CHAPTER 5

Information for Minors Participating in Research Projects: Current Practice and Evaluation of a New Format

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Abstract

Aim: Informing minors participating in medical research is often not focused on their capacity of understanding. The aim of this study is to (1) identify pitfalls in current informed consent practice, (2) obtain feedback from end-users about previously developed new information material, and (3) share recommendations for improvement.

Methods: The previously developed new material and the standard material were evaluated by 12 research nurses of 8 Dutch medical centers and 12 children 8-14 years old and their parents (n=11) participating in a clinical trial.

Results: All nurses expressed that current information is lengthy, complicated and hard to read. Identified pitfalls were timing and a gap in information for children 8-12 years old. All nurses found that the new material was intelligible to children and parents, and were eager to implement it. Children and parents demonstrated good understanding of the new material and were moderately enthusiastic: 12 preferred new material, 7 preferred the standard, 4 had no preference. All participants recommended shortening and simplifying the material.

Conclusion: Current informed consent practice in minors is insufficient to achieve understanding. A shorter, simplified version of our new material should be implemented in order to improve the informed consent procedure for research with minors.

Introduction

When minors are approached to participate in medical research, it is important to provide them with understandable research information. Various international and national laws and regulations provide guidelines to inform minors. The Second Directive 2001/20/EC of the European Parliament and the Council of the European Union states that 'A clinical trial on minors may be undertaken only if […] the minor has received information according to its capacity of understanding (EU, 2001). The U.S. Food and Drug Administration puts forward in the Code of Federal Regulations, sec. 50.55(a): The institutional review board (IRB) must determine that adequate provisions are made for soliciting the assent of the children (Code of Federal Regulations, 2014).

However, numerous studies have indicated that both adult research participants (Kass et al., 2011; Terranova et al., 2012) and minors (Swartling et al., 2011; Tait et al., 2003, 2007) often lack adequate understanding of research information. For example, in one study, half of the children were unaware that their treatment was in fact part of a clinical trial (Unguru et al., 2010). There are many reasons for this lack of understanding, such as timing of the information after receiving a diagnosis, stress in a medical situation, and the degree of interest of the research participant (Chappuy et al., 2008). Another important factor is that the provided written text is too complicated for the average research participant because often highly educated researchers write for participants with a lower average education level (J. B. Green et al., 2003). A recent study by three of the authors indicated that information for minors (age 12-17) was even too difficult to read for adults with an average reading level (Grootens-Wiegers, De Vries, Vossen, & Van den Broek, 2015).

When children are involved in decision-making on research participation, their decisional capacity 'is only as good as the provided information' (Ganzini, Volicer, Nelson, Fox, & Derse, 2004). The use of visuals in complex information can greatly enhance comprehension, and has shown to improve attention, recall and adherence (Houts et al., 2006). Children are also more likely to pay attention to a text with illustrations, and children with a lower reading ability can greatly rely on images in order to understand a text (Brookshire et al., 2002) . Also, illustrations can aid in triggering the memory by looking at the picture after verbal instructions (Houts et al., 2006).

In this chapter we aim to increase awareness among medical practitioners and researchers about the importance of the quality of research information for minors. For this purpose, first, the current informed consent procedure for minors will be illustrated by referring

to an ongoing research study. Next, the development of a new format for information material for minors will be presented and we discuss the evaluation of the new material by research nurses and a subset of children and parents participating in the CoelKids study. We conclude with guidelines for improving the current information practice based on results from our study and on communication theories.

Materials and Methods

Current information process in a study with minors

The CoelKids study is a randomized multicenter study involving children and young adults with celiac disease from the Leiden University Medical Center (LUMC) and 6 participating hospitals in the Netherlands. Celiac disease is a frequent chronic disorder affecting the small bowel and other organs and is treated with a lifelong strict gluten-free diet (Vriezinga, Schweizer, Koning, & Mearin, 2015). The CoelKids study protocol and information material was approved by the medical ethical committee of the LUMC. The CoelKids information was based on the example provided by the Dutch Central Committee on Research Involving Human Subjects. In the Netherlands, a double consent is obligatory if the research participant is aged 12 years or older, meaning that these children have to co-sign the informed consent form with their representatives. For children aged 12 years or older, the text was simplified when possible and the information was addressed to the child. If children were below 12 years of age, the study information addressed their representatives. In both cases, the information leaflet consisted of 3 pages with text only. The only visuals were the study logo on the front page and a flow-chart representing the study outline in the attachment.

New format: comic strip

New information material was previously designed in the form of a comic strip (see figure 1). A comic strip combines both textual and visual information and can be a very intuitive medium for the patient to understand. They have been used in medical education before and proven effective (M. J. Green & Myers, 2010). In order to optimize the material, end-users (pediatricians, research nurses, school children and their parents) have been involved in the previously described process of development (Grootens-Wiegers, De Vries, Van Beusekom, Van Dijck, & Van den Broek, 2015). The comic strip discusses essential research

concepts, such as voluntary participation and why research with children is necessary. In addition, a new informed consent form was developed to accompany the comic strip. The comic strip can be used without the form in order to inform minors, and the form can be used in situations when minors are old enough to provide official consent, or to ask assent. The material is primarily aimed at children from the age of 10 to 14 years, based on research on children's understanding (Ondrusek et al., 1998).

Figure 1. An excerpt from the comic strip, from the chapter on biobanks © Irene Cécile (original version in Dutch).

Evaluation groups

For the present study, two different groups of end-users were consulted for evaluation of a draft of the new research information. The first group consisted of 12 research nurses specialized in pediatric research from 8 large medical centers, who participated in semi-structured focus groups. The focus groups were aimed at describing experiences with the current informed consent procedure and gaining insight in how the material could be adapted for implementation in the clinic. The second group of end-users consisted of children with celiac disease and their parents participating in the CoelKids trial.

A total of 72 children between the age of 8-17 participating in the CoelKids trial and their parents were invited by email to evaluate the new material. After a positive response, parent and child received a separate information letter and survey, the comic strip and a return envelope. The present study was carried out separately from the CoelKids trial. This study was approved by the Medical Ethical Committee of the LUMC.

The survey consisted of two pages with questions on current practice and questions to evaluate the new material. Participants were asked whether they preferred the standard information material as provided in the CoelKids trial, the comic strip, or a mix. Understanding was assessed with true-false questions about voluntary participation, treatment benefit, right to withdraw, randomization, placebo effect, side effects, anonymity, and possible personal benefit. User-satisfaction with the content and lay-out was evaluated with a number of qualitative questions. Additional information needs next to the legally required information were assessed (options were based on previous interviews: fear of needles, fear of the hospital, not knowing how to decide or 'other'). In the survey for the parents, the use of the material as a support for family conversation on research participation was examined.

Results

Evaluation of current practice by research nurses

All nurses expressed that there currently is too much information provided at once, and the information is too complicated and hard to read. Often the documents are longer than the maximum of 4 pages. Or as one of the nurses put it *'sometimes I think 'how could the IRB have approved this?' […] I think that they sometimes approve very complicated patient information forms'*. Another nurse mentioned *'[the information] is approved somewhere and I read it later and I don't know how to explain it'*. The official information is for children from 12 years and older, because they are required to co-decide, but often this information is insufficient to achieve understanding. It was also mentioned that children often do not read the information, and that children younger than 12 years old are not addressed in the information, even though their parents often involve them in decision-making about participation.

Another issue is the importance of timing; an example was provided were a child was very upset after being asked to participate in research shortly after receiving a serious medical diagnosis. All research nurses reported that informing and obtaining consent for research participation is not a single event. Each nurse could describe a situation in which children or parents initially expressed understanding, but appeared completely uninformed or even unaware of participation at a later moment. All research nurses agreed that in order to adequately inform minors and their parents, they needed extra time and used extra

tools. Some of the creative alternatives were: a picture book to show the procedure and medical apparatus; the use of colored beads to visualize red and white blood cells; showing tubes in order to indicate how much blood will be drawn, and a YouTube video. In addition, in some hospitals the nurses would let their own children read the consent material in order to check for comprehensibility.

Evaluation of the comic strip by research nurses

Subsequently it was discussed whether the research nurses thought that the new material could solve a number of the aforementioned issues. All research nurses expressed their enthusiasm about the new material, and said that providing clear information in this way is a sign of respecting the children. All agreed that this material did indeed have the potential to improve the current situation, and it was mentioned that the use of a comic strip might also improve understanding in the parents. The nurses were eager to use the material in daily practice and provided a number of recommendations for improvement and implementation as reported in table 1.

Table 1 Recommendations by the research nurses on how to improve and implement the new material

Limit the amount of information; most children just want to know 'what is going to happen' and in case of research next to treatment 'what [procedure] is extra for the study'
Keep the text **as simple as possible**; some explanations should be more concise
Keep **drawings plain and simple** too, in order to hold the attention
Make sure the information can be **dosed**; e.g. a folder or file where you can select those parts of the information that are suitable for the specific situation and interest level of the child
Make the information available for **children 8-12**, for whom a PIF is not legally obliged, but there is an information need
Use **additional media** to present the information, such as a mobile phone application or a YouTube clip
Make sure that the IRBs agree with the new material, in order to ensure that users are not stopped by lack of **IRB approval**

Evaluation by minors and their parents

In total 20/72 invited children and 17 of their parents (in 2 families, more than 1 child was involved in the trial) responded, of which eventually 11 parents and 12 children returned a completed survey. The age of the respondents ranged from 8-14 years old, with an average age of 11 years.

All children except for one expressed the desire to be involved in the decision on research participation, as the decision concerned 'themselves' and they 'should not be forced'. The children commented that they want to be taken seriously. Most children (n=7) wanted to decide together with their parents, since their parents 'know what it is about'. When asked about the preferred format of information about research participation, 2 children preferred the comic strip and the new form, 2 preferred the comic strip next to a standard form, 4 wanted to have the standard form only, and 4 did not have any preference. Of the parents, 3 preferred the comic strip and the new form, 5 parents would like the comic strip next to a standard form, and 3 preferred the standard form only. The understanding is shown in table 2. Only two children and two parents provided incorrect answers; both children were the only two children who indicated that they did not read all of the information.

Children indicated that they liked the comic strip because it contains a lot of information, and is honest and well-explained. Children mentioned they liked the questions presented in each chapter, which could be used to fill in details on your own personal situation and practice understanding of discussed topics. Parents mentioned that the amount of the information was a strong point. They appreciated that the information was clear, aimed at the target group, and that complicated words were explained carefully. All parents but two responded that the material would indeed be useful as a conversation support to talk about research participation with their child. Recommendations provided by the children and their parents are presented in table 3.

Table 2 Number of correct answers per research topic for children and parents (n=11 as one child did not answer these questions)

	Correct answers	
Research concept	**Children (n=11)**	**Parents (n=11)**
Voluntariness	11	11
Treatment benefit	11	11
Right to withdraw	11	10
Randomisation	9	9
Placebo	11	10
Side effects	11	10
Anonymity	10	11
Personal benefit	11	11

Table 3 Recommendations by children and their parents on how to use and improve the new material

Shorten the amount of information, not to discourage the readers
Some explanations could be **less detailed** (e.g. placebo chapter)
Improve **explanations about blinding and study design** (observational or intervention)
Include information about **fear of needles**
Include information about **how to decide** on research participation
Explain how a **placebo** can be effective
The fully developed example pages of the comic strip have **great color**

Discussion

The results of our study indicate that research information in the format of a comic strip can increase understanding and is well received by different end-users. In addition, the end-users provided us with valuable tips to further improve the material. Accurate study information for minors participating in research is important to increase understanding and empowerment of this specific group.

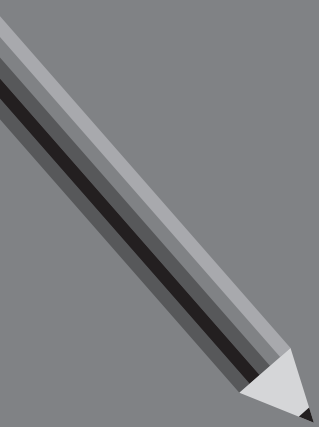
Recommendations for designing study information for minors

Other studies have also demonstrated that interventions such as improving readability, text layout and multimedia formats can effectively improve comprehension in children (O'Lonergan & Forster-Harwood, 2011; Tait et al., 2007). However, evidence of effective methods for children is scarce (Grootens-Wiegers, De Vries, & Van den Broek, 2015) since many interventions have only been studied in adults (Nishimura et al., 2013). Nevertheless, a number of recommendations to improve information practice can be drawn from scientific theory and evidence.

The first recommendation is to keep in mind that the average patient has a reading level different from that of the writer of the research information. Instruments exist to indicate the reading level of a text, such as the Flesch Reading Ease and the Flesch-Kincaid Grade Level, both of which are readily available in most text-writing software and online.

The second recommendation is to include end-users in the development of information material, either in evaluation of comprehension (Barros et al., 2014; Houts et al., 2006), or already in one of the earlier stages of design. This is a promising means to connect to target groups as they are experts on their own preferences and can offer valuable insights in how

to enhance the information (Dedding et al., 2015; C. Hart & Chesson, 1998; Lansdown, 2001; Rudd & Comings, 1994, Grootens-Wiegers, De Vries, Van Beusekom, et al., 2015).
The last recommendation is based upon multimedia theory (Mayer, 2001). According to this theory, information is processed in two distinct channels, auditory/verbal, and visual/pictorial, each with a limited processing capacity. When communication input exceeds the capacity of a channel, this reduces the amount of information taken up and understood by the receiver. In medical research, preventing an overload is a challenge, due to the amount and complexity of the information. As previous studies have indicated that research information for minors often lacks visual support (Menoni et al., 2011; Grootens-Wiegers, De Vries, Vossen, et al., 2015), including images is a promising opportunity to improve understanding. The new information material that is discussed in this chapter has been based on this theory. Our evaluation suggests that the textual/visual combination approach was indeed effective and had a positive effect on comprehension.
Our study has some limitations. While end-users in previous evaluations of the comic strip as well as the research nurses in the present study, have unanimously been very enthusiastic, it is interesting that a relatively large fraction of participants indicated to prefer the standard form. The positive evaluation of CoelKids' standard information may stem from the fact that this study is relatively short and easy to understand, and included a clarifying flow-chart. Nevertheless, it is possible that there was a selection bias towards the most intelligent participants, who may have been more interested in our study. Since we do not have information on the education level of the children and their parents, we were unable to resolve this issue.
The response rate and the return rate of the survey was low, which might have led to a response bias. It is likely that participants with a vested interest or specific opinion about research information responded, and that we are unaware of the preferences of the non-responders. Another reason for the low response might be that the study took place shortly before the summer break, when many families with children are away on holiday. In addition, we did not check whether parents helped the children with questions assessing understanding of the information.
In order to further improve research information for minors, we suggest a randomized trial comparing the comic strip to the current standard information material. This will give more generalizable results among children in a hospital and research context, including the influence of factors currently not applicable to the present study, such as stress due to a hospital visit and limited energy due to illnesses.



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