OR (infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 ag*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti OR ((adolescent/exp OR adolescence/exp OR adolescen*:ab,ti) NOT (adult/exp OR aged/exp OR 'middle aged'/de OR (adult*):ab,ti))) AND (psychology/exp OR 'psychological aspect'/de OR (psychol*):ab,ti) AND (questionnaire/exp OR 'self report'/de OR interview/exp OR 'nonverbal communication'/exp OR observation/de OR 'clinical observation'/de OR (questionnaire* OR ((self OR child*) NEAR/3 report*) OR interview* OR nonverb* OR (non NEXT/1 verb*) OR observ*):ab,ti)

Medline in OvidSP

((annoy* OR anxiet* OR bored* OR emotion* OR fear* OR feeling* OR frustrat* OR helpless* OR irritat* OR mood* OR pleasure* OR regret* OR shame OR sorrow* OR coping OR cope OR coped OR stress* OR distress* OR burden OR perception* OR perceive* OR experience* OR comfort* OR discomfort*) ADJ6 (procedure* OR technique* OR research* OR imaging* OR mri OR anesthe* OR anaesthe* OR intubat* OR surger* OR surgic* OR cannulat* OR infus* OR inject* OR drug administration OR x ray OR dialys* OR invasive OR noninvasive)).ab,ti. AND (exp child/ OR exp infant, newborn/ OR exp child behavior/ OR child psychology/ OR (infan* OR newborn* OR (new ADJ born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under ADJ ag*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*).ab,ti. OR ((adolescent/ OR adolescen*.ab,ti.) NOT (exp adult/ OR (adult*).ab,ti.))) AND (exp psychology/ OR (psychol*).xs,ab,ti.) AND (exp questionnaires/ OR Interviews as Topic/ OR Interview, Psychological/ OR exp nonverbal

communication/ OR observation/ OR (questionnaire* OR ((self OR child*) ADJ3 report*) OR interview* OR nonverb* OR (non ADJ verb*) OR observ*).ab,ti.)

PsycINFO in OvidSP

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APPENDIX B. INTERVIEW SCHEDULE

General experiences

How did you feel about the study in general?
How did you feel before the study?
How did you feel afterwards?
Can you describe your experiences during the study?
Can you describe your experiences during *procedure X*?

Experiences related to discomfort

Can you describe any discomfort you experienced in the study?
Is there any part of the study that you did not like? Which part? Why?
Can you describe any discomfort you experienced because of *procedure X*?

Worst experiences

What was/were the most burdensome/discomforting part(s) of the study? Which part? Why?

Preparation

Who prepared you for the study?
What information did you get about the study? Was this information sufficient?
Did you know what to expect of the study?

Suggestions to reduce discomfort

Can you think of anything that would have made the study easier for you? If so, could you tell me about it?
Can you think of anything that will make *procedure X* less discomforting for you? If so, could you tell me about it?
Can you think of anything that will make *procedure X* more comfortable for you? If so, could you tell me about it?

Future research

Would you participate in this research study again? Why (not)?

APPENDIX C. CHILDREN'S DISCOMFORT DURING RESEARCH PROCEDURES QUESTIONNAIRE AFTER EVALUATION

1. Were you nervous while undergoing procedure X?
¤ I was **not** nervous
¤ I was **slightly** nervous
¤ I was **somewhat** nervous
¤ I was **very** nervous
¤ I was **extremely** nervous

2. Was procedure X annoying?
¤ Procedure X was **not** annoying
¤ Procedure X was **slightly** annoying
¤ Procedure X was **somewhat** annoying
¤ Procedure X was **very** annoying
¤ Procedure X was **extremely** annoying

3. Was procedure X painful?
¤ Procedure X was **not** painful
¤ Procedure X was **slightly** painful
¤ Procedure X was **somewhat** painful
¤ Procedure X was **very** painful
¤ Procedure X was **extremely** painful

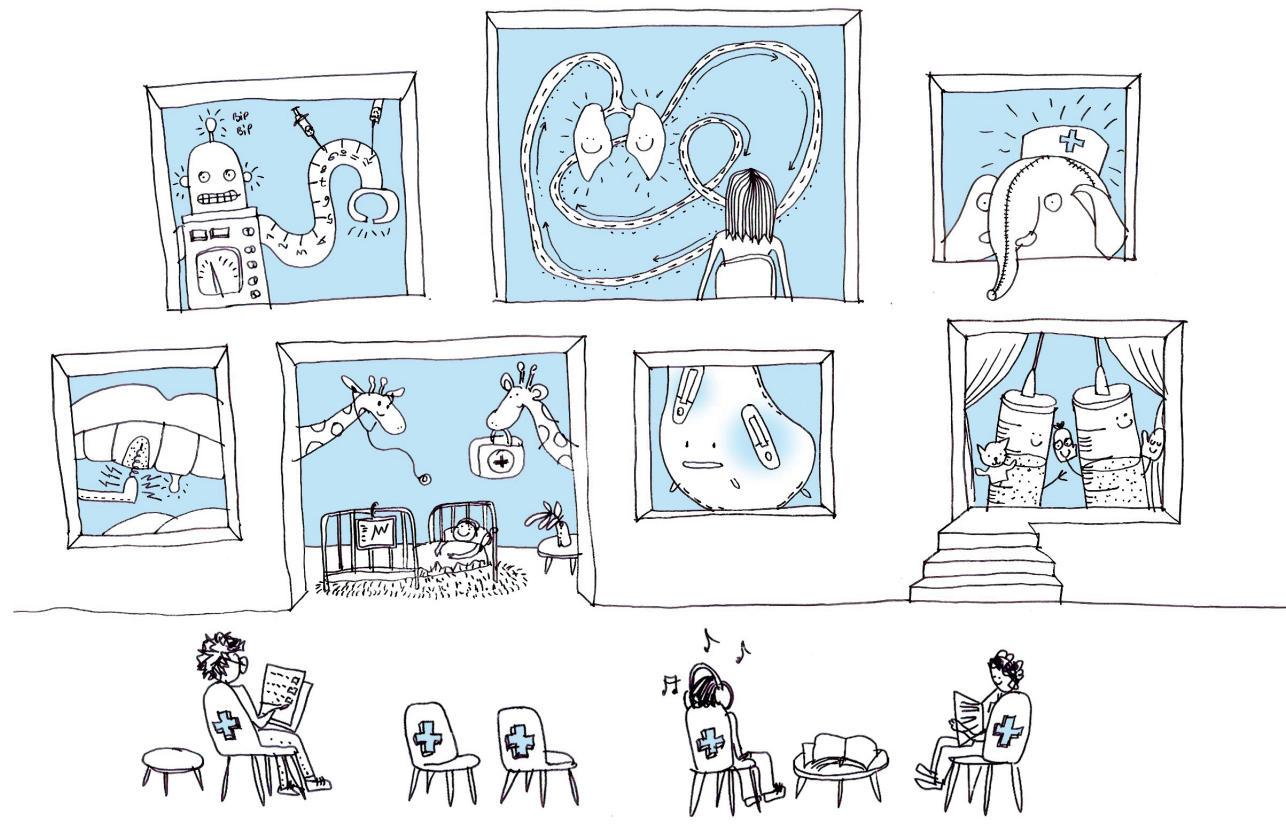
4. Were you frightened while undergoing procedure X?
¤ I was **not** frightened
¤ I was **slightly** frightened
¤ I was **somewhat** frightened
¤ I was **very** frightened
¤ I was **extremely** frightened

5. Were you bored while undergoing procedure X?
¤ I was **not** bored
¤ I was **slightly** bored
¤ I was **somewhat** bored
¤ I was **very** bored
¤ I was **extremely** bored

6. Did you find procedure X tiring?

¤ It was **not** tiring
¤ It was **slightly** tiring
¤ It was **somewhat** tiring
¤ It was **very** tiring
¤ It was **extremely** tiring

7. Do you have any suggestions for making procedure X **less annoying**?



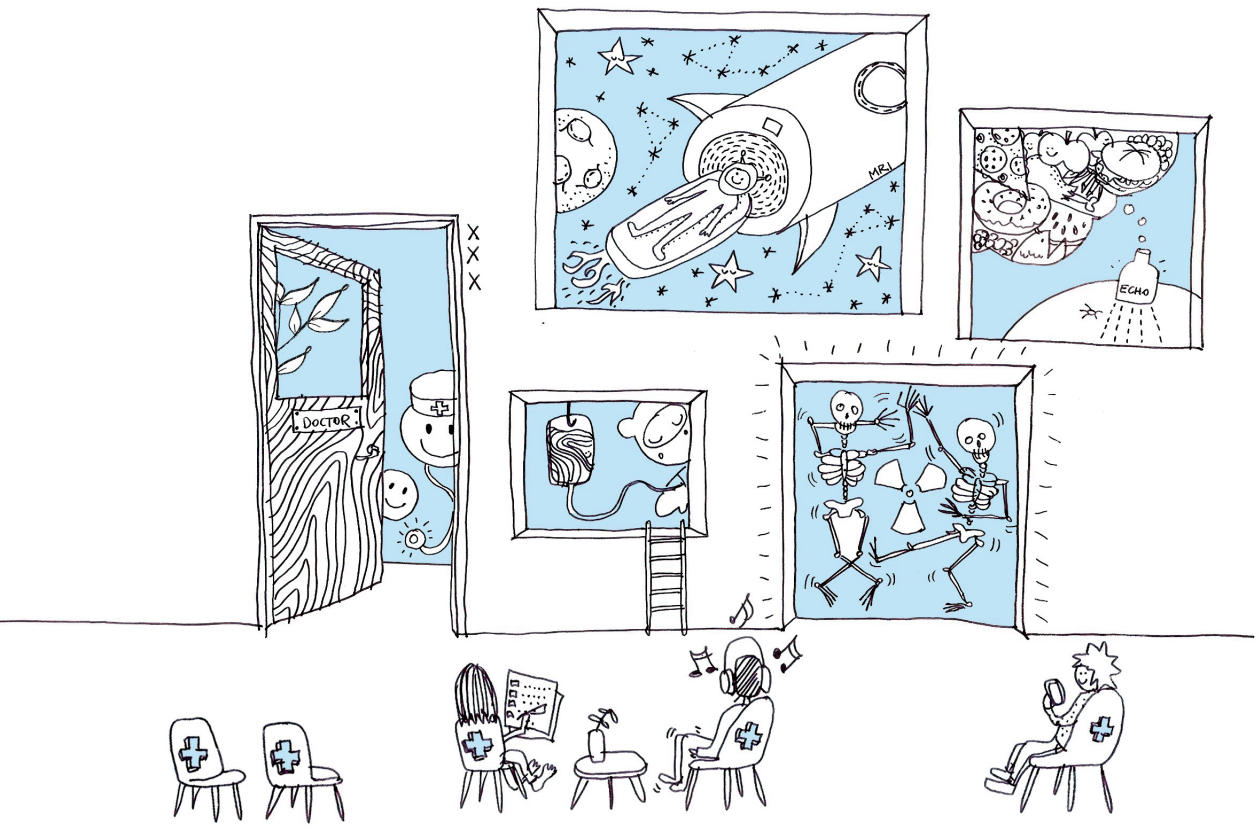
CHAPTER 5.

The child's perspective on discomfort during medical research procedures

MS Staphorst on behalf of the BURDEN-group

BURDEN-group
MA Benninga, M Bisschoff, I Bon, JJV Busschbach, K Diederen, JB van Goudoever, EG Haarman, JAM Hunfeld, VVW Jaddoe, KJM de Jong, JC de Jongste, A Kindermann, M Königs, J Oosterlaan, J Passchier, MW Pijnenburg, L Reneman, L de Ridder, HG Tamminga, HW Tiemeier, R Timman, S van de Vathorst

Submitted



ABSTRACT

Objectives. To describe children's self-reported discomfort during research procedures and to get insight into how discomfort can be reduced. Secondary objectives were to compare discomfort in research to discomfort during dental check-ups, and to explore to influence of age, anxiety-proneness, gender, medical condition, previous experiences, purpose of the procedure (research versus clinical care) on discomfort.

Methods. We enrolled 418 children (8-18 years). We measured discomfort due to six research procedures: buccal swabs, MRI-scans, pulmonary function tests, skin prick tests, ultrasound imaging and venipunctures.

Results. Most children reported limited discomfort during the research procedures (means: 1.0-2.6 on a scale from 1-5). 60.3% suggested providing distraction by showing movies to reduce discomfort. Only anxiety-proneness was positively related to discomfort. The purpose of the procedure affected discomfort differently between the procedures.

Conclusions. The findings of this study support the acceptability of participation of children in the studied research procedures, which stimulates evidence-based research practice.

INTRODUCTION

There is a need to improve treatments and licensed medication for children by conducting pediatric research. For instance, it is estimated that 65% of all prescribed pediatric drugs are used off-label,[1] which exposes children to an increased risk of medication under- or overdose. Pediatric research, however, is complicated by the obligation to protect children against the risks and discomfort of research procedures. It is the responsibility of Institutional Review Boards (IRBs) to estimate the risks and discomfort of research procedures, and evaluate whether these are acceptable for the children. Primarily in case of discomfort, IRBs base this evaluation on their intuition and experiences, which may not necessarily give a representative view of children's experiences.[2-5] Consequently, this can lead to the rejection of studies when discomfort is expected to be excessive but is acceptable for the children, or to the acceptation of studies while discomfort is excessive for the children involved.

Unfortunately, there is a lack on data on children's discomfort. In this study we therefore make a start in describing children's self-reported discomfort during research procedures. These data are an important first step in providing an empirical basis for the evaluation by Institutional Review Boards (IRBs) and eventually providing benchmarks for the level of discomfort that might be expected for children with a given procedure.

We measured discomfort during research *procedures* instead of during a research study *as a whole* to make the results generalizable to children who undergo these procedures in future research and because IRBs often evaluate the research procedures of a study separately.[6-8] By addressing research procedures, this study provides a crucial complement to previous studies that have measured children's overall reactions to participation in research studies, such as the understanding of your rights of being a research participant.[9-12] We compared the outcomes to discomfort of children during dental check-ups, which enabled us to compare discomfort experienced in research with a medical procedure most children encounter ('reference level'). We exploratively compared whether the purpose of a medical procedure (research versus clinical care) influences discomfort. Furthermore, we explored whether age, anxiety proneness, gender, medical condition and previous experiences with the procedure were related to children's discomfort. In addition, children were asked for suggestions to reduce discomfort.

METHOD

Participants

We used a convenience sample in which we aimed to include 50 children for each research procedure, or as much we could enroll within the timeframe of our study.[13] Children were eligible to participate if they met the following criteria: a) aged between

8-18 years, b) fluent in Dutch, c) no current psychological treatment for pain or anxiety disorders, d) no psychosocial problems as diagnosed in the Diagnostic and Statistical Manual of Mental Disorders at the time of enrollment, and e) accompanied by a parent or caretaker. This information was determined by consultation of parent(s) or the child's medical record.

The children were recruited from research studies being conducted at three academic hospitals in the Netherlands. In addition, two other groups of children, for whom the same inclusion criteria applied, were included: 1) children without a known illness who had had a check-up visit to the dentist, and 2) children who had undergone a medical procedure during routine clinical care at one of these three hospitals. Children were enrolled between March 2014 and June 2015.

Procedure

First, the researchers conducting the research studies approached children and their parents if they were willing to participate in our study. Interested children and parents were provided with more information about the study by the first author or a research assistant. After agreement, written consent from parents and written child assent (>12 years) were obtained. Children younger than twelve gave oral assent to participate. Directly after the research procedure, the children completed two questionnaires on an iPad mini tablet to measure discomfort and anxiety-proneness. Parents provided demographic information. All children received a gift card (€7.50) after completing the questionnaires.

Measures

Discomfort

We developed the Children's Discomfort during Research Procedures Questionnaire (CDRPQ) because no appropriate instrument existed for the aim of the current study. Instruments that measure children's self-reported experiences in medical situations often focus on the measurement of pain, distress or anxiety. Discomfort, however, also involves other aspects than pain and distress, as was shown in an interview study we conducted.[14] Measuring various forms of discomfort therefore provides a more thorough measure of the child's discomfort. We aimed for an instrument that measures forms of discomfort that are applicable to all kinds of research procedures. Therefore the CDRPQ can be considered as a generic questionnaire.

The CDRPQ contains: 1) six questions about different types of discomfort (nervousness, annoyance, pain, fright, boredom, and tiredness), which are measured using Likert scales ranging from 1='not discomforting' to 5='extremely discomforting', and 2) one open question about suggestions for reducing discomfort (Appendix A. Note:

The CDRPQ was developed in Dutch and then translated to English for this manuscript). Validity and test-retest reliability were acceptable.[15]

Anxiety-proneness The influence of anxiety proneness on discomfort was measured using the Dutch translation of the trait scale of the State-Trait Anxiety Inventory for Children (STAI-C),[16] or the anxiety scale of the Child Behaviour Checklist (CBCL),[16] depending on which questionnaire was already being used by the participating studies. Previous research shows that there are little differences in measuring anxiety by the trait scale of the STAI-C and the anxiety scale of the CBCL when parent-reported,[17] and that these scales are highly correlated ($r = 0.77$).[18] The trait scale of the STAI-C is self-reported and addresses the frequency and intensity of anxiety symptoms in general. It consists of 20 items (e.g. *"I worry about school"*).[19] The STAI-C trait scale has shown good internal consistency (Cronbach's $\alpha > 0.80$) and acceptable test–retest reliability ($r > 0.65$).[20] The anxiety scale of the CBCL is parent-reported and includes six questions on anxiety problems (e.g. "fear of animals, situations or places"). The CBCL has shown good validity and reliability.[16]

Demographics
Parents provided information on demographics.

Medical procedures

Research procedures
We measured children's experiences during six research procedures: buccal swabs, MRI-scans, pulmonary function tests, skin prick tests, ultrasound imaging and venipunctures (Table 1). The research procedures were selected based on the following criteria: no general anesthesia necessary, perceived by a consulted group of pediatric healthcare professionals as possibly causing discomfort, and performed in the participating hospitals during the timeframe of our study. Almost all children underwent the research procedures for non-therapeutic research purposes, with the exception of the pulmonary function tests and some venipunctures.

Dentist
We measured the experiences of a group of children without a known illness during regular check-up visits to a general academic dental center (Table 1). Fifth-year dentistry students perform supervised dental check-ups on children at this academic dental center.

Procedures in clinical care
We measured the experiences of children undergoing MRI-scans, pulmonary function tests or ultrasound imaging for diagnostic reasons (Table 1).

Table 1. Description of the medical procedures

Procedure	Description
Buccal swab test	Taking mucosal epithelial cells from the inner cheek lining using a small brush.
MRI-scan	Magnetic Resonance Imaging of different parts of the body, particularly of the head. The MRI-scans lasted between 30 and 60 minutes and were performed without sedation.
Pulmonary function test	Regular pulmonary function test that lasted between 15 and 30 minutes.
Skin prick test	Children were tested for 20 allergens. A droplet of each allergen was placed on the inner forearm and penetrated through to the skin using a specially modified lancet.
Ultrasound imaging	Ultrasound imaging used for research purposes was an echocardiogram. For clinical care purposes, ultrasound imaging was particularly an echocardiography and in some cases ultrasounds were made of the lymph nodes, the head or the abdomen.
Venipuncture	One to three 10ml tubes of blood were collected. In one of the two studies children could choose to have EMLA-cream applied before the venipuncture. None of the children had a local anesthetic.
Dental check-up	During the dental check-up a general check was carried out, dental plaque was removed and children were given instructions on how to brush their teeth correctly. A new appointment was made for dental caries or other abnormalities.

Statistical analysis

The data were analyzed using SPSS version 21. For each procedure, we calculated the means of the different forms of discomfort, the percentage who reported the research procedure as 'very' or 'extremely' discomforting, and an average discomfort score based on the six forms of discomfort. As most data were skewed, we used non-parametric statistics. A Kruskal-Wallis Test and Mann-Whitney U tests were used to explore differences between the procedures in the average discomfort score. We used Spearman correlations to explore the relation between the average discomfort score, and age and anxiety proneness. Mann-Whitney U tests were used to explore differences in the average discomfort score between children with and without an illness, boys and girls, children with and without previous experiences, and children in routine clinical care and research. We did a multivariate analysis to measure the variance in discomfort explained by the above-mentioned factors. The first author coded the question 'What would you suggest to make *[procedure X]* less annoying?' into categories. A supervising researcher checked these categories (JH), and disagreements were discussed until consensus was reached.

Ethical approval

The IRB of the VU Medical Center in Amsterdam (The Netherlands) indicated that there was no risk or discomfort associated with this study (i.e. completing the questionnaires), and stated that it is exempt from requiring approval under Dutch Law (2014/010).

All parents and children older than eleven years who agreed to participate gave informed assent/consent for their participation and were aware that their data would be used for research purposes. Children younger than twelve years old verbally agreed to participate.

RESULTS

Participants

528 children were potentially suitable for participation in our study, of which 71 children (13.4%) did not meet the inclusion criteria (24 in research, 33 in clinical care and 14 from the dental clinic): two children did not speak Dutch fluently, five children were not accompanied by a parent and 64 children were too young or too old. Of the 457 children who were invited to participate, 418 children agreed to participate (91.5%). The most frequently mentioned reason for declining was lack of time of the parents (56%), followed by 'no interest' (26%). 307 children were enrolled from clinical research, 61 from clinical care, and 50 from an academic dental clinic. The majority of the children did not have a known illness (73.0%). Mean age was 10.9 years. Further characteristics of the children are presented in Table 2.

Discomfort during research procedures (CDRPQ)

Table 3 shows the discomfort children experienced: the mean of each form of discomfort, and the percentage of children who reported 'very' (score 4) or 'extreme' (score 5) discomfort. For almost all procedures, the mean scores on the different forms of discomfort were low. Exceptions were: children undergoing the buccal swab test generally indicated that they were 'slightly' bored; most children felt the MRI-scan was 'slightly' tiring and 19% felt it was 'very' or 'extremely' tiring.

There were significant differences in discomfort between the procedures ($p < 0.001$). Compared to check-up visits to the dentist, discomfort of buccal swab tests, skin prick tests and ultrasound imaging were less discomforting ($p = 0.002$-0.007), while MRI-scans, venipunctures and pulmonary function tests caused a similar degree of discomfort ($p = 0.05$-0.26).

Suggestions to reduce discomfort

A large group of the children in clinical research (62.6%) suggested that distraction during the research procedures, preferably in the form of a movie, would reduce discomfort (Table 4).

Table 2. Demographics

Demographics	Research (N=307)	Clinical care (N=61)	Dentist (N=50)	Total (N=418)
Gender (%)				
Boy	158 (51.5%)	30 (49%)	27 (54%)	215 (51.4%)
Girl	149 (48.5%)	31 (51%)	23 (46%)	203 (48.6%)
Age (%)				
Mean ± SD	10.5 ± 1.8	12.7 ± 2.8	10.8 ± 1.5	10.9 ± 2.1
< 12 years	273 (88.9%)	26 (43%)	38 (76%)	337 (80.6%)
≥ 12 years	34 (11.1%)	35 (57%)	12 (24%)	81 (19.4%)
Procedure (%)				
Buccal Swab	25 (8.1%)	-	-	25 (6.0%)
MRI	89 (29.0%)	16 (26%)	-	105 (25.1%)
Pulmonary function test	9 (2.9%)	20 (33%)	-	29 (6.9%)
Skin prick test	75 (24.4%)	-	-	75 (17.9%)
Ultrasound imaging	77 (25.1%)	25 (41%)	-	102 (24.4%)
Venipuncture	32 (10.4%)	-	-	32 (7.7%)
Check-up visit at dentist	-	-	50 (100%)	50 (12.0%)
Medical condition (%)				
ADHD/ADD	4 (1.3%)	-	-	4 (1.0%)
Asthma	-	20 (33%)	-	20 (4.8%)
Cystic Fibrosis	6 (2.0%)	-	-	6 (1.4%)
Healthy (i.e. no known illness)	254 (82.7%)	1 (2%)	50 (100%)	305 (73.0%)
Inflammatory Bowel Disease	36 (11.7%)	4 (7%)	-	40 (9.6%)
Metabolic disorder	-	3 (5%)	-	3 (0.7%)
Nephrological condition	-	3 (5%)	-	3 (0.7%)
Oncological condition	1 (0.3%)	8 (13%)	-	9 (2.2%)
Primary ciliary dyskinesia	4 (1.3%)	-	-	4 (1.0%)
Other condition	2 (0.7%)	22 (36%)	-	24 (5.7%)
Previous experience with procedure (%)	148 (48.2%)	35 (57%)	50 (100%)	233 (55.7%)
Trait-anxiety - STAI-C*	**N=82**	**N=61**	**N=36**	**N=179**
Mean ± SD	29.3 ± 5.7	29.1 ± 6.2	28.9 ± 5.7	29.2 ± 5.9
Range	20-44	20-48	22-42	20-48
Trait-anxiety - CBCL*	**N=192**	**N=0**	**N=0**	**N=192**
Mean ± SD	1.0 ± 1.4	-	-	1.0 ± 1.4
Range	0-6	-	-	0-6

* STAI-C = State Trait Anxiety Inventory for Children; CBCL = Child Behaviour Check List

Table 3. Discomfort from child's perspective

Example. *"Were you bored while undergoing the MRI-scan?"*
1 = not
2 = slightly
3 = somewhat
4 = very
5 = extremely

	Nervous		Annoyed		Pain		Frightened		Bored		Tired		Average discomfort score	
	Mean	4+5*	Mean	4+5*	Mean	4+5*	Mean	4+5*	Mean	4+5*	Mean	4+5*	Mean	4+5**
Research														
Buccal swab	1.1	0	1.2	0	1.0	0	1.1	0	2.2	12	1.0	0	1.3	12
MRI	1.8	5	1.4	1	1.1	0	1.3	0	1.7	5	2.3	19	1.6	21
Pulmonary function test	1.2	0	2.1	11	1.2	0	1.0	0	2.6	22	2.4	11	1.8	33
Skin prick test	1.6	3	1.4	1	1.3	0	1.2	0	1.3	1	1.3	1	1.3	7
Ultrasound imaging	1.5	5	1.4	3	1.1	0	1.2	0	1.7	7	1.2	1	1.4	14
Venipuncture	1.9	6	2.1	6	1.9	0	1.5	6	1.8	3	1.3	0	1.7	9
Clinical care														
Dentist check-up	1.6	0	1.6	6	1.4	0	1.2	2	2.0	8	1.5	2	1.6	10
MRI	1.8	0	2.4	19	1.5	0	1.3	0	3.1	44	2.4	13	2.1	63
Pulmonary function test	1.2	0	1.4	0	1.2	0	1.1	0	1.9	5	1.4	0	1.3	5
Ultrasound imaging	1.4	0	1.7	0	1.7	4	1.0	0	1.8	8	1.3	0	1.5	12

* Percentage of children that answered 'very' or 'extremely' on a question ** On at least one discomforting aspect

Potential influencing factors

There was no significant correlation between age and discomfort (p = 0.31), and discomfort and anxiety-proneness, measured with the STAI-C (p = 0.08) and CBCL (p = 0.22). There were no significant differences in discomfort between healthy children and children with a chronic condition (p = 0.78), boys and girls (p = 0.89), and children who had a previous experience or children who underwent the procedure for the first time (p = 0.31). Regarding the multivariate analysis, anxiety-proneness appeared to be significantly related to discomfort (β = 0.305, p < 0.001). The total model was significant, although it only explained 11.5% of the variance of discomfort.

Small differences were found between the experiences of children in research and clinical care. Children reported slightly more discomfort when undergoing a pulmonary function test for research purposes than for clinical care (mean = 1.8 versus mean = 1.3, p = 0.01). Undergoing an MRI-scan for research purposes caused less discomfort than for clinical care (mean = 1.6 versus mean = 2.1, p < 0.001). No significant difference was observed for ultrasound imaging (mean = 1.4 versus mean = 1.5, p = 0.20).

Table 4. Suggestions to reduce discomforts

Suggestion	Number of children	Percentage (%)
(Distraction total)	(192)	(62.6)
- Movie	185	60.3
- Music	1	0.3
- Small talk	2	0.7
- Other form of distraction	4	1.3
Less noise (MRI)	24	7.8
Fewer physical sensations	11	3.6
Warm gel (echoscope)	4	1.3
Warmer room temperature (MRI)	3	1.0
Shorter duration	1	0.3
Receiving present	1	0.3
Other	11	3.6
No suggestion	60	19.5
Total	**307***	**100.0**

* Only children in clinical research

DISCUSSION

This is the first large-scale study investigating children's self-reported discomfort during research procedures. It is in line with the trend of actively involving children in expressing their experiences in medical and research situations. Our study shows that children experienced limited discomfort during the studied research procedures. Although chil-

dren came from diverse backgrounds, the variation in their answers was limited, which supports the idea that our findings are generalizable.

Although the studied research procedures may not be the most invasive ones, it is important to have actual data on the discomfort children experience during these research procedures rather than making assumptions. Besides, research shows that there are significant differences in the evaluation of discomfort of some of these research procedures among IRB members,[21, 22] which supports the importance of self-reported data by children.

Looking at the different forms of discomfort, it is remarkable that the scores of the children in our study on being bored and tired are higher than the scores on the other forms of discomfort. Although a boring or tiring research procedure may not be considered by IRBs as unacceptable, these are important forms of discomfort for children and can be a reason for them to refuse undergoing this procedure (in the future). For this reason, we believe it is important that these forms of discomfort are explicitly taken into account when evaluating discomfort by IRBs.

In several ethics codes and guidelines, minimizing discomfort is a requirement for pediatric research.[23, 24] According to the majority of the children in our study, distraction can help to achieve this. Distraction is proven to be (cost-)effective in reducing discomfort during medical procedures in children of all ages.[25-30] While children preferred to be distracted by movies, during some procedures, it may be more feasible to distract children by providing music, toys, or decoration on walls and ceilings.

Strengths and limitations

The outcomes of this study can help to establish benchmarks for the discomfort of research procedures in children, and thereby assist IRBs, pediatric researchers, parents and children in their estimation of the acceptability of the research procedures for participation. Other strengths of the study are the multi-site enrollment for generalizability; the large number of children in some of the procedures; the comparison with a common 'everyday' medical procedure (i.e. a dental check-up); the use of a specifically developed questionnaire to measure different forms of discomfort (CDRPQ); and the suggestions for reducing discomfort.

As we were dependent on the participating studies, we were unable to include the intended number of children for some procedures, because fewer children took part in these studies than expected, or were included at a later stage than initially planned. This has reduced the power of the outcomes of some research procedures (e.g. pulmonary function tests). On the other hand, the power of the outcomes of other procedures was enlarged because more children were included than planned (e.g. MRI-scans). Because of limited variation in children´s discomfort, we expect that our findings are generalizable.

We used different groups of children to compare discomfort in clinical research with dental check-ups. A design with paired measurements from the same child might have given a better estimation.

Furthermore, the degree of discomfort may be relative to the presence of other research procedures the children underwent in the studies. As there was little variation in their ratings of discomfort, we assume that the other research procedures did not have much influence on children's reports.

All children included in our study assented to undergo the research procedures, which is why our study might be hampered by a selection bias (Note: this is applicable to many pediatric studies). It may be possible that highly anxious children declined to undergo the research procedures because of expected discomfort or anxiousness, or that they may not have been asked to participate for this reason. The fact that we did not have to exclude children with anxiety-disorders (i.e. one of the exclusion criteria) nor that children did have high scores on the anxiety-proneness measures, supports this. The findings of this study therefore cannot just be generalized to children in clinical care.

Future research

For generalizability, future research should include larger numbers and more heterogeneous groups of children, in particular during pulmonary function tests. Future research is also needed to describe children's discomfort during other (more invasive) research procedures. We therefore recommend pediatric researchers to include measures in their studies (e.g. CDRPQ) to investigate discomfort related to the research procedures involved, and also disseminate these results (Note: recently in the Netherlands an addition to the law on research participation was accepted which requires to define and monitor discomfort in pediatric research (parliamentary meeting of October 25th, 2016). [https://www.eerstekamer.nl/wetsvoorstel/33508_verrichten_van_medisch]).

For IRBs and pediatric researchers who evaluate the level of discomfort of (non-therapeutic) research procedures, it is important to know which research procedures involve minimal, a minor increase over minimal discomfort, or more than minimal discomfort. Unfortunately, there are no clear guidelines for this. Future research - in which IRBs, pediatric researchers, children and their parents are consulted - is therefore needed to determine cut-off levels for this.

Conclusion

Our findings support the acceptability of participation of children in the studied procedures for research purposes because children experienced limited discomfort. The results are an important first step in providing benchmarks for discomfort of research procedures in pediatric research, and contribute to the evidence-based evaluation of discomfort in research.

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APPENDIX A. CHILDREN'S DISCOMFORT DURING RESEARCH PROCEDURES QUESTIONNAIRE (CDRPQ)

1. Were you nervous while undergoing procedure X?
¤ I was **not** nervous
¤ I was **slightly** nervous
¤ I was **somewhat** nervous
¤ I was **very** nervous
¤ I was **extremely** nervous

2. Was procedure X annoying?
¤ Procedure X was **not** annoying
¤ Procedure X was **slightly** annoying
¤ Procedure X was **somewhat** annoying
¤ Procedure X was **very** annoying
¤ Procedure X was **extremely** annoying

3. Was procedure X painful?
¤ Procedure X was **not** painful
¤ Procedure X was **slightly** painful
¤ Procedure X was **somewhat** painful
¤ Procedure X was **very** painful
¤ Procedure X was **extremely** painful

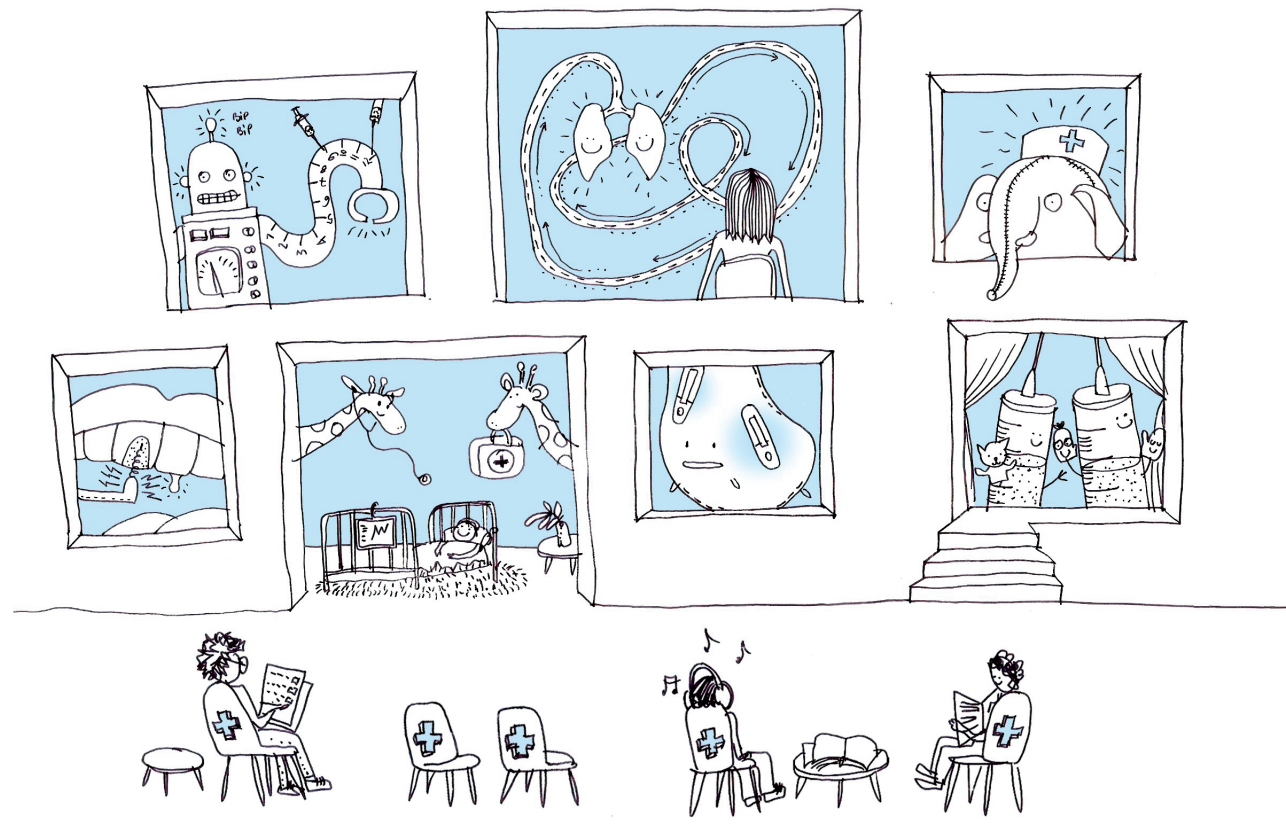
4. Were you frightened while undergoing procedure X?
¤ I was **not** frightened
¤ I was **slightly** frightened
¤ I was **somewhat** frightened
¤ I was **very** frightened
¤ I was **extremely** frightened

5. Were you bored while undergoing procedure X?
¤ I was **not** bored
¤ I was **slightly** bored
¤ I was **somewhat** bored
¤ I was **very** bored
¤ I was **extremely** bored

6. Did you find procedure X tiring?

¤ It was **not** tiring
¤ It was **slightly** tiring
¤ It was **somewhat** tiring
¤ It was **very** tiring
¤ It was **extremely** tiring

7. Do you have any suggestions for making procedure X **less annoying**?

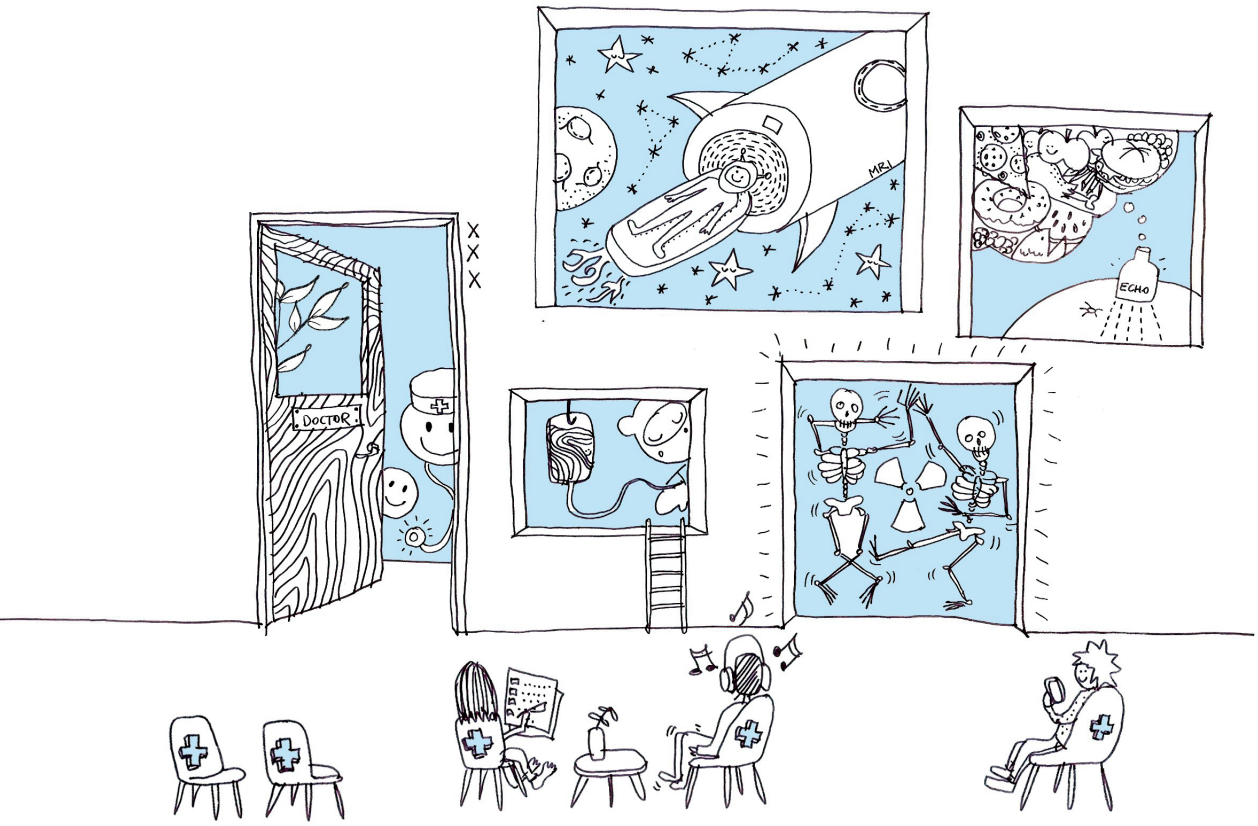


CHAPTER 6.

The risk of children on clinically relevant stress due to research procedures

MS Staphorst, JAM Hunfeld, R Timman, J Passchier,
JJV Busschbach, JB van Goudoever

Submitted



ABSTRACT

Objectives. We exploratively studied children's long-term clinically relevant stress due to research procedures. We also explored whether age, anxiety-proneness, discomfort during research, gender, and medical condition were related to traumatic stress symptoms.

Methods. We enrolled 100 children (8-18 years). The research procedures that children underwent were buccal swabs, MRI-scans, pulmonary function tests, ultrasound imaging, or venipunctures. We used the Children's Revised Impact of Event Scale (CRIES-13) to measure stress symptoms. A score of ≥30 on the CRIES-13 was seen as clinically relevant stress.

Results. None of the children showed clinically relevant stress, except for one who underwent a venipuncture. Discomfort during research procedures, anxiety-proneness, and being a girl were significantly related to stress symptoms.

Conclusions. We cautiously conclude that for the studied procedures, Institutional Review Boards (IRBs) do not need not be concerned about clinically relevant stress, since our study reveals that is it largely absent.

INTRODUCTION

One of the conditions of pediatric research is that the risks are acceptable in relation to the benefits (i.e. in the case of therapeutic research), or should be minimal (i.e. in the case of non-therapeutic research). Study risks can be categorized into five categories: physical, psychological, social, legal, and economic risks.[1] The risk estimation by ethics committees of clinical research is primarily based on the potential physical harm.[2] While research participation typically does not pose economic, legal, or social problems to children, it can pose psychological risks.[2] Psychological risk can be operationalized in various ways and is not acceptable in clinical research if it involves clinically relevant stress, meaning a psychological state for which professional help is needed. Studies on stress in routine pediatric care show that medical procedures can cause fear, phobia and sometimes even trauma in children, which in turn may lead to medical non-adherence and treatment refusal.[3-6] In a recently published review, stress in relation to pediatric medical traumas was defined as "a set of psychological and physiological responses of children and their families to pain, injury, serious illness, medical procedures, and invasive or frightening treatment experiences".[7] This review indicates that research in pediatric medical situations has grown significantly, but this does not hold for studies looking at stress due to research participation. It is important to specifically have data on stress symptoms in pediatric research rather than generalizing data from pediatric clinical care because children in research differ from children in clinical care settings. Children in clinical research, who generally do not benefit from the study, make a deliberate decision for participating in clinical research, while children in clinical care often have no choice for undergoing medical procedures. Therefore a selection takes place in which the most vulnerable children generally will be excluded from clinical research.

Several articles discuss the psychological risks of research participation,[e.g. 2, 8] but self-reported data on the psychological risks of research on children are rare,[9] particularly on long term risks. We only noted one small study that investigated the psychological impact of clinical research (examination for sexual development, intravenous insertion, blood draws and staying overnight in the hospital) on children.[10] Approximately 10% of children were advised not to participate due to expected proneness for stress symptoms; none of the other children exhibited psychological problems after participating.

In this explorative study, we studied if children are at risk for clinically relevant stress in pediatric research one month and one year after undergoing a medical research procedure, using self-reported data on (long-term) stress symptoms. We explored whether age, anxiety-proneness, discomfort children experienced during the research procedure, gender and medical condition were related to clinically relevant stress symptoms.

METHOD

Participants

Data were collected as part of a study regarding children's discomfort during medical research procedures.[11] To be eligible, children had to be a) between 8 - 18 years old, b) fluent in Dutch, c) without current psychological treatment for pain or anxiety disorders, d) without severe psychosocial problems such as anxiety disorders and depression at the time of enrollment of the initial study, and e) accompanied by at least one parent or caretaker. We enrolled both children with and without a known illness. Children were recruited between March 2014 and June 2015 from research studies at three academic hospitals in the Netherlands.

Procedure

Written parental consent and child assent (≥ 12 years) were obtained. Children younger than twelve years orally agreed to participate. Children filled in two questionnaires directly after undergoing a research procedure: 1) Children's Discomfort during Research Procedures Questionnaire (CDRPQ) and 2) State-Trait Anxiety Inventory for Children (STAI-C). Parents provided demographical information.

Parents received an email for their child after a one-month period. We could only send this email to a subsample due to possible interference with the outcomes/logistics of some of the medical research studies on which our study was 'piggybacked'. This email contained an online link for the child to complete the Child Revised Impact of Event Scale (CRIES-13)[12] for measuring long-term clinically relevant stress symptoms related to the research procedure. For evaluating stress symptoms after one year, we included an additional group of children one year after they underwent a research procedure. All children received a gift card (€7.50) after completing the questionnaires, which was sent to their home. We removed both email and personal addresses afterwards.

Measures

Children's Revised Impact of Event Scale (CRIES-13)

Clinically relevant stress due to research procedures was measured by the Dutch version of the CRIES-13,[12] which is a child's self-report scale about the frequency of event-related (traumatic) distress. The CRIES-13 consists of 13 items that are rated on a 4-point Likert scale: 0 = 'not at all', 1 = 'rarely', 3 = 'sometimes', 5 = 'often'. The total score can range from 0 to 65. When a child has a total score of 30 or above on the CRIES-13, this child is considered to have clinically relevant stress symptoms.[13] The CRIES-13 demonstrates satisfactory to good psychometric characteristics.[14] It has good internal consistency for the total score (Cronbach's $\alpha = 0.80$).

Children's Discomfort during Research Procedures Questionnaire (CDRPQ)
Discomfort during the research procedure was measured using the CDRPQ. The CDRPQ contains questions about six different forms of discomfort (nervousness, annoyed, pain, fright, boredom and tiredness), which are measured using 5-point Likert scales ranging from 1 = 'not discomforting' to 5 = 'extremely discomforting'. An average discomfort score can be calculated with these six forms of discomfort. The CDRPQ was developed based on literature, interviews with children about discomfort in clinical research,[15] and in consultation with pediatricians, ethicists, psychologists, nurses and parents from patient associations. The CDRPQ was well received by the children. Convergent validity and test-retest reliability were acceptable.[16]

State-Trait Anxiety Inventory for Children (STAI-C)
We measured anxiety-proneness by the trait scale of the Dutch translation of the STAI-C.[17, 18] The STAI-C is a valid questionnaire, which measures state and trait anxiety. The trait scale addresses the frequency and intensity of anxiety symptoms in general, and consists of 20 items, e.g. *"I worry about school"*. The higher the scores on this scale, the more children tend to interpret situations as threatening. There is no official cut-off score for the STAI-C. In a Dutch norm population the STAI-C trait scale has shown good internal consistency (Cronbach's $\alpha > 0.80$) and acceptable test–retest ($r > 0.65$).[17]

The STAI-C is used for children between 8 - 15 years. We also used this questionnaire for older children (16 - 18 years) as it has been suggested that the child-version may be more useful for adolescent populations than the adult version (STAI), given that even older adolescents may have difficulty understanding some of the vocabulary of the adult version.[19] Literature shows that the Dutch version of the STAI-C is reliable and valid for adolescents between 12 - 18 years old.[20]

Medical research procedures

We measured clinically relevant stress in children in relation to five medical research procedures: buccal swab test, MRI-scan, pulmonary function test, ultrasound imaging and venipuncture. An elaborate description of the procedures is described elsewhere.[11] The research procedures were selected on the following criteria: no general anesthesia, pediatric healthcare professionals we consulted found that it possibly caused discomfort, and the availability of research procedures in the cooperating hospitals during the time frame of our study. Almost all children underwent the research procedures for non-therapeutic research purposes, except for pulmonary function tests and some of the venipunctures.

Statistical analysis

The data were analyzed using SPSS version 21. As the data were skewed, we used non-parametric statistics. We determined the medians, interquartile ranges, and percentage of children who had clinically relevant stress (≥ 30 on the CRIES-13). We conducted a Kruskal-Wallis test respectively a Mann-Whitney U test to measure whether differences exist in stress symptoms between the different research procedures after one month respectively after one year. Spearman correlations were calculated between age, anxiety-proneness, and discomfort on the one hand and stress symptoms on the other hand. Discomfort was measured using the average discomfort score of the CDRPQ. Mann-Whitney U tests were used to evaluate differences in stress symptoms between children with and without an illness, and between boys and girls. A multivariate regression analysis was conducted to measure the variance explained in stress symptoms by age, anxiety-proneness, discomfort, gender, medical condition (with or without having a medical condition), and the time of measurement (one month versus one year after undergoing a research procedure). As stress symptoms scores had a non-symmetrical distribution, a log-transformation was applied first.

Ethical approval

The Institutional Review Board of the VU University Medical Center in Amsterdam (the Netherlands) evaluated this study and indicated that there was no risk or discomfort associated with it (2014/010) and stated that the study was exempt from getting approval under Dutch Law.

All parents and children older than eleven years who agreed to participate gave informed assent/consent for their participation and were aware that their data would be used for research purposes. Children younger than twelve years old verbally agreed to participate.

RESULTS

Participants

A total of 100 children were included in this study. 66 children completed the CRIES-13 one month after undergoing a medical research procedure, and an additional group of 34 children filled out the CRIES-13 one year after undergoing an MRI-scan or venipuncture for research purposes. The children's demographics are described in Table 1.

Table 1. Demographics and characteristics of the children

Demographics	After one month (N=66)	After one year (N=34)
Age (8-18 years)		
Mean ± SD	12.4 ± 2.7	12.4 ± 2.3
< 12 years	35 (53%)	20 (58.8%)
≥ 12 years	31 (47%)	14 (41.2%)
Gender (%)		
Boy	35 (53%)	24 (70.6%)
Girl	31 (47%)	10 (29.4%)
Research procedure		-
Buccal Swab	21 (31.2%)	17 (50%)
MRI	13 (19.7%)	-
Pulmonary function test	6 (9.1%)	-
Skin prick test	-	-
Ultrasound imaging	1 (1.5%)	17 (50%)
Venipuncture (without EMLA)	25 (37.9%)	
Previous experience with procedure	56 (84.8%)	10 (29.4%)
Child's medical condition		
ADHD/ADD	4 (6.06%)	-
Cystic Fibrosis	3 (4.5%)	-
Healthy	24 (36.4%)	34 (100%)
Inflammatory Bowel Disease	30 (45.5%)	-
Oncological condition	1 (1.5%)	-
Primary ciliary dyskinesia	3 (4.5%)	-
Other condition	1 (1.5%)	-
Trait-anxiety - STAI-C*		
Mean ± SD	29.2 ± 6.1	30.7 ± 6.4
Range	20-44	22-43

* STAI-C = State Trait Anxiety Inventory for Children

Clinically relevant stress symptoms (CRIES-13)

After one month (N=66)

The total scores on the CRIES-13 in this group varied between 0 - 29 (median = 6; IQ range = 2-11). None of the children showed clinically relevant stress symptoms (total score ≥ 30) related to the research procedures (Table 2). A Kruskal-Wallis test showed that there were no significant differences in stress symptoms between research procedures ($p = 0.166$).

After one year (N=34)

After one year, total scores on the CRIES-13 varied between 0 - 32 (median = 9; IQ range = 5.85-12) (Table 2). One child showed clinically relevant stress (score: 32) due to a venipuncture. A Mann-Whitney U test showed that children's stress symptoms did not differ between research procedures ($p = 0.986$).

Table 2. Medians and interquartile-ranges (IQ 25-75%) on the CRIES-13 after one month (N=66) and one year (N=34)

	One month	One year
Buccal swab	4 (1-6.5)	-
MRI-scan	4.3 (1.5-10)	9 (6-12)
Pulmonary function test	9 (3.25-17.25)	-
Ultrasound imaging	12	-
Venipuncture	7 (4-14)	9 (4.5-14)
Total	6 (2-11)	9 (5.85-12)

Potential influencing factors

As only one child had a clinically relevant stress score (CRIES-13 score ≥ 30), we describe the relation between several potential influencing factors and stress symptoms (instead of *clinically relevant* stress symptoms).

Anxiety-proneness was correlated with stress symptoms ($r = 0.426$, $p < 0.001$), indicating that more anxiety-prone children experience more stress symptoms. Spearman correlations showed a moderate relation between discomfort and stress symptoms ($r = 0.494$, $p < 0.001$) (Table 3), indicating that the more discomfort children experienced, the more long-term stress they experienced. Examining the individual questions of the CDRPQ (i.e. different forms of discomfort), Spearman correlations showed weak to moderate positive relations between nervousness, feeling annoyed, pain, fright, and being tired ($r = 0.257$ - 0.419; $p < 0.05$). Boredom was not related to stress. Mann-Whitney U tests showed significant differences in stress symptoms between boys and girls ($p < 0.001$), with girls having higher scores on the CRIES-13 than boys.

Spearman correlations showed no relation between age and stress (p = 0.929). Mann-Whitney U tests showed no differences in stress symptoms between children with and without a known illness (p = 0.769).

Table 3. Spearman correlations between discomfort (CDRPQ) and stress symptoms (CRIES-13) (N=100)

	Nervous	Annoyed	Pain	Fright	Bored	Tired	Average discomfort score
Total score CRIES-13	.419**	.365**	.257*	.360**	-.056	.314**	.494**

* p-value ≤ 0.05 ** p-value ≤ 0.001

Multivariate analysis

The regression analysis of the log-transformed CRIES-13 including the covariates age, anxiety-proneness, discomfort, gender, medical condition, and time of measurement had an R^2 of 35.1%. Discomfort experienced during the procedure (beta = 0.384, p < 0.001), anxiety-proneness (beta = 0.265, p = 0.005), and gender (i.e. being a girl) (beta = 0.225, p = 0.012) were significant and unique indicators of stress symptoms.

DISCUSSION

This is the first study to explore long-term clinically relevant stress symptoms in children due to medical research procedures. Our study shows that clinically relevant stress from the studied research procedures is almost absent. As these research procedures were found to be associated with low discomfort,[11] these results did not surprise us. The positive relationship between discomfort during the procedure and long-term stress, and the results of the regression analysis in which discomfort appeared to be a good indicator for long-term stress, suggest that clinically relevant stress symptoms might be manifest as a result of more intrusive research procedures.

We found that more anxiety-prone children experience more stress symptoms, which is in line with previous studies.[e.g. 21] Studies in medical settings often found that younger children (i.e. younger than approximately eight years) experienced more pain, anxiety, and distress during medical procedures than older children.[22, 23] In our study, we did not find a relation between age and stress, which might be explained by the inclusion of relatively old children (> 8 years).

The research procedures appeared to cause more stress symptoms in girls than in boys. Other studies show that girls are more prone to posttraumatic stress than boys, while boys show behavioral symptoms.[24] Girls are also more likely to report physical and psychological symptoms than boys, which can be explained by girls experiencing more symptoms or being more aware of these symptoms than boys, who are less supposed to express their emotions as it might be considered a sign of 'weakness'.[25]

We found no relation between medical condition and stress symptoms, which suggests that children with a medical condition are not at higher risk for developing stress symptoms than healthy children (or vice versa).

Limitations and future research

A limitation of our study is the limited number of children in some research procedures, particularly during ultrasound imaging and pulmonary function tests. This is why we address this study as an explorative study. However, the limited variation in the reported stress symptoms indicates that the results are generalizable to other children undergoing these procedures in research settings. We therefore cautiously conclude that clinically relevant stress was largely absent as children reported relatively few stress symptoms.

As we only included children who had assented to undergo the research procedures, the study might be hampered by a selection bias (note: this applies to many research studies). It is possible that children who expect to experience stress symptoms did not participate in the research studies we cooperated with. Therefore, along with measuring clinically relevant stress symptoms caused by research participation, prescreening for expected psychological risk is also important. McCarthy et al. developed a screening protocol to identify children who are potentially at risk for stress symptoms during non-therapeutic research participation.[10] They identified that if trait-anxiety – which can be measured using the STAI[18] - is considered high (i.e. more than one standard deviation above the mean of the study population), potentially provoking experiences such as invasive medical procedures may cause harmful stress reactions in children. They stated that children who have high trait-anxiety scores should not participate in non-therapeutic research as it may put them in potential anxiety-provoking situations needlessly.

In this study, only one child was considered to have clinically relevant stress one year after undergoing a venipuncture. It should be noted that this stress might not be caused by the research procedure. For future research, we therefore recommend a shorter interval than one year to measure stress after research participation. We also recommend repeated measurements in the same child to see the development of the stress symptoms over a longer period of time.

We are aware that the research procedures in this study are not the most invasive ones, thus it is expected that almost no clinically relevant stress was demonstrated. Our study shows that there is a significantly positive relation between discomfort and long-term stress symptoms, which justifies future research on clinically relevant stress symptoms in children who underwent more invasive research procedures, such as lumbar punctures. Also, stress symptoms of younger children (< 8 years) and children with life-threatening medical conditions in clinical research should be investigated, as they may be more prone to clinically relevant stress.

Practical implications

The risk of clinically relevant stress symptoms from other (invasive) research procedures should be measured, and results disseminated by pediatric researchers, which in turn can facilitate IRBs' decision-making on (psychological) risk. It would therefore be helpful if IRBs recommend pediatric researchers to measure clinically relevant stress due to the research procedures of their studies, and disseminate the findings to other researchers, IRBs, and parents and children.

Since our study showed that discomfort is related to long-term stress symptoms for children, minimizing discomfort (which is mandatory in many codes and regulations on research participation) may decrease the risk on clinically relevant stress symptoms. Pediatric researchers can minimize discomfort by incorporating practical suggestions of the children themselves, which we provided in a previous study.[11]

Conclusion

We cautiously conclude that children in clinical research are not at risk for clinically relevant stress from the research procedures we investigated. As discomfort during research procedures and long-term stress symptoms were positively related, we recommend to investigate clinically relevant stress from more invasive research procedures.

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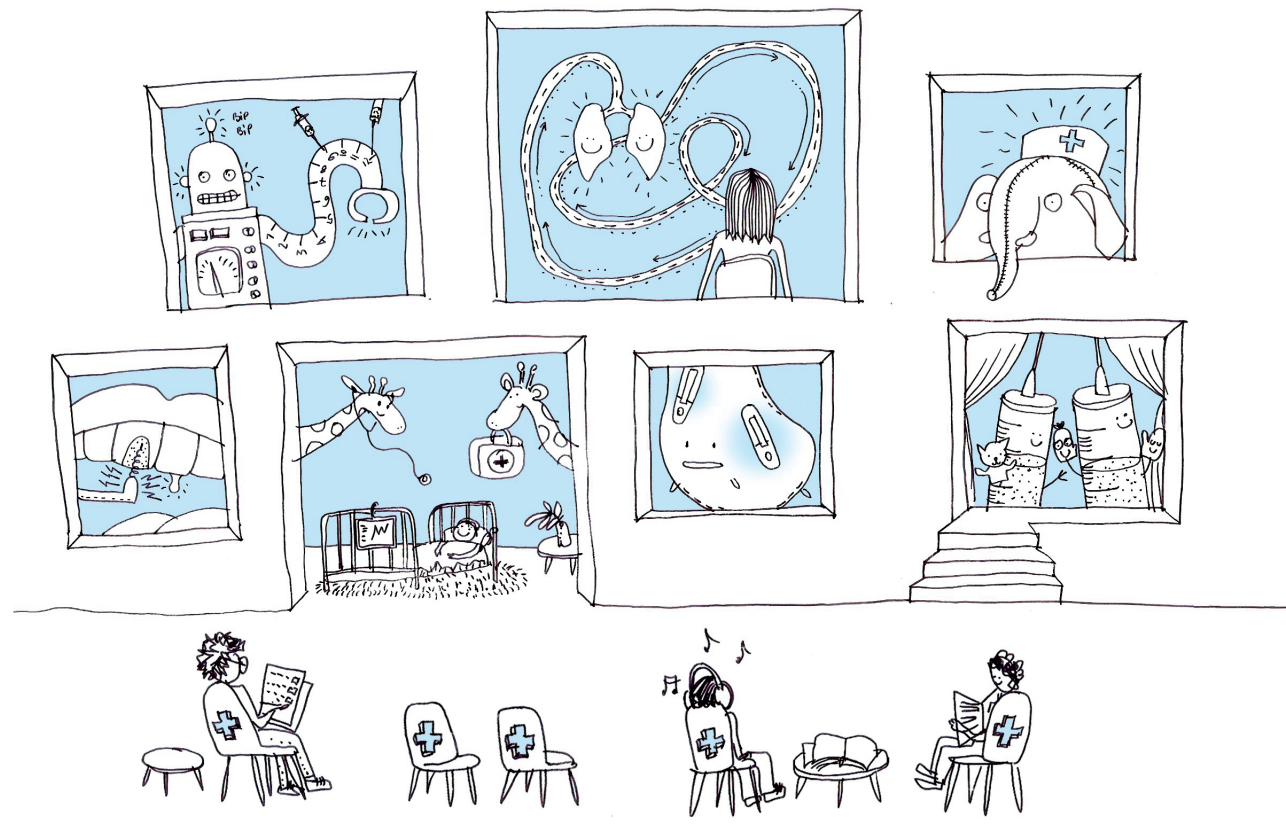

CHAPTER 7a.

Are positive experiences of children in non-therapeutic research justifiable research benefits?

MS Staphorst, JAM Hunfeld, S van de Vathorst

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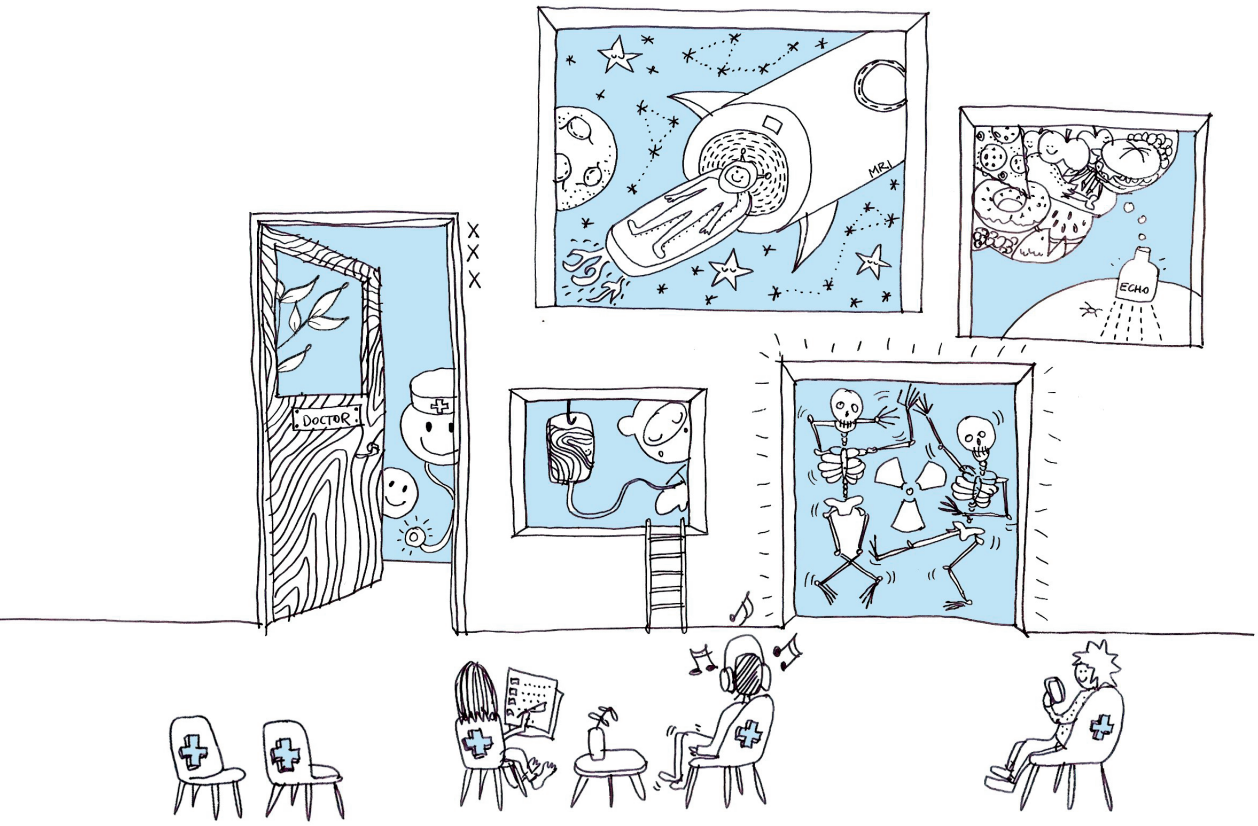

ABSTRACT

Background. Conducting non-therapeutic research is ethically challenging because participation conveys risks and burden and no health benefit. In this paper we report the positive experiences of a diverse group of healthy and ill children (6-18 years) who participated in non-therapeutic research studies, and discuss whether these positive experiences can justifiably be viewed as benefits.

Methods. We used semi-structured interviews from an earlier study about children's experiences in clinical research and did a secondary analysis on the positive experiences of the children in the non-therapeutic studies (N=30). Interviews were analyzed using 'thematic' analysis.

Results. The interviewed children most frequently mentioned as positive experiences of non-therapeutic research participation: helping others and the gratification that comes with it, possible health benefits in the future, having fun, and new/increased knowledge about the human body, hospitals, and doing research. Less frequently mentioned were getting a present, not having to go to school and getting extra attention from health-care staff.

Conclusion. Our study shows that children participating in non-therapeutic research have various positive experiences while taking part. We argue that some of these justifiably could be taken into the risk-benefit analysis in certain situations, or maybe even as a standard part of this analysis. This may help to increase the number of (crucial) non-therapeutic studies with children.

INTRODUCTION

Next to therapeutic research, non-therapeutic research is also necessary to improve healthcare for children. However, conducting non-therapeutic research is ethically challenging because children may experience burden and risks when participating, and these are not balanced by health benefits. Most guidelines and regulations therefore state that non-therapeutic studies are only acceptable if they convey minimal burden and risk.[1-3] The debate on the risk-benefit analysis in pediatric research primarily focuses on the degree and nature of both burden and risk. During our study on the experiences children have during their participation in research, we stumbled upon the fact that children who participate in non-therapeutic research also report many positive experiences. Can these positive experiences be seen as a benefit, to be weighed in the risk-benefit analysis of study protocols? If so, this could tip the scale. In the absence of benefits, risk and burden weigh heavily, but in relation to (certain) benefits they may be acceptable.

Almost fifteen years ago King argued that there should be a clearer description and definition of benefits in research because of the misconception about what a constitutes a benefit in clinical research.[4] According to King three categories of benefit can be identified: 1) direct benefit (i.e. health or medical benefit from receiving the intervention being studied), 2) collateral benefit (i.e. benefit from being in a study, e.g. a free physical exam, free medical care, personal gratification of altruism) and 3) aspirational benefit (i.e. benefit to society and to future patients, which arises from the results of the study).[4] However, in practice these distinctions are probably not applied. In a study into the appreciation of benefit by Institutional Review Boards (IRBs), it was shown that about 60% of the IRB chairpersons considered added psychological counseling that was not necessary for research purposes, to be a direct benefit.[5] Ten percent of the IRB chair respondents even considered participant payment as a direct benefit of research. This leads to the question, also raised by Cave,[6] whether in addition to medical benefits, non-medical benefits (e.g. social, economic and emotional benefits) can qualify as direct benefits?

Few studies investigated the benefits children experience during research participation.[7-10] These studies primarily focused on the quantitative measurement of benefits. Although they give important information on the percentages of children that experience a certain benefit, these studies give limited insight into the variety of children´s benefits. Recently, Luchtenberg et al. conducted a qualitative study on the benefits adolescents experienced during their participation in clinical trials.[10] The adolescents in their study positively valued helping others (e.g. future patients, their doctors and parents) and experienced personal benefits (e.g. improved health). Their study provides important additional information to the quantitative data of previous studies. Their study however primarily focused on adolescents in therapeutic studies. In this report we give insight into the positive experiences of a more diverse group of children (healthy and ill children

between 6 and 18 years) that participated in non-therapeutic research studies, and we will discuss whether these positive experiences can justifiably be viewed as benefits that can be taken into account into the risk-benefit analysis of IRBs in non-therapeutic research.

MATERIALS AND METHODS

Subjects

For this paper, we used a subsample of the interviews from an earlier study on children's discomforts in clinical research.[11] We purposefully selected a broad range of children (in age and medical condition) undergoing various types of medical research procedures to assure a wide range of experiences, influences and attitudes.[12] The children were enrolled until saturation was reached, i.e. until no new topics related to children's experiences were mentioned during the interviews.[13] For this analysis on the positive experiences, we only used the interviews of the children in the five non-therapeutic studies (mostly observational studies).

Procedure

The researchers of the cooperating studies first informed parents and children about our interview. Parents and children also received an information letter. Parents and children had an opportunity to ask questions about the interview in a face-to-face conversation with the interviewer, which was prior to the start of the study on the day of the child's research visit. If willing to participate, written parent consent and child assent (children ≥ 12 years) were obtained. Children younger than twelve years verbally agreed to participate. All children received a gift card (€7.50) after the interview.

Interviews were conducted in a private room at the hospital, directly after the children's participation in the research studies by the first author (MSS), who has a degree in health psychology and was trained in interviewing children. Parents were present during most interviews, although they were kindly requested not to intervene in the interviews as the focus was on the child's perspective.

Instruments

The interviews were semi-structured and were focused on discomfort during clinical research. We also asked the children about general experiences during the studies. We did not specifically ask about positive experiences; children spontaneously mentioned these. The interview schedule can be found in Appendix A.

Data analysis

Audiotaped interviews and field notes were transcribed verbatim. After initial transcription by trained 3rd year psychology students, the first author (MSS) checked the transcripts for accuracy and analyzed the data using NVivo 10.0. For this report, we did a secondary analysis on a subsample of the interviews and specifically looked at children's positive experiences during non-therapeutic research participation. We used 'thematic analysis' to identify themes related to positive experiences.[14] The supervising author (SvdV) independently analyzed a third of the interviews to ensure agreement on the coding. Note: for additional information on the children and methods we used, we refer to the initial article.[11]

RESULTS

Participants

For this paper, we used the interviews of 30 out of a total of 46 children. These 30 children (6-18 years; mean=11.9 years) participated in non-therapeutic research studies; the other 16 children all participated in therapeutic research. Among them were both children with mild or severe chronic conditions (60%), and healthy children (40%). An equal proportion of girls and boys participated: 15 girls and 15 boys. A description of the children is provided in Table 1.

Positive experiences

All children mentioned positive experiences, and we categorized these into seven different types. Most frequently mentioned were 'helping other children' and the gratification that comes with it; having fun; (future) health benefits; and gaining new knowledge. Other, less frequently mentioned positive experiences were receiving a present; not having to go to school; and getting attention from healthcare staff and researchers.

Helping other children (altruism)

Children, and in particular the children with a severe chronic condition, frequently reported that they think it is important to help other children (with the same medical condition) to get better treatments in the future. *"I don't benefit from it myself […] for me it's important that other children can benefit from it, that they can get the right medicines immediately and that they can live a normal life and in good condition […]. If it helps other children to suffer as less as possible, then for me it's no issue to participate"* **(girl #4)**. Through helping others by participating in research, children reported to feel good about themselves *"It gives you a good feeling when you participate"* **(girl #31)**.

The interviewed children for whom the research procedures and their normal care could be combined (e.g. extra blood samples, couple of minutes extra in the MRI for re-

Table 1. Description of the children in non-therapeutic research

ID*	Gender	Age in years	Health condition
01	Girl	7	IBD**
02	Boy	6	Healthy
03	Girl	6	Healthy
04	Boy	17	IBD
05	Boy	8	IBD
06	Boy	6	Healthy
07	Boy	17	IBD
08	Boy	6	Healthy
09	Girl	11	Asthma
12	Boy	14	IBD
13	Boy	15	IBD
16	Girl	17	IBD
19	Boy	6	Asthma
22	Girl	8	Asthma
27	Girl	11	IBD
29	Girl	16	IBD
31	Girl	16	Asthma
32	Boy	13	Healthy
33	Girl	12	Healthy
35	Boy	17	IBD
36	Boy	12	Healthy
37	Girl	6	Healthy
38	Girl	12	Healthy
39	Boy	15	Healthy
40	Girl	15	IBD
41	Girl	12	Healthy
43	Girl	12	Asthma
44	Boy	12	Healthy
45	Girl	16	Asthma
46	Boy	16	Asthma

* ID: Identification number of the initial study
** IBD: Inflammatory Bowel Disease

search purposes), said the researchers made it very easy for them to help others because it took minimal effort and time "*It only takes five extra minutes in the MRI. Why wouldn't I participate if I may help someone else? It takes minimal effort and for others it may be helpful"***(boy #12)**.

Having fun

Many children mentioned 'having fun' during the research procedures, in particular the pulmonary function tests, MRI-scans, measuring blood pressure, and the cognitive capacity tests (Wechsler Intelligence Scale for Children, WISC) *"There was a game I had to do [one of the tests of the WISC]. You get different cards and you have to make a story with these [...]in the right order as fast as you can. I found that the most fun part [of the study]"***(boy #32)**. Children particularly enjoyed the research procedures that were framed as a game. For instance, during the pulmonary function test, children had to blow as hard as they could in order to virtually blow up a balloon *"It [the cognitive test] has a scientific objective, but it was really fun to do!"***(boy #32)**. The children who mentioned the MRI as fun said it was because it was exciting to them, and/or because they could listen to music or watch a movie.

Future health benefits

The majority of the chronically ill children positively valued possible health benefits in the (near) future. They hoped that better medicines were found, or that there will be increased knowledge about their diseases, so that they could benefit from these developments in the future *"Well, if they find a better medicine by doing research, I'll help others and maybe myself too"***(girl #29)**. Additionally, the children indicated that they would like to know in detail how the results of the study can be used in the future. Some children reported that they considered having an extra medical check-up as a benefit of participating in research.

New or increased knowledge

About half the children, the healthy ones in particular, mentioned they enjoyed learning something about their physical and/or cognitive capacities, for instance how well their lungs work by undergoing pulmonary function tests or what level their blood pressure is. In most of the research studies, the children and parents received the individual outcomes of research procedures, such as the test results on the pulmonary function test. The healthy children who underwent an MRI also received a picture of the child's head.

A couple of children were interested in learning about hospitals, the medical procedures, healthcare staff and doing research *"I like to see what they [healthcare staff at the pediatrics department] are doing (…) because I want to become a pediatrician myself"***(girl #38).**

Receiving a present

Most children received some kind of present after their participation (e.g. crayons, coupon for the movies). The majority indicated that they very much appreciated this present, although they it was not an incentive for them to participate. In one study, the

parents of the children received money for their participation. The parents of one of the children promised their child that he could have the money. The child indicated that this was the most important reason to participate.

Not having to go to school

A couple of children, in particular the healthy children and children with a mild chronic condition, mentioned that they would rather participate in research than go to school *"Tuesday is an annoying day at school. I'd rather do this"***(boy #32)**.

Getting attention

A few chronically ill children mentioned getting (extra) attention from healthcare staff as something positive. The children who explicitly mentioned that the research team was friendly were in general more positive about the study they participated in than children who did not mention whether they liked the research team.

DISCUSSION

Our study shows that children (6-18 years) participating in non-therapeutic research have various kinds of positive experiences. We argue that three of these (learning, altruism and fun) can be justifiably qualified as benefits of research participation and can (conditionally) be used in a risk-benefit analysis. Exclusive focus on the potential risk and burden of participation tends to ignore the positive effects of participation, which our study shows is an important aspect for children. In general, researchers can sometimes be overly cautious when including vulnerable populations in their research because they think it will only burden them, while in fact these patients positively value the opportunity to contribute to society.[15, 16]

In our opinion, learning about yourself, medical procedures and/or doing research should certainly count as a benefit. A study that adds to children's knowledge of the human body/medicine is 'better' than one in which children do not experience this. Previous research also shows that children want to be actively involved in research and are interested in the results of a study.[10] We think learning something from participation (e.g. about science, biology or the human body) is a justified benefit that should be maximized. We therefore concur with Wendler's view that educational benefits can justify non-therapeutic pediatric research.[17]

We also think that 'helping other children' is acceptable as a benefit for children as it indicates an altruistic attitude, which we value positively. Altruism has been documented in previous studies about the experiences of children in (non-therapeutic) pediatric research,[7-9, 18] and should be an important motivation for participating in any research (therapeutic and non-therapeutic). Adolescents (≥12 years) and chronically ill children

frequently mentioned altruism, and some younger children with a chronic condition also mentioned altruism. According to Piaget's formal operations stage, children aged 12 or over are able to understand ethics and morals, and would therefore be inclined to mention altruism.[19] The younger children in our study who mentioned helping others as a positive experience, may be influenced by their parents.[20] However, young children with a (chronic) illness may be more mature than their healthy peers concerning aspects of healthcare, and therefore show altruism in medical situations at an early age.

Having fun, which was mentioned in particular by the healthy children, can be seen as a benefit because it improves the experience of children in research. If children's experiences improve, children may be more likely to participate in future research, which in turn may increase participation rates.

However, not all the reported positive experiences are desirable benefits or even acceptable as a benefit from an ethical perspective. The benefit of 'getting extra attention from healthcare staff' is dubious from a moral viewpoint. Adults and children may feel that by participating in research they get attention they would otherwise not have received from the healthcare staff, but this should not be the case. Care should be taken to ensure that routine clinical care is sufficiently attentive and that there is no need for patients to feel that only participation in research would give them the care they need. We also regard receiving a present or money as a dubious benefit, especially when it is the primary benefit for participating. It could tempt researchers to give the child more money as compensation for a higher risk and burden level of their study.[21] However, giving a small present as a token of appreciation may be acceptable, particularly if children do not know this beforehand. This small gift may help children feel appreciated. Researchers however should make sure that the incentive is not the overriding reason to participate and it should never compensate for risk.

The future benefits that the children mentioned can be regarded as 'hope'. In previous research, hope for (future) health benefits is often mentioned as a motivation or benefit of non-therapeutic research participation.[10, 22] Hope can be interpreted as therapeutic misconception (i.e. blind optimism),[23] or as therapeutic optimism (i.e. hope that does not result in despair).[24] Based on the interviews, we assume that this hope for future health benefits can be categorized as therapeutic optimism, however, this is an assumption and we do not know whether it may be (mixed with) therapeutic misconception. Although therapeutic optimism may be a reasonable and balanced form of optimism, we think 'hope' should not be incorporated into the risk-benefit analysis because there is a thin line between a therapeutic misconception and therapeutic optimism, and it may not be obvious which form of hope is experienced.

Should positive experiences be seen as benefits in all studies?

Knowing that children may experience (non-medical) benefits, and that the expectation of these benefits might and should motivate them to participate is one thing. The appreciation of the positive side effects of research participation is in those cases a strictly personal choice. However, before they can make this choice, IRBs have to do a risk-benefit evaluation in order to decide whether the study as a whole is acceptable (and therefore open for individual appraisal by parents and children). That is an entirely different matter. Should IRBs take possible benefits into account, and weigh these against the risks and benefits of non-therapeutic studies? We propose two scenarios.

Scenario 1. Only in certain situations non-medical benefits should be taken into account

Research by Westra et al. shows that ethics committees can struggle with the minimal risk/discomfort threshold, and sometimes allow more than minimal risk/discomfort in studies that formally should be rejected.[25] This is particularly the case when the studies are thought to be crucial, but the risks and burden are expected to be slightly above minimal. Weighing certain non-medical benefits in these situations can help to make exceptions for these crucial studies. The non-medical benefits could then be the factors tipping the balance to a favorable risk-benefit ratio. Including these benefits also helps to make the evaluation more transparent. Please note that the benefits we deem acceptable are classified by King as collateral or aspirational benefits.[4] We thus accept that certain collateral and aspirational benefits are, in these exceptional cases, weighed into the risk/benefit analysis.

Scenario 2. Non-medical benefits should always be taken into account

This would be a more general approach. The advantage of always taking into account certain non-medical benefits, is its simplicity: no need to decide whether in this particular case this is acceptable or not. Another argument in favor of this, is the fact that these non-medical benefits are, if present, always experienced by the research participant him/herself, and are not - as is mostly the case with medical benefits - a benefit for a future child. The downside is that less crucial research, entailing more than minimal burden or more than negligible risks might be justified by these non-medical, and non-direct benefits. In fact this implies that the distinction between medical and non-medical (collateral or aspirational) benefits becomes vacuous.

For both scenarios, there are several other considerations to take into account. Similar to the medical benefits, non-medical benefits cannot be guaranteed. In addition, the benefits are not applicable to all children. Children need to have the cognitive capacity to experience these benefits, which we estimate to be from approximately six years onwards (assuming that the child has no cognitive or psychological problems). Although we cannot draw any conclusions about differences between healthy and ill

children based upon our empirical work, it is likely that some positive experiences/ benefits are more important for certain groups of children, and less important for others. It might be argued that, once these groups are identified based on firm quantitative research, IRBs could and should take different benefits into account for different groups of participants. The same goes for different types of research studies. For instance, in non-therapeutic studies in ill children, altruism (and future benefits) are of importance, while in non-therapeutic research with healthy children 'increased knowledge' and 'having fun' may play a more important role. We therefore have a preference for the first scenario, of selectively deciding to allow non-medical benefits to tip the scale, in order to avoid that non-medical benefits justify too much risk and burden.

Recommendations

To better take into account non-medical benefits in non-therapeutic research participation, and in order to incorporate these benefits into the risk-benefit analysis, we have recommendations for several groups involved in pediatric research.

Institutional Review Boards

We recommend that IRBs take the non-medical benefits that we argued are justifiable into account when weighing the risk-benefit analysis of non-therapeutic research participation. We state a preference for the first, cautious scenario, where these benefits can tip the scale when crucial studies are at stake, but there are no medical benefits justifying the slightly over-minimal risks and burden. In those cases, IRBs should check whether the research set-up is done in such a way that the possibilities for non-medical benefits are maximized.

Policy makers

Policy makers in the field of pediatric research participation can contribute to this discussion by revising the regulatory framework to allow certain non-medical benefits into the risk-benefit analysis. This will support IRBs to incorporate non-medical benefits into the risk-benefits analysis in specific cases and make their evaluation justified and transparent.

Pediatric researchers

Based on the interviews with the children, there are two things for pediatric researchers to focus on. First, pediatric researchers could use empirical information on positive experiences during the informed consent process. Information about the positive effects is often lacking in study protocols and patient information brochures. Researchers may be reluctant to provide information about possible non-medical benefits because they do not want to persuade parents and children to participate based on non-health benefits. We are of the opinion that all information, including that on positive experiences, is necessary to make a well-informed decision on whether to participate in research.

Second, we advise pediatric researchers to improve children's experiences and set up their study in such a way that non-medical benefits are maximized. Meeting the needs of children to learn new things during research (i.e. educational benefit) provides researchers with an opportunity to use non-therapeutic research to teach children about science, and thus to create more support for science among the general public. There are several ways in which this can be achieved, examples include giving the child-participants a booklet in which they can register the results of the research procedures in a way that appeals to them, or giving them feedback on the results of a study in an attractive way, or presenting the research procedures in the form of an interactive game.

Limitations and future research

We studied children's positive experiences in a retrospective design following a secondary analysis of interviews that we conducted. Future research should specifically aim at exploring the self-reported positive experiences of children during research participation in order to gain more in-depth information (i.e. directly asking children about their positive experiences). We found that the emphasis of the positive experiences mentioned by the healthy children and by children with a chronic condition differed. Healthy children were more likely to mention 'having fun', 'increased knowledge' and 'not having to go to school' as a positive aspect of research participation, while the ill children mentioned 'helping others', 'future health benefits' and 'extra attention' more often. Quantitative research is needed to establish whether this difference can be supported, as well as other differences between children (e.g. differences in age). The Reactions to Research Participation Questionnaires for Children (RRPQ-C) as well as the survey by Wendler et al. could be used to measure whether children experience certain benefits of research participation in a quantitative way.[18, 26] Since we did not interview children with acute life-threatening conditions, we do not know whether our findings can be generalized to them.

Conclusion

In general, we argue that there is (too) much focus on the protection from risks and burden of children in non-therapeutic clinical research, and (too) little focus on the positive experiences and benefits that are important for these children. Our study shows that children taking part in non-therapeutic research have various positive experiences during research of which some could justifiably be considered to be benefits of research participation.

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APPENDIX A. INTERVIEW SCHEDULE

General experiences

How did you feel about the study in general?
How did you feel before the study?
How did you feel afterwards?
Can you describe your experiences during the study?
Can you describe your experiences during *procedure X*?

Experiences related to discomfort

Can you describe any discomfort you experienced in the study?
Is there any part of the study that you did not like? Which part? Why?
Can you describe any discomfort you experienced because of *procedure X*?

Worst experiences

What was/were the most burdensome/discomforting part(s) of the study? Which part? Why?

Preparation

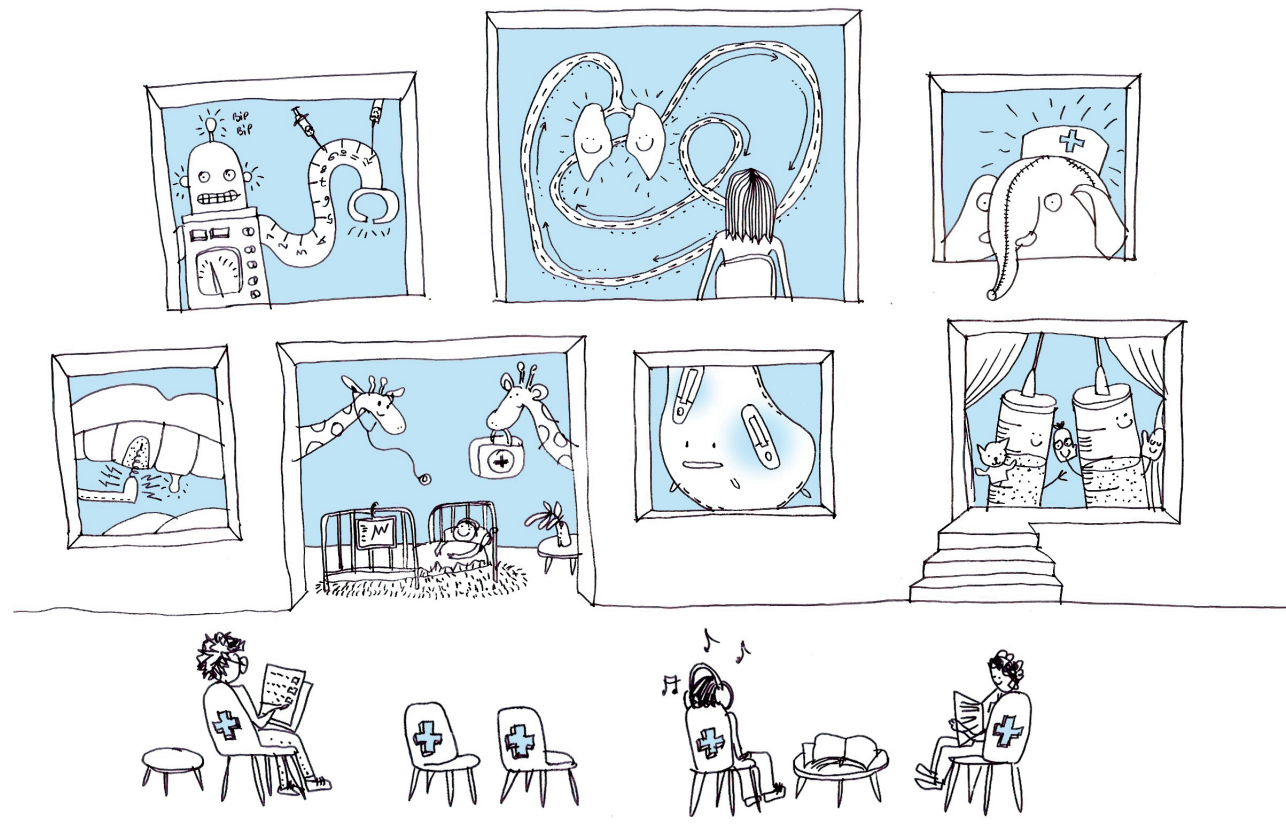
Who prepared you for the study?
What information did you get about the study? Was this information sufficient?
Did you know what to expect of the study?

Suggestions to reduce discomfort

Can you think of anything that would have made the study easier for you? If so, could you tell me about it?
Can you think of anything that will make *procedure X* less discomforting for you? If so, could you tell me about it?
Can you think of anything that will make *procedure X* more comfortable for you? If so, could you tell me about it?

Future research

Would you participate in this research study again? Why (not)?

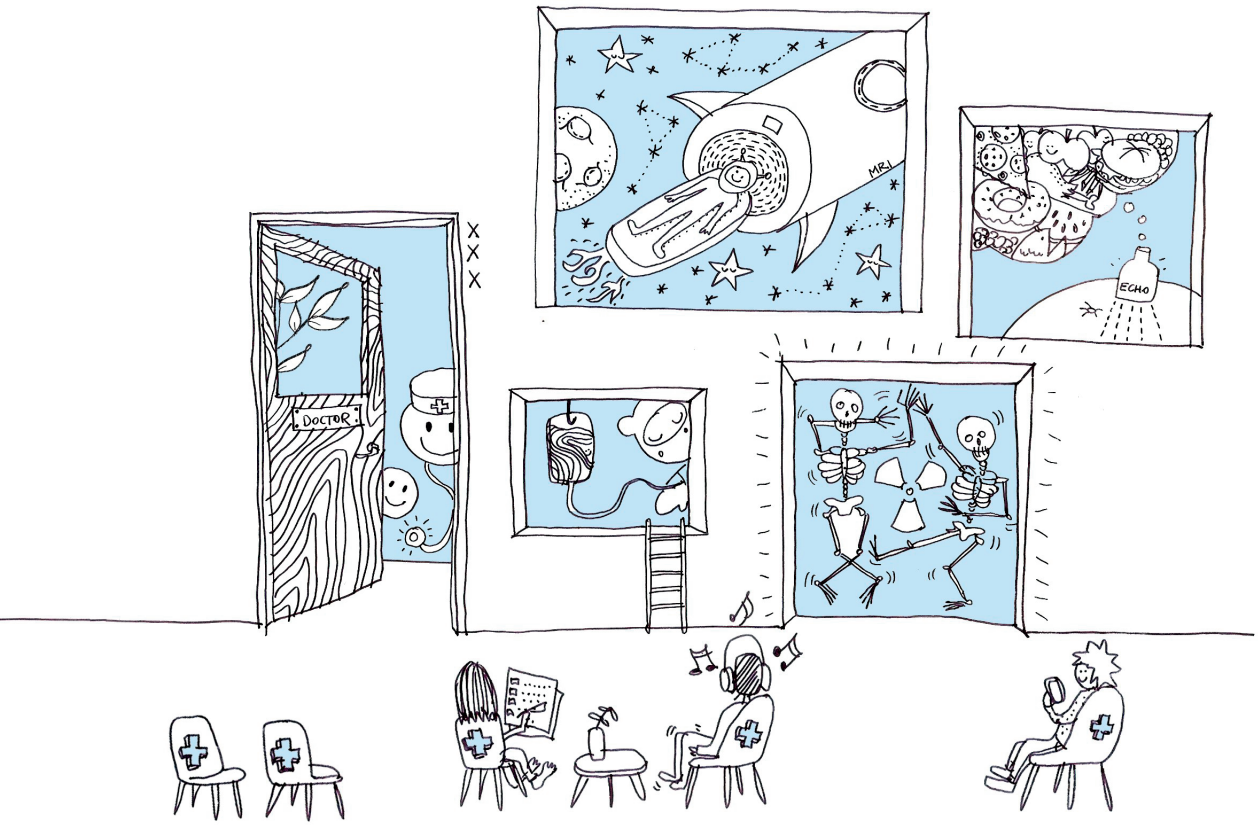


CHAPTER 7b.

Empirical data on benefits children experience in clinical research

MS Staphorst, S van de Vathorst

American Journal of Bioethics (2015), 15:20-21



EMPIRICAL DATA ON BENEFITS CHILDREN EXPERIENCE IN CLINICAL RESEARCH

An important group is often excluded from taking part in discussions about benefits in pediatric research: the children themselves. Luchtenberg and colleagues (2015) rightly point out that previous studies investigated the benefits children experience in research; however, these studies are biased in that the researchers came up with the answer categories, instead of using input from the children to identify relevant topics. To get an idea of the benefits relevant to them, it is important to hear their voices and let the children indicate the benefits they actually experience. The authors took an important step forward and provided a broader picture of what we already know about benefits in pediatric research by interviewing children in clinical trials.[1]

RESEARCH BENEFITS EXPERIENCED BY OTHER GROUPS OF CHILDREN

In an interview study focusing on the benefits children mention directly after participating in clinical research studies (N=46, 6–18 years), most of the benefits we found were similar to those in the target article.[2] Our study provides additional information about the benefits children experience, because we targeted a different group: We studied children in various research studies, not only those in clinical trials.

Young children

The children interviewed in the target article were relatively old (11–23 years). It is interesting that most of the benefits mentioned in the target article (helping other children, feeling good about oneself because of altruism, and personal health benefits) were also mentioned by the younger children in our study (22 of the 46 children interviewed in our study were between 6–11 years old). It is important to recognize that even children as young as 6 years are capable of reporting benefits they experience during research participation. Contrary to the development theory of Piaget in which young children generally are not considered to be capable of altruism or of feeling a moral duty,[3] our findings indicate that young children participating in research, including 6-year-olds, think it is important to help other children. An explanation for this could be that sick children may be concerned about children with similar conditions and therefore their condition may have rendered them capable of altruism at a younger age than their healthy peers.

Healthy children

Luchtenberg and colleagues (2015) mentioned that they included both healthy and sick children in their study. However, only two of the children included were actually healthy. Interesting benefits mentioned by the healthy children in our study were "having fun"

and "learning about oneself" (N = 12). They often enjoyed undergoing research procedures such as a magnetic resonance imaging (MRI) scan, intelligence tests (Wechsler Intelligence Scale for children), and even pulmonary function tests. These procedures were often passed off as a game, and the children thought they were fun. Another important benefit for the healthy children was to learn more about their cognitive and physical capacities. These children were interested in knowing how they would fare on a certain procedure, and what their anatomy looks like in an MRI. Although "having fun" and "learning about oneself" are not recognized as direct benefits of research in existing ethics guidelines, our study shows that these are important benefits for healthy children participating in research.

Children in non-therapeutic research

Although not explicitly stated by the authors, we deduce that most children in the target article participated in therapeutic studies. The majority of the children we interviewed participated in nontherapeutic studies, giving interesting information from the perspective of children who are not expected to benefit as defined by current ethics guidelines. Even though nontherapeutic research does not aim to provide health benefits, some sick children in these studies did mention health benefits such as extra medical checkups and better monitoring of their disease. In addition, almost all the children experienced benefits related to helping other children (and maybe even themselves in the future). The children with a chronic condition in particular thought it was really important to help other children. We therefore think that the term 'network of exchange', which the authors introduced when describing 'helping others in general', particularly concerns sick children.

HOW CAN PROFESSIONALS INVOLVED IN PEDIATRIC RESEARCH USE THE EXPERIENCES OF CHILDREN?

The target article and our own study show that both young children and adolescents,[2, 4] including healthy children and children in non-therapeutic research, experience a variety of benefits from research participation. Based on the findings of these studies, we think an important message for professionals involved in pediatric research is to recognize that non-health benefits also play an important role for children participating in a study, in therapeutic as well as nontherapeutic research.

Pediatric researchers

Pediatric researchers may be reluctant to mention benefits other than health benefits during the informed consent procedure because it may feel like pushing parents and children to participate. However, to obtain a complete picture of what participation in a

study will be like, it is important that parents and children be informed of the different kinds of benefits.[1] Furthermore, if pediatric researchers are aware of important research benefits for children, they can try to maximize these benefits when designing their studies. For instance, they could make the study more fun for the children by making the procedures more like an interactive game. If researchers make an effort to make a study beneficial in the eyes of the children, this may help to increase patient participation.

Institutional Review Boards (IRBs)

According to the definitions in existing ethics guidelines, research benefits are seen as health benefits. King (2000) argues that we should distinguish different kinds of benefits: direct health benefits, collateral benefits, and aspirational benefits.[5] According to King, many of the benefits found by Luchtenberg et al. (2015) and those in our own study would be categorized under collateral benefits (e.g. having fun, satisfying your curiosity, learning about oneself). Shah et al. (2004) showed however that the chairs of IRBs sometimes perceive collateral benefits as direct benefits,[6] which, according to the benefits that are important for the children, may actually be justified in some cases.

The findings of the target article and of our own study can help IRBs in recognizing what the benefits of a study are from the perspective of the children themselves. We would advise institutional review boards to also take the reported benefits in these studies into account when evaluating the risk–benefit ratio of study protocols. This supports Cave's view that if research will not directly benefit the child's health, other (collateral) benefits, such as altruism and having fun, can be viewed as direct benefits.[7]

FUTURE RESEARCH ON CHILDREN'S BENEFITS IN CLINICAL RESEARCH

Although both the target article and our own study give an insight into relevant benefits for children, it would be interesting to investigate in a larger sample size the percentage of children that experience certain benefits and whether the benefits for children depend on the type of study (nontherapeutic vs. therapeutic) or the severity of the child's condition (life-threatening vs. chronic condition vs. healthy).

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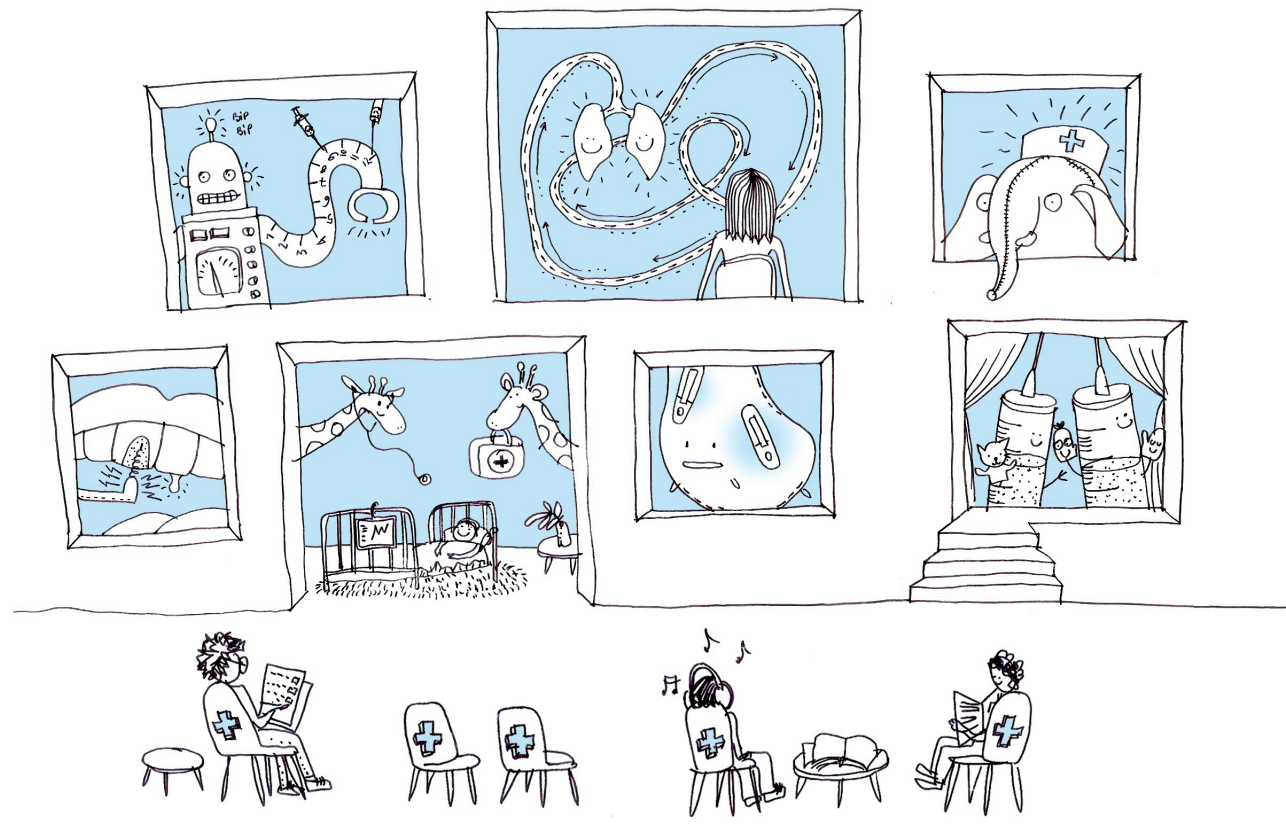
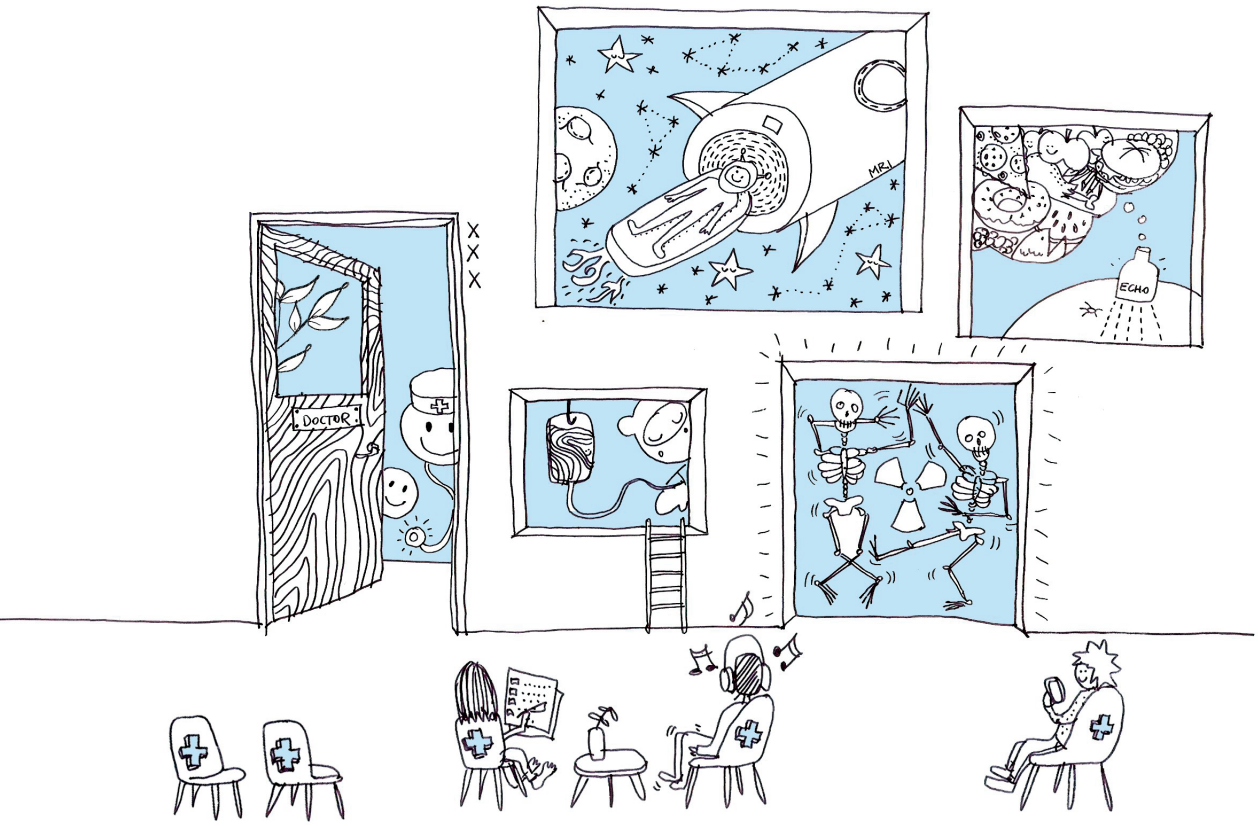


CHAPTER 8.

GENERAL DISCUSSION



The need to protect children from discomfort and risks in clinical research outweighs the need for the development of evidence-based drugs and treatments. While children obviously need protection against discomforting research procedures, children's discomfort in medical settings can be overestimated,[1, 2] which can lead to the rejection of important pediatric studies.

The aim to meet the need for more pediatric research[3, 4] - leading to better pediatric healthcare - forms the basis of this thesis. We primarily focused on providing evidence-based data on children's discomfort during several common research procedures. For this, we developed an instrument for measuring discomfort of research procedures. Our eventual goal is to develop an online database with data on children's self-reported discomfort, for which this thesis lays the foundation.

RESEARCH QUESTIONS

1. What is the degree of discomfort of common medical research procedures?
2. Do children experience clinically relevant stress symptoms due to common medical research procedures in the long-term?
3. Do age, anxiety-proneness, gender, medical condition and previous experiences with the procedures influence discomfort?
4. Are there differences in discomfort of the same medical procedures that are conducted for research purposes versus clinical care?
5. What are children's suggestions to reduce the discomfort of research procedures?

Research question 1. Children's self-reported discomfort during medical research procedures

In order to answer our main research question, we first needed to know what discomfort for children in clinical research means because there is no clear description (**Chapter 3**). A restricting factor was that most children did not understand the meaning of the word discomfort ('belasting' in Dutch). Therefore we had to change our approach slightly, and asked children about their experiences instead, focusing on the negative ones. What we learned from the interviews is that discomfort is not a one-dimensional but rather a multidimensional construct that involves different kinds of physical and mental experiences. Although children came from diverse backgrounds and underwent different research procedures, their experiences were remarkably similar, for instance boredom, tiredness, nervousness.

The second step to get insight in children's discomfort during research procedures was to standardize the measurement of it, for which we developed a questionnaire together with several pediatric healthcare professionals and input from literature: the Children's Discomfort during Research Procedures Questionnaire (CDRPQ) (**Chapter 4**).

Since we aimed to develop an instrument that could be used for all kinds of research procedures, it was important to use forms of discomfort that are relevant to most research procedures (i.e. a generic questionnaire). The final version of the CDRPQ involves six questions about children's discomfort, with each question involving five levels of discomfort, and an open question about children's suggestions for reducing discomfort.

For the final step, we asked children in clinical research to complete the CDRPQ. Given our restricted time and resources, we included six common research procedures: buccal swabs, MRI-scans, pulmonary function tests, skin prick tests, ultrasound imaging, and venipunctures (**Chapter 5**).

Children reported limited discomfort related to these procedures. These results may be not surprising as the procedures are quite common, which may be an indication that they are not (very) invasive and children may be familiar to undergoing these procedures. On the other hand, there appears to be ambiguity about the degree of discomfort of some of these research procedures (e.g. some consider MRI-scans as minimal discomfort, while others view this procedure as more than minimal discomfort).[5,6]

We were surprised by the relatively high scores on the questions about being bored and being tired, independent of the research procedures. Measuring children's negative experiences in medical situations rarely seems to focus on these experiences. This indicates that boredom and tiredness may be underestimated forms of discomfort for children in medical settings.

Research question 2. Psychological risk on clinically relevant stress

Literature shows that painful and distressing procedures can have a significant psychological impact on children, for which psychological help is required.[7,8] In **Chapter 6** we showed that the risk on long-term *clinically* relevant stress due to common research procedures is almost absent. As children already experienced limited discomfort during these research procedures (**Chapter 5**), these results did not surprise us. There is, however, a significant positive relation between discomfort during the procedures and long-term stress symptoms, suggesting that more discomforting research procedures may have a significant psychological impact on children. Measuring risk on clinically relevant stress is therefore of particular importance during very or extremely discomforting research procedures, which we think will be primarily used in therapeutic research, because there is no a priori upper limit for the level of discomfort as long as it is in proportion to the potential benefits.

Research question 3. Factors influencing discomfort

Discomfort of a certain procedure may be experienced differently in different children and/or across different situations. We therefore exploratively[d] studied the influence of several potential factors on discomfort (age, anxiety-proneness, gender, medical condition and previous experiences) to identify groups of children that are more prone to experience discomfort and consequently might need special precautions (**Chapter 5**). We focused on these specific factors because research in clinical care shows that these can influence children's experiences, and ethics committees often take these factors into consideration when evaluating discomfort.

Except for anxiety-proneness, our results showed no relation between the above-mentioned factors and discomfort. There are several explanations for this absence. First of all, children's discomfort scores were relatively low, making it difficult to find a relation between these factors and discomfort. Second, we think the population of children in research differs from children in routine clinical care (in which the influence of these factors on discomfort was found). Contrary to the general pediatric population in routine clinical care, our study sample had a high percentage of healthy children, relatively old children (>8 years), and trait-anxiety levels were relatively low. Third, skewedness of some of the data (age and health condition) may have prevented to find a relation between these factors and discomfort. Since the explorative nature of this research question, it is needed to investigate the influence of these factors in larger study samples.

Research question 4. Research versus clinical care

It is important to know if children in research experience less discomfort during the medical procedures than children in clinical research. Children in research generally undergo medical procedures voluntary,[e] which is why they possibly experience less discomfort during the same medical procedure. If proven, this information can lead to more acceptability of children in clinical research. We therefore exploratively studied whether the purpose of a medical procedure (routine clinical care versus research) influenced discomfort. The results were inconclusive. Significant differences were found for MRI-scans and pulmonary function tests, although the differences were small. Although we expected the procedures less discomforting in research, it may be (partly) dependent of the procedures whether children experience it as less (or more) discomforting in research settings than in clinical care. More research is therefore needed.

d This was exploratively studied because our sample size was too small for a reliable outcome on the influence of factors on discomfort

e There are exemptions: sometimes children may not know that they are participating in a research study, and sometimes the parent makes the decision to enroll.

Research question 5. Children's suggestions to reduce discomfort

Getting insight into children's discomfort is one step; actually doing something to minimize this discomfort is a second one. Minimizing discomfort is even obligatory in several codes and regulations on pediatric research participation.[9, 10] To help researchers reducing discomfort of the procedures in their studies, we described children's suggestions for reducing discomfort (**Chapters 3, 5**). Since we think these suggestions are an essential part of measuring discomfort, we added a question about reducing discomfort to the CDRPQ.

Distraction was, by far, the most mentioned suggestion to reduce discomfort, independent of the research procedures. Distraction has proven to be effective in reducing discomfort of medical procedures in children of all ages,[11-15] and it is also cost-effective because of the relatively low start-up and maintenance costs.[16] It can be provided in different forms, such as showing short movies, listening to music or small talk. Our study shows that children prefer distraction by showing a movie.

Distraction is often provided during potential painful procedures, or when children are anxious. However, based on the relatively high scores on the CDRPQ on 'bored' and 'tired', it is recommended to also provide distraction during lengthy procedures and extensive study visits.

STRENGTHS

The debate on discomfort in pediatric research generally takes place from the perspective of adults, while the most important group is often excluded: the children themselves. This thesis aimed for hearing their voices about their experiences in research, and disseminating these data. This thesis is the first doing so on a relatively large scale, with respect to the number of research procedures and the number of children undergoing these procedures.

The necessity of getting insight into children's self-reported experiences in clinical research is mentioned frequently. More than a decade ago, researchers like Kassam-Adams developed instruments to map up children's experiences in research. Unfortunately, these initiatives never reached large-scale support by healthcare professionals. We were unable to find a clear reason for this. We believe it is because these researchers focused on discomfort of complete research *studies*, which makes it difficult to generalize the findings because studies are rarely similar. We therefore have chosen to focus on discomfort of research *procedures*, making it possible to generalize the findings of a certain procedure to children undergoing this same procedure in different studies.

It needs to be noted that – many years after the attempts by previous researchers[17,18] – our project benefits from recent Dutch and European developments within pediatric research. For instance, the Dutch government is promoting and subsidizing research on

the ethical, juridical and psychological aspects of children in research, and also invested in the development of a (ethics) guideline for pediatric researchers about the care of the children involved in their studies. Moreover, the Dutch government recently accepted a law that expands the possibilities for pediatric research, in particular for children in non-therapeutic research. This law largely follows recommendations by the Committee Doek[4] for expanding the legislation on pediatric research and is in accordance with the renewal of the European regulation on clinical trials in children. Proof of the importance and relevance of this thesis is the fact that the law (Wet Medisch Wetenschappelijk Onderzoek met Mensen, WMO) now states that discomfort of children in research has to be defined and monitored. For this reason, we believe the time is ripe to measure children's self-reported discomfort.

Furthermore, data on children's self-reported discomfort and their suggestions for reducing discomfort provide useful information for those involved in pediatric research. The dissemination of this information will benefit the general area of pediatric research by providing an empirical basis for the evaluation of discomfort, facilitating cross-study comparisons of the impact of various procedures, and eventually helping to provide benchmarks for the level of discomfort that might be expected for children undergoing a given procedure. This thesis also offers an instrument (CDRPQ) for measuring children's discomfort, which can help to establish these benchmarks.

LIMITATIONS

This thesis has several limitations to take into account. The most important ones are mentioned below.

Participants

Since we were dependent on the research procedures conducted at the participating hospitals, and the time given for our research project, we were unable to include the intended number of children (N=50) for some research procedures, because fewer children took part in these studies than expected, or were included at a later stage than planned. This has an effect on the power and generalization of the outcomes. Because of this and skewedness of the data (i.e. age and medical condition), no definitive conclusions can be drawn about the influencing factors on discomfort, such as whether younger children need special precautions in clinical research.

We only included children who had assented to undergo the research procedures; therefore the study might be hampered by a selection bias. It is possible that some children declined to undergo a research procedure because of expected discomfort. Unfortunately, we do not have information on the pool of children that was eligible for participation for the studies from which we recruited children, the sampling and

inclusion of these studies, and the percentage of children that actually participated (e.g. for some studies sampling is still ongoing). Studies on children's motivations for (not) participating in clinical research could help to gain a general insight into the percentage of children that decline to participate because of the expected discomfort.[19-22] However, selection bias basically is not only a problem for this thesis, but for many pediatric studies because selection takes place due to, for instance, gatekeeping by researchers and parents.

Measuring discomfort

While the children mentioned various forms of discomfort, we only included forms of discomfort into the CDRPQ that were most frequently mentioned by the children and are applicable for all kinds of research procedures (e.g. 'feeling short of breath' is only relevant for certain procedures, while 'boredom' can be part of many). Hence, the CDRPQ should be seen as a generic questionnaire. This has advantages, such as making comparisons possible between discomfort of different research procedures, as well as disadvantages. It can give an incomplete view of the overall discomfort because important specific forms of discomfort are not measured for some procedures.

A solution could be to develop a procedure-specific questionnaire on discomfort, involving the questions of the CDRPQ and additional questions about specific forms of discomfort related to a certain procedure. Of course, it is needed to validate this procedure-specific questionnaire first. It also needs to be noted that adding more questions will burden children more (an often heard criticism of research is the large amount of questionnaires) and therefore might influence the response-rate.

Children's Discomfort during Research Procedures Questionnaire (CDRPQ)

Next to the above-mentioned limitations about measuring discomfort, limitations of the CDRPQ are the - so far - limited psychometric analyses.

IMPLICATIONS AND RECOMMENDATIONS FOR THOSE INVOLVED IN PEDIATRIC RESEARCH

Data on children's self-reported discomfort and suggestions for reducing discomfort provide useful information for several groups involved in pediatric research. Below, we describe the relevance of the results of this thesis for each group and how these can be incorporated in practice.

Ethics committees

Evaluating discomfort

In **Chapter 5**, we describe the discomfort of some common medical research procedures, which helps make the evaluation of discomfort evidence-based. We encourage ethics committees to use these data when evaluating discomfort. We strive for information on the discomfort of other research procedures in the near future.

Recommending pediatric researchers to measure discomfort

To be able to use children's self-reported information on discomfort, it is needed that these data are collected and disseminated. Ethics committees can play a key role in this by requiring these data as part of a study protocol and recommending pediatric researchers to register children's experiences.

Evaluating benefits

Currently, only health benefits are taken into account in the risk-benefit analysis of pediatric research. In our opinion, there are situations in which "increasing knowledge about the human body and doing research," "having fun," and "altruism" can also be taken into account as benefits in the risk-benefit analysis (**Chapters 7a, 7b**). These benefits can tip the scale when crucial studies are at stake, but when the medical benefits cannot justify the slightly over-minimal risks and discomfort.

Pediatric researchers

Measuring discomfort

We recommend that pediatric researchers routinely include a brief assessment of the impact of the research procedures of their studies by asking the participating children, for which the CDRPQ could be used (**Chapter 4**). To avoid overloading pediatric researchers with extra work and responsibilities during a study visit, it would be ideal if children can report their experiences directly on a website/app. As such, pediatrics researchers can limit their tasks to emphasizing the opportunity and importance of reporting these experiences to children (and their parents) and to refer them to this website/app.

Informed consent process

During the informed consent procedure, we encourage researchers to provide parents and children with information on expected discomfort of research procedures based on empirical data, in order to facilitate their decision-making for participation.

Reducing discomfort

It is important that discomfort in pediatric research is reduced as much as possible. This can be achieved by standard asking children - next to discomfort - for their suggestions

to reduce discomfort (i.e. one of the questions of the CDRPQ), and - if feasible - to apply these in their studies. As we showed in **Chapters 3 and 5** many children undergoing different procedures suggested providing (more) distraction, for instance by showing short movies.

Maximizing positive experiences

When designing a study, pediatric researchers are encouraged to have an eye for the positive experiences that are important for the children, and are acceptable from an ethical point of view, such as their interest in science/human body (**Chapters 7a, 7b**). Improving the positive experiences may also improve participation rates, and maybe even awake an interest in science among children.

Children and parents

Facilitating decision-making

For children (and parents) who are approached for research participation, it can be helpful when they have access to information on discomfort of research procedures of children in previous research. It provides them with additional information on what to expect from undergoing research procedures from the perspective of their peers. This information can facilitate decision-making for (parts of) research participation, as they will be better informed. For instance, if the majority of children do not experience a specific research procedure as discomforting, it may be a reason for others to agree with undergoing this procedure too.

Self-reported data on discomfort

The availability of children's self-reported data on discomfort is dependent on the willingness of children to report on their experiences during research participation. As we learned from the studies in this thesis, our experience is that most children are willing to report these experiences as long as it does not require much extra time. We think that it would be useful if children can report their experiences (anonymously) on a website (e.g. using the CDRPQ), which they could access without (extensive) registration to make it as easy as possible for them.

FUTURE DIRECTIONS

Implementation

It is important that the evaluation of ethics committees on discomfort is evidence-based. This thesis made a start in describing discomfort during research procedures. Additional research is needed to measure discomfort in larger and more heterogeneous sample sizes (e.g. more variation in age, medical condition), and related to other research pro-

cedures. For this, we developed an implementation plan that is supported by several prominent stakeholders involved in pediatric research in the Netherlands (e.g. Dutch Society for Pediatrics, Dutch Society for Ethics committees, Nefarma, the Ministry of Health) and recently received financial support by ZonMw. In short, we plan to develop a website where children can report their experiences using the CDRPQ; the data on discomfort will be anonymously published in a database on this website. The website will be accessible for children, parents, ethics committees, researchers and others who are interested. To promote this website, we continue to work on the development of a network in which physicians, researchers, ethics committees, parents and children are involved. We aim for a network in the Netherlands first, and if proven successful, we will expand this to other countries as well.

Eventually, we hope the website can be used as a platform where data on discomfort are disseminated, experiences of research participation are shared, videos are showed in which children explain some essential concepts of participating in research, et cetera. The United Kingdom already established such a platform, which we see as an example for the Netherlands.

Child participation

We consulted children at different stages of our research project: during the interviews they were consulted about their experiences and were asked about the word discomfort; they were also asked about which response options they prefer; they provided feedback on the concept-version of the CDRPQ. When looking at Hart's Ladder of Participation,[23] there are possibilities for improvements in child-participation in our project, leading to more empowerment of the children and thus to the successfulness of the project. As we cannot turn back time, we plan to more actively involve children during the follow-up project, for instance by setting-up a child-council ('kinderraad') who can help design the webpages for the children, who can test the website and provide feedback, who can advise us to expand the website to a platform, et cetera.

Levels of discomfort and their meaning

For ethics committees and pediatric researchers who evaluate the level of discomfort of (non-therapeutic) research procedures, it is important to know which research procedures involve 'minimal discomfort'. In this thesis, we provide data on different degrees of discomfort, but we do not provide which degree corresponds with the categories of discomfort used in legal documents and regulations (e.g. minimal discomfort, minor increase over minimal discomfort). One of the reasons why we did not do this is because the jurisdiction on the level of discomfort depends on the country where the research is being conducted. In **Chapter 5** we discuss a recommendation by Westra et al., in which they suggest that minimal risk is when "at most a quarter of the persons (25%)

concerned will experience considerable risk".[24] Although this definition is meant for risk (involving both risk of harm and risk of discomfort), a cut-off level of 25% for minimal discomfort seems like a reasonable percentage. However, it is needed that future research investigates if taking a percentage is indeed an acceptable way of determining different levels of discomfort, and if so, which percentage is an acceptable cut-off level according to ethics committees, researchers, and of course children and their parents.

Additional validation

Future research is needed for additional validation of the CDRPQ. For instance, it would be helpful to measure convergent validity based on all questions of the CDRPQ on the child's discomfort. Also, the CDRPQ was developed in the Dutch language and then translated to English for this thesis. For using this questionnaire abroad, it is needed to validate the CDRPQ in other languages first. Furthermore, future research is needed to investigate whether the CDRPQ can also be used in younger children (< 8 years).

CONCLUSION

This thesis aimed for making the evaluation of discomfort in pediatrics research evidence-based by providing information on children's self-reported discomfort. It makes a start in reporting and disseminating children's self-reported experiences, and lays a foundation for an online database on children's discomfort in clinical research. With the recent additions in Dutch law to define and monitor children's discomfort in research, aiming to increase the acceptability of children in clinical research, the time is ripe to build this database and make the evaluation of discomfort evidence-based.

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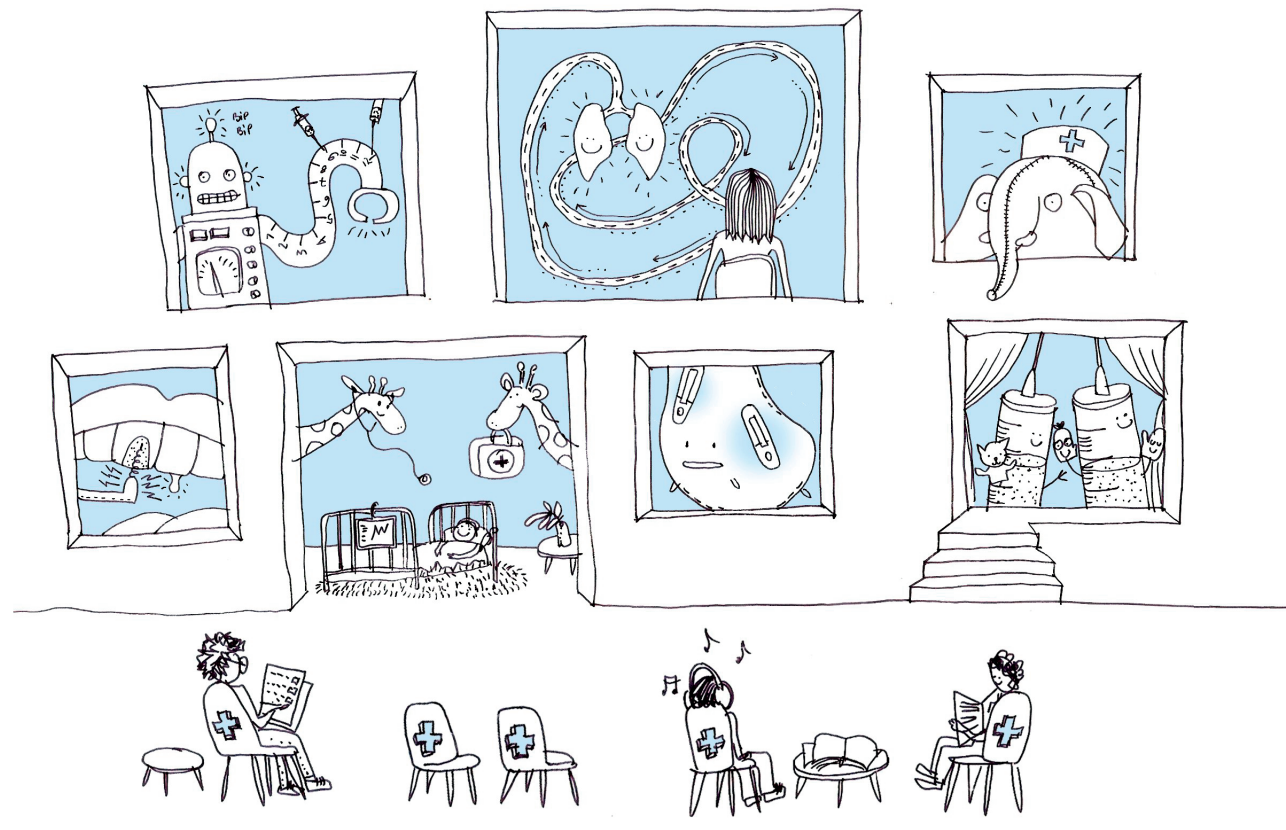
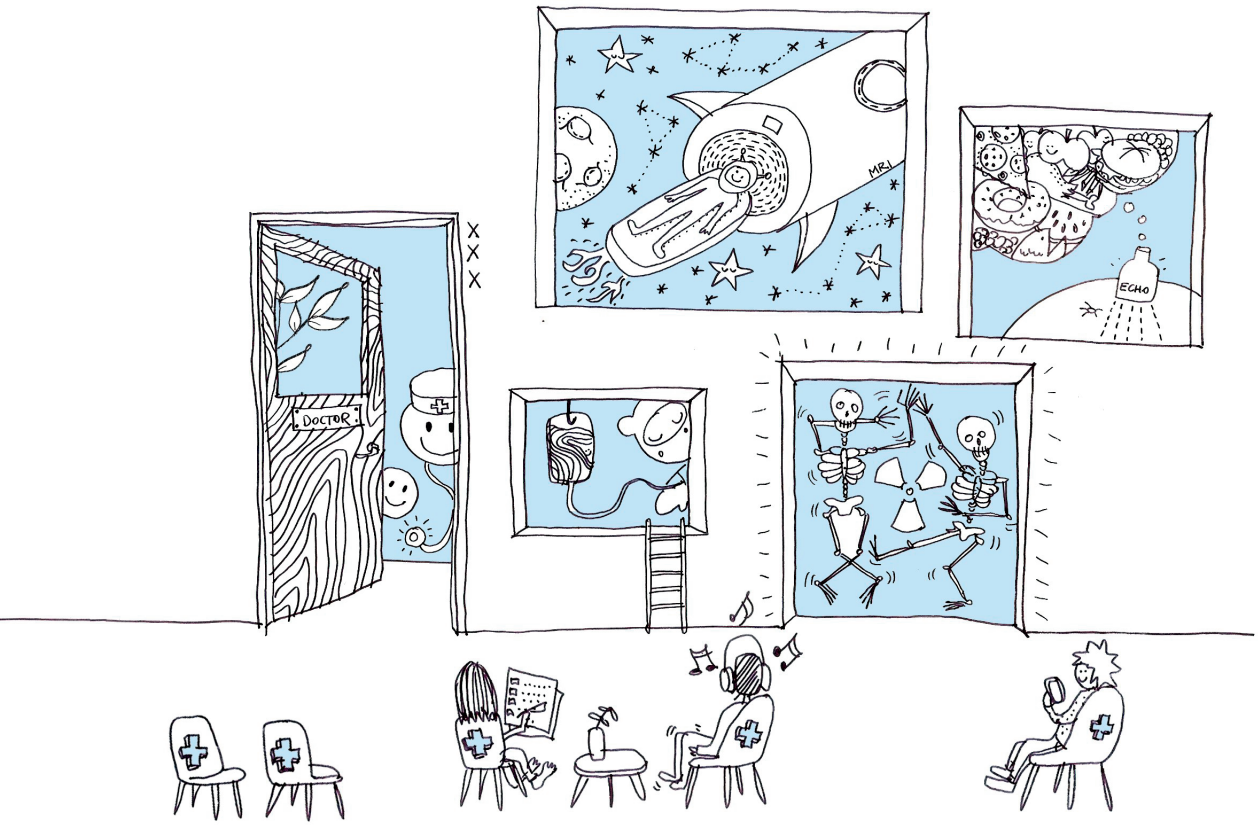
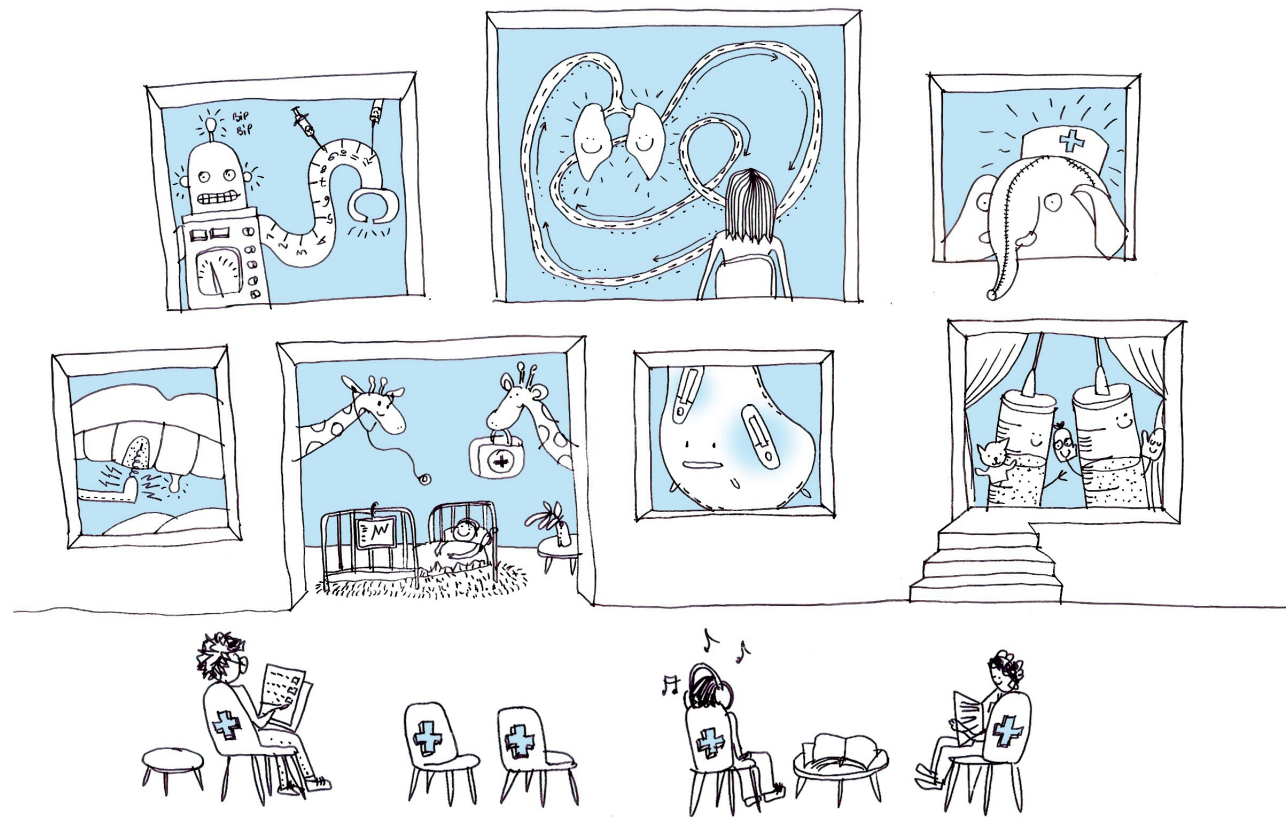
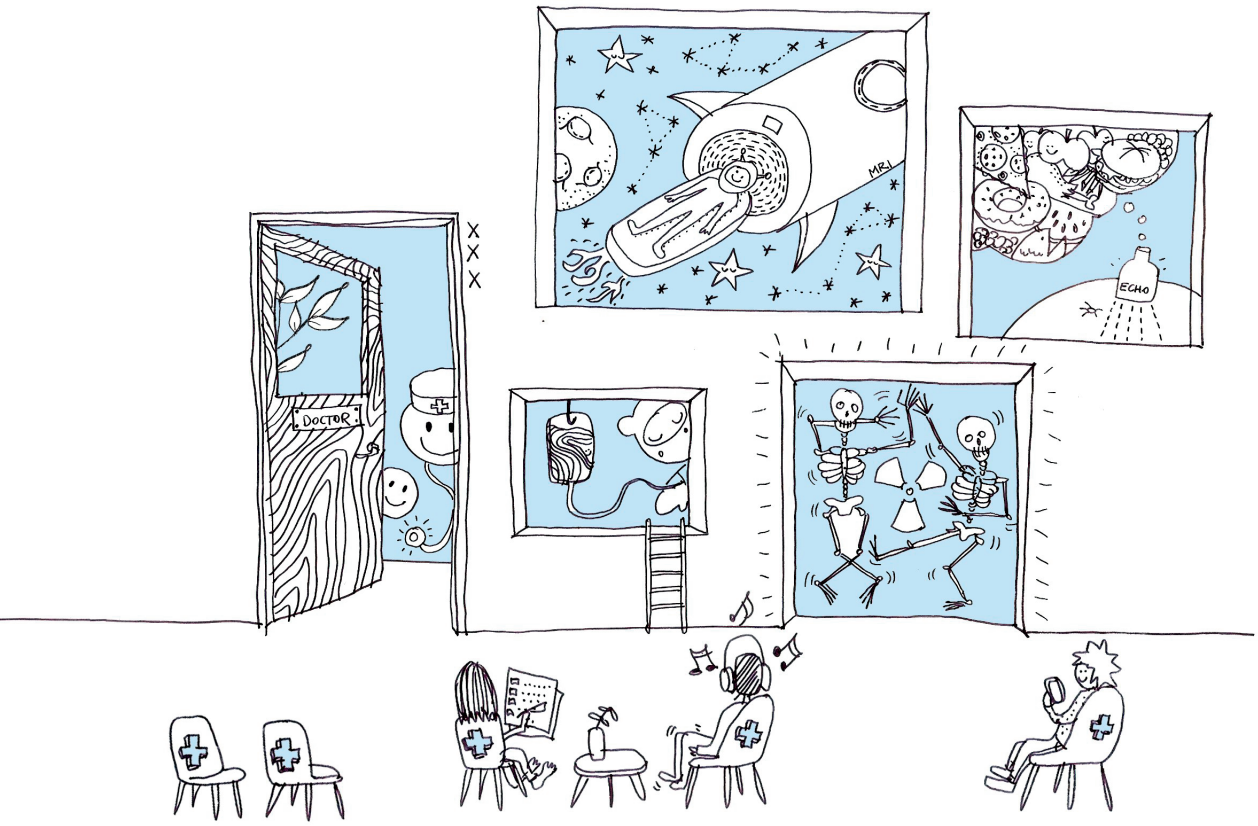


ADDENDUM





SUMMARY



Chapter 1 introduces the topic of children participating in clinical research. Children's health is at risk because of unlicensed and off-label medicines and other treatments (i.e. it is estimated that approximately 65% of treatments and medicines for children are unlicensed and/or off-label). Clinical research is needed to get access to tested and licensed medication and treatment, yet children are restricted from participating because of the risks and discomfort it causes. It is striking that the guidelines for protecting children might actually bring their health at risk.

To find an optimal balance in conducting clinical research and protecting the child, it is necessary to have empirical data on children's self-reported experiences in clinical research. Until now, these data are scarce. The general aim of this thesis was to get insight into children's experiences in clinical research, and make a start with collecting self-reported data on discomfort of children during medical research procedures. Although the focus is primarily on discomfort, positive experiences and benefits are addressed as well.

The studies described in this thesis were carried out at the Academic Medical Center in Amsterdam, VU University Medical Center in Amsterdam, Erasmus University Medical Center in Rotterdam, and the Academic Center of Dentistry in Amsterdam/Almere (ACTA).

The main research questions of the thesis were:

1. What is the degree of discomfort of common medical research procedures?
2. Do children experience clinically relevant stress symptoms due to common medical research procedures in the long-term?
3. Do age, anxiety-proneness, gender, medical condition and previous experiences with the procedures influence discomfort?
4. Are there differences in discomfort of the same medical procedures that are conducted for research purposes versus clinical care?
5. What are children's suggestions to reduce the discomfort of research procedures?

Chapter 2 describes the study protocol of a two-phase study measuring children's self-reported experiences during research procedures. The first phase consisted of an interview study with a diverse group of children about their experiences during research procedures. In the second phase, the development of a questionnaire, measuring children's experiences during research procedures in a quantitative way, is described. This questionnaire is based on literature, input from pediatric healthcare experts and the interview outcomes of the first phase. Next, we measured the experiences of children during common medical research procedures using this questionnaire. Finally, we measured long term (clinically elevated) stress symptoms due to research procedures.

Chapter 3 provides insight into children's discomfort during clinical research procedures and their suggestions to reduce possible discomforts. We interviewed a group of 46 children (aged 6-18) participating in clinical research studies. The forms of discomfort of the interviewed children could be divided into two main groups: physical and mental forms of discomfort. The majority experienced physical discomforts during the research procedures: pain, shortness of breath, nausea, itchiness, and feeling hungry, which were often caused by needle procedures, some pulmonary procedures, and food provocation tests. Mental discomforts included anxiousness because of anticipated pain and not knowing what to expect from a research procedure, boredom and tiredness during lengthy research procedures and waiting, and embarrassment during Tanner staging. Children's suggestions to reduce the discomforts of the research procedures primarily were providing distraction (e.g. watching a movie or listening to music), providing age-appropriate information and shortening the duration of lengthy procedures.

In **Chapter 4** we described the development of a generic, short and child-friendly instrument to measure children's self-reported discomfort during research procedures: the Children's Discomfort during Research Procedures Questionnaire (CDRPQ). The CDRPQ is based on literature, the interviews we held with children and input from several pediatric healthcare experts. It consists of six questions about different forms of discomfort children experience (nervousness, annoyance, pain, fright, boredom, tiredness) and an open question on how discomfort can be reduced. An average discomfort score can be calculated based on the six different forms of discomfort. Convergent validity and test-retest reliability were acceptable. Internal consistency was low, as expected given the variety in forms of discomfort. The CDRPQ was well received by the children.

In **Chapter 5** we investigated children's self-reported discomfort during research procedures and their suggestions how discomfort can be reduced, using the CDRPQ. We measured discomfort of six medical research procedures: buccal swabs, MRI-scans, pulmonary function tests, skin prick tests, ultrasound imaging and venipunctures. We compared the findings to children's discomfort during dental check-ups, and explored whether age, anxiety proneness, gender, medical condition, previous experiences and the purpose of the procedure (research versus clinical care) affected discomfort.

For this study, we included 418 ill and healthy children (8-18 years): 307 from research, 50 from dental care, and 61 from clinical care. Most children reported limited discomfort during the research procedures. When compared with dental check-ups, buccal swab tests, skin prick tests and ultrasound imaging were less discomforting, while MRI-scans, venipunctures and pulmonary function tests caused a similar degree of discomfort. Only anxiety-proneness was positively related to discomfort. It was inconclusive whether the purpose of the procedure (research versus clinical care) affected discomfort. The

majority of the children (ca. 60%) suggested providing distraction by showing movies to reduce discomfort.

Clinical research can cause different types of risk: physical, psychological, social, economic and legal risks. In **Chapter 6,** the psychological risk that research procedures can have on children is investigated. We operationalized psychological risk as clinically relevant stress symptoms, measured with the Children's Revised Impact of Event Scale (CRIES-13). A score of ≥ 30 on this scale was considered as clinically relevant stress. We measured stress symptoms of children (N=66) who underwent buccal swabs, MRI-scans, pulmonary function tests, ultrasound imaging and venipunctures after one month. We asked an additional group of 34 children about the stress symptoms caused by MRI-scans and venipunctures after one year.

None of the children had clinically relevant stress symptoms, except for one child who reported to have clinically elevated stress symptoms one year after undergoing a venipuncture. Discomfort during research, trait-anxiety and gender (i.e. being a girl) were significantly positively related to long-term stress symptoms, indicating that children who experience a considerable degree of discomfort during research, girls, and children with high trait-anxiety scores are more likely to experience long-term stress-symptoms due to research procedures.

Contrary to the previous chapters on children's discomfort, **Chapters 7a and 7b** address positive experiences and potential benefits of children in clinical research.

Recruiting children for non-therapeutic research is ethically challenging because participation conveys risks and discomfort and no health benefit. In **Chapter 7a** we give insight into the positive experiences of a group of healthy and ill children (6-18 years) who participated in non-therapeutic research studies, and discuss whether these positive experiences can be viewed as benefits. We argue that helping others, having fun, and new/increased knowledge could justifiably be valued as benefits. We present two scenarios how ethics committees could incorporate these benefits into the risk-benefit analysis of study protocols. The first scenario discusses that these above-mentioned benefits should be incorporated in the risk-benefit analysis in studies that are thought to be crucial, but the risks and burden are expected to be slightly above minimal. In the second scenario, we propose that these benefits should be a standard part of the risk-benefit analysis.

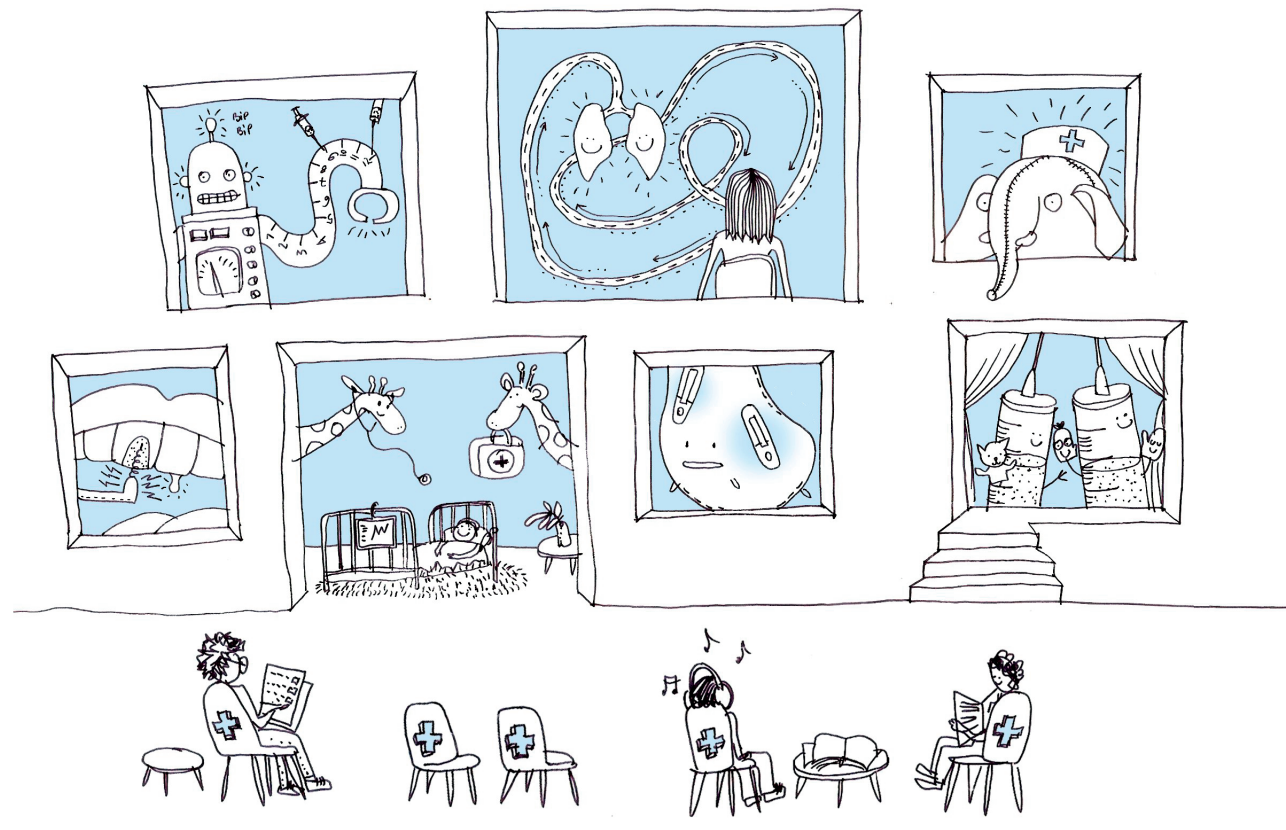
Chapter 7b is based on the findings of **Chapter 7a**. It consists of an open peer commentary on the article *"Young people's experiences of participation in clinical trials: reasons for taking part"* by Luchtenberg et al. (2015). They conducted a qualitative study about

the benefits adolescents experience in clinical trials. In our commentary, we support the different benefits that Luchtenberg et al. found in their study, based on hearing the voices of the children in a more varied (in age, medical condition, and study types) study sample.

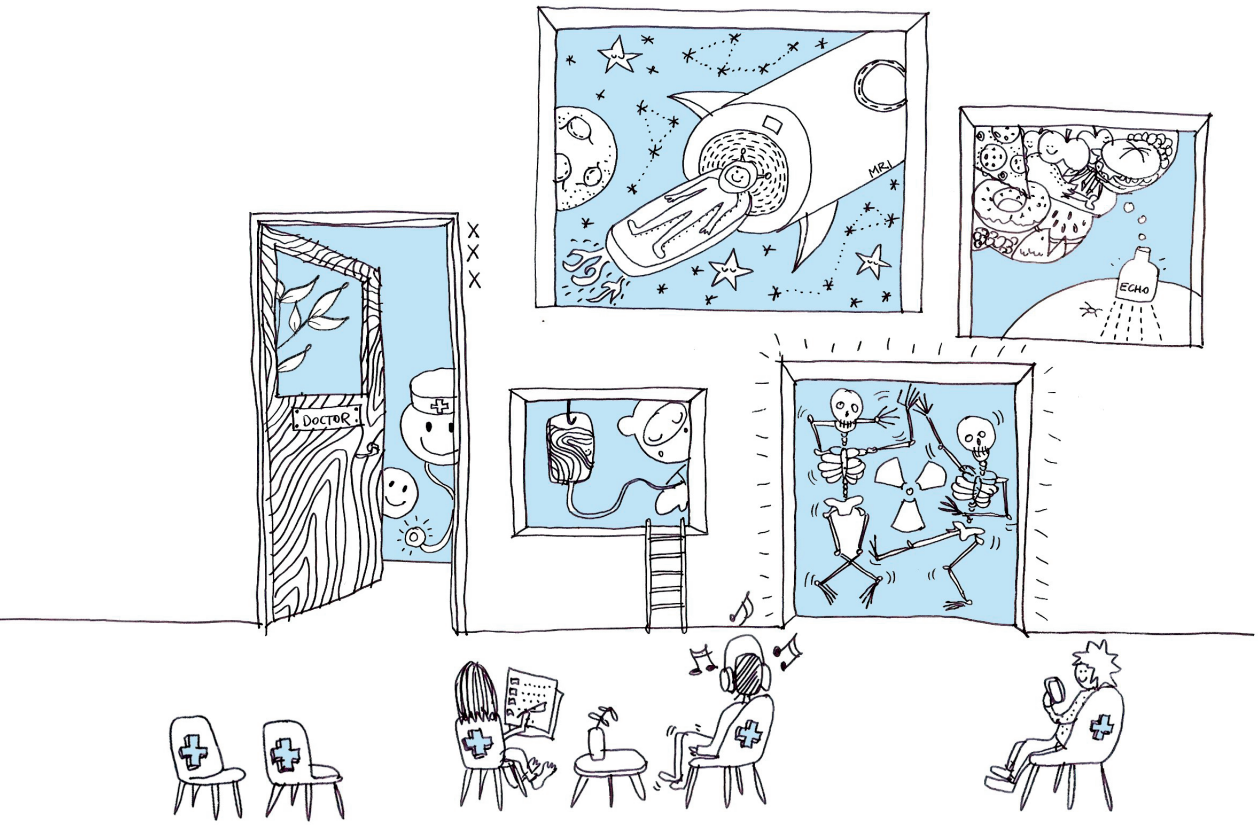
Chapter 8 constitutes a general discussion on the main findings of the studies presented in this thesis. This thesis aimed to make decisions in clinical research evidence-based by providing information on children's self-reported discomfort during several research procedures. These data are a first step in providing benchmarks for discomfort of various research procedures in pediatric research.

Summarized, children experience limited discomfort and long-term stress symptoms during the investigated research procedures. This supports the acceptability of undergoing these research procedures.

Based on the findings of this thesis, recommendations and implications for different groups involved in pediatric research are given (i.e. pediatric researchers, ethics committees, children and their parents). Also recommendations are given for future research. For instance, more data are needed on the discomfort of research procedures, in particular of research procedures not described in this thesis. For this, we designed an implementation plan to collect and disseminate these data, for which we recently received a grant by ZonMw.



SAMENVATTING



In **Hoofdstuk 1** wordt een toelichting gegeven op de deelname van kinderen aan wetenschappelijk onderzoek. De gezondheid van zieke kinderen loopt gevaar vanwege niet geregistreerde en niet goed onderzochte medicijnen en behandelingen. Wetenschappelijk onderzoek is nodig om ervoor te zorgen dat kinderen toegang krijgen tot geteste medicatie en behandelingen, maar kinderen worden vaak uitgesloten van deelname vanwege de risico's en belasting die het onderzoek met zich meebrengt. Het is opmerkelijk dat de regelgeving die (zieke) kinderen moet beschermen tegen wetenschappelijk onderzoek, aan de andere kant hun gezondheid op het spel lijkt te zetten.

Om een optimale balans te vinden om wetenschappelijk onderzoek te kunnen doen én tegelijkertijd kinderen te kunnen beschermen tegen belasting (en risico's) van het onderzoek, is het nodig om empirische data te hebben over de ervaringen van kinderen in wetenschappelijk onderzoek zoals kinderen die zelf rapporteren. Tot op heden zijn deze data nauwelijks beschikbaar. Het doel van dit proefschrift was daarom om inzicht te krijgen in de ervaringen van kinderen in wetenschappelijk onderzoek, en een start te maken om de belasting die kinderen ervaren tijdens medische procedures in wetenschappelijk onderzoek in kaart te brengen. Hoewel de focus van dit proefschrift vooral op belasting is gericht, wordt ook ingegaan op de positieve ervaringen en voordelen die kinderen ervaringen tijdens onderzoek.

De studies die zijn beschreven in dit proefschrift zijn uitgevoerd bij het Academisch Medisch Centrum in Amsterdam, het VU Universitair Medisch Centrum in Amsterdam, het Erasmus Universitair Medisch Centrum in Rotterdam, en het Academisch Centrum voor Tandheelkunde in Amsterdam/Almere (ACTA).

De belangrijkste onderzoeksvragen van dit proefschrift waren:

1. Wat is de mate van belasting van veel voorkomende medische procedures in wetenschappelijk onderzoek?
2. Ervaren kinderen klinisch relevante stress symptomen op de lange termijn vanwege medische procedures in wetenschappelijk onderzoek?
3. Beïnvloeden leeftijd, angst-predispositie, geslacht, medische conditie en eerdere ervaringen met een medische procedure de belasting van kinderen in wetenschappelijk onderzoek?
4. Zijn er verschillen in belasting tussen een zelfde procedure die wordt uitgevoerd in het kader van wetenschappelijk onderzoek versus als deze wordt verricht voor diagnostiek- en behandeldoeleinden?
5. Wat zijn suggesties van kinderen om belasting van medische procedures in wetenschappelijk onderzoek te verlichten?

In **Hoofdstuk 2** wordt het studieprotocol van een twee-fase onderzoek over de zelf-gerapporteerde ervaringen van kinderen tijdens wetenschappelijk onderzoek

beschreven. De eerste fase van het onderzoek bestaat uit een interviewstudie waarin een diverse groep van kinderen over hun ervaringen tijdens medische procedures in wetenschappelijk onderzoek wordt gevraagd. In de tweede fase wordt de ontwikkeling van een vragenlijst beschreven waarmee de ervaringen van kinderen in wetenschappelijk onderzoek kunnen worden gekwantificeerd. Deze vragenlijst is gebaseerd op literatuur, input van kindergeneeskundige experts, en de resultaten van de interviews uit de eerste fase van het onderzoek. Een volgende stap was om daadwerkelijk de ervaringen van kinderen tijdens verschillende onderzoeksprocedures te meten, waarbij gebruik werd gemaakt van de bovengenoemde vragenlijst. Als laatste is gekeken naar stress symptomen van de kinderen op de lange termijn als gevolg van het ondergaan van onderzoeksprocedures.

Hoofdstuk 3 geeft inzicht in de belasting die kinderen ervaren tijdens wetenschappelijk onderzoek en hun suggesties om deze belasting te verminderen. We hebben hiervoor 46 kinderen (6-18 jaar) geïncludeerd die meededen met een wetenschappelijke studie. De belasting die kinderen ervoeren, hebben we ingedeeld in twee hoofdcategorieën: fysieke en mentale belasting. De meerderheid van de kinderen ervoer fysieke belasting tijdens de onderzoeksprocedures, bestaande uit pijn, kortademigheid, misselijkheid, jeuk en honger hebben. Deze ervaringen werden met name veroorzaakt door naaldgerelateerde procedures, longfunctiemetingen, en voedselprovocatietesten. Mentale belasting betrof met name het angstig zijn vanwege geanticipeerde pijn en omdat het kind niet wist wat het te wachten stond, zich vervelen en moeheid tijdens langdurige procedures en wachten, en schaamte tijdens puberteitsonderzoek. Kinderen gaven aan dat de belasting van de onderzoeksprocedures verminderd kon worden door afleiding (bijvoorbeeld naar een film kijken of naar muziek luisteren), het geven van leeftijdsadequate informatie over het onderzoek en het verkorten van langdurige procedures.

In **Hoofdstuk 4** wordt de ontwikkeling beschreven van een generieke, korte en kindvriendelijke vragenlijst om de zelf-gerapporteerde belasting van kinderen tijdens medische procedures in wetenschappelijk onderzoek te meten: Children's Discomfort during Research Procedures Questionnaire (CDRPQ). De CDRPQ is gebaseerd op literatuur, interviews met kinderen en input van verschillende kindergeneeskundige professionals. De vragenlijst bestaat uit zes vragen over verschillende vormen van belasting (zenuwachtig, vervelend, pijn, eng, saai, moe) en een open vraag over hoe de belasting verminderd kan worden. Een gemiddelde score kan worden berekend op basis van de zes vragen over belasting. De convergente validiteit en test-hertest betrouwbaarheid waren acceptabel. Interne consistentie was - zoals verwacht - laag, vanwege de variëteit in vormen van belasting. De CDRPQ werd goed ontvangen door de kinderen.

In **Hoofdstuk 5** hebben we de zelf-gerapporteerde belasting van kinderen tijdens wetenschappelijke onderzoekprocedures onderzocht en de suggesties van kinderen om deze belasting te verminderen. We hebben hierbij gebruikt gemaakt van de door ons ontwikkelde vragenlijst: de CDRPQ. We hebben de belasting gemeten van zes onderzoeksprocedures: wangslijmvliesafnames, MRI-scans, longfunctietesten, allergietesten, echoscopieën en bloedafnames. De belasting van deze procedures hebben we vergeleken met de belasting die kinderen tijdens een controle-afspraak bij de tandarts ervaren. Ook hebben we exploratief gekeken of de leeftijd van de kinderen, angst-predispositie, geslacht, medische aandoening, eerdere ervaringen met de procedures, en het doel van het onderzoek (wetenschappelijk onderzoek versus zorg) van invloed waren op de belasting tijdens het onderzoek.

Voor deze studie hebben we 418 zieke en gezonde kinderen geïncludeerd (8-18 jaar oud), waarvan 307 kinderen meededen met wetenschappelijk onderzoek, 50 kinderen die een controle bij de tandarts ondergingen en 61 kinderen werden geïncludeerd vanuit de klinische zorg. De meeste kinderen rapporteerden een beperkte mate van belasting tijdens de wetenschappelijke procedures. Wanneer we de belasting vergeleken met die van de kinderen tijdens de tandartscontroles waren de wangslijmvliesafnames, allergietesten en echoscopieën minder belastend, terwijl MRI-scans, bloedafnames en longfunctietesten een vergelijkbaar niveau van belasting lieten zien. Verder was alleen angst-predispositie positief gerelateerd aan belasting. Het was onduidelijk wat voor invloed het doel van de procedure (wetenschappelijk onderzoek versus zorg) had op de belasting. De meerderheid van de kinderen (ca. 60%) gaf als suggestie om voor afleiding te zorgen tijdens de onderzoekprocedures, met name door middel van het kijken naar films.

Wetenschappelijk onderzoek kan verschillende soorten risico met zich mee brengen: fysieke, psychologische, economische en juridische risico's. In **Hoofdstuk 6** hebben we gekeken naar de psychologische risico's voor de kinderen in wetenschappelijk onderzoek. We hebben psychologisch risico geoperationaliseerd als klinische relevante stress. Deze hebben we gemeten met de Children's Revised Impact of Event Scale (CRIES-13). Een score van ≥ 30 op deze vragenlijst werd gezien als klinisch relevante stress. Na één maand, hebben we de stress symptomen van 66 kinderen die een wangslijmvliesafname, MRI-scan, longfunctietest of bloedafname ondergingen gemeten. Een additionele groep van 34 kinderen hebben we één jaar na het ondergaan van een MRI-scan of bloedafname gevraagd naar hun stress symptomen.

Geen van de kinderen rapporteerde klinisch relevante stress, met uitzondering van één kind dat een jaar daarvoor een bloedafname had ondergaan. Belasting gedurende het onderzoek, angst-predispositie en geslacht (meisje) hadden een significant positieve relatie met lange-termijn stress symptomen. Kinderen die aanzienlijke belasting

tijdens het onderzoek ervaren, meisjes en kinderen die van nature angstig aangelegd zijn, lijken meer kans te hebben om lange-termijn stress symptomen te ervaren door deelname aan wetenschappelijk onderzoek.

In tegenstelling tot de voorgaande hoofdstukken over belasting, gaan **Hoofdstukken 7a en 7b** over de positieve ervaringen van kinderen in wetenschappelijk onderzoek en de mogelijke voordelen die zij ervaren van onderzoekdeelname.

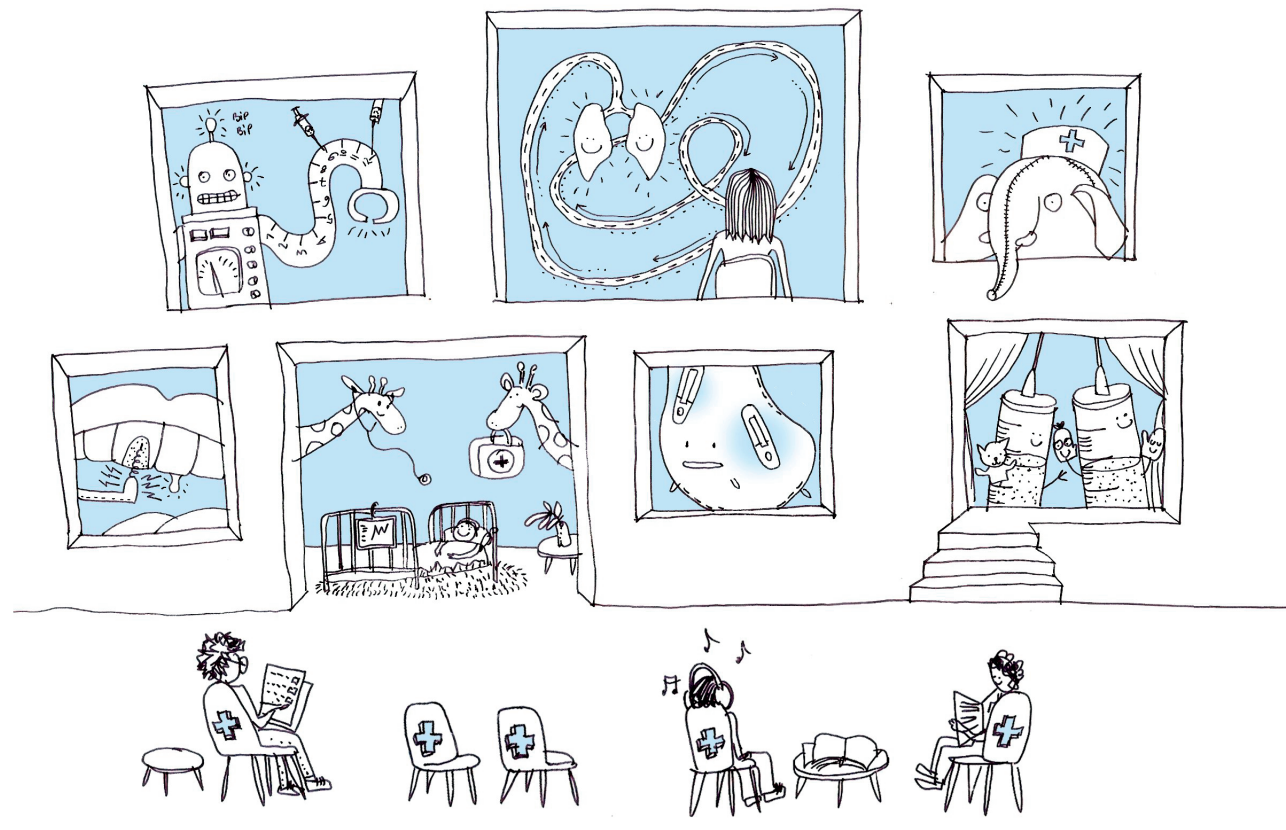
Het includeren van kinderen voor niet-therapeutisch wetenschappelijk onderzoek is een uitdaging omdat deelname risico's en belasting met zich meebrengt, maar tegelijkertijd geen gezondheidsvoordelen voor het deelnemende kind biedt. In **Hoofdstuk 7a** geven we inzicht in de positieve ervaringen van een groep zieke en gezonde kinderen (6-18 jaar) die deelnemen aan niet-therapeutische studies. We bediscussiëren of deze positieve ervaringen gezien kunnen worden als voordelen van onderzoekdeelname, en als zodanig in de besluitvorming een doorslaggevende rol kunnen spelen ten gunste van deelname aan medisch onderzoek. We beargumenteren waarom het helpen van anderen, plezier hebben en het verwerven van nieuw en verbeterde kennis hiervoor in aanmerking komen. We presenteren twee scenario's hoe ethische commissies deze voordelen mee kunnen nemen in de "risk-benefit" analyse van onderzoeken. In het eerste scenario wordt beschreven dat de bovengenoemde voordelen alleen moeten worden meegenomen in deze analyse wanneer het gaat om een cruciale studie waarbij de risico's en belasting iets meer dan minimaal zijn. In het tweede scenario pleiten we ervoor om deze voordelen mee te nemen in de risk-benefit analyse van alle onderzoeken.

Hoofdstuk 7b is gebaseerd op **Hoofdstuk 7a**. Het betreft een commentaar op het artikel *"Young people's experiences of participation in clinical trials: reasons for taking part"* door Luchtenberg et al. (2015). De auteurs van het stuk geven aan dat zij een kwalitatief onderzoek hebben gedaan naar redenen voor kinderen om deel te nemen aan wetenschappelijk onderzoek en de voordelen die zij ervaren van onderzoekdeelname. In ons commentaar onderschrijven wij de voordelen die Luchtenberg et al. noemen, waarbij wij ons baseren op ons eigen onderzoek met een meer gevarieerde onderzoekspopulatie (meer variatie in leeftijd, medische aandoeningen en studie types).

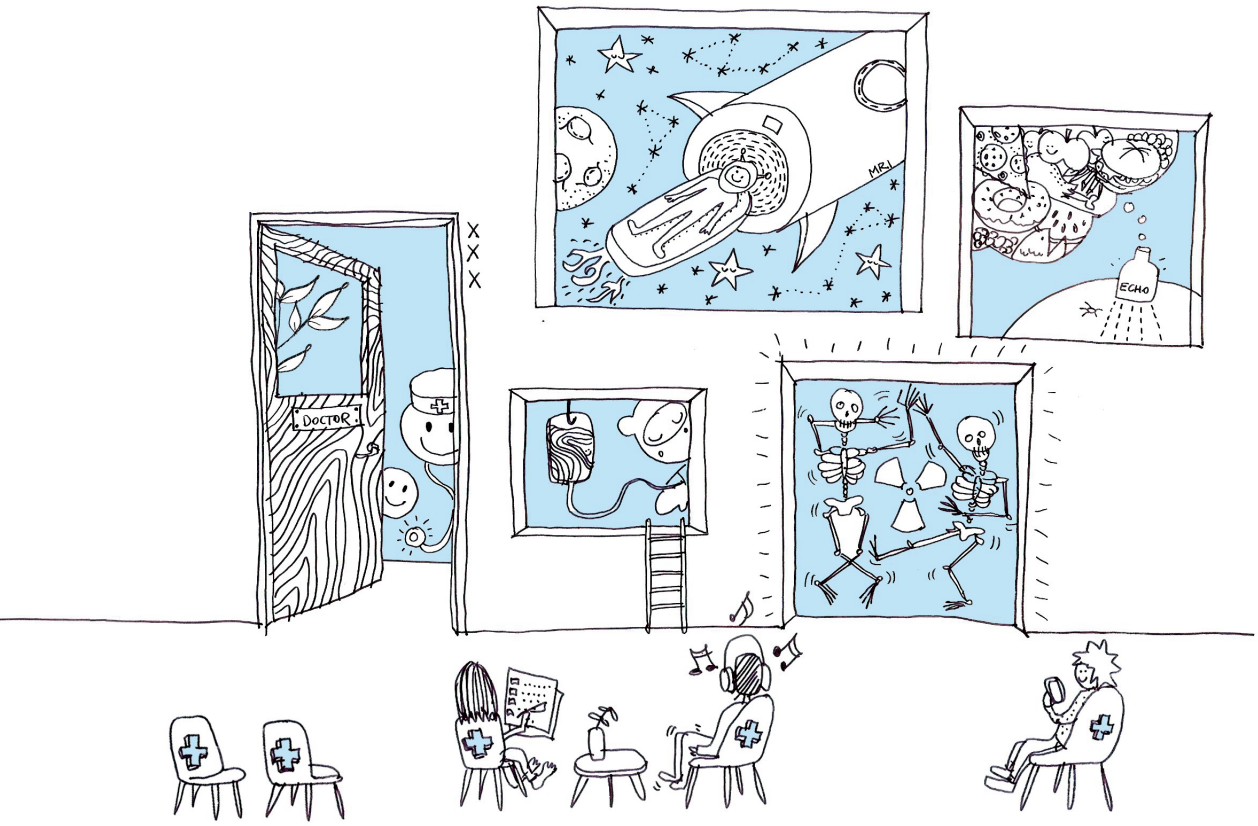
Hoofdstuk 8 bevat een discussie over de belangrijkste bevindingen van de studies in dit proefschrift. Dit proefschrift had als doel om de beslissingen over deelname aan wetenschappelijk onderzoek evidence-based te maken door informatie te verschaffen over de zelf-gerapporteerde belasting van kinderen tijdens onderzoeksprocedures. Deze gegevens vormen een eerste stap voor een referentiepunt van de belasting van onderzoeksprocedures in kindergeneeskundig onderzoek.

Samenvattend kan worden gezegd dat kinderen weinig belasting en lange-termijn stress ervaren door de door ons onderzochte procedures in wetenschappelijk onderzoek. Deze resultaten onderstrepen dat het - in het algemeen – aanvaardbaar is om kinderen deze procedures te laten ondergaan in het kader van wetenschappelijk onderzoek.

Verder staan in dit hoofdstuk aanbevelingen en implicaties voor verschillende groepen die betrokken zijn bij kindergeneeskundig onderzoek, zoals onderzoekers, ethische commissies, kinderen en ouders. Ook worden aanbevelingen gegeven voor toekomstig onderzoek. Zo is er meer onderzoek nodig over de belasting van de onderzoeksprocedures, met name over de belasting van onderzoeksprocedures die niet beschreven zijn in dit proefschrift. Wij hebben een implementatieplan opgesteld om deze gegevens te verzamelen en te verspreiden, en hebben hier recent een subsidie van ZonMw voor ontvangen.



PHD PORTFOLIO



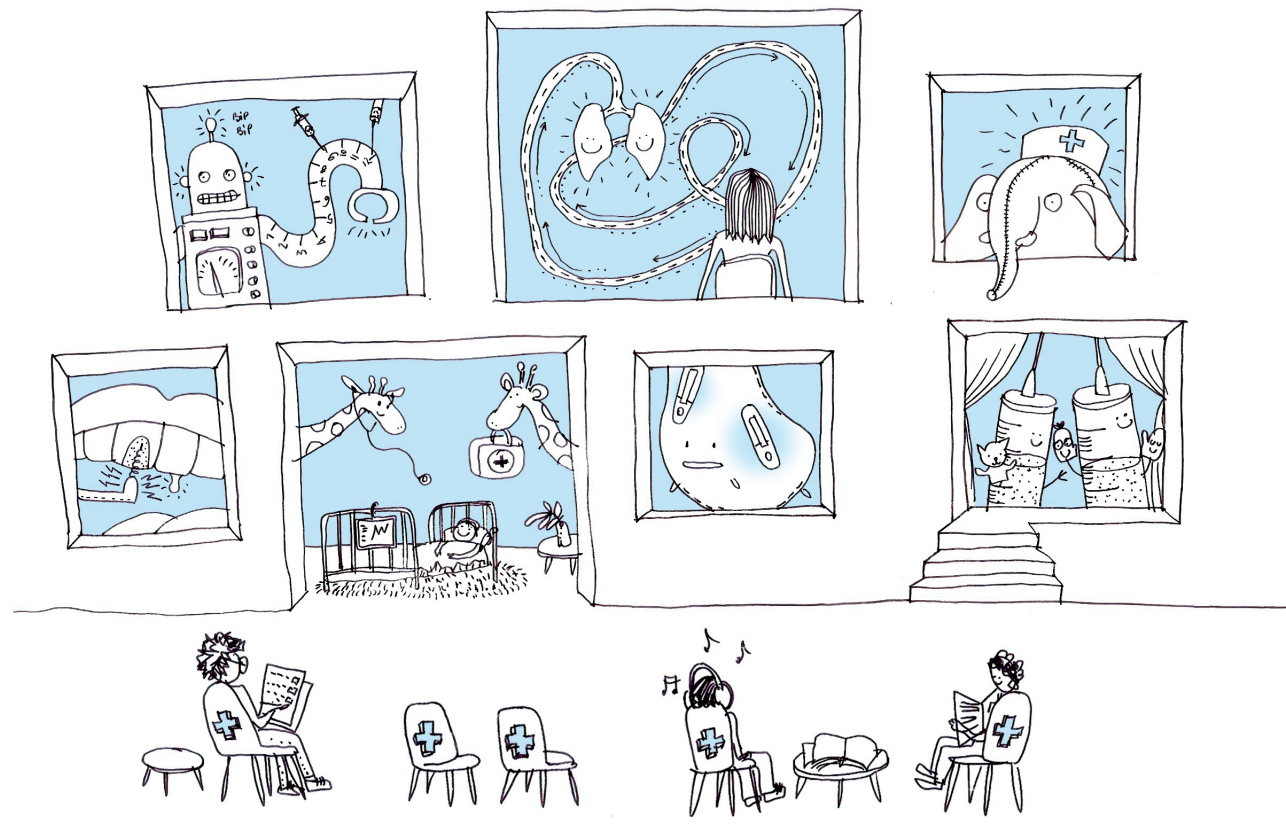
Name	Mira Sophie Staphorst
Department	Psychiatry, section Medical Psychology & Psychotherapy, Erasmus MC, Rotterdam, The Netherlands
PhD period	2012 – 2016
Promotors	Prof.dr. J.J. van Busschbach Prof.dr. J.B. van Goudoever Prof.dr. J. Passchier
Supervisor	Dr. J.A.M. Hunfeld

PHD TRAINING	**Year**	**Workload**
General research skills		
Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers BROK . Erasmus MC, Rotterdam	2012	20 hrs
Endnote. Erasmus MC, Rotterdam	2012	4 hrs
Systematical literature in PubMed. Erasmus MC, Rotterdam	2012	4 hrs
Systematical literature in other databases. Erasmus MC, Rotterdam	2012	4 hrs
Writing a scientific article. VU Taalcentrum, Amsterdam	2013	24 hrs
Introduction to clinical research. NIHES, Rotterdam	2014	0.7 ECTS
Biostatistics for clinicians. NIHES, Rotterdam	2014	0.7 ECTS
Integrity in research. Erasmus MC, Rotterdam	2014	0.3 ECTS
Research impact and relevance: how to publish a world class paper. Erasmus University, Rotterdam	2014	3.5 hrs
Research ethics. Medical Ethics & Philosophy, Erasmus MC, Rotterdam	2015	5 hrs
Grant Writing, 12C approach©. Erasmus MC, Rotterdam	2015	1.5 hrs
Recertification BROK	2016	4 hrs
In depth courses		
Qualitative interviewing. Evers Research Institute, Rotterdam	2013	16 hrs
Qualitative analyses. Evers Research Institute, Rotterdam	2013	16 hrs
Foundations of survey research. Utrecht University and Statistics Netherlands (CBS)	2013	1.5 ECTS
Regression analyses. NIHES, Rotterdam	2014	1.9 ECTS
Introduction in multilevel analysis. Utrecht University	2015	1.5 ECTS
CONFERENCES – PARTICIPATION AND PRESENTATIONS	**Year**	**Workload**
2nd Amsterdam Kindersymposium, Amsterdam	2013	8 hrs
Kinderen en jongeren actief in wetenschappelijk onderzoek. Nederlands-Vlaams Platform Researching Children, Leiden	2013	8 hrs
Presentation 'Discomfort of children in clinical research: a qualitative study'. 3rd Amsterdam Kindersymposium, Amsterdam	2014	1 ECTS
Symposium 'Ethiek in the picture!' Dilemma's blijvend in beeld. Commissie Ethiek en Kind, Juliana Kinderziekenhuis, Den Haag	2014	4 hrs
Poster and presentation (Award 'most promising research'). 2nd International Paediatric Psychology Conference, Amsterdam	2014	1 ECTS
Presentation 'Children's discomfort during clinical research - interview study'. Sophia Research Day, Erasmus MC, Rotterdam	2015	8 hrs

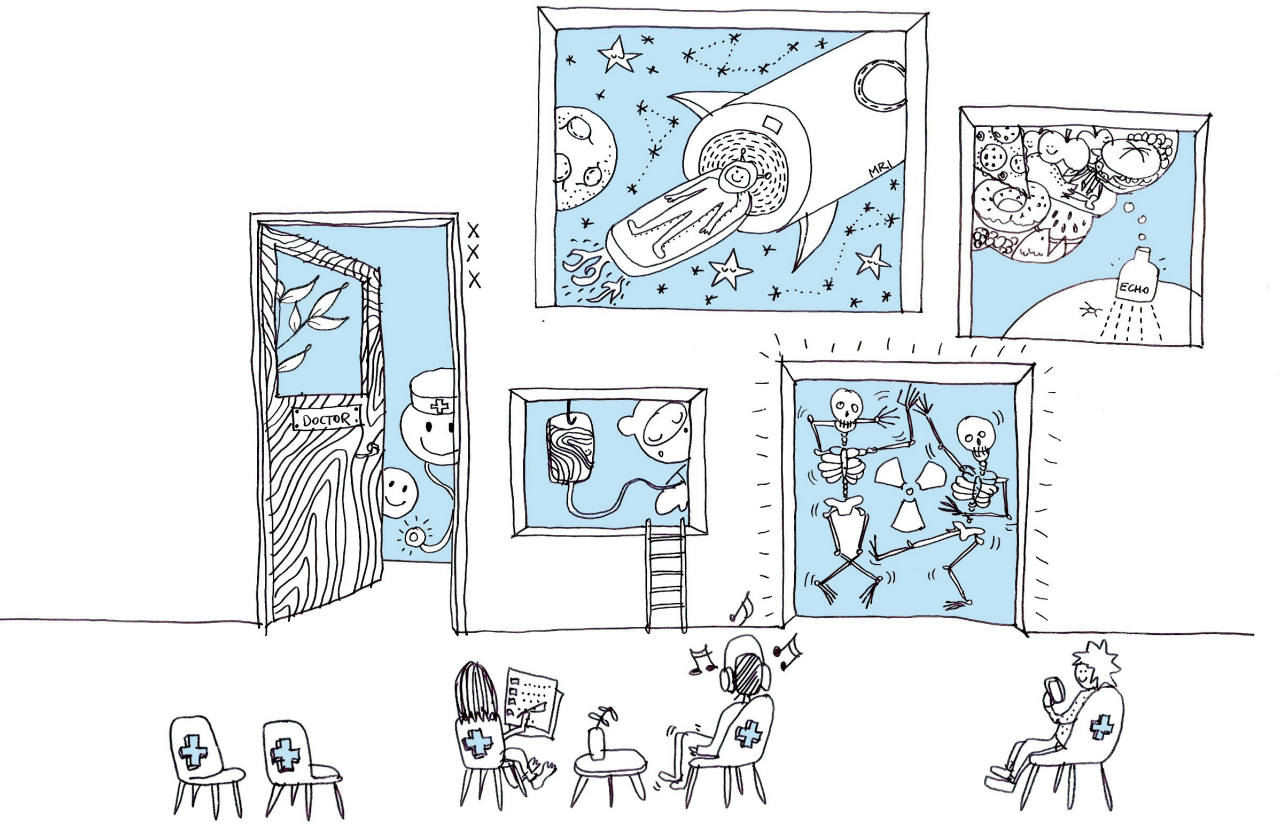
Presentation 'De belasting die kinderen ervaren in wetenschappelijk onderzoek – interviewstudie'. NVK Congres, Veldhoven	2015	1 ECTS
Presentation 'Voordelen die kinderen zelf ervaren na deelname aan wetenschappelijk onderzoek'. NVK Congres, Veldhoven	2015	1 ECTS
Presentation 'Children's discomfort in clinical research', EAPS Conference, Genève	2016	1 ECTS
OTHER PRESENTATIONS	**Year**	**Workload**
Medical psychology, Erasmus MC, Rotterdam	2012	1 hrs
Pediatric pulmonology, AMC, Amsterdam	2012	1 hrs
Pediatric gastroenterology, AMC, Amsterdam	2013	1 hrs
Minor medical psychology, Erasmus University, Rotterdam	2013	1 hrs
ZonMw Priority Medicines Children, The Hague	2013	1 hrs
Pediatric gastroenterology, AMC, Amsterdam	2014	1 hrs
Psychiatry, Erasmus MC, Rotterdam	2014	1 hrs
Pediatric pulmonology, Erasmus MC, Erasmus MC, Rotterdam	2014	1 hrs
Nederlandse vereniging voor METCs (NVMETC), Utrecht	2015	1 hrs
Research nurses, UMC Utrecht.	2015	1 hrs
European working group 'EU guideline - Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population', Ministry of Health, Welfare and Sports VWS, Den Haag	2016	1 hrs
TEACHING	**Year**	**Workload**
Basiskwalificatie onderwijs (BKO). Erasmus MC, Rotterdam	2012	40 hrs
Coordination simulation patients. Erasmus MC, Rotterdam	2012	25 hrs
Lecturer of communication skills and medical psychology in the medical curriculum. Erasmus MC, Rotterdam	2012-2016	0.2 fte
Coach training and intervision. Erasmus MC, Rotterdam	2015	8 hrs
Coach for 8 medicine students. Erasmus MC, Rotterdam	2015-2016	24 hrs
MISCELLANEOUS	**Year**	**Workload**
Working group. National ethics guideline for psychological and behavioral science research.	2012-2014	0.1 fte
Research meetings with related researchers from the ethics projects within Priority Medicines Children (ZonMw). Erasmus MC, Rotterdam	2012-2014	5 hrs
Working group. National guideline "Zorgvuldigheidscriteria rondom onderzoek met kinderen " Nederlandse Vereniging voor Kindergeneeskunde (NVK)	2012-2014	320 hrs
Research meetings. Medical psychology, Erasmus MC, Rotterdam	2012-2016	1 ECTS
Volunteer medicine program. IMC Weekendschool, Amsterdam Noord	2013	20 hrs
Coordination and organization research meetings. Medical psychology, Erasmus MC, Rotterdam	2013-2016	1 ECTS
PhD-day. Erasmus MC, Rotterdam	2013, 2014	12 hrs
Seminar career orientation. Promeras, Erasmus MC, Rotterdam	2014	4 hrs
Research meetings. Pediatric psychology, Erasmus MC, Rotterdam	2014-2015	6 hrs
Masterclass strategy consultancy in healthcare. Gupta Strategists, Utrecht	2015	12 hrs

Reviewer. Journal of Empirical Research on Human Research Ethics	2015	6 hrs
Reviewer. Social Science and Medicine	2016	6 hrs
Grant (€50.000,-) Verspreidings- en implementatie Impuls, ZonMw	2016	36 hrs

1ECTS (European Credit Transfer System) is equal to a workload of 28 hours.
1fte (full time equivalent) is equal to a working week of 36 hours.



LIST OF PUBLICATIONS



THIS THESIS

MS Staphorst, JAM Hunfeld, R Timman, J Passchier, JB van Goudoever (2015). Hearing the voices of children: self-reported information on children's experiences during research procedures – A study protocol. BMJ Open, 5:e009053.

MS Staphorst, JAM Hunfeld, S van de Vathorst, J Passchier, JB van Goudoever on behalf of the BURDEN-group (2015). Children's self reported discomforts as participants in clinical research. Social Science & Medicine, 142:154–162.

MS Staphorst, S van de Vathorst (2015). Empirical Data on Benefits Children Experience in Clinical Research. American Journal of Bioethics, 15:20-21.

MS Staphorst, JAM Hunfeld, S van de Vathorst (2016). Are positive experiences of children in non-therapeutic research justifiable research benefits? Journal of Medical Ethics, 0:1–5.

OTHER PUBLICATIONS

MS Staphorst. Kind & Ziekenhuis K&Z Magazine. Stichting kind en ziekenhuis, april 2014. Onderzoek Belastend? De mening van kinderen zelf. April 2014.

MS Staphorst. Interne nieuwsbrief Generation R, Erasmus MC. Onderzoek naar MRI ervaringen. September 2014.

MS Staphorst. Externe nieuwsbrief Generation R, Erasmus MC. Uitgelicht: Generation R onderzoekt de ervaringen met de MRI. No. 31 2015.

MS Staphorst. Kinderarts & Samenleving. Nederlandse vereniging voor Kindergeneeskunde (NVK). Hoe belastend vinden kinderen onderzoek? September 2015.

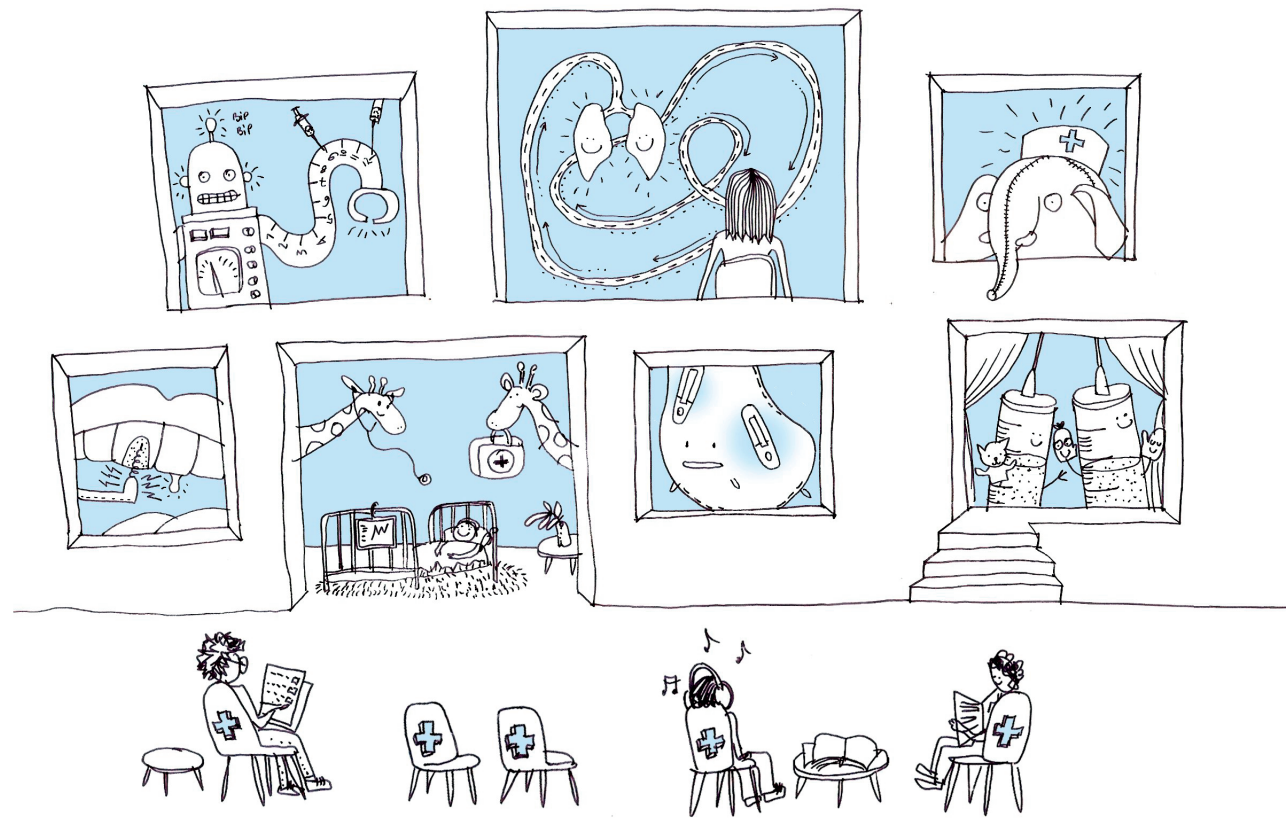
SUBMITTED

MS Staphorst, R Timman, J Passchier, JJV Busschbach, JB van Goudoever, JAM Hunfeld. The development of the 'Children's Discomfort during Research Procedures Questionnaire' (CDRPQ).

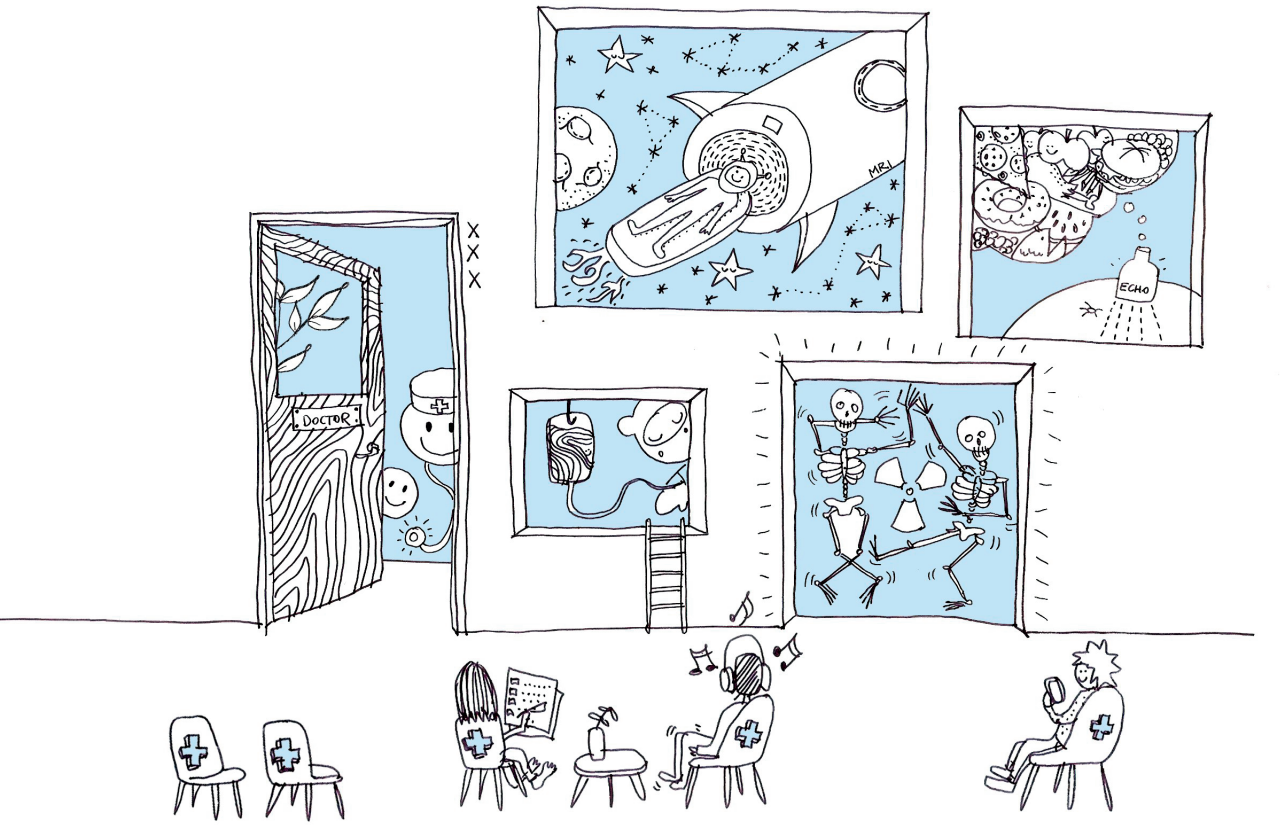
MS Staphorst on behalf of the BURDEN-group. The child's perspective on discomfort during medical research procedures.

MS Staphorst, JAM Hunfeld, R Timman, J Passchier, JJV Busschbach, JB van Goudoever. The risk of children on clinically relevant stress due to research procedures.

MS Staphorst. Hoofdstuk over belasting bij kinderen in onderzoek. Richtlijn Zorgvuldigheidscriteria bij kinderen in onderzoek. Nederlandse vereniging voor Kindergeneeskunde (NVK).



LIST OF CO-AUTHORS AND COLLABORATORS



Wim van Aalderen - Department of Pediatrics, Emma Children's Hospital, Academic Medical Center (AMC), Amsterdam, the Netherlands

Nora Adriaens - Department of Pediatrics, Emma Children's Hospital, Academic Medical Center (AMC), Amsterdam, the Netherlands

Marc Benninga - Department of Pediatrics, Emma Children's Hospital, Academic Medical Center (AMC), Amsterdam, the Netherlands

Fenny Beukers - Department of Pediatrics, Emma Children's Hospital, Academic Medical Center (AMC), Amsterdam, the Netherlands

Margriet Bisschoff - Departments of Pediatrics and Child Psychiatry, Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands

Irma Bon - Department of Pediatrics, VU University Medical Center (VUmc), Amsterdam, the Netherlands

Jan van Busschbach - Department of Psychiatry, section Medical Psychology and Psychotherapy, Erasmus University Medical Center, Rotterdam, the Netherlands

Kay Diederen - Department of Pediatrics, Emma Children's Hospital, Academic Medical Center (AMC), Amsterdam, the Netherlands

Hans van Goudoever - Department of Pediatrics, Emma Children's Hospital, Academic Medical Center (AMC), Amsterdam, the Netherlands. Department of Pediatrics, VU University Medical Center (VUmc), Amsterdam, the Netherlands

Eric Haarman - Department of Pediatrics, VU University Medical Center (VUmc), Amsterdam, the Netherlands

Simone Hashimoto - Department of Pediatrics, Emma Children's Hospital, Academic Medical Center (AMC), Amsterdam, the Netherlands

Lies Hulshof - Department of Pediatrics, Emma Children's Hospital, Academic Medical Center (AMC), Amsterdam, the Netherlands

Joke Hunfeld - Department of Psychiatry, section Medical Psychology and Psychotherapy, Erasmus University Medical Center, Rotterdam, the Netherlands

Vincent Jaddoe - Departments of Pediatrics and Child Psychiatry, Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands

Karin de Jong - Department of Pedodontology, Academic Centre Dentistry Amsterdam (ACTA), Amsterdam, the Netherlands

Nicolette de Jong - Departments of Pediatrics and Child Psychiatry, Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands

Johan de Jongste - Departments of Pediatrics and Child Psychiatry, Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands

Angelika Kindermann - Department of Pediatrics, Emma Children's Hospital, Academic Medical Center (AMC), Amsterdam, the Netherlands

Marsh Königs - Section of Clinical Neuropsychology, VU University, Amsterdam, the Netherlands

Suzanne Mugie - Department of Pediatrics, Emma Children's Hospital, Academic Medical Center (AMC), Amsterdam, the Netherlands

Charlotte Nusman - Department of Pediatrics, Emma Children's Hospital, Academic Medical Center (AMC), Amsterdam, the Netherlands

Jaap Oosterlaan - Section of Clinical Neuropsychology, VU University, Amsterdam, the Netherlands

Jan Passchier - Department of Clinical Psychology/EMGO+, VU University, Amsterdam, the Netherlands

Mariëlle Pijnenburg - Departments of Pediatrics and Child Psychiatry, Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands

Liesbeth Reneman - Department of Pediatrics, Emma Children's Hospital, Academic Medical Center (AMC), Amsterdam, the Netherlands

Lissy de Ridder - Departments of Pediatrics and Child Psychiatry, Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands

Hyke Tamminga - Department of Pediatrics, Emma Children's Hospital, Academic Medical Center (AMC), Amsterdam, the Netherlands

Henning Tiemeier - Departments of Pediatrics and Child Psychiatry, Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands

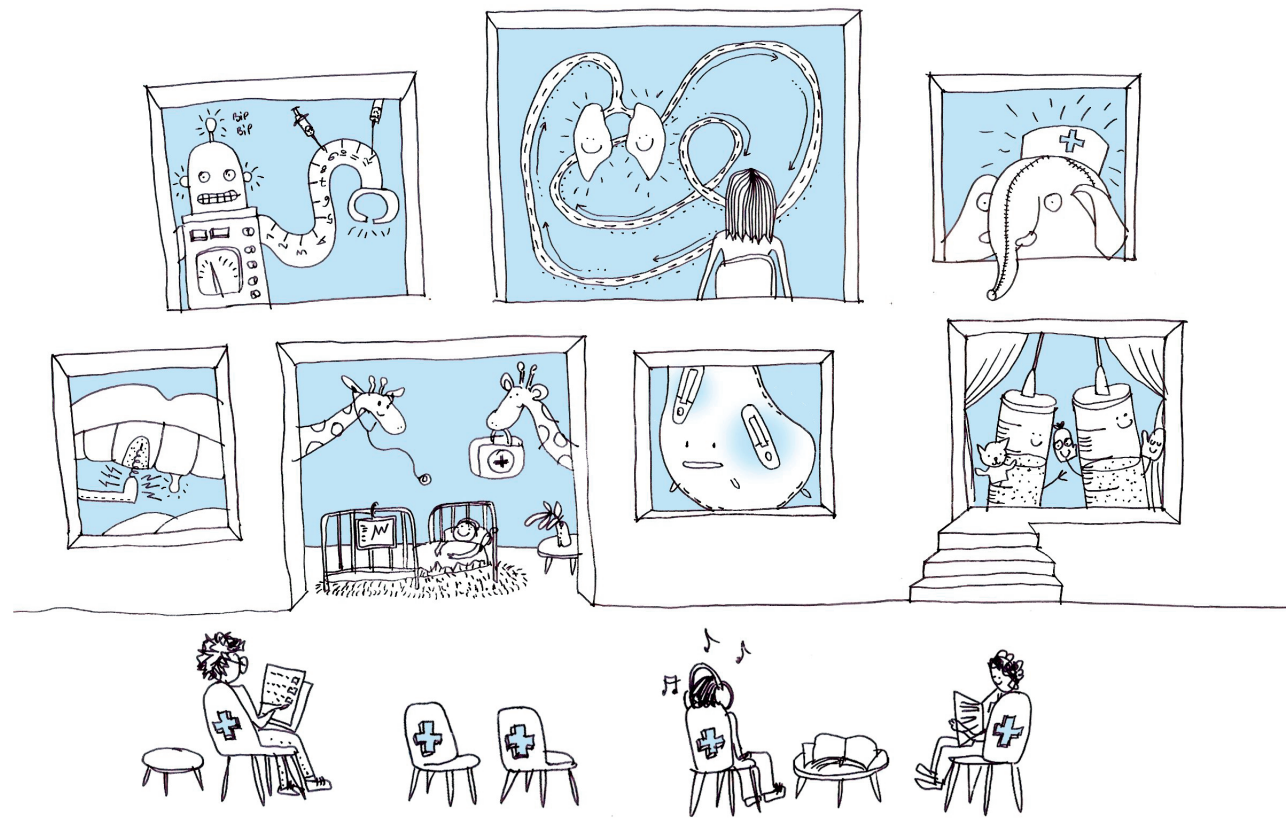
Reinier Timman - Department of Psychiatry, section Medical Psychology and Psychotherapy, Erasmus University Medical Center, Rotterdam, the Netherlands

Hannah van der Valk - Departments of Pediatrics and Child Psychiatry, Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands

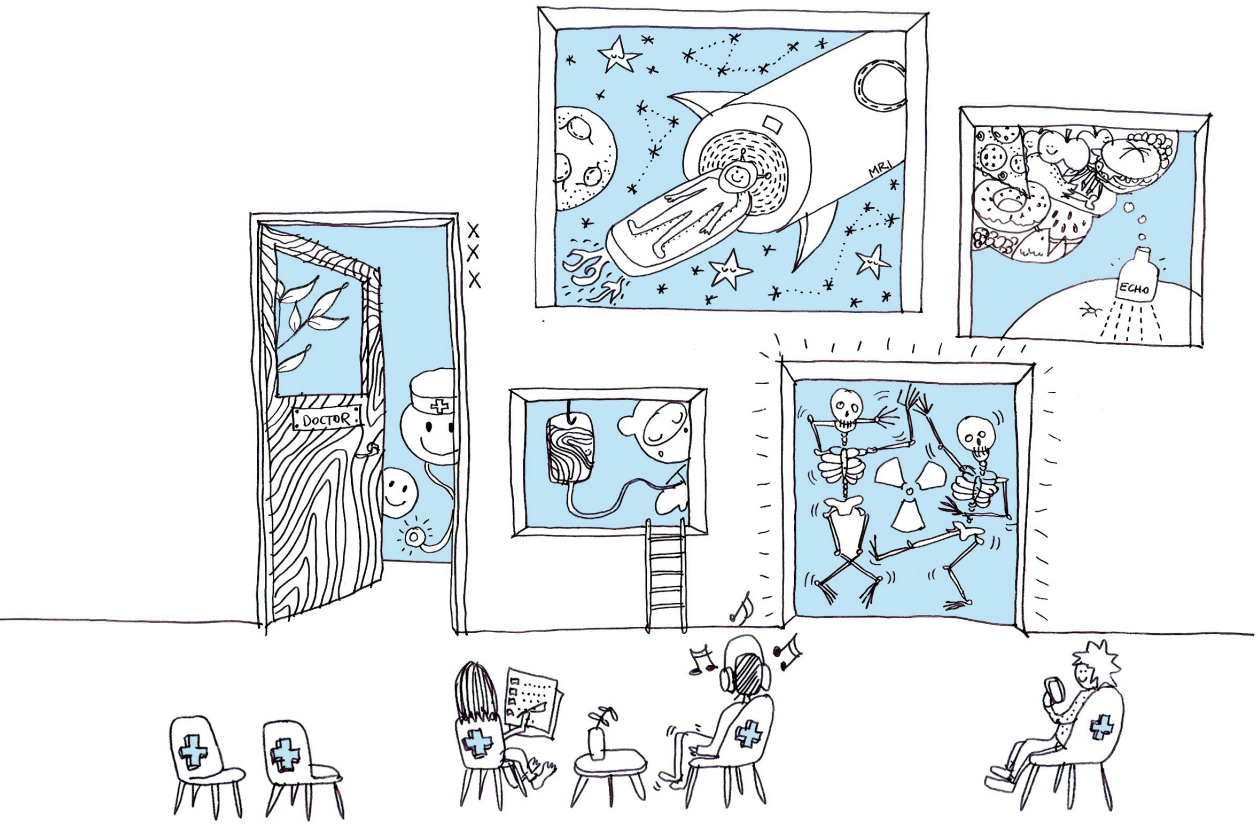
Suzanne van de Vathorst - Department of Ethics and Philosophy, Erasmus University Medical Center, Rotterdam, the Netherlands

Ilja de Vreede - Department of Pediatrics, Emma Children's Hospital, Academic Medical Center (AMC), Amsterdam, the Netherlands

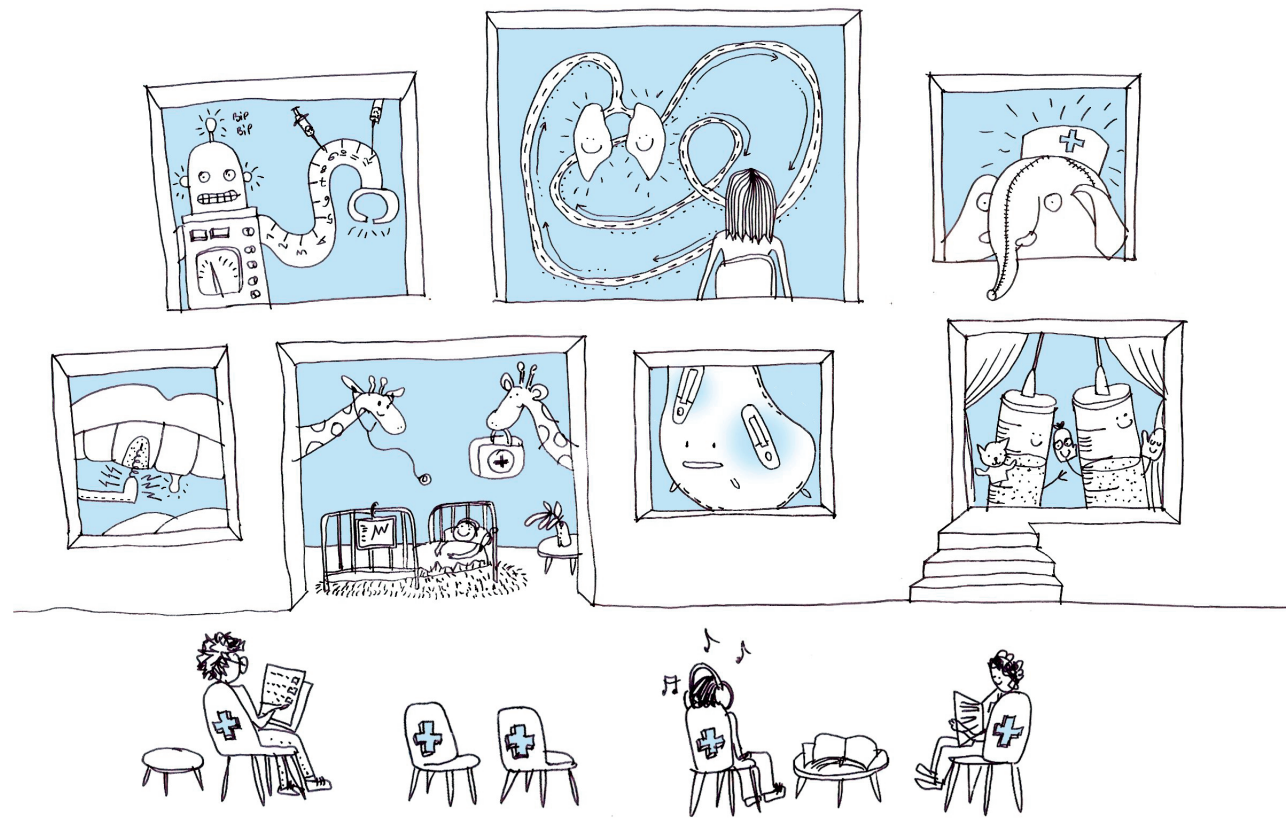
Aleid van Wassenaer - Department of Pediatrics, Emma Children's Hospital, Academic Medical Center (AMC), Amsterdam, the Netherlands



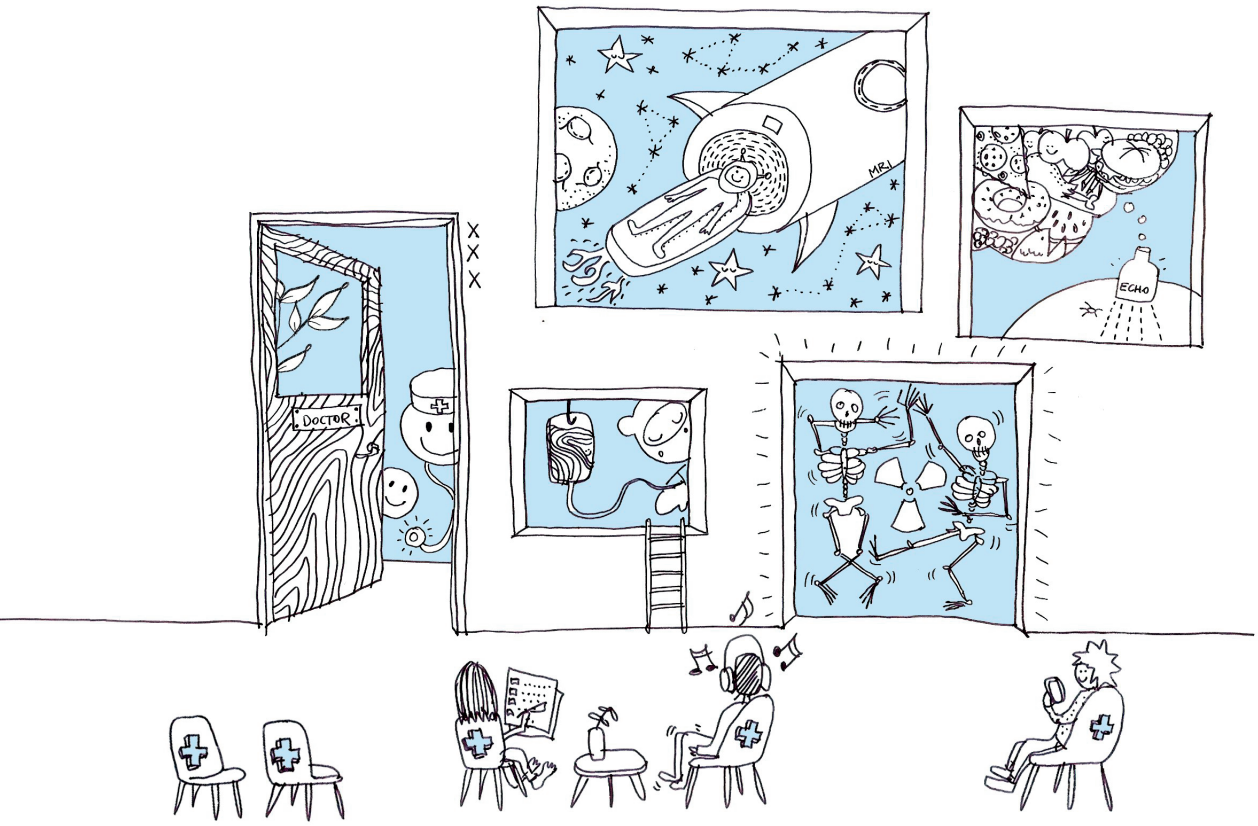
CURRICULUM VITAE



On November 28th 1986, Mira Sophie Staphorst was born in Leiden (the Netherlands). In 2005, after finishing grammar school (Stedelijk Gymnasium Leiden), she began studying psychology at Leiden University. After attaining her bachelor's degree, she moved to Canada for a semester, and followed an exchange program in public health at Queen's University in Kingston. Upon returning to Leiden, she continued her studies in health psychology, completing a master's degree in 2010. Between 2010-2016, she worked for the section of Medical Psychology and Psychotherapy at the Erasmus University Medical Center in Rotterdam, where she started as a lecturer in communication skills and medical psychology. After 1,5 years, she switched to research and worked on a research project focusing on the experiences of children in clinical research. The results of this project are described in this thesis. Mira currently works as a policy advisor for research and education at the Julius Center (UMC Utrecht), and as a post-doc researcher at the Academic Medical Center (AMC) in Amsterdam for the follow-up project of this thesis.



DANKWOORD



Graag wil ik iedereen bedanken die op een directe of indirecte manier heeft bijgedragen aan het tot stand komen van dit proefschrift.

Allereerst wil ik alle kinderen (en hun ouders) bedanken voor deelname aan de onderzoeken in dit proefschrift. Bedankt voor jullie openheid over jullie ervaringen in wetenschappelijk onderzoek.

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Prof. Passchier. Beste Jan, ik heb ontzettend veel geleerd van jouw ruime ervaring als onderzoeker in de medische psychologie. De manier waarop jij eindeloze mogelijkheden ziet om onderzoek te doen, vind ik inspirerend. Je hebt zelfs onze vragenlijst naar het Indonesisch laten vertellen; never say never! Bedankt voor je nauwe betrokkenheid bij het project en je betrokkenheid op persoonlijk vlak.

Prof. Van Goudoever. Beste Hans, elke keer nadat ik bij jou was geweest om de vorderingen om het project te bespreken, stapte ik vol goede moed en motivatie de deur uit. Jouw kracht om te relativeren en te motiveren, en lastige vraagstukken te vergemakkelijken (en dat ook nog eens op een super efficiënte manier) vind ik enorm bewonderenswaardig.

Prof. Van Busschbach. Beste Jan, in het laatste jaar werd jij officieel mijn promotor, ondanks dat je deze rol al ruime tijd daarvoor 'officieus' vervulde. Jouw nuchtere kijk heeft het onderzoek goed gedaan. Ik waardeer het enorm dat je zoveel tijd hebt gestoken om mij 'de kunst van het weglaten' te leren ('Hier heden verse eieren te koop').

Dr. Hunfeld. Beste Joke, ik heb je als een ontzettend betrokken copromotor ervaren die dag en nacht voor mij klaar stond. Je hebt ervoor gezorgd dat ik de grote lijnen van het project voor ogen bleef houden en niet teveel in details verzandde – een bekende valkuil van mij. Dank voor de zorgvuldigheid waarmee je aan het project hebt gewerkt en dank voor je vertrouwen in mij.

Prof. Rings, Prof. Knibbe, Prof. Willems, Prof. Kalverboer en Prof. Oosterlaan: hartelijk dank voor de tijd en moeite die jullie hebben genomen om mijn proefschrift kritisch te beoordelen. Ook dank ik jullie voor de bereidheid om aan de promotiecommissie deel te nemen.

Prof. Van de Vathorst. Beste Suzanne, dank voor de enthousiaste manier waarop jij vanuit ethisch oogpunt een bijdrage hebt geleverd aan dit proefschrift. Ik heb met veel plezier met jou samengewerkt, en dat heeft ons ook nog eens een paar mooie publicaties opgeleverd!

Dr. Timman. Beste Reinier, ik wil je bedanken voor jouw statistische ondersteuning en jouw geduld om mij dingen uit te leggen. Ontzettend praktisch dat je in de kamer naast mij zat en dat ik altijd even tussendoor mocht komen met mijn vragen.

Graag wil ik alle betrokken (kinder-)artsen, verpleegkundigen, onderzoekers, ethici en tandartsen bedanken voor de hulp bij mijn onderzoek. Bedankt voor de mogelijkheid om aan de kinderen uit jullie studies te vragen hoe zij dit hebben ervaren, jullie kritische blik bij het ontwikkelen van de vragenlijst, jullie uitleg en kennis over de kinderen in jullie onderzoeken en het kritisch lezen van mijn manuscripten.

Denise, Francien en Noortje: dank voor jullie hulp bij het uitwerken van de interviews. Claartje, José, Kerime, Mariette, Marlou, Nicoletta en Sarina: dank voor jullie hulp bij het afnemen van de vragenlijsten. Zonder jullie was ik nu nog steeds data aan het verzamelen! Kerime, jou wil ik in het bijzonder bedanken voor je lieve briefjes en chocola; een welkome afleiding tijdens het schrijven!

Lieve oud-collega's van het Erasmus MC: jullie hebben mijn eerste jaren op de arbeidsmarkt tot een bijzondere tijd gemaakt, waar ik met veel plezier op terug kijk. Dank voor alle gezelligheid, interesse én vooral ook jullie hulp de afgelopen jaren. Een paar mensen wil ik in het bijzonder bedanken. Benno, ik ben je erg dankbaar dat je mij destijds hebt aangenomen als docent bij de Medische Psychologie. Met veel genoegen kijk ik terug op onze gesprekken over onderwijs, muziek en kunst. Annemerle en Noor, wat fijn om twee van die toppers als kamergenoten te hebben gehad. Het 'support'-filmpje dat jullie voor mij hebben gemaakt, heb ik vaak bekeken. Sintyha, dank voor je hulp bij allerlei onderwijszaken, maar nog meer voor de gezellige shopsessies, etentjes en natuurlijk alle bara's die je voor me mee hebt genomen. Hanneke, mijn mede-Amsterdammer in Rotterdam, ik kijk met veel plezier terug naar onze roadtrips en uitstapjes door het land. (Ex-)junior onderzoekers van de MPP, dank voor alle steun, jullie gezelschap, jullie hulp en natuurlijk ook het delen van promovendus-perikelen. Wilfred, mijn onderwijspartner-in-crime, ik kijk met veel plezier terug op de leuke lessen die wij samen hebben gegeven. Ik wil je ook bedanken voor je hulp om mij in contact te brengen met artsen/onderzoekers in het Sophia. Jouw advies 'kaftje er omheen' heeft zijn vruchten afgeworpen; daarna lag het proefschrift (relatief) snel bij de drukker! Maya, bedankt voor je hulp

om de lessen te verzetten als 'er weer eens iets belangrijks tussen was gekomen voor mijn onderzoek'. Hetty, dank voor jouw helpende hand bij allerhande logistieke zaken.

Divisie Vrouw-Kind van het AMC: hartelijk dank voor de gastvrijheid om ook bij jullie aan mijn proefschrift te kunnen werken.

Mijn collega's van het Julius Centrum (UMC Utrecht), met name kamer Str 7.101, wil ik bedanken voor de interesse en steun bij de laatste loodjes van mijn onderzoek. Wat heerlijk om zulke fijne collega's te hebben.

Iwona, dank voor de prachtige omslag van mijn proefschrift.

Lieve vrienden, vriendinnen en familie, dank voor jullie oprechte belangstelling in mijn onderzoek, jullie positiviteit en de welkome afleiding naast mijn onderzoek.

Lieve Bibi, ik vind het heel bijzonder dat jij aan mijn zij staat bij de verdediging van mijn proefschrift. Sinds we samen in Leiden psychologie zijn gaan studeren, ben jij een belangrijk persoon in mijn leven. Je bent een goede vriendin, studiegenoot, clubgenoot, oud-huisgenoot, schoonzus, en nu ook paranimf!

Lieve Annette, Mark en Willem, en de rest van de Stalen en Van Driellen, bedankt dat jullie mij zo liefdevol hebben opgenomen in jullie familie. Dank voor jullie interesse in mijn onderzoek en de nodige ontspanning.

Lieve Irene, mijn lieve bommetje, waar zou ik zijn zonder jou? Door jou leer ik dingen los te laten, te relativeren en - niet geheel onbelangrijk - voor mijzelf op te komen. Jij houdt mij een spiegel voor waar dat nodig is en bent mijn rots in de brandig. Ik ben ontzettend blij dat jij mijn lieve zus en paranimf bent!

Lieve papa en mama, jullie hebben mij de vrijheid gegeven om mijn eigen keuzes te maken in het leven en hebben mij het vertrouwen gegeven dat ik meer kan dan dat ik zelf denk. Bedankt voor al jullie onvoorwaardelijke liefde, geduld en support. Papa, dank voor al je wijze adviezen. Lieve mama, dit proefschrift draag ik op aan jou.

Lieve Rogier, woorden schieten te kort als ik moet beschrijven hoe dankbaar ik jou ben. Jij bent degene die er altijd voor mij is; wat ben ik blij dat jij en ik samen wij zijn. Ik houd van jou!