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Informed Participation and Patient Empowerment: A Patient-Centered Approach to Improve Pediatric Clinical Research

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Additional information is available at the end of the chapter

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Abstract

Over the last years, a Europe-wide trend toward a patient-focused approach is developing and is influencing the decision-making process related to the clinical research. This new vision aims to draw on patient knowledge and experience in order to deliver benefits for all stakeholders of the drug development process, optimizing the clinical study design. In this context, the “patient empowerment” concept has been developed as an approach encouraging the active participation and self-determination of the patients in the caring procedure. For this reason, in 2016, European Patients’ Academy (EUPATI) launched a public consultation that ended in September 2016 with the release of the EUPATI guidance for patient involvement in the medicine research and development process. Likewise, the recommendations on the “Summaries of Clinical Trial Results for Laypersons” for the Implementation of Regulation (EU) No 536/2014 recommended a clear and comprehensible communication of the clinical trial results to the patients. However, rarely, all these attempts for the patient involvement pay attention to the pediatric population needs. An innovative approach for the patients’ involvement in pediatric clinical research is represented by the **Young Persons Advisory Groups**, an organization composed of youths, patients, and carers, actively participating in clinical research and advising researchers and their teams.

Keywords: patient empowerment, patient involvement, patient-centered approach, child-friendly approach, age-tailored information, patient advocacy, YPAGs—Young Persons Advisory Groups

1. Introduction: patient empowerment and involvement

In 1998, the World Health Organization (WHO) released the second edition of the WHO Health Promotion Glossary, where, for the first time, the concept of “Empowerment of the health” was described [1]. **WHO defines empowerment as “a process through which people gain greater control over decisions and actions affecting their health.”** In addition, the document makes a difference between community or individual empowerment according to the involvement of individuals acting for themselves or collectively to influence social, economic, and physical conditions impacting their health and quality of life. The WHO Glossary goes on underling that this process, which can be social, cultural, psychological, or political, allows individual or social groups to shed light on what are their needs making clearer what are the efforts required to achieve their goals in life. In this context, the WHO definition also includes a description of health promotion as the process able to create the favorable conditions to convert efforts of individuals and groups into health outcomes as described above [1].

Actually, the concept of empowerment is somewhat complex and includes several psychological and social components that, over the last years, have been studied empirically. In particular, Peter Schulz and Kent Nakamoto underlined the need to distinguish and separate the concepts of empowerment and high health literacy. They are often mismatched, but it is necessary to recognize that they are conceptually and empirically distinct. High literacy, in fact, does not necessarily entail empowerment and vice versa. Furthermore, in order to be sure that the empowerment process is successful, it is important to have both a high literacy and a high degree of mastery. At the same time, the impacts of health literacy and patient empowerment are deeply intertwined, considering that the prevalence of one of them could bring to nonoptimal health outcomes: high levels of health literacy without an adequate degree of patient empowerment can make the patient too dependent on health professionals; while, on the contrary, high degree of empowerment may bring to unsafe health choices if not associated with an appropriate level of health literacy (**Figure 1**).

Finally, the achievement of empowerment by the patient depends on some personal abilities as well as the environmental conditions. In fact, some *life skills* of the patient, such as the scientific approach and the wisdom, are fundamental to acquire the proper knowledge to interact with their healthcare provider. On the other hand, it is essential that the external environment stimulates the patient propensity to be an active protagonist of the healthcare process. The

		Psychological Empowerment	
		Low	High
Health Literacy	High	Needlessly Dependent Patient	Effective Self-manager
	Low	High-needs Patient	Dangerous Self-manager

Figure 1. Relationship between empowerment and health literacy.

healthcare provider should encourage the patients to participate in the care process, avoiding that the patient acts as a passive user.

Overall, four components have been identified as being fundamental to the process of patient empowerment: (1) acquisition by patients of sufficient knowledge to be able to engage with their healthcare provider, (2) patient skills, (3) the presence of a facilitating environment, and (4) understanding by the patient of his/her role.

The transition from empowerment to **patient involvement** implies an important change of attitude: healthcare actors are no longer giving patients their information and allowing them to control the outcomes, but rather they are now actively working to engage patients in their healthcare. In particular, patient participation refers to the involvement of the patient in decision-making or expressing opinions about different treatment methods, which includes sharing information, feelings, and signs, and accepting health team instructions. As a result, the focus has gone from a patient-driven process to a healthcare provider-driven one.

Generally, several studies and European initiatives carried out over the last years have revealed that such patient-centered approach may raise the adequacy of exams and care and reduce the risk of litigation and expenses [2].

2. Patient empowerment: a new frontier in the European scenario

2.1. The European Patients' Academy on therapeutic innovation (EUPATI)

In Europe, the patient-focus approach is becoming a key point in the decision-making process related to the clinical research and an important element of pharma companies' business models and research ethics committees who advocate for the protection of patients in clinical trials. It requires new strategies, new organizational structures, and a culture change across the pharma sector as well as a direct link with patient experts who are capable of providing advice on the value of treatments and on what health outcomes are relevant to patients.

Over the last years, in fact, several initiatives have been carried out with the scope to sensitize the clinical world and encourage the patient involvement in the clinical research. One of the most significant initiatives is the **European Patients' Academy (EUPATI)** [3], funded within "Call 3" of the Innovative Medicines Initiative (IMI) in the period from February 2012 to January 2017, with the scope to prompt a major reflection on the importance of the patient involvement in the medicines development process. EUPATI is a Paneuropean project implemented as a public-private partnership by a collaborative multistakeholder consortium from the pharmaceutical industry, academia, not-for-profit, and patient organizations. Its main activities include the education and training on medicines development, clinical trials, medicines regulations, and health technology assessment, to increase the capacity of patients to understand and contribute to medicines research and development and even improve the availability of objective, reliable, patient-friendly information for the public. For this purpose, EUPATI provides several tools for the patients training such as the toolbox medicine development and English language patient expert training courses. EUPATI's interest in raising

awareness of the clinical world on the patient empowerment has led to the launch of a public consultation, which ended in September 2016 with the release of the EUPATI guidance for patient involvement in the medicines research and development process [4]. Each guidance suggests an area where at present there are opportunities for patient involvement, and in particular:

- industry-led medicines R&D,
- ethical review of clinical trials,
- regulatory processes,
- health technology assessment (HTA).

The necessity to have a clear guidance on patient involvement in different areas of the medicines development process originates from some needs and lacks in the clinical research, such as:

- existing code of trial conduct does not describe the involvement of the patients,
- patients and patients' organizations should be involved proactively during early discovery, development, and postapproval stages and not only in the clinical development,
- overarching guidance on meaningful and ethical interaction is missing.

For these reasons, the guidance is devoted to provide recommendations for all stakeholders aiming to interact with patients, for example by delivering a clear and complete definition of "patient" (patients, carers/family representatives, expert patient advocates, etc.), establishing the operating procedures for a long-term interaction and explaining the key elements of a written collaboration agreement.

In particular, the guidance provides the following definitions:

- **"Individual patients"** are persons whose main contribution is represented by their personal experience of a disease or treatment regardless of whether they may or may not have specific knowledge in the medicine research and development process.
- With personal experience of living with a disease, they may or may not have technical knowledge in **"Carers"** who are paid or volunteer persons helping "individual patients."
- **"Patient advocates"** are persons who have knowledge and competences to gather patients living with a specific disease and to support them regardless if they may or may not be affiliated with an organization.
- **"Patient organization representatives"** are persons within a patient organization on a specific disease or issue, who have been designated to represent the point of view of the organization itself.
- **"Patient experts"** are patients with experience of living with a specific disease that, differently from "individual patients," have also specific knowledge in research and development

(R&D) and/or regulatory affairs achieved through training activities such as courses provided by EUPATI on the full spectrum of medicines R&D.

All these procedures are aimed to draw on patient knowledge and experience and understand what it is like to live with a specific condition, how care is administered, and the day-to-day use of the medicines. As a result, they allow to incorporate patient needs and priorities in an optimized drug development process as well as to achieve a constructive dialog with the patient and a functional exchange of information, fundamental to speed up a successful clinical process.

2.2. Summaries of clinical trial results for laypersons

On April 16, 2014, the European Parliament and the Council of the European Union (EU) released the Regulation EU No 536/2014 [5] on clinical trials on medicinal products for human use, to ensure that the rules for conducting clinical trials are identical through the EU. The aim of the Clinical Trial Regulation is to favor the conduction of the clinical trials in accordance with the highest standards of patient safety for all the EU Member States. These goals are achieved through some harmonized procedures for authorization, specific sponsor obligations, and simplified reporting procedures. Furthermore, such regulation foresees a section dedicated to communication of the results to patients. In particular, the article 37 requires sponsors to provide summary results of clinical trials in the EU Portal and Database in a format understandable to laypersons and the Annex V of the regulation outlines 10 elements that must be considered in the lay summary writing.

In this context, from June 1, 2016 to August 31, 2016, the Directorate General for Health and Food Safety, DG SANTE launched a public consultation on the “Summary of Clinical Trial Results for Laypersons,” developed by the expert group on clinical trials, in order to collect comments and suggestions by all the stakeholders involved in clinical research to implement the Clinical Trials Regulation (EU) No 536/2014. The main objective of this document is to provide recommendations and templates for the production of a summary of clinical trial results for laypersons by sponsors and investigators, in accordance with Annex V of the EU Clinical Trials Regulation. Despite not mandatory, this document intends to make the summaries more accessible to the lay persons.

The **recommendations of the clinical trials expert group on the “Summaries of Clinical Trial Results for Laypersons”** [6], which have been published on January 2017 in EudraLex Volume 10, Chapter V, provide the following principles:

- develop the summary for a general public audience and do not assume any prior knowledge of the trial,
- develop the layout and content for each section in terms of style, language, and literacy level to meet the needs of the general public,
- keep the document as short as possible,
- focus on unambiguous, factual information,

- ensure that no promotional content is included,
- follow health literacy and numeracy principles, and
- consider involving patients, patient representatives, or advocates in the development and review of the summary information to ensure that it truly meets their needs.

In particular, the document provides detailed information about the health literacy level to consider in the summary, the readability specifying the size of the serif font, and the use of plain language, numeracy, and visuals. As the International Adult Literacy Survey identifies five levels of proficiency ranging from level 1 (lowest level) to level 5 (highest level), the document suggests that the text should be suitable for people with a low/medium average level of literacy (level 2 or 3). However, as readability scores are useful but not in themselves enough to ensure that a text is easy to understand, sponsors should consider, where feasible, testing the readability of an initial version of the study results' summary with a small number of people who represent the target population. Depending on the nature of the study, this could be patients with a particular disease or it could be members of the public. For example, studies, which affect the general public such as vaccine studies, would benefit from input from members of the public rather than patients. Their feedback and suggestions can be crucial in developing a summary that lay people will understand.

Moreover, the Annex I of the recommendations offers the templates with user-friendly equivalent headings, useful to prepare the summary, and even giving examples of wording more comprehensible for the target population.

Despite all attempts of increased awareness for the patient involvement in clinical research, rarely these initiatives pay attention to the pediatric population.

Children's active participation in the decision-making process is necessary not only in the daily clinical practice, but also and especially in all the activities related to the development and use of drugs. In the last years, the idea that children's preferences should always be taken into consideration is also agreed upon among parents. For this reason, healthcare professionals have to consider children and families' active participation as a fundamental step to reach consensus and compliance to treatments and research.

Furthermore, in 2012, following a large consultation phase, the Pediatric Committee (PDCO) issued a "concept paper on the involvement of children and young people" in its activities, with the children's best interests as primary consideration [7]. It has to be also highlighted that the setup of a child-friendly approach implies a collaborative and continuous action involving pediatricians and healthcare professionals, psychologists, families, and children.

Children and parents should be involved not only in the revision of clinical study protocols but also during the whole study development. Finally, it is necessary to recognize that a standard model of information is not valid for all age groups, above all for extreme groups.

2.3. Ethical considerations for clinical trials on medicinal products conducted with minors

The need to involve children actively in the decision-making process related to a clinical trial is clearly underlined also in the updating guideline "Ethical considerations for clinical trials

on medicinal products conducted with minors” [8]. The document was released by a group chaired by the European Commission with the aim to develop guidelines to implement the Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. The document, opened for consultation from June to August 2016, provides recommendations on various ethical aspects of clinical trials performed in children from birth up to the legal age of adulthood and will contribute to the protection of all children who are the subject of clinical trials.

Moreover, it underlines that “the investigator and protocol writer should ensure that there is involvement of children (suffering from the relevant condition) and families in the development of informative material and where feasible, also in the design, analysis, and conduct of the trial.” Consequently, even if the pediatric population is not specifically cited by the EU Clinical Trials Regulation 536/2014 (Article 37) requiring sponsors to provide summary results of clinical trials in a format understandable to laypersons, children cannot be excluded by the advantages of this obligation.

By definition, children (minors) are unable to consent (in the legal sense), but they should be involved in the process of informed consent as much as possible, using appropriate age information. In the ethical review, in fact, drawing on the pediatric expertise allows to balance the benefits, risks, and burden of research in minors. Moreover, the difference between minors and adults as research participants has implications on the design, conduct, and analysis of trials, which should also include pediatric expertise.

The Regulation EU 536/2014 provides a series of definitions in order to clarify some important concepts for the patient interaction and patient involvement and in particular the age groups. Defining the age range is necessary to have a guidance regarding the proper involvement of minors of different ages in the informed consent process. Subsets of the pediatric population as defined in ICH E11 (ICH Harmonized Tripartite Guideline—Clinical Investigation of Medicinal Products in the Pediatric Population E11) [9] are partially adopted, and the age groups of 2–11 years and 12–17 years have been redefined as follows:

- **preschoolers** (2–5 years)
- **schoolers** (6–9 years)
- **adolescents** (from the age of 10 up to but not including above 18 years)

Regardless of the age and with an appropriate communication, the clinical trial regulation states that the child should be involved in the process of informed consent. The article 2 of clinical trial regulation defines the “**Informed consent**” as the document expressing the will of a subject to participate in a particular clinical trial; the subject, after having received information on all the aspects of the clinical trial in which he/she will be involved, expresses his/her decision in a free and voluntary way. In case of minors and of incapacitated subjects, it is intended as an authorization or agreement from their legally designated representative to include them in the clinical trial [5].

Moreover, the article 29(8) of the clinical trials regulation adds that also a minor should assent firsthand to participate in the clinical trial in cases in which he/she is capable of forming an

opinion and evaluating the information received, without prejudice to national law and in addition to the informed consent signed by the legally designated representative [5]. The ethical considerations document supports and highlights the legal value of the assent, suggesting that assent should be understood as a legally required expression of the minor's will to participate in a clinical trial, dependent on Member State law. According to this view, the assent should be considered in the same way as the consent of the parents/legally designated representative since it expresses with legal value the willingness of the child to participate in the clinical trial [8]. However, a minor who expresses the assent to join to a clinical trial cannot participate in it in absence of the informed consent signed by the parents/legally designated representative [8]. In addition, the consultation document introduces the term **agreement**, used in accordance with the term "assent," to describe the expression of will to participate in a clinical study given by the minor. The document also recommends systematically requiring the agreement when it is not legally mandatory and explains that the modalities to obtain it, in contrast to the legally required assent, are not age dependent but are related only to the [8]. If the minor is considered not mature enough to express his/her will to participate in a conscious manner, the lack of agreement does not necessarily mean the child will not participate in the clinical trial. However, dissent should be taken into due account in line with Article 32(1c) of the clinical trial regulation, when the minor, despite having proven his/her maturity, expresses his/her will not to participate [8].

Another important aspect discussed in the document is the importance to estimate to what extent a child is able to provide agreement. It is recommended to consider not only the chronological age, but also and especially **the developmental stage, intellectual capacities, and life/disease experiences** of the minor. The evaluation should be made after a careful discussion among the investigator, the parents/legally designated representative, and the child [8].

3. Patient and public involvement: the role of advocacy

Patient and public involvement (PPI) represents the active involvement of patients and/or individuals from the general population in scientific research with the aim to enhance quality and relevance of the research itself. Indeed, PPI strategies have shown in the last year to be key instruments to improve the conduction, the communication, and the prioritization of the research.

The involvement of service users in research has risen internationally, with patients' engagement in all the aspects of health and social care research. PPI plans have been included successfully in many clinical trial grant applications foreseeing patients' engagement in all the phases of clinical research: initial stages, undertaking phase, analysis and write-up, dissemination, and implementation [10].

Jo Brett et al. [11] carried out a systematic search of electronic databases and health libraries to identify the impact of PPI on health and social care research. The authors pointed out that PPI can have positive impact on research, enhancing its quality and ensuring its appropriateness and relevance. They also suggested that PPI strategies, to engage users in the initial stage of a medical research, are to be preferred since patients and lay people involvement in this step can shape the entire study and, users may have more freedom to influence the aims and

methods of the study. Moreover, they underlined that a clear definition of the roles of all the professionals and users involved through a precise planning and procedure, and training activities are important factors determining the success of the PPI.

Also, challenges to the development of plans for PPI have been described including issues regarding their purpose, difficulties in ensuring sufficient resources and in the recruitment of service users, the long-term commitment needed from service users, and the time and cost limits imposed on studies. Nonetheless, all the challenges mentioned above can be avoided by a precise planning of the PPI strategy, especially in the early stage of a proposed study [10, 11].

Among the current policies to encourage public involvement, strategies based on the concept of advocacy are spreading all over the world.

The World Health Organization (WHO) gave a definition of Advocacy for Health in the Health Promotion Glossary published in 1998 as “a combination of individual and social actions designed to gain political commitment, policy support, social acceptance, and system support for a particular health goal or program” [1].

According to this definition, advocacy stands for acting or doing something to influence private and public policy choices’ in order to achieve an individual or community objective.

Advocacy is one of the three strategies underpinning health promotion as described in the WHO Health Promotion Glossary mentioned above, and many strategies have been described to reach this goal including the use of the mass media and multimedia, direct political lobbying, and community mobilization through, for example, coalitions of interests around defined issues.

3.1. An innovative approach for the patient involvement: advisory groups in pediatric clinical research

When it comes to consider patient’s involvement in the pediatric field, more challenges have to be faced since the engagement of children requires appropriate means and language and it is also necessary to take into due account all the relevant legal and ethical aspects.

Despite these challenges, children have the right to be involved and informed, to know in advance which medicines they need and why and to get access to the resulting evidence-based medicinal products. Their point of view has to be taken into due account in the design and planning of a clinical study, and they should be allowed to express their own views and granted the right to participate in the decision-making process concerning their own health.

An innovative approach for the patients’ involvement in pediatric clinical research is represented by the **Young Persons Advisory Groups** widespread through the world. A Young Persons Advisory Group (YPAG) is an organization composed of youths, patients, carers, and people interested in a health condition or in research, actively participating as partners, advising researchers and their teams in a full range of activities in various research projects and initiatives.

After educational and training activities, the youths become able to help researchers in trial design, prioritizing future researches, improving communication with the target population, and increase awareness on clinical research through the different means of communication.

Many advisory groups have been founded, and all together they constitute the **International Children's Advisory Network (iCAN)** [12], a worldwide consortium of children's advisory groups or chapters working together to provide a voice for children and families in health, medicine, research, and innovation through synergy, communication, and collaboration. Within the consortium, various types of groups can be described, all working together for advocacy purposes in pediatric medicines:

- **Kids and families impacting disease through science, (KIDS):** Advisory groups of children, adolescents, and families focused on understanding, communicating, and improving the process of medical innovation for children. KIDS groups have been created in Connecticut, Georgia, Missouri, Ohio, Illinois, Michigan, Texas, Florida, Barcelona, Australia, France, and recently in Italy and Albania.
- **Young Persons Advisory Groups:** a set-up in Great Britain (Liverpool, Birmingham, London, Bristol, and Nottingham) as Generation R [13] with the aim to increase the input and influence of children and their families or carers into the development of clinical research.
- **Kids Can** (Vancouver): promoting a direct engagement of young people in research and the **ScotCRN Young Persons Group** (Scotland) aimed to support clinical research to improve the safety and efficacy of children's medicines and healthcare.

Advocating for children in healthcare globally is the main purpose of the network as well as taking into due account the children and families' needs and willingness in health, research, medicine, and innovation in order to improve clinical research. iCAN's chapters work both locally in partnership with their local children's hospitals and communities and collaborate together network-wide to have a global impact.

Their slogan is: Together, we can improve the future of pediatric medicine!

The European chapters of iCAN (KIDS Barcelona, YPAG Birmingham, YPAG Bristol, KIDS France, YPAG Liverpool, YPAG London, YPAG Nottingham, YPAG Scotland) have recently established a **European YPAGs' network, or eYPAGnet** [14], under the coordination of Hospital Sant Joan de Déu (Barcelona) as part of the iCAN umbrella organization. This network arose from the need, recognized by the Enpr-EMA (European Network of Pediatric Research at the European Medicines Agency), to promote cooperation among European groups with the mission to improve the capacity of collaboration with the different actors who participate in the research and development process of innovative drugs in Europe.

Enpr-EMA has promoted several actions with the aim to foster engagement of young people and families in clinical research. A survey on the involvement of young people and family members in Enpr-EMA pediatric research networks was launched in August 2012 and highlighted that only three out of the 39 networks participating to the survey had developed strategies or guidelines for the involvement of young people and families. A second survey was conducted in November 2016 to investigate the point of view of the Pediatric Committee (PDCO) members in relation to the involvement of young people and families in the activities of the Committee. Moreover, a working group on young patient advisory groups has been established in order to develop harmonized procedures for a more European-oriented approach of YPAGs.

The working group has launched two surveys to investigate the characteristics of the existing YPAGs with the final aim to create a European network of young advisory groups and to define the best practices to address issues in the framework of the EU multilanguage YPAGs. Within these initiatives, eYPAGnet has been created and admitted, during 2017 annual meeting, as member of Enpr-EMA of category 4.

Among the main scopes of eYPAGnet, there are development of clinical research initiatives and empowerment training programs for children on a European level and the promotion of new chapters' set-up. Indeed, since June 2017, two new chapters, KIDS Bari and KIDS Albania have been created in Europe and are coordinated by Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) and the TEDDY Network (European Network of Excellence for Pediatric Clinical Research).

CVBF is a not-for-profit organization aimed to perform research in life science at European level with a special focus on drug development for small populations (pediatric and rare diseases). It provides scientific, economic, and regulatory consultancy in pediatric clinical research and a research management support in national and international research projects. Particular interest is given to promote educational activities supporting the consortium's areas of expertise and to favor knowledge and access to the results of biomedical research and accelerate their use by patients. The consortium has developed a considerable expertise in communication and dissemination field, leading and managing these activities in several EU-funded projects (GAPP, DEEP, CloSed, and InNerMeD).

The TEDDY Network was born as an EC-FP6-funded Network of Excellence (NoE) and now is an independent multidisciplinary and multinational network including 50 members in 20 EU and non-EU countries aimed to favor the integration of the pediatric pharmacological research activities, the implementation of adequate health policies, and a social awareness on the importance of the pediatric medicines across Europe covering different specialty areas (hematology, oncology, infectious diseases, respiratory diseases, intensive care, pain, endocrinology, rare diseases, neonatology, etc.).

TEDDY is a category 1 network member of Enpr-EMA and collaborates with existing pediatric networks and research organizations with the goal to promote and foster scientific and technological excellence in the pediatric research in Europe.

3.2. Advisory group contribution in pediatric clinical research

Existing advisory groups and initiatives have shown to be an effective form of patient and public involvement in the pediatric field providing fresh perspectives on pediatric clinical research and promoting changes of attitudes about the involvement of young people in all the aspects of medicines research.

The activities carried out by all the advisory groups across the world are aimed at contributing to raise awareness of the importance of patient and public involvement in the development of research trial.

The education and, in particular, the peer education is a fundamental aspect of the advocacy strategy. The **peer education** is an educational approach, recommended by modern development psychology, based on teaching and sharing information, values, and behavior relating to health promotion among lay people. Through this approach, advocacy groups aim to provide children

and families with resources and opportunities to express their feedback and inputs about studies and products intended for children.

iCAN is a free resource available to any organization, company, or group, which seeks the input of children and families in their projects. iCAN chapters utilize online-based surveys, focus groups, forums, and more to engage all of the youth advisory groups in their network to provide specific feedback about clinical trials or any other process of medical innovation for children.

Moreover, many groups work on research projects on their own and participate in science conferences to disseminate their results and to highlight the importance of their involvement in research. Just to mention some examples of projects carried out by iCAN chapters, Kids Can developed a mobile application “Mobile Kids” [15] to encourage physical activity in kids aged between 8 and 13 years with the use of mobile technology.

Kids Can and Kids Connecticut participated in the development of guidelines aimed to standardize reporting of clinical trial protocol (SPIRIT-C) [16] and trial reports (CONSORT-C) [17] across pediatric studies.

Members of US, Canada, and UK young patients’ advisory groups provided their contribution responding to a survey launched by the Global Alliance for Pediatric Therapeutics Assent Project [18], a project aimed to evaluate current practices, challenges, and unmet needs associated with the achievement of pediatric assent for clinical trials.

KIDS Barcelona group provided recommendations [19] to be taken into account by the sponsor of a clinical trial and ethics committee of the research center to make the assent form more understandable for children. The recommendations are collected in a guideline, available in Spanish and English, approved by iCAN and EUPATI and included in the guidelines for the design of a pediatric clinical trial by Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Moreover, the Spanish group has developed a series of eight different funny comics [20] to explain several matters of the clinical research using a language more familiar for the children.

Furthermore, YPAGs have given their useful contribution in the revision of informed consent/assent template prepared by Enpr-EMA within the activities of the working group 4 on ethics providing their thoughts and ideas to make the template more understandable by a wide range of ages.

By many activities and initiatives performed, the young advisor groups spread all over the world are able to help the professionals involved in the clinical trials to overcome some tough issues of the clinical research. For example, they could help to open and complete on time the trials or could improve the recruitment of patients to the agreed target and the retention of patients to completion. In general, through the YPAGs, the clinicians involved in the trials could meet the needs of the patients, designing the study according to their necessities.

4. Patient-centered approach to improve pediatric clinical research: some good practices

It is universally established that written communication, combined with verbal interaction, may enhance children’s understanding of their participation in a clinical research [21] as well

as the contents and styles of documents addressed to children are elements that largely influence their understanding of written documents.

As an example, it has been demonstrated that the use of pictures, following appropriate recommendations, improves the quality of communication, especially for patients with very low literacy skills. However, available data and publications show that ad hoc informative strategies for empowering minors in clinical trials are rarely produced. In addition, the difficulty increases in multicenter trials, involving countries with different cultural and educational backgrounds.

This is the assumption at the basis of the development of age-tailored information booklets, assent forms, and videos prepared in the framework of the DEferiprone Evaluation in Pediatrics [22] (DEEP) and GAbapentin in Pediatric Pain [23] (GAPP) projects, two EC-FP7 funded projects coordinated by Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF).

All the materials have been developed with a language and a wording appropriate to age, psychological and intellectual maturity, taking into account the cultural and linguistic differences, in a collaborative effort among pharmacologists, pediatricians, child psychologists, and illustrators.

In the framework of the GAPP project, aimed to confirm the efficacy and safety of gabapentin in pediatric patients affected by chronic pain with a neuropathic component, three booklets and two videos (**Figure 2**) have been created to inform the child participant on the study objectives and procedures. Two assent forms have been released to obtain his/her consent to



Figure 2. GAPP projects' video: in the framework of the GAPP project activities, two videos have been developed to inform the child participant on the study objectives and procedures according to two age ranges (for children on the top and for teenagers on the bottom).



Figure 3. DEEP project booklets: the pages extracted from the three booklets, developed for three different age ranges (age range 0–6, 6–10, and 10–17, respectively, in the top, middle, and bottom pages), explain how the clinical trial will be carried out.

participate in the study. A patient diary has also been developed to register specific daily data on the use of the Investigational Medicinal Products (IMPs), rescue and concomitant medication, pain scores, and adverse effects when the patient is at home. It also contains instructions for the use of the IMP, troubleshooting, and contact details of the study’s medical staff.

For the young participants of the DEEP project, aimed to marketing a new formulation of deferiprone for the treatment of iron overload in pediatric patients affected by congenital

anemia, three different booklets (**Figure 3**) explaining clinical trial aims and procedures and what they are going to experience, and two different assent forms were prepared. For both projects, all these informative materials are available in all the languages of the project.

Informative videos (a spoonful of info helps the medicine go down) [24], specifically addressed to children between 4 and 7 years old explaining some main concepts on drugs and their use, have also been developed by the TEDDY Network of Excellence for Pediatric Clinical Research within the empowerment activities addressed to young patients in the healthcare field.

5. Conclusions

There is a need to change attitudes in order to make the patients' empowerment a priority in the clinical research field. Patients have to take an active role in activities or decisions that will have consequences for the patient community, because of their specific knowledge and relevant experience as patients. Children's active participation in the decision-making process is needed not only in the daily clinical practice, but also in all the activities related to the development and use of drugs. Minor shall take part in the informed consent procedure in a way adapted to his/her age and mental maturity.

Patients/families need to be considered as "co-managers" of their condition and participate in decisions related to their healthcare according to their capacity. Moreover, patients (individually and) collectively have to play a role in improving healthcare services for all patients by contributing with their specific experiences as learning and educational tools to inform and (re-) design of services.

However, the involvement must be planned, appropriately resourced, carried out, and evaluated as to its outcomes, impact, and the process itself, according to the values and purposes of all participants. Engaging children early in the research process and educating the world about the importance of participating in clinical research could increase the level of participation in pediatric clinical trials, thus reducing the patients' retention and fostering treatment compliance. Moreover, a patient-centered approach can improve the capacity of collaboration with the different agents, who participate in the research process and in the development of innovative drugs.

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References

- [1] WHO Health Promotion Glossary. 1998. Available from: <http://www.who.int/healthpromotion/about/HPR%20Glossary%201998.pdf>
- [2] Angelmar R, Bermann BP. Patient empowerment and efficient health outcomes. *Financing Sustainable Healthcare in Europe*. 2007:139-162
- [3] EUPATI. Official Website. Dec 1, 2016. Available from: <https://www.eupati.eu/>
- [4] EUPATI. Guidance Documents on Patient Involvement in R&D. Dec 14, 2016. Available from: <https://www.eupati.eu/guidance-patient-involvement/>
- [5] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Apr 16, 2014. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf
- [6] Summaries of Clinical Trial Results for Laypersons. Recommendations of the Expert Group on Clinical Trials for the Implementation of Regulation (EU) No 536/2014 on Clinical Trials on Medicinal Products for Human Use. Jan 26, 2017. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_01_26_summaries_of_ct_results_for_laypersons.pdf
- [7] EMA Concept Paper on the Involvement of Children and Young People at the Paediatric Committee (PDCO). Sep 17, 2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/09/WC500132555.pdf
- [8] Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Minors. Recommendations of the Expert Group on Clinical Trials for the Implementation of Regulation (EU) No 536/2014 on Clinical Trials on Medicinal Products for Human Use. Jun 2, 2016. Available from: https://ec.europa.eu/health/sites/health/files/files/clinicaltrials/2016_06_pc_guidelines/gl_1_consult.pdf
- [9] ICH Harmonised Tripartite Guideline. Clinical Investigation of Medicinal Products in the Pediatric Population. E11. Nov 15, 2005 Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/Step4/E11_Guideline.pdf
- [10] Buck D, Gamble C, Dudley L, et al. From plans to actions in patient and public involvement: Qualitative study of documented plans and the accounts of researchers and patients sampled from a cohort of clinical trials. *BMJ Open*. 2014;**4**:e006400. DOI: 10.1136/bmjopen-2014-006400
- [11] Brett J, Staniszewska S, Mockford C, Herron-Marx S, Hughes J, Tysall C, Suleman R. Mapping the impact of patient and public involvement on health and social care research: A systematic review. *Health Expectations*. Oct 2014;**17**(5):637-650. DOI: 10.1111/j.1369-7625.2012.00795.x [Epub Jul 19, 2012]. Review. PubMed PMID: 22809132; PubMed Central PMCID: PMC5060910

- [12] iCAN Official Website. Dec 28, 2016. Available from: <https://icanresearch.org>
- [13] Generation R Official Website. May 10, 2015. Available from: <http://generationr.org.uk/about/>
- [14] KIDS Barcelona Official Website. Jan 18, 2017. Available from: <https://www.kidsbarcelona.org/en/eypagnet>
- [15] KidsCan Young Persons Advisory Group webpage. Dec 18, 2014. Available from: <http://bcchr.ca/kidscan/mobilekids>
- [16] SPIRIT-C Project Webpage. Nov 28, 2013. Available from: <http://www.sickkids.ca/Research/EnRICH/Research-Projects-and-Initiatives/SPIRIT-C/index.html>
- [17] CONSORT-C Project Webpage. Nov 28, 2013. Available from: <http://www.sickkids.ca/Research/EnRICH/Research-Projects-and-Initiatives/CONSORT-C/index.html>
- [18] Global Alliance for Paediatric Therapeutics Webpage. May 18, 2016. Available from: <http://www.pediatricinnovation.org/drug-reformulation/>
- [19] Guidelines for a Design Focused on the Children are Available at the KIDS Barcelona Official Website. Jan 18, 2017. Available from: https://www.kidsbarcelona.org/sites/default/files/aaff_eupati_english.pdf
- [20] Comics are Available at the KIDS Barcelona Official Website. Jan 18, 2017. Available from: https://www.kidsbarcelona.org/sites/default/files/comic_ensayos_clinicos.pdf
- [21] Ungar D, Joffe S, Kodish E. Children are not small adults: Documentation of assent for research involving children. *The Journal of Pediatrics*. 2006;**149**:s31-ss3
- [22] DEEP Official Website. Sep 02, 2017 Available from: <https://www.deepproject.eu/>
- [23] GAPP Official Website. May 26, 2017. Available from: <https://www.pediatricpain.eu/>
- [24] TEDDY Videos are Available at the TEDDY Official Website. Feb 15, 2017. Available from: <https://www.teddynetwork.net/teddy-videos-drug-use-explained-to-children/>

