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Report on patient engagement and perspective integration

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Contact: Jacques Demotes
ECRIN-ERIC Director General
European Clinical Research Infrastructure Network
BioPark, 5-7 rue Watt
75013 Paris, France
Tel: +33 180058646
Jacques.demotes@ecrin.org
www.ecrin.org

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1. List of Authors

Name	Institution
Eric Vermeulen	Dutch Patient Association for Rare and Genetic Diseases (Vereniging Samenwerkende Ouder- en Patiëntenorganisaties VSOP)
Martine Jansen- van der Weide	Dutch Patient Association for Rare and Genetic Diseases (Vereniging Samenwerkende Ouder- en Patiëntenorganisaties VSOP)
Kim Karsenberg	Dutch Patient Association for Rare and Genetic Diseases (Vereniging Samenwerkende Ouder- en Patiëntenorganisaties VSOP)
Cor Oosterwijk	Dutch Patient Association for Rare and Genetic Diseases (Vereniging Samenwerkende Ouder- en Patiëntenorganisaties VSOP)
Begonya Nafria Escalera	Fundació Sant Joan de Déu (FSJD)
Joana Claverol Torres	Fundació Sant Joan de Déu (FSJD)
Pamela Dicks	National Health Service Grampian, Scottish Children's Research Network
Salma Malik	European Clinical Research Infrastructure Network (ECRIN)

2. Executive Summary

Deliverable 5.13 consists of three parts.

- The first part provides an introduction to the children's participation in clinical research.
- The second part shows the time schedule and actions of Task 5.4 in more detail.
- The third part gives an overview (Quick scan) of tools that could be appropriate for engagement activities and patient empowerment, and a summary of topics that might be relevant to patients to address.

3. Introduction and background

Historically, children and young people have been protected from participation in medical (drug) research, and as a consequence medications have not been appropriately labelled for them [1]. To help change this situation, the Paediatric Regulation in the European Union (EU) was implemented in 2010 and provides incentives for pharmaceutical companies to investigate new drugs in children. However, off-label dosing recommendations for currently marketed drugs also need to be revisited [2] especially for older, off-patent medications [3]. The initiative to gather empirical evidence about older drugs can be undertaken by non-commercial (academic) paediatric clinician-scientists [4]. The revision of the Directive of the European Commission (EC) in 2014 [5] highlights the role of paediatric networks to help consolidate available knowledge about medicines and translate it into practice. Paediatric drug research poses challenges, but innovations in trial design and pharmacology prompt some [6] to conclude that ‘there has never been a better time for conducting drug studies in children’.

PedCRIN aims to develop tools for international pediatric research and work package 5 (WP5) is to deliver consultation methods to involve children and parents in clinical research. There is a need to involve children/parents in research design, the preparation of patients’ documentation and information materials to improve research protocols and enhance research participation. There are examples of struggling or failed RCT’s in the field of pediatric medicine that have had significant difficulties with the recruitment of pediatric patients [7, 8]. Another recent study showed that less than half of the clinical research projects succeeded in recruiting 80% of confirmed participants at the planned closing date [9]. Mistrust in research, logistical aspects and disruption of daily life are some of the aspects that play a role in the refusal or withdrawal of research participation [10]. Furthermore, informed consent information can be misunderstood leading to consent that is not fully informed in some cases, and to disappointment and possible withdrawal from the study in other cases [11]. Early involvement of these patients in the trial protocol may result in identification of trial aspects that might be less acceptable or unclear for participants. Also, it stimulates more patient-oriented health research by including patient-relevant outcome measures, and offering the opportunity to check the relevance and scope of the research to be conducted [12].

Patient involvement in adult studies is becoming more and more state of the art, being a starting point with the identification of priorities and patient’s needs, as this is what research is aiming at: improving patients’ lives [13, 14]. However, there still is not a standard procedure in how to involve patients/patient representatives when designing a clinical trial. Especially, concerning pediatric patient involvement more insights are needed in what children consider important in the clinical trial process. Therefore, in this task the role of patients/parents/patient representatives will be identified through consultation with advocacy groups and Young Persons Advocacy Groups (YPAGs), for which education and empowerment activities will be put in place. In the next section the schedule and actions of task 5.4 are explained in more detail.

4. Schedule and actions task 5.4

The goal of Task 5.4

To investigate how patients/parents/patient representatives can be involved in the design, execution and finalization of clinical trials and to assess the impact of the patient engagement activities.

The work on task 5.4 consists of five phases

- Overview of available methodology
- 'Walking through' a trial protocol
- Education and empowerment activities during pilot trials funded by PedCRIN
- Evaluate patient involvement/engagement in the pilots
- Report of activities and impact assessment of the empowerment activities (D 5.14)

4.1. Overview of available methodology (tools)

Time Schedule: M 4-6

Relevant methods that promote and facilitate patient engagement in paediatric clinical trials will be selected either from literature, trusted sources and/or from (European) projects about patient involvement in clinical trials (performed during the last 10 years). These relevant patient engagement methods will be presented in an overview (section 5. Quick scan) and if appropriate used and tested during the pilot trials (This activity will be done during M 9-23, see 4.3).

4.2. 'Walking through' a trial protocol

Time schedule: M 9-12

Patients/parents/patient representatives with knowledge about and or experience with the three pilot trial diseases will be invited to participate. Patients/parents/patient representatives who will be invited for the consultation process will also receive general information about clinical trials and a short questionnaire (for more details section 4.3: education and empowerment activities during pilot trials). The general information about clinical trials will contain only those elements that are relevant for the pilot trial they are selected for. For example with regard to trial design: randomisation, placebo or standard treatment, choice of control arm (comparator), outcome measures, design, informed consent, practical issues during the trial, etc. In the short questionnaire they will be asked in which elements of the clinical trial process they would like to be involved, and what their contribution would entail. Also, their level of experience with (their child) participating in a clinical trial and in clinical trial design is requested. The goal of this questionnaire is to explore in which way patients/parents wish to be involved in clinical trial design, execution and communication and what tools are most appropriate according to them. Also, we would like to investigate who is the most appropriate patient/parent/patient representative to consult for future empowerment activities. Their responses on these questions will be incorporated in the consultation procedure (section 4.3).

4.3. Education and empowerment activities during PedCRIN funded projects

Time schedule: M 9-23

In July 2017 from the 13 applications received, 3 pilot trials were selected for PedCRIN funding. If needed clinicians involved in these pilot trials or (local) clinicians with knowledge about the disease can give explanations to patients/parents/patient representatives and YPAGs about the trial protocol, informed consent document, outcome measures and communication activities regarding research results. Patients/parents/patient representatives and YPAGs will be invited to provide an active feedback on all relevant trial elements. Following pilot trial implementation suitable patients, parents, patient organisations and patient representatives will be contacted to participate in the consultation activities. In parallel the current YPAGs, members of eYPAGnet (see 5.1.3) are going to be involved. The main goal of this WP5 task is to find an answer to the questions: in which aspects regarding clinical trial design, execution and reporting of clinical trials do patients/parents/patient representatives and YPAGs want to be involved and which methodology for involvement is the most appropriate? What is the impact of the patient engagement activities on trial design, execution and report?

The following paragraphs will describe in more detail, who will be involved, which procedures will be followed, which topics will be discussed and what will be done with task results.

4.3.1. Selected pilot trials

PedCRIN will support three pilot trials (Table 1) with services for trial management outside the coordinating country. The services consist of regulatory and ethical submissions, trial monitoring, pharmacovigilance, support to insurance contracting, product and biosample management. In addition the trials will be used to test the tools developed in WP3

4.3.1.1. Botulinum toxin in children with cerebral palsy (BoNT-A-CP study)

Objectives: To evaluate whether injections of BoNT-A in the calf muscles make walking easier in children/adolescents with cerebral palsy (CP) within a time span of 6 months, and to evaluate whether an improvement in energy cost during walking is associated with increased daily activity, increased walking capacity, less pain and perceived improved performance and satisfaction.

Study design: A double blinded, multi-center, randomized, placebo-controlled trial, parallel-group design (Phase IV). The study was evaluated by the Norwegian Research Council and got a full score (excellent).

State of affairs: The study has already started in Norway. Approval for the study has to be sought in other countries.

4.3.1.2 Prophylactic oropharyngeal surfactant for preterm infants (POPART study)

Objective: To determine, among infants born before 29 weeks of gestation, whether oropharyngeal surfactant at birth, compared to no intervention, reduces the rate of endotracheal intubation for respiratory failure within 120 hours of birth.

Study design: A non-blinded, multi-centre, randomized controlled trial, parallel group design. Parents with experience with preterm birth (and clinical trials) were involved in the study design.

State of affairs: This study has yet to start and approval has to be obtained in other countries. Possible relevant aspects for consultation phase: Parents are asked for consent antenatal if possible. This pilot trial can only be discussed with parents – possibly parents with experience in neonatal care. So this trial will be consulted with patients advocates' groups in Europe consisting of parents and if possible patient representatives from the concerning patient organisations.

4.3.1.3. Oxytocin treatment in infants with Prader-Willy Syndrome (OTBB3 trial)

Objectives: To assess the effect of OXT administration versus Placebo on sucking/swallowing after 1 month of 4IU intranasal OXT treatment administered every other day among neonates with Prader Willi Syndrome (PWS) aged less than 3 months at inclusion.

Study design: A double blinded, multi-center, randomized, placebo-controlled trial, parallel-group design (Phase III)

State of affairs: The study has already started in France. Approval for the study has to be sought in other countries. Because this study is a regulatory trial with approval by the EMA, making changes to the protocol on the basis of the consultations is not very likely. Phase 1&2 of this study were also performed by the same study team. [15, 16]

4.3.1. Consultations about the PedCRIN pilot trials

The consultations of the patients/parents and/or patient representatives will be held with specific groups appropriate for the specific pilot trial. Here we describe what kind of consultations with specific groups will be held.

Who to involve

The VSOP will invite young patients/parents and/or patient representatives (for example via VSOP –network, child and hospital (a Dutch organisation), and youth councils (of Dutch academic hospitals). The VSOP will include patients with the disease in question, when children are too young to be consulted, parents will be invited to participate and/or patient representatives. The VSOP will work with the PI's from the PedCRIN funded trials to assess the possibilities of consultations with patients and parents in other countries.

VSOP will initially start two (Dutch) patient advocates' groups consisting of either parents/patient representatives for POPART and OTBB3 study). If possible within time and budget an additional (Dutch) patient group will be formed, consisting of (young) patients with Cerebral Palsy.

All groups will consist of between 6-10 participants. The group meetings will last a maximum of 3 hours for the groups consisting of adults (parents and patient representatives) and 2 hours for the group consisting of children. Three meetings will be divided in two sessions and in between sessions there will be a 30 minute break. The agenda of the meeting will include the following elements.

- Welcome (by project leaders)
- Introduction (project leaders and participants)
- Pilot introduction (outcome measures, design, informed consent, communication, etc.)
- Discussion of the pilot trial and formulating recommendations regarding: comparator, outcome measures, design, informed consent, practical issues during the trial and information after the trial has ended

- Evaluation of the consultation and the methodology used

It is unlikely that all topics can be addressed during the discussion of the pilot trials. The number and subject of topics will depend on the pilot type, the results/responses from the patients during the walking through pilot trial and the time available during the meeting. The Power model (section 5) will be used during the whole process of consulting parents/patient representatives.

A part of the consultation will also be a follow-up contact with participating youth/parents to address possible stress caused by the discussions in the face to face meetings.

The YPAG from the European YPAG network, led by Fundació Sant Joan de Déu, will be consulted. (Spain, England, Scotland and France). The methodology to be used by the YPAGs will be developed according to the materials of the pilot trials.

Procedure

The young person advisory groups (YPAGs) will be consulted in one pilot trial. In the Netherlands different groups will be established (Dutch patient advocates' groups) who will give feedback on selected topics of all pilot trials. These different groups YPAGs and Dutch patient advocates' groups will be consulted during face-to-face meetings. Efforts will be made to make virtual participation possible when a child (and/or parent) that is motivated to participate and can give a valuable contribution, but is unable to be physically present. The reason for selecting these face to face meetings for consulting patients/parents/patient representatives and retrieving their input is described in more detail in section 5 (Quick Scan).

How and what to ask

Based on the quick scan of available methods to consult patients/parents/patient advocates, the most appropriate methods will be chosen, the consultations by the VSOP will be face to face meetings (focus groups) because of the interaction that can take place between the participants - where necessary and possible other methods will be added (questionnaire and interviews).

Comments and response:

In the situation the YPAG's and/or the Dutch patient advocates' group retrieve different feedback, the chances of those differences being the result of methodology are decreased and made transparent. In the situation that patients, parents and or patient advocates taking part in a Dutch group aren't able to be physically present during the face to face group efforts will be made for the parent/patient or patient advocate to be virtually present via Skype etc. The group meetings (YPAGs and Dutch patient advocates' groups) are going to use 'face-to-face' methodology [17]. In the case young children aren't able to attend the group meeting (face-to-face or virtually), but are willing to participate, an alternative method could be to perform individual interviews to collect their feedback. The possible topics that could be addressed are:

- Choice of control arm (comparator)
- Outcome measures
- Design
- Informed consent
- Practical issues during the trial
- Information after the trial has ended

Report

The results will be presented in an overview after the patient representatives have agreed on the final version of the overview. This overview will be reported back to the pilot trial investigators/clinicians. As the PedCRIN funded pilot trials have already started it will not be possible to change the protocol according to the patients' wishes recorded in the consultations. We will, however, discuss the findings from the consultations with the investigators and record their response (See 4.4.) (Table 1).

Table 1. Pilot studies: characteristics and possibilities for consultations

Project : Objectives	Phase & Design	Countries	Inclusion Criteria	No. of Patients	Investigational Medical Product (IMP)	Follow-up End points	Start Date	End Date	Outcome measures
BoNT-A-CP Study - Does botulinum toxin A make walking easier in children with Cerebral Palsy within a time span of 6 months - To evaluate whether an improvement in energy cost during walking is associated with increased daily activity, less pain and perceived improved performance & satisfaction.	Phase IV A double blinded placebo controlled randomized parallel-group design. Multicenter study.	<i>Norway</i> France (Nice) Poland (Zagórze)	- Diagnosed with unilateral or bilateral CP in their medical record - Level I or II according to Gross Motor Function Classification System - Must be at least 4 years of age. - Identified spasticity in the calf muscles, clinically judged as grade 2 or 3 (Tardieu Scale)	96 20 already recruited	-Botox® (onabotulinumtoxin A), sterile vacuum-dried powder for reconstruction with sterile, non-preserved 0,9% Sodium Chloride injection USP. -Sterile 0,9% Sodium Chloride injection	24 weeks 4,12 and 24 weeks	01/01/2015	30/06/2018	- Evidence for the efficacy of BoNT-A in the calf muscles on walking - Improvement in energy cost during walking - Improvement in performance, satisfaction and fatigability, and social participation - Recurrent musculoskeletal pain - Identification of characteristics of responders and non-responders
Available materials to discuss in consultations			Patient involvement in design phase?			Possibilities to adapt the protocol			
- Materials have to be translated to English (for YPAG) and Dutch (for patient groups) - Protocol available in English			- Patient involvement is not formally included in the protocol			- No, research has already started. - Ethical approval has to be sought in Nice and Poland. - PIF has to be written for the added countries			
POPART study - To determine whether, among infants born before 29 Weeks of gestation, does, oropharyngeal surfactant at birth compared to no intervention reduce the rate of endotracheal intubation for respiratory failure within 120 hours	Phase 3 Randomized, parallel group, controlled trial	<i>Ireland</i> Czech Republic Norway	- Infants born before 29 weeks of gestation - Initiation of intensive care	250	Curosurf (Chiesi Farmaceutici, Parma, Italy) 120mg or 240mg given by injection into the oropharynx	Infants will be followed up until discharge from hospital	01/06/2017	31/05/2019	- Incidence of endotracheal intubation for respiratory failure within 120 hours of birth.

of birth		Portugal, Sweden Italy Denmark							
Available materials to discuss in consultations		Patient involvement in design phase?				Possibilities to adapt the protocol			
- Materials and protocol are available in English, have to be translated to Dutch (for patient groups)		Yes - PI contacted a parent				- No, but the research has yet to start. - PIF has to be written for the added countries			
OTBB3 study - Oxytocin treatment in babies with Prader-Willi syndrome: effects of intranasal administrations of oxytocin in infants aged from 0 to 3 months vs. placebo on sucking and swallowing (phase III clinical trial)	Phase 3 Multicentre, prospective, randomized, placebo-controlled, double-blind clinical trial	France Germany Belgium Italy Netherland	- Male or female infants, with PWS genetically confirmed - Age ≤ 3 months - Signed informed consent obtained from the parents - Parents willing and able to comply with all study procedures	52	Syntocinon: spray nasal (5ml; 40 UI/ml) Victoria Apotheke Pharmacy	5 months	01/11/2017	01/11/2020	Is sucking/swallowing assessed after 1 month of treatment by the Neonatal Oral-Motor Assessment Scale (NOMAS) scored on videos. The proportion of neonates/infants with a quasi-normal score (≤10) will be compared between treatment groups.
Available materials to discuss in consultations		Patient involvement in design phase?				Possibilities to adapt the protocol			
- Materials and protocol are available in English, have to be translated to Dutch (for patient groups) - This trial is regulatory, with involvement of EMA		- No, but researchers conducted a phase 1 / 2 study in the same patient group.				No - Regulatory trial. Already EMA approval obtained - PIF has to be written for the added countries			

Table 2. Methods and activities WP 5

Study	Type of consultation	Groups to be consulted	Available methods	Topics to be discussed with YPAGS/patient groups	Goals of patient consultation	Investigators consultation
BoNT-A-CP study	YPAGs Advocacy group (NL)	YPAG (Youth) Children with CP Age groups: 10-11 years 12-18 years Parent group	- In person (Face to face group) questionnaire - Face to face groups Questionnaire	1.Design 2.Protocol 3.Informed consent procedure 4.Outcome measures 5.Comparator 6.Practical issues during the trial 7.Information after the trial has ended	- Obtain information about topics from the perspective of youth and/or patient representatives - Learn how youth and/or patients want to be involved in clinical studies in the different phases - Learn and test different tools to consult youth and/or patient representatives	<i>Interviews with (principal) investigators</i> Goals: - Considerations of researcher to consult patients before study. - Which tools are needed to consult patient before study? - Response to the opinions of the patient conclusions
POPART study	Parent group (connected to YPAGs) Advocacy group (NL)	Parents (Specific group? [parents of premature born children]) Parents (Parents premature born children [VOC])	- In person (Face to face group) Questionnaire - Face to face groups Questionnaire	1.Design 2.Protocol 3.Informed consent procedure 4.Outcome measures 5.Comparator 6.Practical issues during the trial 7.Information after the trial has ended	- Obtain information about topics from the perspective of youth and/or patient representative - Learn how youth and/or patients want to be involved in clinical studies in the different phases - Learn and test different tools to consult youth and/or patient representatives	<i>Interviews with (principal) investigators</i> Goals: - Considerations of researcher to consult patients before study. - Which tools are needed to consult patient before study? - Response to the opinions of the patient conclusions
OTBB3 study	Parent group (connected to YPAGs) Advocacy group (NL)	Parents (Specific group? [rare disease]) Parents (P-W Stichting) Youth (P-W Stichting) Age group: 12-18 years	- In person (Face to face group) Questionnaire - Face to face groups Questionnaire	1.Design 2.Protocol 3.Informed consent procedure 4.Outcome measures 5.Comparator 6.Practical issues during the trial 7.Information after the trial has ended	- Obtain information about topics from the perspective of youth and/or patient representatives - Learn how youth and/or patients want to be involved in clinical studies in the different phases - Learn and test different tools to consult youth and/or patient representatives	<i>Interviews with (principal) investigators</i> Goals: - Considerations of researcher to consult patients before study. - Which tools are needed to consult patient before study? - Response to the opinions of the patient conclusions

4.4. Evaluation patient involvement/engagement in the pilot trials

Time schedule: M 21-36

As the pilot trials have already started and/or cannot be changed, the outcomes of the consultations with patients/parents/patient representatives cannot alter the study protocol and therefore the impact of patient involvement cannot be evaluated.

To evaluate the impact of the patient engagement activities, a consultation (per pilot trial) with the pilot trial investigators will be organised. During this consultation we will ask whether elements in the clinical trial process, discussed during the consultation with patients/parents/patient representatives and YPAGs, have been adjusted after the investigators received the feedback. For example: how the decision making process regarding the adjustment to these trial elements took place; if they initiated an amendment and if so, how much time the amendment procedure took; and how they would like to see patient involvement in clinical trials in the future.

The most relevant topic in this consultation will be to discuss which tools they need to stimulate patient engagement in clinical trial design and development, and how the engagement activities proposed by the patients/parents/patient representatives could be incorporated in the future.

This consultation will be done by means of interviews. If possible a face to face meeting with the investigators will be organised because this would enable discussion among those involved. However, most trials take place outside of the Netherlands and organising such a meeting may not be possible.

4.5. Report of activities/impact assessment of empowerment activities (D 5.14)

Time schedule: M 36-48

A report will be written describing the results and conclusions from the empowerment activities. If possible a layman version will be developed for the patients, parents, patient advocates and YPAG's.

5. Review of available methodology

Several tools are available to stimulate patient engagement in clinical research. Below a selection of the possible **methods to retrieve information** from patients/parents, patient representatives and YPAGs and **methods to engage** these patients/parents and patient representatives **in the design, execution and communication regarding clinical** trials are addressed. Finally, possible relevant topics to discuss during a consultation of patients/parents and patient representatives are described.

5.1. Possible methods to retrieve information

5.1.1. Interviews

Interviews are a suitable way to explore the child's perspective, methods papers give advice about interviews[18]. Irwin and Johnson (2005) provide specific advice how to interview children of different ages. It is for example important to 'build rapport' with the child before beginning the interview: to become a trusted conversational person. In general it can be concluded that interviewing of children poses extra demands on the structure of the interview, open ended questions may not be suitable for all children and special attention should be given not to pose leading questions. The presence of parents is to be decided upon, their presence may be necessary when interviewing young children, but they also interfere with the personal perspective of the child when they want to aid the answering of children[19]. When many children will be interviewed, the process of interviews and analysis may pose challenges in time management/ could be time consuming which needs to be taken into account.

Due to these reasons it is unlikely this method will be used in task 5.4. Only in the case a child is unable to be (physically or virtually) present during a group meeting of one of the pilot trials this method may be considered in the case the child is really motivated and his feedback is of added value. For example in the case her/she is the only child with the disease represented in the discussed pilot trial.

5.1.2. Questionnaires

Children and parents can be asked to complete questionnaires [20, 21]. Questionnaire research is considered to be more difficult with children. Barakat et al. (2013) have tested a questionnaire concerning the benefits and barriers to paediatric clinical trials participation [22].

In the case of task 5.4 it is unlikely patients/parents and patient representatives will be consulted by questionnaire. When retrieving information about topics like outcome measures, informed consent material and practical issues during a trial the facilitator requires to interact, talk and discuss the topics with the participants. Questionnaires limit the responses to questions set by the researcher, whereas facilitated meetings with young people, open the possibility to ask questions the young people feel are relevant.

However, it is important to also consider using questionnaires as a useful tool, as well designed questionnaires can be used by investigators to write the research protocol according to the wishes of CYP and their parents/carers. Therefore during the consultations with the YPAG's and/or Dutch patient groups we will ask the participants if they consider a questionnaire is a good tool/method in certain circumstances such as, if the researcher wants to know which information, according to the patient/parent/patient representative should be present in (for example) informed consent material.

5.1.3. Focus Groups

Focus groups are another possibility to retrieve information from patients/parents/patient representatives. The patients/patient representatives /YPAGs can be informed about a certain topic and give their views. The existence of a group process can be an advantage or disadvantage for the opinions that might be given. Some patients might be overwhelmed by the opinion of others. On the other hand, some might be encouraged by other patients to share their own views. When choosing this type of involvement it is important to be aware of that.

Focus groups in general do not have to be 'face-to-face', they can also be organized via the internet; 'online focus groups' [17]. Online focus groups can have two forms: synchronous and asynchronous. The (dis)advantages are described by Nicholas et al. (2010) [17]. Other publications on Focus Groups for young persons are also available [23-25].

5.1.4. Young Persons Advisory groups (YPAGs)

The YPAG is a group of children and young people, generally aged between 12 and 18 year, who are or have been patients and have an interest in research. They have received training in drug discovery, clinical trial design and ethics. The members actively participate as partners, advising researchers and their teams on a full range of activities in various research projects and initiatives. (<http://journals.sagepub.com/doi/abs/10.1177/2168479015601344?journalCode=dijc>) [26]. As a group they regularly give feedback on trial protocols, practical aspects of trial conduct and on the age appropriateness of patient documentation. This type of consultation has shown to be effective in improving patient engagement and the clinical trial process.

In regard to task 5.4, face to face groups and the YPAGs are the means for retrieving information from patients/parents/patient advocates. During the face to face groups / YPAG meetings the advantages and disadvantages of a group process will be taken into account. For example by giving each individual participant the chance to give his/her opinion regarding a topic. This can be achieved by facilitating the discussion, breaking down in to smaller groups and encouraging less confident members to offer their opinion.

5.1.5. Consultation through a platform discussion

Patient organisations often organize platforms, eg. via Facebook. Via such a platform members can be asked to respond to a question or topic and views on the question or topic can be discussed among the members. The entries (texts) can be analysed by researchers. The advantages are that participants do not need to travel and can respond at a time they choose [27-29]. If researchers have access to the platform, they can also ask specific members for explanations or further information on their entries. The disadvantage of this tool is that it may be hard to pose difficult questions and participation may very well be biased to patients who are very active.

For task 5.4 consultation through a platform discussion, due to the lack of direct interaction and discussion, isn't the most preferred tool. It might however be a suitable tool/method when researchers want feedback, for example, on informed consent material they have developed. Like in the case with the questionnaires during the performance of task 5.4 the participants of the group meetings will be asked whether platform discussions are a suitable tool/method when research want to receive feedback from patients/parents/ patient advocates on informed consent material, list of outcome measures, protocol procedures, etc.

5.2 Methods to engage in the design, execution and communication regarding clinical trials

In order to use the tools mentioned above, a plan has to be put in place in which preparations are made to optimize patient involvement. Such preparations could be, among other things, finding the most appropriate patients for the consultation, practical arrangements, and possible training. The following tools and models are considered below.

5.2.1. The "Power model"

One of the possibilities available is the power model. The 'Power model' [30] that has been developed in another European project (Asterix) could serve as a tool to include patient and parent

opinion. The goal of this tool is to provide guidelines for researchers to include the patient opinion in the choice of outcome measures in the trial design stage. The model is intended for use in the research stage when a specific trial is in the design phase. It is assumed that the research agenda has already been set, preferably in collaboration with patients. The model consists of several steps including the identification of and contact with participants (which patient representatives), consultation on the most relevant outcome measures (how to consult) and the choice and use of the outcome measures in the clinical trial.

5.2.2. The “Wulf” method

Another option is information from Wulf et al. (2012). They described four relevant topics in patient involvement:

1. Involvement should be a process, with continuity over the whole clinical research, not a one-off meeting or even several one-off meetings for every research phase. It is important to create a partnership environment to secure communication between the investigator team and the child and parents/carers. Wulf et al. (2012) describe this notion but do not propose a frame for this involvement [11].
2. Involvement should be specific for distinct participants: children of different age groups, parents/carers with different capabilities to engage in the involvement [11].
3. Specific medical staff members (investigators / research physicians / nurses / research assistants) have different roles in the involvement of children and parents/carers and should be trained accordingly [11].
4. Involvement may differ according to the type of study (phase 3 RCT (with placebo or with two already used medicines), smaller phase 2, cross over research)

Also during the process of consultation/patient involvement strategies to promote question-asking are needed to include the young patient in the decision-making process [11].

A continual dialogue needs to be established which gives young patients and their parents the opportunity to exchange information about the study as well as reports how they would be affected by participating in the trial [11].

5.2.3. The “Fargas/Malet” method

Fargas Malet et al. (2010) [31] describe methodological issues and techniques but foremost they stress that for children confidentiality/vulnerability is important. When planning a research project, it is important to bear in mind that the research context might affect what children will talk about. It is also very important to provide privacy and confidentiality. The setting may steer children towards saying what they think adults want them to say.

A radical solution to this may be to put a child in charge of the consultation (for example a face to face group meeting) Fargas Malet et al. (2010) Also allowing them to use drawing and photography to describe their ideas Photography is recommended in the Kind en Ziekenhuis brochure (in Dutch) [32], Fargas Malet et al. (2010) also describes among ‘participatory techniques’ the ‘grouping and ranking exercises’: children are given a set of cards or photographs of activities or issues to rank in order of importance.

5.3. Topics to be addressed

With regard to the topics to address during the consultation of patients, the clinical trial process can be categorized in several phases in which patient involvement can be worthwhile. These phases consist of the *design, conduct, and report phase*.

5.3.1. During the design of the study

5.3.1.1. Possible designs

When a trial is being designed, different designs exist to choose from. For example, besides the standard 2-arm randomized controlled trial, there are also options to use three or more arms. Other options (not extensive) are: a crossover clinical trial in which each patient is assigned to a sequence of treatments, including at least two treatments (of which one "treatment" may be a standard treatment or a placebo), an adaptive clinical trial in which certain adaptations are possible during the trial, and a cluster randomized controlled trial in which groups of subjects (as opposed to individual subjects) are randomised (for example per centre). Also differences in type of randomization (ratio for division 1:1, or 1:2 for example), or how to assess the effect of the intervention (is it expected that the experimental treatment will be better (superiority), or is it expected that the experimental treatment has the same effect, but gives lesser side-effects (non-inferiority)) are possible. Patients might have good arguments to prefer a specific type of design, or refute (another) one.

5.3.1.2. Choice of control arm (comparator)

For patients the type of comparator that is used in a trial in general is very important. For example, Tromp et al. showed that parents may be afraid that their children would be placed in the group with ineffective treatment. (Reference Edwards et al. (2011) [42] for an alternative study design. Therefore, parents or children should be involved in this decision-making process to understand the reasons for choosing a specific control arm, and to share their ideas on possible alternatives.

5.3.1.2. Outcome measures

The choice of outcome measures is also a topic that patient would like to have influence on. That patient involvement in research leads to better outcome measures for research has been demonstrated in research [33].

Other examples are:

1. <http://medicaleconomics.modernmedicine.com/medical-economics/news/engaging-patients-decrease-costs-and-improve-outcomes>
2. <http://catalyst.nejm.org/patient-engagement-report-improved-engagement-leads-better-outcomes-better-tools-needed/>
3. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4854260/>

5.3.2. During the conduct of study

5.3.2.1. Informed consent

It is apparent from research that it is difficult to inform parents and children about clinical research [11].

Children need age-specific and experience specific information. Children's participation in designing the documents can improve the subsequent comprehension and assent [34, 35]. For example, informed consent can be sought through the use of comic strips. Grootens et al. (2015) developed Informed consent material in the form of a comic book [35].

Others have developed games that can be used to involve children in the process of clinical trial (<http://www.axon-com.com/clinical-trials-for-children-a-real-game-changer/>) (another example of a game (however, a *board* game [far too dull for children?] – for biobanking) is: https://www.researchgate.net/profile/Ahmed_Samir_Abdelhafiz/publication/308919355_Targeting_future_customers_Introductory_Biobank_course_for_undergraduate_medical_students/links/57f79d7908ae886b89834739.pdf

Information about reasons for consent/dissent for clinical research is given in a review by Wulf et al (2012) [11], a review by Tromp et al. (2016) [10] a study by Hein et al. (2015) [36] and a review by Hunfeld et al. (2011) [37].

5.3.3. During the study

A continual dialogue needs to be established which gives child and parents the opportunity to exchange information. This can be done by an ongoing evaluation of patient (parent) experiences by means of a small questionnaire [11].

Children and parents indicate that they wish to be asked about their experiences during the clinical trial. A continual dialogue needs to be established which gives child and parent the opportunity to exchange information. This can be done by an ongoing evaluation of patient (parent) experiences by means of a small questionnaire [11]. This tool to evaluate the experiences of patients can be very simple, consisting of only a few questions with a time schedule for researchers to ask patients and parents about their experiences during the clinical trial. The physicians/researchers may consider this a bureaucratic procedure but if in fact this helps patient involvement during the trial it could promote retention of children in the study – which could motivate physicians and researchers. Woolfall et al. (2014) provide an example of a method to involve parents in a controversial RCT at a PICU [38].

Methods for the involvement of children, youth and parents can be based on several publications [18, 32, 39-41]. There are also guiding documents targeting adults, but still relevant for this project [13, 14].

5.3.4. Report of study

Patients often expect to be informed about the results of the study.

It should be explored how patients can be involved in the communication process regarding study results. It might be depending on study design and/or type of disease studied at what point in time patients want to be informed and about which results they want to receive information. Involvement

should explore how this can be done. An extended communication procedure providing patients and their families with study results is crucial. Lay summaries are part of that.

Study materials are often stored and can be used again. Patients should be informed about this. In regard to task 5.4 during the group meetings (YPAG's and Dutch groups) it will depend on the type of pilot trial which of the above mentioned methods to engaged patients/parents and patient representatives in clinical trials will be used. The ambition of the Dutch group is to work according to the power Model.

We need to define specifically the different activities performed with patients/parents and YPAG related to the pilot trials of PedCRIN. A table that summarizes this plan will be useful to know in detail about the action plan of patient engagement of the project.

5.3 Why is patient/parent/patient representative's participation in the design, execution and report of clinical trials needed?

Participation of patients/parents/patient representatives in the design, execution and report of clinical trials is essential to make clinical trials patient centred. Participation can help, among other things, to overcome practical and logistical issues. Participation will help researchers to focus on health issues that are important for researchers, clinicians AND patients/parents/patient representatives. For patients participation can result in better implementation of study results. Secondly the inclusion procedure in a clinical trial will probably be easier. In the next paragraphs the quick scan results about these two aspects will be described.

Why do children decline/assent to trial participation?

Age, educational level, experience with disease were determinants of the willingness of children to participate in a research project.[36] Younger children, children with less disease experience, and children deciding on participation in less complex research with less risk were more prone to decline research participation. Time constraints and direct burdens from the research procedures were the main reasons for not participating expressed by children of 9 years and older. Altruism was a subjective reason for research participation in children aged 10–18 years, and well-informed adolescents of 14 years and older were not subject to therapeutic misconceptions. Unfamiliarity, limited information provision for parents and young children, and logistic burdens are factors that negatively affect research participation; therefore, strategies should be aimed at these issues. Campaigns directed at convincing the professionals and general public of the value of research for clinical practice should include informing patients about the use of data and efforts to improve quality when entering the hospital. Logistic burdens should be minimized by coaching and guiding of children and parents and by improving accessibility. Involving children and families in advisory boards is a way to improve research awareness among eligible participants and to align research procedures with the participants' preferences. Directives for future research include evaluation of the actual experience of research participation as well as research on how paediatric patients and their parents evaluate proportionality in decisions on research participation.

The 'willingness to participate construct' (European Commission. Cordis) shows that there are four factors important to explain the decision to participate in a clinical trial [42]:

Control. Participants want to have control: not only do they want precise information about the trial, they also want to have a say in the study as part of their participation.

General concerns. Participants want to have attention for their general concerns, such as their worries about the effort involved to participate.

General interest in clinical research. Participants have altruistic reasons to be involved in clinical research.

Personal benefits. The degree of willingness to participate depends greatly on the extent of personal gain respondent assumes to derive from participation.

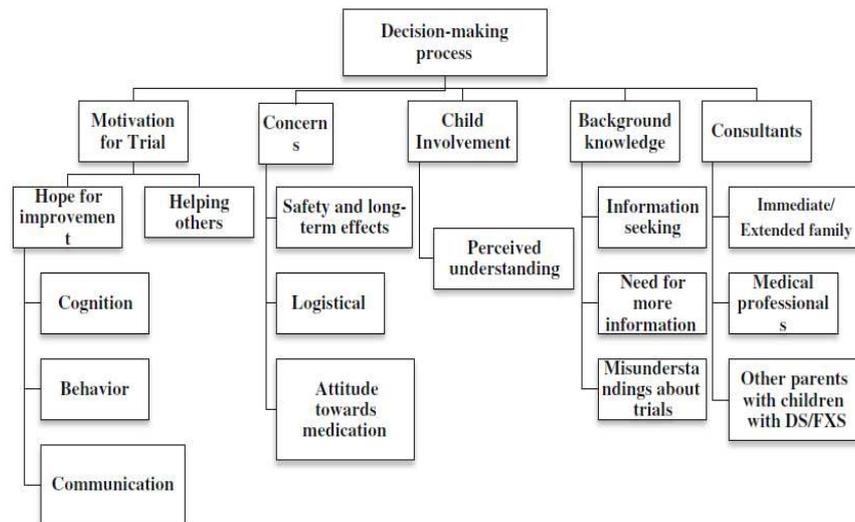
The study shows that allocation to a control group may be reason not to consent to participation in a trial.

The project delivered a range of tools: interview protocols, face to face groups, a questionnaire for parents, children and patient organisations.

They also explored the role patient organisations should have in clinical trials. POs should take a supporting role and support the children to be active. POs should be involved in the very onset of children trials and help in the production of the research protocol. POs should be informed that a trial in their field is being planned.

Reines et al. (2017) [43] show that among other things, parents would like to discuss trial participation with persons other than the medical staff. We could suggest that hospitals have a person available that can be consulted by parents/children before and during the clinical trial. This study also shows that randomisation to a placebo arm is a parental concern. This effect has been called ‘the therapeutic misconception’ (a professional’s phrase, from a patient perspective this is not a misconception but an expectation) Explaining this, Reines et al. conclude, would prevent patients to quit the study disappointedly. The authors provide a schema (below) that shows the elements of the decision making process for clinical trials.

Fig. 2 Decision-making process for pharmacological clinical trials



Edwards et al. (2011) [44] show that parents prefer a study design with a protocol that ensures that all children eventually receive the experimental treatment. This is of course especially important for studies with new drugs and less important for most investigator driven studies that study two already known medicines (that are used but have not been studied in children). Other items to address are on the extremes of patient involvement in the clinical research: being consulted about outcome measures and being informed about research results.

Perspectives of children

Cooperation of children with treatment can be enhanced by appreciating the agency (autonomy) of children [45]. Children do not simply accept the recurrent health education from medical professionals. Instead, they attribute their own personal meaning to their disease and treatment.

Drawing from their years of experience with the disease and health care and the image of a passive and vulnerable child, they actively find ways to balance personal goals with medically defined goals. Efforts to facilitate child participation should be based on insights into the ways in which children enact agency in the clinical encounter. Studies have been done to elicit the perspectives of children on participation in clinical trials [46-49].

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