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Hearing the voices of children: self-reported information on children's experiences of medical research procedures – A study protocol

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ABSTRACT

Introduction: In pediatric research there is a tension between what you can ask from a child and what is needed for the development of evidence-based methods for the 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 of research procedures.

Methods and analysis: In the first phase of our study we aim to interview 40 children (6-18 years) about their self-reported experiences after participating in clinical research. In the second phase, we will develop a questionnaire for the quantification of the experiences during a number of research procedures. We use the outcomes of the interview for the development of this questionnaire. The next step is to measure the experiences of children (6-18 years) during seven research procedures by using this questionnaire. A one-month follow-up is conducted to investigate possible long-term impact of the research procedures on the children. The children will be recruited from different research studies in three academic children's hospitals in the Netherlands.

Discussion: The findings of our study will give us 1) self-reported information on children's experiences of a number of research procedures, including differences between subgroups of children (e.g. age, health condition, anxiety-proneness); 2) children's recommendations for decreasing discomfort during these research procedures; 3) an instrument for the quantification of the self-reported experiences of research procedures which can be used to monitor children's discomfort related to research procedures.

The findings of our study can facilitate evidence-based decision-making about the participation of children in clinical research for Institutional Review Boards, pediatric researchers as well as for children and their parents.

Strengths and limitations of this study

- This study gives insight into the experiences of research procedures in children, as seen from the perspective of children themselves.
- We develop an instrument to register children's self-reported experiences during research procedures and their suggestions to decrease possible discomforts.
- In this study, we identify children who deserve special attention during research because of their (mental) vulnerability (based on age, health condition and anxiety-proneness).
- We study children's experiences during a limited number of research procedures as well as a limited number of medical conditions of the children. Future research is needed to study the experiences of other research procedures with children from all kinds of medical backgrounds.

INTRODUCTION

In 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 they are (legally) unable to give informed consent. For instance, there are scarce data about dosage and effect of medicines for children, which amounts to 65% of all prescribed drugs. More pediatric 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 benefit 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. pediatricians, pediatric nurses, ethicists). Literature shows, however, that pediatric nurses, pediatricians, psychologists and parents are likely to overestimate, e.g.[3 4], or underestimate, e.g.[4 5], children's discomfort in medical settings. It is therefore crucial to 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 the discomforts of research procedures.[6]

The measurement of children's experiences in pediatric research

Hunfeld & Passchier reviewed the literature on discomfort of medical procedures in pediatric 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 for having empirical data about the experiences of children in 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 however concerns *perceived* benefits and barriers to pediatric clinical trials participation. The other questionnaire, 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 generalize. 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 main aim of these studies is to get insight into the self-reported experiences of children when undergoing research procedures. Since there is limited

information about this topic, the first phase of our project consists of a qualitative study to explore the experiences of children in clinical research. The second phase is a study in which we measure children's experiences during research procedures in a quantitative way.

Research questions

Our research questions are:

1. What are children's experiences during (common) research procedures?

2. What is the emotional impact of research procedures for children caused after one month?

3. To what extent are children's experiences and emotional impact determined by the child's anxiety-proneness?

4. Are there differences in experiences and emotional impact of research procedures between a) healthy children and children with a chronic condition and between b) young (<12 years) and older children (≥12 years)?

5. Are there differences in experiences of the same medical procedures that are conducted in the context of clinical research versus diagnostics and therapies?

METHODS AND ANALYSIS - INTERVIEW STUDY

Design

In the first phase of our study, we will start with semi-structured interviews to explore the children's experiences with research procedures, their suggestions to reduce potential discomfort caused by the procedures, and their understanding of the word 'discomfort'. In addition, children will answer a few written questions about their experiences with the research procedures. They fill in each question on a Likert-scale and two visual analogue scales (VAS) to find out their preference for a specific response option. We will use the

outcomes from this phase for the development of a questionnaire to measure children's experiences in the second phase.

Population

In the interview study we aim to include 40 children, or until saturation is reached.[10] The focus of the interviews is to explore the experiences of a diverse group of children participating in various research studies in order to get information from subjects with various characteristics (e.g. in age, health status). Children are eligible to be interviewed if they meet the following criteria: a) aged between 6 – 18 years, b) fluent in Dutch, c) no current psychological treatment for pain or anxiety disorders, d) no severe psychosocial problems, e) accompanied by at least one parent or care-taker. Children will be excluded if they have impaired cognitive ability or have an inability to communicate verbally which will be determined by the researchers of the medical studies on which our study is "piggybacked".

We aim to include children from four different pediatric departments: gastroenterology, pulmonology, nephrology and oncology to cover a large variety of research procedures and to include children from a broad range of diseases. The children will be recruited from three academic hospitals in The Netherlands: Sophia children's hospital (Erasmus University Medical Center) in Rotterdam, the department of Pediatrics of the VU Medical Center in Amsterdam, and Emma children's hospital (Academic Medical Center) in Amsterdam.

Procedure

Children who participate in a clinical research study from the above mentioned departments and their parents will be approached by the researchers of the studies we will cooperate with. If they are 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 questions about the interview in a face-to-face conversation with the interviewer, which will probably be on the day of the child's research visit. Once parents and children agree to participate, written parent consent and child assent (children ≥ 12 years) will be obtained. Children younger than twelve 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 a specific training in interview skills by experts in the field of medical psychology. Children will receive a gift-card (7.50 euros) for their participation. Interviews will be conducted in a private room at the hospital, directly after the children's participation in the research studies. Parents can 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 complete a brief survey about the child's demographics and medical history.

Instruments

Demographics

We will collect demographics from the child's medical record which include gender, date of birth, ethnicity, educational level, pediatric disease and medical history.

Interview

The interviews will be semi-structured and will be focused on the discomforts the child experienced during a clinical research study, in particular in relation to the research procedures involved. We will ask children about their understanding of the word 'discomfort' and how they would describe this word. Children will also be asked about suggestions to decrease possible discomfort. The interview questions will be based on literature, a review

about discomfort of children in clinical research [7] as well as on input from several pediatricians, psychologists and pediatric nurses.

In addition, children will fill in a 'pilot questionnaire' with a couple of (written) questions about their experiences with the research procedures. To find out children's preferences for a response option for the answers of the questionnaire in the second phase, children fill in each question on: a 5-point Likert scale, a 100mm colored visual analogue scale (VAS) and a simple 100mm VAS.

Analyses

The interviews will be audio-recorded and transcribed verbatim. The transcripts will be analyzed using 'thematic analysis' in QSR NVivo 10. 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.[11]

The outcomes concerning children´s experiences on the written questions will be exploratively analyzed using SPSS version 22. For each question the means, medians and standard deviations will be calculated as well as the frequencies of the answers on the Likert-scale. We will investigate children´s preference for a response option by using frequencies. We will also calculate Spearman correlations on each question between the three different response options to investigate whether the answers on the different response options are (highly) correlated.

METHODS AND ANALYSIS - QUESTIONNAIRE STUDY

Design

In the second phase of our study for the quantitative measurement of children's experiences, we will first develop a questionnaire based on the information gathered in the interview study

as well as in an expert meeting with different health care professionals involved in pediatric research (pediatricians, pediatric nurses, ethicists, psychologists, pedagogics and parents). Next we will measure children's experiences during seven research procedures by using this questionnaire.

Population

To determine the number of children we need to include for this phase, we will perform a power analysis based on the statistics of the numeric VAS in our pilot study. For the determination of scores on the questions about the research procedures, we consider a 95% confidence interval of +/- 10mm on the 100mm VAS as acceptable. For the testing of a difference between the experiences of different research procedures, our parameters are: α = .05, power = .80. We consider a difference of at least 20mm on the 100mm VAS to be significant. Dependent of the preference of children for the Likert or the VAS scale, we will choose one of these for the questionnaire study. In this case, the sample sizes found with the numeric VAS should be corrected as the Likert scale is a ranking scale. According to a general rule of thumb this can be done by adding 15% to the number of participants.[12] Recruitment is based on the same criteria as previously mentioned for the interviews

Again the children will be recruited from the previously mentioned departments from three academic children's hospitals in the Netherlands. In addition, healthy children (6-18 years) will be included to measure their experiences after a check-up visit at the dentist. With this subsample we aim to measure the experiences of a medical procedure in a child's 'daily life'. This number of children will also be calculated by a power-analysis based on the statistics of the questions on the numeric VAS in the first phase of our study (α = .05, power = .80).

Procedure

Parents and children from the above mentioned departments who undergo one of the procedures for research purposes will be approached by the researchers of the studies we will cooperate with. If they are interested, parents and children will receive an information letter, which will adapted for children (6-11 years) and adolescents (12-18 years). Parents and children will also have an opportunity to ask questions about our study in a face-to-face conversation with the PhD student, who will administrate the questionnaires. This will probably be on the day of the child's research visit. Once parents and children agree to participate, written parent consent and child assent (children ≥ 12 years) will be obtained. Children younger than twelve years have to verbally agree to participate.

Directly after undergoing the research procedure, the child will complete the *'What do you think of ...?'-questionnaire* (fill out the name of the clinical research procedure concerned on the dotted line), 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 one month, the child receives an email with the link to fill in the follow-up questionnaires online. These questionnaires include *'What do you think of ...?'-questionnaire* again and the Child Revised Impact of Event Scale (CRIES-13) for the assessment of the impact of the clinical research procedure. After having completed all questionnaires, children will be sent a gift-card (7.50 euros) 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.

Research procedures

For the present study we will measure children's experiences during seven research procedures. The research procedures are selected based on an expert meeting with pediatricians and members of IRBs, and also on what procedures are conducted in research studies in the hospitals we cooperate with during the timeframe of our study.

Instruments

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

Children's experiences during seven research procedures will be measured using the *'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 general in which the child participates; 3) whether the child would undergo the clinical research procedure again in the future; 4) an open question to ask children about suggestions for decreasing discomfort of the research procedures. 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. The questions in this *'What do you think of ...?'*-questionnaire will be based on the topics on children's experiences from the interviews and from professionals during the expert meeting.

We will study children's suggestions for decreasing possible discomfort of research procedures by an open question in the *'What do you think of ...?'*-questionnaire. The answers of the children will be coded into categories.

Zelfbeoordelings Vragenlijst voor Kinderen (ZBV–K)

Anxiety-proneness of the children will be measures by the *Zelfbeoordelings Vragenlijst voor Kinderen* (ZBV–K).[13] The ZBV-K is a Dutch translation of the State–Trait Anxiety Inventory for Children (STAI-C)[14] 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 anxious symptoms. The child was instructed to rate the frequency with which he or she experiences anxiety symptoms in general on a 3-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 $\alpha > 0.80$).[13] The total ZBV-K score for trait-anxiety range between 20 and 60. Test–retest reliability for both children and adolescents has been found to be acceptable (Dutch norm population: $r > 0.65$).[13] 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.

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).[15] 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.[16] 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 $\alpha = 0.60$), e.g. 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.[17]

Demographics

Demographics that we will collect include the child's age, gender, health status, ethnicity, previous experiences with the medical procedure, how the child is prepared for the study, who performed the procedure (e.g. pediatrician, lab worker, PhD student), the duration of the procedure, and whether the child had local anesthetics. This information will asked from the parents or derived from the child's medical record.

Analyses

Depending on the choice of scales (VAS or Likert scale) of the questionnaire, parametric or non-parametric tests will be used. Concerning the *'What do you think of...?'*-questionnaire, the mean respectively median scores of the individual questions will be calculated. (Non)parametric tests will be used to measure the differences in the subgroups of children's anxiety-proneness, age, health condition and other demographics on the *What do you think of...?'*-questionnaire. 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 seven different research procedures will be tested by one-way ANOVAs respectively Kruskal-Wallis one-way ANOVAs. Similar analyses will be carried out on the CRIES-13 scores. For each clinical research procedure, the percentage will be calculated of children willing to undergo a similar procedure again. Suggestions for improvements of the research procedures will be coded and listed in an table.

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 of both studies 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 pediatric 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 a number of research procedures. The primary aim of our project is to get insight into the experiences of research procedures in children, as seen from the perspective of children themselves. Our second aim is to develop a standardized instrument to register children's self-reported experiences of research procedures and their suggestions to decrease possible discomforts and to provide this information in a database which will be accessible for stakeholders, such as parents, children, IRBs and researchers. Finally, we will explore which children deserve special attention because of their (mental) vulnerability (based on age, health condition and anxiety-proneness). The outcomes of our study will give IRBs, researchers, parents and children information about children's self-reported experiences related to research procedures, which can support their decision-making whether or not to

participate in (certain procedures of) clinical research.

Limitations

A limitation of our study is that we cannot acquire a complete overview of the experiences of all research procedures and subgroups of children, 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 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 pediatric study protocols, we decided to focus on these factors

Conclusions

The outcomes of our project described in this manuscript are:

1. An overview of the experiences and impact of seven common research procedures as reported by children themselves and the differences in experiences between subgroups of children (e.g. age, health condition, anxiety-proneness).

2. Suggestions given by the children to decrease discomfort of the seven research procedures investigated in our study.

3. Information about the optimal way to measure discomfort during research procedures.

ABBREVIATIONS

CRIES-13: Children's Revised Impact of Event Scale – 13 questions

IRB: Institutional Review Board

STAI-C: State-trait anxiety inventory for children

VAS: Visual Analogue Scale

ZBV-K: Zelfbeoordelings Vragenlijst voor Kinderen (Dutch version of the STAI-C)

AUTHORS' CONTRIBUTIONS

Mira S. Staphorst

MS will carry out the data collection and analysis of both studies, she will draft the initial manuscripts of the articles. She approved the final version of this study protocol.

Joke A.M. Hunfeld

JH conceptualized and designed the study. She will supervise data collection at the different hospitals, will critically review and revise manuscripts. She approved the final version of this study protocol.

Jan Passchier

JP conceptualized and designed the study. He will critically review and revise manuscripts. He approved the final version of this study protocol.

Johannes (Hans) B. van Goudoever

JG conceptualized and designed the study from the medical/pediatric perspective. He will critically review and revise manuscripts. He approved the final version of this study protocol.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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ABSTRACT

Introduction: In pediatric research there is a tension between what you can ask from a child and what is needed for the development of evidence-based methods for the 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 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 pediatric 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.

Strengths and limitations of this study

- This study gives insight into children's experiences during research procedures, as seen from the perspective of children themselves.
- This study provides suggestions of children to reduce discomforts related to research procedures.
- This study provides an instrument to measure children's self-reported experiences during research procedures.
- This study explores whether certain children experience more discomfort during research based on age, health condition and anxiety-proneness.
- We study children's experiences during a limited number of research procedures as well as a limited number of medical conditions of the children. Future research is needed to study the experiences of other research procedures, and with children from all kinds of medical backgrounds.

INTRODUCTION

In 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 they are (legally) unable to give informed consent. For instance, there are scarce data about dosage and effect of medicines for children, which amounts to 65% of all prescribed drugs. More pediatric 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. pediatricians, pediatric nurses, ethicists). Literature shows, however, that pediatric nurses, pediatricians, psychologists and parents are likely to overestimate, e.g.[3, 4], or underestimate, e.g.[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 pediatric research

Hunfeld & Passchier reviewed the literature on discomfort of pediatric 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 for having 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 pediatric 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 generalize. 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. 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 that 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 caused after one month?

Secondary research questions:

3. 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?

4. Are there differences in experiences between medical procedures that are conducted for research purposes or routine clinical care?

5. 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 outcome of this interview study are the different discomforting aspects during research procedures that children experience. These aspects will be categorized 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 option 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 aim for numerical representativeness. We will interview children from six years of age because literature shows that children from six years and older are cognitively capable and have language capacities to accurately verbalize 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 (MS) in consultation with other members of the project group (JH and JP). Children are eligible to be interviewed if they meet the following criteria: a) aged between 6–18 years, b) fluent in Dutch, c) no current psychological treatment for pain or anxiety disorders, d) no severe psychosocial problems (such as anxiety disorders and depression), e) accompanied by at least one parent or care-taker and f) 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 Pediatrics 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 pediatric 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 twelve 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 a specific training in interview skills by experts in the field of medical and pediatric psychology. Children will receive a gift-card (7.50 euros) 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, pediatric disease and medical history. If the parent cannot provide 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 for suggestions to decrease possible discomfort. The interview questions are based on literature, a review about discomfort of children in clinical research,[7] and input from several pediatricians, psychologists and pediatric 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 literature. We will ask the children to fill in each question on three response options: a 5-point Likert scale, a 100mm colored visual analogue scale (VAS) and a simple 100mm 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 analyzed 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 health care professionals involved in pediatric research (pediatricians, pediatric 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 one 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 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 eight years of age 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 one 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 euros) 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. 5-point Likert scale, 100 mm colored 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 $\alpha = 0.60$), e.g. 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 3-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. (1996) 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. pediatrician, lab worker, PhD student), the duration of the

procedure, and whether the child had local anesthetics. 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, feces testing, MRI-scan, pulmonary function test, buccal swab, skin prick test (allergy test), and venipuncture. The research procedures are selected based on an expert meeting with pediatricians, pediatric 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 pediatric 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 other persons who are interested. The findings of our project can help IRBs and pediatric 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 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 pediatric study protocols, we decided to focus on these three factors.

ABBREVIATIONS

CRIES-13: Children's Revised Impact of Event Scale – 13 questions

IRB: Institutional Review Board

STAI-C: State-trait anxiety inventory for children

VAS: Visual Analogue Scale

ZBV-K: Zelfbeoordelings Vragenlijst voor Kinderen (Dutch version of the STAI-C)

AUTHORS' CONTRIBUTIONS

Mira S. Staphorst

MS will carry out the data collection and analysis of both studies, she will draft the initial manuscripts of the articles. She approved the final version of this study protocol.

Joke A.M. Hunfeld

JH conceptualized and designed the study. She will supervise data collection at the different hospitals, will critically review and revise manuscripts. She approved the final version of this study protocol.

Reinier Timman

RT supported with the methodological and statistical aspects of the study. He approved the final version of this study protocol.

Jan Passchier

JP conceptualized and designed the study. He will critically review and revise manuscripts. He approved the final version of this study protocol.

Johannes (Hans) B. van Goudoever

JG conceptualized and designed the study from the medical/pediatric perspective. He will critically review and revise manuscripts. He approved the final version of this study protocol.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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