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# Chapter 4

A qualitative study about children's vulnerability in  
medical research: protection and empowerment

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## Abstract

**Background:** Medical research guidelines often label children as vulnerable. This may cause both overprotection and underprotection, resulting in unnecessary exclusion of children from medical research. Additionally, it may lead to children being unable to safeguard their own interests. A contextual and dynamic approach to vulnerability, such as the layered approach, could help to provide more appropriate protection. Our aim was to explore how this layered approach could help in practice to address children's vulnerability. To that end, we explored children's experiences in research and used them to provide practical guidance for researchers and REC members.

**Methods:** Qualitative study of 52 interviews with children aged 9 to 18 about their experiences while participating in medical research. Interviews were audiotaped or videotaped, transcribed verbatim, and analyzed using Atlas.ti software. Themes were derived from what children considered important and from their recommendations to researchers and future participants.

**Results:** Children focused mainly on improving their participation rather than on protection. Both personal as well as contextual factors played a role and often interacted. Burden due to interventions or timing of procedures were important in children's consideration. Disease or previous research experiences could foster decision-making. Tailored information and support from parents, peers, and professionals made children feel at ease and taken seriously. All factors contributed to children's knowledge, capability, and confidence in making decisions about participation in research as well as during participation.

**Conclusions:** In exploring vulnerability we found that children do not focus so much on protection as on support that leads to empowerment. The layered approach to vulnerability provides a way to not only protect children, but also to empower them. We identified four potential layers of vulnerability related to (1) information, (2) burden involved in participating in research, (3) having a disease or (4) participating as a healthy volunteer without any acquaintance with research. If we want to support children in their evolving capacity, we should give sufficient weight to their voices. This makes them greatly dependent on the responsibility of others such as researchers and parents. Based on the identified layers, we formulated responsibilities relating to involvement, support, and information supply.

## Background

Children have the right to receive good health care and the right to be protected. They also have the right to be involved in all matters that concern them, including participation in medical research.<sup>1</sup> Medical research is needed to provide children with the best possible health care. Nevertheless, health professionals sometimes feel reluctant to recruit children for medical research because of their supposed vulnerability.<sup>2-4</sup> Children are deemed incapable of giving informed consent. In addition, there is the perception that research interventions may have a greater impact on them compared to adults.<sup>5</sup> This has resulted in a legal framework and guidelines whereby children are highly protected.<sup>5-8</sup> In traditional guidelines, children are considered as an undifferentiated and vulnerable group categorized by age. This one-size-fits-all approach may result in overprotection and underprotection of children alike. When focusing only on group characteristics that render children vulnerable, such as their lack of capacity to give informed consent, researchers and research ethics committees (RECs) might overlook contextual and individual features constituting vulnerability. Contextual features regard for example the study interventions (e.g. injections), the institutional environment, or social or economic context.<sup>9</sup> Personal experiences in relation to these contextual features could render children more vulnerable in some situations and not in other situations (e.g. experienced trauma for injections but not for undergoing an MRI). Children with positive experiences with such interventions may be less burdened than average when undergoing study procedures. If they would also have above average decision-making capabilities due to their illness experiences, they might be unnecessarily excluded from research that is considered harmful for the average child, thus being overprotected by following the one-size-fits-all approach. The opposite may lead to underprotection. Inappropriate protection based on group vulnerability could make children unable to safeguard their own interests as a result of their evolving capacity to give informed consent.<sup>10</sup> Besides, focusing only on how to overcome risks and burdens could obscure the balance with potential benefits and personal interests of children. Research-related benefits mostly relate to health benefits but may also contribute to patients' quality of life.<sup>5</sup> In a previous study we found that participation in research taught children a lot about their diseases and some of them gained more confidence. It made them feel good knowing that they were helping other people.<sup>11</sup> RECs experience difficulty assessing what risks and benefits in research comprise and their practices vary widely.<sup>12</sup> They regularly use adult standards when assessing which information should be provided to children. When RECs do have a method for assessing children's capacity to

give assent it is based on an age cutoff, in other cases they rely on researchers' clinical judgement.<sup>13</sup> Researchers on the other hand, might also face problems with ensuring adequate support for children, especially when they are new in the field of pediatrics. A study about REC websites showed that many offer little guidance on how to address ethical issues such as proving protection and ways to seek for assent from children.<sup>14</sup> Therefore, there is a need for practical guidance for REC members and researchers. Such guidance will enable them to offer appropriate protection while acknowledging benefits of research and support children in their developing capacity of providing informed consent or assent. This guidance benefits from a clear conceptualization of vulnerability.

Several attempts have been done to re-conceptualize vulnerability in a way that it does justice to potential participants, both in terms of protecting them and supporting them to participate, to overcome the problems described above for classic concepts of vulnerability based on chronological age group.<sup>9,15-20</sup> The International Ethical Guidelines for Health-related Research Involving Humans propose an individual and dynamic approach and considers Luna's account.<sup>10,21</sup> Luna's layered model distinguishes different sources of risks or potential harms, called 'layers' of vulnerability, rather than labelling all members of a research group as vulnerable. Layers can be acquired over time depending on the person's development and changes in contextual factors. The more layers of vulnerability children acquire, the more vulnerable they are, and the more protection or support they need. In general, layers may be related to problems regarding the risk of exploitation, differences in cultural background, problems with informed consent or information, autonomy, or disrespect for human rights.<sup>22</sup> The two-step approach to the layers of vulnerability offers a way of identifying aspects of vulnerability and evaluating these aspects in detail. Step one consists of identifying the layers and their stimulus conditions. These are the cause of the layer to be triggered or actualized and harm that person. This step also includes identifying potential cascading effects, which is that layers may generate other layers. These may render the person more and more vulnerable. In step two, layers are evaluated and strategies formulated to eradicate, minimize or overcome layers (especially those that may be very harmful and very likely to occur). These strategies may also involve empowerment of the participants.<sup>20</sup> We believe the layered concept might be helpful for understanding children's participation in research because it accounts for individual differences and because it is a dynamic approach which makes it possible to address changes in contextual factors but also in children's developing capacity. Yet, to implement this approach, we need to document how children experience research in practice.

The aim of this study was to explore how the layered approach could help in practice to address children's vulnerability. To that end, we explored children's experiences in research. This includes how they can best be protected and supported while participating, but also what they needed to make decisions about their participation in research. We apply children's experiences to the layered approach to vulnerability to provide practical guidance. This could help researchers while developing their research proposals, and help RECs that review those proposals to find a balance between providing sufficient protection while supporting children in their developing capacity.

## Methods

This is a secondary analysis study in which we combined two qualitative datasets from the UK and the Netherlands about children's participation in medical research. The research teams consisted of two social science researchers (Louise Locock and Lesley Powell) from the Health Experiences Research Group (HERG) at the University of Oxford, and a pediatrician (Eduard Verhagen), ethicist (Els Maeckelberghe), and MD (Malou Luchtenberg) all based at University of Groningen, Beatrix Children's Hospital, University Medical Center Groningen (UMCG), the Netherlands. The UK data were used in a previous analysis on young people's reasons for taking part in research.<sup>11</sup> The analysis of the UK dataset prompted exploration of new themes. The previous analysis included children's advice on how to improve research. This drew our attention to how they perceived their position in research. This pointed to finding a balance between providing protection and supporting participation, taking into account how research participation could benefit their lives. The development of the Dutch study was based on these insights.

### Recruitment and sampling

In both the UK and Dutch studies from which the datasets are derived, potential participants were approached through nationwide patient support groups, social media, word of mouth, and via health care professionals. They had all been invited to participate in medical research as a patient or healthy volunteer. Recruitment aimed for a maximum variation sample based on age (9 to 18 in the Dutch study and 10 to 25 in the UK study), sex, state of health, the types of research they were invited to take part in, and whether they had decided to participate in a study.<sup>23</sup> English (for the UK) or the Dutch (for the Netherlands) did not have to be children's first language, as long as they were capable of expressing themselves in narrative. To aim for a maximum variation sample in the Dutch

study, this included children with health conditions that can be accompanied by an affected cognitive function, such as Prader-Willi Syndrome. We did not want to exclude children solely based on their potential limited capacity because they could add a valuable perspective to the discussion and they deserve to be heard too. We only invited children who were considered sufficiently capable of expressing themselves verbally, which was determined by their treating physician and parents.

### **Informed consent**

In both the UK and Dutch study, potential participants were given information leaflets for themselves and their parents separately. Written assent from the child was obtained in addition to parental consent. Young people over 16 years old signed informed consent themselves. The consent given for the UK study included permission for secondary analysis.

### **Data collection and analysis**

The datasets comprised semi structured in-depth interviews, which took between 30 and 100 minutes to conduct, with children about their experiences with taking part in research. A topic guide was developed to guide the interviews. The topic guide used for the Dutch interviews was informed by the results of the UK study. Interviews were conducted at home between January 2010 and December 2011 in the UK and between May 2017 and January 2019 in the Netherlands. The interviewers (LP of the British children and ML for the Dutch children) were trained at HERG. They had not met the participants prior to the interviews. The interviews were either audiotaped or videotaped, transcribed verbatim, and subsequently returned to the participants to check and remove any sections they wished to be excluded for further analysis. Atlas.ti software was used to organize and analyze anticipated and emergent themes. Names of persons and locations were removed from the transcripts.

Our secondary analysis combined an amplified analysis (an enlarged dataset compared to a single study) and a supplementary analysis. The latter was a more in-depth investigation of emergent themes that were not fully addressed in the original study.<sup>24</sup> The topic guide for the Dutch interviews included asking children if they felt vulnerable, or if they felt differently from children who do not have disease or research experience (e.g. questions like “Some people say that children are vulnerable, or weaker, as compared to adults. What do you think they mean by that?”, “Do you feel different from other children who do (not) have experience with being ill or taking part in research?”, “Do you think that matters when you

are asked to participate in research?”, “Is there something that makes you weaker or stronger than others?”). They reported they found the term ‘vulnerable’ rather vague and not adequate to describe their position in research. They rather spoke about what they considered important to optimize their participation. With this in mind, we re-analyzed the UK data. Therefore, our initial analysis involved identifying themes that the children themselves had described as important. This was based on answers they had given to the questions to summarize their overall experiences (e.g. “How would you summarize your overall experiences?” or “What do you think was most important for you when being asked to take part in research?”), or to explain what they thought were the most important topics discussed in the interviews (e.g. “What do you think were the most important things that we discussed in this interview about your research participation?”). These themes were chosen inductively by ML and EM after reading and discussing the answers to those questions. Consequently, transcripts were coded to further explore the themes. This included looking for related experiences that helped to refine the themes and to find associations between the themes. The first five transcripts were coded by ML and EM, and ML completed the coding. Coding was discussed regularly with EM and LL (for the UK data) to reach agreement on emerging themes to the level that everyone could support the themes as derived from the data. At various stages of the process the themes were presented and discussed with the entire research team.

## Results

A total of 52 participants aged 9 to 18 years were included in the study, 29 from the UK and 23 from the Netherlands. To prevent adult interpretation of childhood experiences three participants from the original UK dataset had been excluded because they were over 18. Only children who are native speakers decided to participate. During some interviews a parent was present. None of the views aired by the parents were considered with exception of one Dutch case in which the mother assisted her child with Prader-Willi Syndrome to help him express himself. Participant characteristics are shown in Table 1.



**Table 1. Participant characteristics**

Characteristics	UK data n* (%)	Dutch data n* (%)	N* (%)**
<i>Sex</i>			
Girl	18 (62)	9 (39)	27 (52)
Boy	11 (38)	14 (61)	25 (48)
<i>Age</i>			
9,10 years	1 (3)	4 (17)	5 (7)
11, 12 years	8 (28)	6 (26)	14 (27)
13, 14 years	8 (28)	9 (39)	17 (33)
15, 16 years	4 (14)	3 (13)	7 (13)
17, 18 years	8 (28)	1 (4)	9 (17)
<i>Disease</i>			
Acute diseases (acute lymphoblastic leukemia, brain tumor, Hodgkin's lymphoma)	4 (14)	3 (13)	7 (13)
Common chronic diseases (DM1, Crohn's disease, asthma, arthritis, migraines)	13 (45)	7 (30)	20 (38)
Rare chronic diseases (peanut allergy, glycogen storage disease, hypophosphatemic rickets, vasculitis, lupus, Wegener's granulomatosis, osteogenesis imperfecta, cystic fibrosis, Grave's disease, overlap connective tissue disease, tuberous sclerosis complex)	7 (24)	8 (35)	15 (29)
Other conditions/syndromes (congenital heart condition, Prader-Willi Syndrome, restricted growth)	1 (3)	3 (13)	4 (8)
<i>Healthy</i>	4 (14)	2 (7)	6 (12)
Participants decided to			
Participate	27 (93)	19 (83)	46 (90)
Not participate	1 (3)	3 (13)	4 (8)
Withdraw	1 (3)	1 (4)	2 (4)

\* Number of participants: UK data n = 29, NL data n = 23, total N = 52.

\*\* Rounded to nearest whole number

Our analysis identified the following facilitating and obstructive factors to participation from children's perspectives: burden of and benefit from participation, disease experience, information, relationship with others, and the desire and ability to help others. These factors often interacted with each other. It was noticeable that children focused mainly on how their participation in research could be enabled, rather than how they could be protected, and they expressed a strong wish to help others by taking part in research. Burden as a result of interventions involved or timing of procedures were important in children's consideration whether to participate. Disease or previous research

experiences, positive or negative, could also foster a decision to participate in research. Negative or no previous experiences made children rely more on support of others, and they needed more information to be able to make a decision. Tailored information and support from parents, peers, and professionals made them feel at ease and taken seriously during research participation. To a certain extent most factors were important for all the children. They contributed to children's knowledge, capability, and confidence in making decisions about taking part in research and during research participation. We discuss each factor below.

### **Burden of and benefit from participation**

Children reported that the type of intervention and the resulting burden was one of the most important aspects in considering research participation. Whether the actual intervention was perceived as burdensome was related to several factors, such as personal preferences, disease, or previous research experience. Children acknowledged that some studies could not be done without certain procedures and if the perceived benefits outweighed the burden, they felt it was acceptable. Some participants reported that they disliked going to the hospital because of a certain procedure like blood taking, and sometimes the intervention was the reason to withdraw.

*“Not necessarily nice because I have to lie in bed and glycoside did not taste nice and that’s why I stopped.”* (Child01; boy aged 10 with glycogen storage disease, Dutch dataset)

For others the research intervention did not seem to be making them more vulnerable because they had learned from experience how to deal with them.

*“Because... then for that research, we already have a lot of experience. The hospital, injections...”* (Child02; boy aged 13) *“That is why it was, of course, easy for us to say yes to that, right?”* (Child03; girl aged 14) *“Because if I were to say to somebody, a little kid, would you take part in that, then they want, of course they don’t understand what that is, but, um, they would think, injections and stuff? No, that’s not ... But because we already have the experience, because we... we used to have to, when we were little kids and little babies. Then we didn’t really have a will of our own in that. No, blood just had to be taken. Yes, and then you get used to it. So, I think for the other children who have not experienced that, that it is a step, or a step more difficult, to take part in such a research. Because*

*you don't really have experience with...*" (Child02; brother of Child03, both siblings have hypophosphatemic rickets, Dutch dataset)

Duration and timing of the procedures were important factors in the decision whether children wanted to participate. It also depended on disease and personal preferences. If a study procedure was planned on a separate day than a regular treatment visit, some children foresaw the extra traveling time as too much of a burden after a long day of intensive treatment and decided not to participate. Conversely, two siblings welcomed the deviation from their daily routine. This shows that children have different needs regarding protection against being overly burdened in research.

*"It wasn't so bad; we have to go to [city]. Well, nice, another hour and a half in the car."* (Child02; boy aged 13) *"It was just an outing [laughs] actually."* (Child03; girl aged 14) *"No, it was actually just four years we will go to [city] on an adventure again."* (Child02) *"Cozy."* (Child03) *"Out of your daily routine. Yes, it worked.... Because yes, of course we now have a new medicine. And we have already improved a lot. But I think it is also good for us that we go out of our daily routine."* (Child02; brother of Child03; both siblings have hypophosphatemic rickets, Dutch dataset)

The difference in attitudes towards time commitment could be the result of the type of disease or the type of study, but could also be the result of differences in personal preferences. This was also noticeable in how children experienced taking part in a study. Whereas some saw it as a new and exciting adventure, others experienced it as boring because the study procedure required them to wait or lie down for a long time. Children suggested making procedures more fun by, for example, providing the possibility of playing games while waiting for a next appointment, or watching a video while undergoing MRI. Time investment on the part of the researcher was also mentioned as important in comforting children. One girl advised researchers to adjust their time investment to the individual child, reacting to signs of discomfort or anxiety.

*"That [researchers] will look at them. That instead of 'a research project is performed on number 104', it will really be oriented towards that person. Look, let's say that person finds it a bit scary, then you should spend more time on this child, like that."* (Child04; girl aged 16 with congenital heart disease, Dutch dataset)

### Disease experience

The experiences reported by children with a chronic disease revealed that they were familiar with interventions, such as getting injections, taking medicines, or blood taking. This made it relatively easy to tolerate the interventions in a study, and thus less vulnerable than children without such familiarity. Having this disease experience also made children feel better able to consider taking part in research themselves, because of the knowledge they had gained over the years of being a patient. The same was expressed for previous research experience, especially when this had been positive. One participant, for example, mentioned that her long-term relationship with the medical team made her feel more empowered because it had made her feel better able to express her wishes and asking questions about the research. Besides, the research team could easily approach her.

*“I think they feel that they were more able to come up to me because they can, I’m more approachable. Because they know me very well and I’ve been there a long time and they know that I’ll help anything that they need to do. But I think they, I think they still would ask anyone, even if they were just new diabetics. I don’t think that really had much of an impact. But they were just able to talk to me more about it. ...I felt more comfortable saying like, I could say what I think in front of them and they won’t take anything the wrong way. Or if I need to ask questions, no matter how stupid it is, they’ll just answer it.”* (Child05; girl aged 17 with Type 1 diabetes, UK dataset)

Ill children without previous disease experience, for example, if they were recently diagnosed, reported finding some interventions burdensome or overwhelming because everything was new to them. Children reported that being invited to participate in research by someone familiar such as the treating doctor made them feel more supported in considering taking part. Taking part in research was also mentioned by young people as a way of helping them overcome the shock of their diagnosis and helping them to manage their disease. Participants also said it made them to feel empowered because they could help others, which distracted them from being a patient.

*“Yes, um I’d say to them, “Definitely take part.” Just, I’d say, “Even if you do, even if you just think, ‘Oh, no, that’s nothing to do with me.” It’s like I’d say, “Even it, it helps, it helps every, everyone trying to get over it and get used to it. Because everyone who gets diagnosed and didn’t know, it’s a big big shock to them, and just a different, change of lifestyle. And taking part in research, it’s not*

*only helping themselves, it's helping everyone to deal with it. ...Yes, it just, yes, it gets you through it and makes you think, "At least I'm helping other people as well." So, yes, I think it's, I think the research is brilliant."* (Child06; boy aged 15 with Type 1 diabetes, UK dataset)

One participant (mother) explained that how a child reacted to an intervention could also be explained by the child's own state of health, implying that in some cases healthy children are more vulnerable compared to children with a disease or poor state of health.

*"I think that healthy children who participate in a study are more vulnerable at certain levels than [my son], um... I name a few such as taking blood samples. I just know that children, some children will really have a trauma for that the rest of their lives, especially if they have to be held by multiple people because they really don't want to but they have to. He [son] is not bothered by that, he finds it annoying, but he is just sitting there like that, I am sitting here and he usually squeezes my hand and the other one is just like that. And if it really hurts, then he does "mmm," and that's it. He has never cried with blood tests..."* (Child07; Mother of boy aged 11 with Prader-Willi syndrome, Dutch dataset)

Healthy volunteers themselves, however, felt that having no illness made them less susceptible to intervention-related burden.

*"If I were sick, it would probably have been much harder, it would have taken longer, I think, it would have taken much more effort to do all of that [lung function tests]. Compared to as I am healthy now, so yes, I think it was much easier, yes."* (Child08; girl aged 16, healthy volunteer, Dutch dataset)

## Information

Children wanted to be properly informed about what they could expect was going to happen during the study. Not knowing what was going to happen could make them vulnerable. The girl in the following example illustrates the importance of providing enough details about interventions, in this case emphasizing the need to tailor the information to sex. Not knowing that she had to take her bra off for an ECG was not a reason for her to decline to take part, but it had made her needlessly vulnerable for a moment.

*"I think it would be really smart to just tell exactly everything that is going to happen, what is awaiting them, because children want to know that. For*

*example, that they say with an ECG: pay attention, your top must be exposed, with this you have to do this, with that you have to do that. That you also prepare them. Because children can react badly when a surprise is no fun. Well, I had that when I had forgotten about that with the ECG and when my mother got a petite bra, hoping that, you know, they could stick next to it and then I was a bit: [makes a squeak ] I do not want anymore.” (Child04; girl aged 16 with congenital heart disease, Dutch dataset)*

Wanting to be well informed about study procedures was not only related to the content of the information, but also to the support provided by those involved in explaining procedures to the children. Parents, for example, played an important role in making sure their children felt comfortable. They showed support during the research procedures, provided them with additional information, or reminded children about what was going to happen. Children reported on the importance of interplay between parents, doctors, and themselves. Most children seemed to think it was self-evident that their parents should be involved in the decision as a matter of protection, but they wanted to have a say in the matter as they were the ones to undergo the procedures. Therefore, they expressed the importance of the researcher explaining the study to them, and not just to their parents.

*“I mean they should talk to them and I’ve said this from when my treatment started. Doctors and researches should not talk to the parents they should talk to the children because it’s their lives not their parents. I mean they should talk at their level, they should learn they should be trained to be able; if they’re working in pediatrics they should be able to explain anything to a child of any age because surely that should be a qualification of a pediatric doctor. Any pediatric doctor should be able to bring it down to a child’s level.” (Child09; girl aged 12 with acute lymphoblastic leukemia, UK dataset)*

If children were not properly involved in the process or did not fully understand information that was given to them, they were more vulnerable. The girl in the following example explained how she felt more insecure and wondered whether she was herself to blame for not asking more questions, as well as the doctor for not explaining it better. She carefully expressed the wish for her doctor to take more responsibility to target information to her needs, instead of to her parents’ needs.

*“Eh yes, if he had ask me like..., if I..., you know, maybe I should put it on me because I could have asked: what is this about [?], instead of... but perhaps the doctor could have explained it a bit easier with less difficult words, let’s say it like that.”* (Child10; girl aged 13 with Crohn’s disease, Dutch dataset)

### **Relationship with others**

Children appreciated health care professionals who were willing to help them in whatever way they needed, and who actively involved them in the research. Some children said it felt like a true collaboration and made them look forward to their next appointment.

*“Um, a lot of collaboration. And, explain well what you are going to do and such. And yes, because we really have done many things together, with all of them, with a team and such. And that made it all very pleasant, you know? It became much more humane. You were not doing an investigation with numbers or something. You were just doing something together. Um, with the doctors, and people who injected us and other people who were in the study with us, say, who were also going to do the same. Which we therefore met; it was all very nice.”* (Child02; boy aged 13 with hypophosphatemic rickets, Dutch dataset)

Simple gestures from health professionals made children feel more involved in the research, for example, pedagogical employees who played a game with children, or a doctor who made funny jokes.

*“Well, there are also pedagogical staff and they usually do fun things with you and such, like games or something... and sometimes there are just stupid doctors. ...Well, um, just then he’s a bit stupid or something, then he’s just not that much fun. ... Um, just how he does it. [a nice doctor is]...Well, [someone] that makes a little joke but also not too stupid jokes and, um, just a little bit, that you can also help yourself a little and such.”* (Child11; boy aged 9 with leukemia, Dutch dataset)

It helped if doctors and nurses were friendly, open, and honest. One mother explained how she felt that the impact of staff behavior varied depending on the individual child.

*“I think that children can also be very vulnerable if they are treated very unkindly, if there are nurses in their department who are, um, yes, who are*

*simply not friendly and who cannot picture themselves as a child. And one child is more troubled by this than another and one person also picks up such signals faster than another. He [son] will just pick up those signals much less quickly than one of our daughters.”* (Child07; Mother of boy aged 11 with Prader-Willi syndrome, Dutch dataset)

Friends and family played a role in supporting children in research in addition to parents and health professionals. Some young people suggested they would like to have the possibility of meeting other participants during the research for peer support, or to be able to bring a friend. They reported it would help them to feel less alone.

*“If like other people know that like loads of other people doing it and like maybe like you could do it together type of thing it will make it better because you like know other people’s experiences, you see not just sitting on your own thinking like I’m the only person out of my group of friends that has this. And I don’t like to, you know, like slow them down or having to do stuff that, like I can’t do stuff that they can because like you feel like really left out. But it would be nice, you know, like if other people were there and obviously so then you know that you’re not alone type of thing.”* (Child12; girl aged 15 with chronic juvenile idiopathic arthritis, UK dataset)

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### **Desire and ability to help others**

Children wanted to help others, such as peers or future patients, their treating physician, or science and society in general by participating in medical research. Helping others was a way of showing that they were more than just patients. Support from and familiarity with the researchers at the time of recruitment was important for children to feel strengthened in their choice to participate for the welfare of others. Children that chose not to participate in research did acknowledge the benefit for others, but they perceived this did not outweigh the expected burden for them.

We found a distinct difference between healthy volunteers and patients in the extent to which the desire to help others emerged from their narratives. This not only seemed related to being ill, but also to familiarity with health care and health professionals. Most patients were invited during one of their hospital consultations. Healthy volunteers, who did not have these consultations, had more trouble finding research opportunities. Helping others as a reason to



participate was more explicitly mentioned by patients, while healthy volunteers also had other reasons, such as being interested in research or making some money. Their wish to help others seemed to become stronger during and after participation. One of the healthy participants speculated that they were less aware of the situation of children that would benefit from the research, because they did not have disease and research experience.

*“I think there are also more people who have had an illness or are sick, that they have participated more in those types of research than people who, yes, are just being healthy. Because they are less likely to have a connection with that. ... because, look, when you were in a hospital, you sometimes hear of research. But as a healthy person, then you don’t actually ever go to the hospital. So then... you don’t hear about it and there are not posters everywhere saying “yes, join in” and things like that.”* (Child13; boy aged 13, healthy volunteer, Dutch dataset)

Healthy volunteers depended more on their parents who helped them to find opportunities. Both ill and healthy participants recommended there should be increased public information about research in order to encourage healthy volunteers to participate and appreciate how they could learn from research and help others. They hypothesized that a more balanced view of the positive and negative side of research could enable healthy children to become interested in research participation. From their perspective, sharing positive experiences with the public as a means of countering the oft-heard negative side of taking part in research was important. While they emphasized on the importance of taking responsibility and being aware that research takes time and involves certain risks, they said it would help to explicitly mention the contribution children make towards the welfare of others, while at the same time embarking on an interesting adventure themselves. They wanted honest information to be publicly available including positive information that might foster a desire to help others.

*“And then, oh, that is really cool such a study. And then they might get a bit like that from me, that seems wonderful: “wow, that really is a very big adventure.” And yes, maybe they then ...maybe also dare to take the step sooner of maybe I will also participate in such a research. ...because you often hear in the news, for example, the research went wrong. I just say something. But you don’t actually hear so often that it went well.”* (Child02; boy aged 13 with hypophosphatemic rickets, Dutch dataset)

## Discussion

We explored how children spoke about their experiences with participating in medical research to inform us about how they perceive their vulnerability. The children's reports revealed that the balance between the burden of and the benefit from research was important to them. Both personal and contextual factors played a role in finding this balance. Children illustrated that, for example, disease experience could make a difference between making them feel overwhelmed and anxious, or at ease when undergoing an intervention. More support from parents or tailored information that goes beyond what is outlined in regulations (e.g. tailored towards their sex) appeared to be needed to decrease children's sense of being vulnerable.

### Protection and empowerment

Children's disease and research experiences not only point towards how they can more appropriately be protected and supported, they also draw attention to other interests of children that relate to their wish to have their opinions taken into account. It appeared that children who were more experienced in their own condition and because of prior research participation needed less protection and support from others (e.g. their parents and doctor) because their increased knowledge made them feel more confident and more able to make decisions about their participation. In contrast with children with less illness experience, such as healthy volunteers, they more often expressed the wish to help others by taking part in research. They felt better able to consider what their own participation could mean for others within society, and they felt more engaged and strengthened in their wish to help others by participating in research. This can be understood in terms of feeling empowered. The definition of empowerment is ambiguous and mostly described for adult patients. Yet, the concept of empowerment is widely studied and often explained in terms of a process or outcome that involves collaborative decision-making or participation, capacity-building and gaining control over a person's life or getting access to resources.<sup>25-28</sup> The World Health Organization defines empowerment as: "a process through which people gain greater control over decisions and actions affecting their health. Empowerment may be a social, cultural, psychological or political process through which individuals and social groups are able to express their needs, present their concerns, devise strategies for involvement in decision-making, and achieve political, social and cultural action to meet those needs".<sup>25,p6</sup> In a systematic review, Barr and colleagues identified several constructs within four main domains for the assessment of (adult) patient

empowerment. These domains and examples of constructs within those are (1) patient states, experiences and capacities (e.g. self-confidence); (2) patient actions and behaviors (e.g. learn from past experience); (3) patient self-determination within the healthcare relationship (e.g. collaboration) and (4) patient skills development (e.g. sense of healthcare providers empowering behavior).<sup>27</sup> The factors that children expressed in our study resonate with these four domains.

### **Practical guidance using the layered approach**

We will now use the layered approach to frame the concerns and advice children reported in this study. The approach resonates well with our findings because it is a dynamic approach involving personal and contextual aspects. In addition, it provides guidance for others' responsibilities not only in terms of protection but also in terms of empowerment.<sup>17,20</sup> This is particularly important in the case of pediatric research, because children are dependent on several stakeholders including researchers and their parents for information and decision-making. Children's needs with regard to information and decision-making might be different from their parents' needs, which makes their situation complex compared to adult research, in which participants receive information and make decisions by themselves. Thus in pediatric research besides the usual protections and safeguards such as parental consent, we should also consider special preferences and needs of the children and work with them to empower them. Based on our findings, we identified four potential layers of vulnerability. These layers relate to insufficient information about research, to excessive burden due to interventions that is not in balance with potential benefits, to physical or psychosocial harm caused by a disease or health condition, and to the risk of not being sufficiently supported as healthy volunteer because of unfamiliarity with research and health care.

#### *Information layer of vulnerability*

The information layer of vulnerability points to a lack of proper information to make a well-considered decision about taking part in research. A stimulus or trigger of this layer is lack of sufficient information (Child10), information that does not prepare children for what they might face when taking part in research, or information that is beyond their scope of understanding. Grootens et al found that patient information leaflets for pediatric research are often not attuned to children's reading ability, and little is known about which format works best.<sup>29</sup> The information layer of vulnerability could be harmful because potentially it could cascade towards coercion<sup>30</sup> or therapeutic misconception,<sup>31,32</sup>

leading in turn to more vulnerability. If the information does not entail a proper explanation of what to expect in terms of how interventions may affect children, a cascade effect towards the excessive burden layer of vulnerability is likely to occur. Therefore, it is crucial to avoid this layer or to minimize it.

Our participants mentioned the importance of tailoring the information towards the children's level (Child09), considering individual needs according to, for example, their sex and experience (Child04). A last strategy that children mentioned was to place more information on a public website in addition to examples of previous research and opportunities,<sup>11</sup> as well as sharing positive experience with the public to counter negative experience broadcast in the media (Child02).

#### *Excessive burden layer of vulnerability*

The excessive burden layer of vulnerability relates to the potential risk of being harmed by interventions. It occurs when the burden of interventions is off balance with the benefits, but it can also be related with the timing, duration and ways of interacting with the child when the procedure is done. Stimuli or triggers for this layer are a combination of factors that include the type of intervention, influence of disease, negative experience in the past, and lack of information and support. As our participants mentioned, children were more susceptible for vulnerabilities when, for example, they had been diagnosed recently (Child06). Our participants also showed that having disease experience could make an intervention such as blood taking less stressful or not burdensome at all if a child is used to it (Child02-03 and Child07), while it could be much more burdensome for others without experience or with a negative experience. Some participants did experience discomfort but realized that the research could not be carried out otherwise. This confirms a study by Barned et al in which young people are willing to endure a painful procedure because it outweighed the benefit of helping others.<sup>33</sup> If benefits do not outweigh burden we intuitively expect that adverse experiences related to hospital visits will have the effect of cascading towards anxiety, and in the long-term perhaps even health care evasive behavior. If children are not well informed about interventions, or if they do not feel confident to ask questions about procedures, interventions can be perceived as more harmful.

Strategies to overcome or prevent the excessive burden layer involves taking more time and patience to accommodate the individual needs of a child. For example,

timing of procedures should be adjusted to children's individual needs. Other strategies suggested by the children were for health professionals to provide support and distraction when children undergo procedures and to empower children by involving them in the process of the research (Child02 and Child11). Strategies for providing distraction, appropriate information, and shortening procedures confirm those mentioned by children in a study by Staphorst et al.<sup>34</sup> In addition, our participants suggested that being allowed to bring along a friend on a visit to the hospital, or to come in contact with peers who were undergoing the same procedure, could help to focus more on the benefits rather than the burden of participating in research (Child06).

#### *Disease layer of vulnerability*

The disease layer of vulnerability relates to being more susceptible to harm as a result of the child's state of health or illness. Some participants experienced physical or psychosocial harm, for example, when they had been recently diagnosed. When children were invited to participate in research at such a moment, they were less able to capture information and consider participation. Consequently, it was more difficult for professionals to inform and involve them. As a result, interventions may cause greater harm. The disease layer thus had a potential cascade effect on the information layer and may generate an excessive burden layer of vulnerability.

The stimulus or trigger of this layer, the disease itself, cannot always be taken away. Nevertheless, in the layered approach obligations not only point to eradicating layers, but also to minimizing layers of vulnerability. In order to minimize the effect of the disease layer children should be safeguarded from feeling more ill or weaker because of their taking part in research. Practical adjustments should be arranged, such as not enrolling children directly after diagnosis or combining research meetings with doctors' consultations planned around school times so children do not miss out on important parts of their education. Having a quiet place in the hospital to do homework also helps children to cope with missing school. As our participants implied, it is important to realize that personal preferences might not be the same for every child and family. Doctors and parents should discuss with the children what they value and prefer soon after diagnosis.

#### *Lack of acquaintance layer of vulnerability*

Healthy volunteers who do not have a disease or research experience may face the lack of acquaintance layer of vulnerability. Whereas in an everyday sense children

who are ill tend to be more vulnerable compared to healthy children, in a research setting different kinds of vulnerability are addressed.<sup>15</sup> This was confirmed by our patient participants who explained that their health and research experience helped them to feel empowered. While one healthy volunteer (Child08), for example, assumed that some tests might be more burdensome if she were sick, the opposite might in fact be true. Even though the lung test in this example was probably more difficult to perform for children with asthma, this child would have experienced them before, while for a healthy volunteer it is difficult to imagine what doing such test implies. Hein et al also found that little prior disease experience is an important predictor for not participating in research.<sup>35</sup> In addition, healthy children might have more difficulty understanding the information, because they are less familiar with the greater context. It is harder for healthy volunteers to picture who will benefit from the research because they probably do not know anyone who has the condition the research is investigating (Child13). Therefore, healthy children only realize at a much later stage what their participation could mean for others. This seems to point to a lack of empowerment rather than a potential vulnerability.

A strategy to prevent this layer is, as was suggested by our participants, sharing more information about research experiences, both positive and negative with the general public, alike (Child02). This may help healthy children to make a more deliberate decision about taking part in research.

### **Giving due weight to children's voices**

There is increasing recognition for children's rights in international policy documents such as the Convention on the Rights of the Child.<sup>1</sup> One of those rights is children's right to share their opinions and to be listened to (article 12). But how much weight should we give to their voices? In this study we advocate to give as much weight to children's voices as possible to do justice to their developing capacity. Our findings suggest that in doing so, we should not only focus on protecting children, but also look for ways to empower them in research. Yet we acknowledge the possibility that children's expressions are a reflection of their immaturity and undeveloped capacity and sometimes they would not be able to oversee the consequences of their actions. Children's position in research is complex and the exact weight that should be given to their voices always depends on individual situations (e.g. capacity of the individual child, previous experiences and health setting) and its assessment by professionals and parents of children. In an acute health setting, for example, it might be more challenging for parents and professionals to give due weight to children's own

views while also protecting their other interests.<sup>36</sup> This complex situation makes that children greatly depend on adults' responsibility and we hope this could be the start of a discussion with other professionals, parents and children about how to give more weight to children's perceived interests in research.

### **Limitations and future research**

This qualitative research seeks to find reality as it is represented by the interviewees. We must always remain critical about self-reported experiences as only one perspective on 'the truth'.

Our interviews covered a wide range of experiences with medical research in the UK and the Netherlands from widely varying participants. Our aim was to enlarge our dataset and thereby to extend the variation in our sample rather than to look for differences between the two datasets. Nevertheless, there were variations between the UK dataset and the dataset from the Netherlands that invite further consideration. A greater proportion of the children in the Netherlands sample had rare chronic diseases or other conditions, while a greater proportion of the UK children had experienced common chronic diseases. In addition, we have chosen a relatively large age range extending from 9 to 18 years. The perceived position of a child in research might vary depending on the child's age, the type of disease and the type of research the child is invited to. Our analysis showed that disease or research experience in itself had a positive influence of how capable children felt to make decisions about research participation, but we did not find clear find a clear difference of the type of disease, for example between common or rare chronic diseases, neither did we find a distinct difference based on age. Because all these factors seemed to be interacting with each other, it was not possible within our analysis to address the influence of these factors separately. We believe this needs future studies with a more quantitative or mixed methods approach.

We did not address all possible variations within the pediatric population. The few participants with a health condition that may involve cognitive impairment or diminished ability to express oneself verbally is also a limitation of our study as those children too deserve the chance to be heard. Further research is needed to provide more insight into their perspectives. The emphasis on supporting participation and being empowered rather than being protected may reflect the nature of the sample, which was predominantly children who had agreed to take part in research. Children in our sample who chose not to participate also

acknowledged factors contributing to this empowerment, including the benefit for others, but it was not sufficient to outweigh the expected burden for them as a result of interventions and timing of procedures. More research with children who decline is required.

We did not interview children in a palliative research setting, children from different cultural backgrounds, or children from low-income countries. Therefore, we might have missed potential layers of vulnerabilities in our analyses relating to, for example, financial considerations, language, or cultural differences.

#### *Financial motivations*

Our participants reported that a financial reward did not play a major role in their decision to participate in medical research. To them a substantial financial compensation in return for participation seemed strange and unnecessary.<sup>11</sup> If a financial motivation becomes the main or only reason for taking part in medical research, participants (children or parents) may fail to consider the possible harm, and a financial layer of vulnerability could occur. Another trigger of this financial layer might be gaining access to a certain drug through a clinical trial to which they would otherwise not have had access. For people without health insurance participation in medical research might be their sole means of entering the medical circuit. This latter situation is more likely in countries without access to health care and in case of poverty. Future research is required to elaborate on this layer and its potential implications.

#### *Language and cultural differences*

In our recruitment efforts for the Dutch interviews, none of the children with foreign parents whom we approached agreed to participate. A language layer of vulnerability may have acted as a barrier for them to consent to participate in our research. Language is known to be a significant barrier for medical specialists in the regular health care setting in their consultations with patients and can lead to misunderstanding or cause problems such as lack of empathy<sup>37-39</sup> A potential strategy when recruiting children and parents with a different native language is to hire a translator to help with recruitment. Yet, if a study lacks the financial resources to support participants with translation services, researchers are more reluctant to invite a non-native speaker to participate in medical research.<sup>40</sup> and this may exclude non-native speakers (for example recent migrants) from important research. Asking family interpreters might be a cost-effective solution, but this could potentially lead to miscommunication or distrust on account of



power imbalances.<sup>41</sup> We have taken language as just one example to show how aspects that constitute or relate to someone's cultural beliefs or background could cause a layer of vulnerability. Nevertheless, we acknowledge that language is not the same as culture. Investing in training and knowledge of different cultural beliefs before beginning to recruit participants might be a helpful strategy to minimize layers of vulnerability relating to culture.

## Conclusions

In exploring vulnerability we found that children do not focus so much on protection as on support that leads to empowerment. The layered approach to vulnerability provides a way to not only protect children, but also to empower them. We identified four potential layers of vulnerability: 1) relates to information; 2) considers the burden involved in research; 3) ponders the suffering from a disease and 4) the impact of the lack of acquaintance with research. Some layers may overlap or interact with one another. If we want to support children in their evolving capacity, we should give sufficient weight to their voices. Importantly, this greatly depends on the responsibility of others such as researchers and parents. Based on the identified layers, we formulated responsibilities that relate to involvement, support, and supply of information, while keeping in mind the individual differences among children. We believe these insights can be useful for researchers and RECs to provide them with more tangible guidance when developing or assessing research proposals that are tailored towards children's needs and wishes. Other potential layers, such as those related to financial motivation, language, and other cultural aspects were not present in our dataset but should be included in future research.

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*“I thought it could be fun and I had never done such a thing before, and I like to help people, and perhaps I want to become a doctor in the future so I thought it would be fantastic!”*

*“It actually felt a bit like I was a researcher myself”*