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COMMENTARY

Involve Children and Parents in Clinical Studies

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There is a need for more and good pediatric research because many treatments are still not evidence based. Pediatric studies often fail so guidance for pediatric drug research, as given by Shakhnovich *et al*.,[1] is very welcome. This commentary argues for an addition to their advice: involve children and parents in the (design of) clinical studies. There is evidence that patient involvement enhances research, also in pediatrics.

In their important paper, Shakhnovich *et al*.[1] describe the essential elements of pediatric drug research, discussing current guidelines and literature concerning pediatric clinical research. A possible addition to their advice to improve clinical research in pediatrics could be to involve children and parents in the design of the clinical study. We hope that by adding some of the literature about experiences and policies we can help improve pediatric clinical research even more.

The involvement of (adult) patients has been shown to prevent research waste and to improve inclusion/retention rates and, therefore, to prevent failed clinical trials.[2] Involvement, therefore, also reduces costs.[2] The need to involve children/parents in research design, the preparation of patients' documentation, and information materials to improve research protocols and enhance research participation is widely acknowledged.[3] The failure of almost one in five pediatric trials, mainly due to recruitment problems, as referred to by Shakhnovich *et al*.[1] (Pica and Bourgeois),[4] might have been at least partly prevented by engaging/involving parents and children in the design stage. Early involvement of patients in the trial design may result in identification of trial aspects that are less acceptable or unclear for potential participants. Adaptation of these aspects may enhance the willingness to participate in the trial.[5] There is evidence that recruitment increases with patient engagement, and that patient engagement enhances the quality of research (e.g., by the choice of relevant outcome measures).[2] Patient involvement should be seen as an integral part of designing a study.[6]

The need to involve children/parents in research design, the preparation of patients' documentation, and information materials to improve research protocols and enhance research participation is widely acknowledged. The US Food and Drug Administration (FDA) wants to integrate the patient's perspective in drug development, a policy described in Mullin *et al*.[7] There are many examples of involvement of children and parents in research.[8] Patient engagement is, for example, arranged via members of the Children's Advisory Network and Young Persons Advisory Groups (YPAGs)[9] with specific tools for involvement.[10]

In the United States, engagement (in general, not specific for pediatrics) is attained and promoted in (for example) Patient-Centered Outcomes Research Institute (PCORI) in Boston (https://www.pcori.org/about-us/our-programs/engagement/public-and-patient-engagement/engagement-resources#content-4029). In Canada, patient engagement in research (in general) is promoted via Strategy for Patient-Oriented Research (SPOR; (http://www.cihr-irsc.gc.ca/e/41204.html)) and (http://www.cihr-irsc.gc.ca/e/45851.html). Great Britain has, as part of the National Institutes of Health Research, the institute INVOLVE with guidance, resources, and literature about patient engagement in general and specifically for children (https://www.invo.org.uk/current-work/involving-children-and-young-people/), which also shows further literature on the matter (https://www.invo.org.uk/current-work/involving-children-and-young-people/references-on-involving-children-and-young-people-in-research/). In Europe, guidance for patient involvement in pediatrics is given through the project RESPECT (https://issuu.com/respect_patient_needs/docs/respect_book?viewMode=doublePage). Further, in Europe, there are research networks that integrate patient engagement in research: European Paediatric Translational Research Infrastructure (EPTRI; (https://eptri.eu/)), Paediatric Clinical Research Infrastructure Network (PedCRIN; (https://www.ecrin.org/projects/pedcrin)), and Conect 4 children (C4C; Collaborative Network for European Clinical Trials for Children (https://conect4children.org/)).

As an example, in PedCRIN, the (potential) role of children and/or parents is identified through consultations of YPAGs and patient groups by means of a focus group; a group meeting in which clinical studies that are supported by PedCRIN (https://www.ecrin.org/projects/pedcrin/call-outcome) are discussed. During a focus group, children and/or parents are informed about a certain topic and they can give their views, with the idea that participants learn from each other and that, therefore, more diverse responses are generated. PedCRIN has developed a concise meeting guide for consulting parents and children that is available on request from the authors, as well as more literature about the topic.

One of the PedCRIN-deliverables deals with pediatric patient involvement in research (https://www.ecrin.org/sites/

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default/files/PedCRIN/PedCRIN%20Deliverables/WP5%20D5.13%20Patient%20engagement%20and%20perspective%20integration%20.pdf) and provides more guidance and literature concerning the following topics.

POSSIBLE METHODS TO RETRIEVE INFORMATION

Interviews

Interviews are a suitable way to explore the child's perspective. 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.

Questionnaires

Children and parents can be asked to complete questionnaires. Well-designed questionnaires can be used by investigators to write the research protocol according to the wishes children and their parents/carers.

Focus groups

Focus groups are another possibility to retrieve information from patients/parents/patient representatives. Focus groups, in general, do not have to be "face-to-face," they can also be organized via the internet; "online focus groups."

Consultation through a platform discussion

Patient organizations often organize platforms (e.g., 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 analyzed by researchers. The advantages are that participants do not need to travel and can respond at a time they choose.

Interviews and focus groups imply a "one time consultation" in which the patient opinion is explored and determined. However, patient 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.

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

These phases consist of the design, conduct, and report phase.

During the design phase of the study

Possible designs. When a trial is being designed, different designs exist to choose from. Patients might have good arguments to prefer a specific type of design, or refute (another) one.

Choice of control arm (comparator). For patients, the type of comparator that is used in a trial, in general, is very important. Parents may be afraid that their children would be placed in the group with ineffective treatment. 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.

Outcome measures. The choice of outcome measures is also a topic that patients would like to have influence on. That patient involvement in research leads to better outcome measures for research has been demonstrated. The FDA acknowledges the importance of determining the patient perspectives by means of PROMs, as described in the study of Mullin *et al.*[7]

During the conduct of study

Informed consent. Children need age-specific and experience-specific information. Children's participation in designing the documents can improve the subsequent comprehension and assent.

A continual dialogue needs to be established that gives children 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. Children and parents indicate that they wish to be asked about their experiences during the clinical trial. A continual dialogue needs to be established that gives children and parents the opportunity to exchange information.

Report of study. Study participants 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 on which they want to receive information, and from whom. 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.

In conclusion, pediatric drug research should not be the sole domain of professionals, but should also include patients and parents as stakeholders along the drug development continuum. Patient associations can and do play an important role in initiating and supporting patient involvement, as was shown by, for example, the study by EURORDIS-Rare Diseases Europe, an alliance of rare disease patient organizations (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3531929/pdf/msy-0003-0237.pdf). The European Patients Forum shows the value of patient organizations (in research) (http://www.eu-patient.eu/globalassets/library/publications/epf_added_value_report_final.pdf). There is guidance for patient involvement in pediatric research available and professionals could consider whether the study would profit from "one-time involvement" by a consultation or rather attempt to keep patients (representatives) involved during the whole research process.

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