Executive Summary:

The RESPECT consortium responded to a call from the EU 7th Framework programme for a coordination study concerning Identifying patients' needs in the clinical trials context (HEALTH-2007-4.1-4). This call requested that three questions be answered:

1) How can patients be better mobilised and empowered?

2) How can patients get the clinical outcomes that really matter to them?

3) How can the patients' needs be integrated into clinical trials?

Methods

A mixture of qualitative methods was used. Case study interviews were conducted with the children; focus groups with parents and clinical staff were undertaken; interviews with pharmaceutical company staff were made; online surveys and a series of workshops were held in five European states. An action research method was used in the workshops where data collection and dissemination was carried out.

Results

The RESPECT project found that the reasons for participation reflected the needs of the participants and although these reasons varied there were a number of recurring themes. The first theme was that most respondents believed that they would get better medication by participating in a trial and hence were disappointed if they were allocated into the control arm. Although clinical trial research is based on the principle of equipoise, clinical trial researchers saw paediatric trials as a special case where many new medications have been previously tested on adult populations. The second theme to emerge was that families appreciated the opportunity for additional monitoring and specialist care for their child. The third theme was the social obligation which the participant's families felt; this was referred to by many who expressed a wish to either 'pay back' the health care system for providing health care for their child previously or helping other children with the same condition illustrating a sense of group membership. A fourth theme was that parents included their child in order to learn more about the condition themselves or to help the child learn more. Many of the reflections of the families could be characterised as concerning a need to be actively involved in the care of their child. These needs were modified by several factors related primarily to the risks involved in participation, i.e. greater risk was balanced by greater personal need, but also to their trust in the doctor or medical profession and the concern of a good parent that they must do what is best for the child. Another factor which related to need and risk was the inconvenience of participation, i.e. the greater the need the more inconvenience was tolerated.

Conclusion

The project concluded that participation issues are resolved where the family including the child has more say in the clinical trials process. In order to achieve this a partnership model emerges in terms of empowerment based on five elements: 1) a mutual respect which encourages cooperation; 2) access to

information and the opportunity to acquire knowledge; 3) active involvement through self-determination; 4) independent monitoring of the patients' reported outcomes and 5) accountability of the clinical trial team to the patient. Thus, although information provision about a particular trial is a necessary precondition for making an informed decision about participation, it is also necessary to ensure that research and ethical review practices are transparent and accessible so that the child's representatives, including their patient organisation, can be included in the process and hold accountable these practices when meeting the needs of the child. The challenge is to empower parents to make truly informed decisions on behalf of their children. This can be achieved by going beyond informed consent to the education process that is needed to prepare people for participation and making practices transparent. By moving towards the realisation of this empowerment model the child's needs are met.

Project Context and Objectives:

The RESPECT project

The European RESPECT project set out to explore the expectations and needs related to the participation and empowerment of children in clinical trials. The partners in the project were the following:

- Sahlgrenska Academy at University of Gothenburg, Göteborg Pediatric Growth Research Center. The coordinator of the project. An academic and clinical partner conducting clinical trials with children.
- Good Clinical Practice Alliance - Europe. A consultancy group active in the area of ethics as related to clinical trials research.
- University Medical Centre Hamburg-Eppendorf. An academic partner with access to trainee medical staff who will in the future conduct clinical trials with children.
- European Patients' Forum. A European umbrella NGO representing 44 chronic disease-specific patient organisations operating at EU level and with national coalitions of patients organisations.
- University Children's Hospital Ljubljana - Dept of Paediatric Neurology

A clinical partner conducting clinical trials with children, particularly children with epilepsy and mitochondrial disease.

- Consorzio per le Valutazioni Biologiche e Farmacologiche. A clinical research organisation (CRO) conducting and monitoring clinical trials particularly with Thalassaemia patients and coordinator of the TEDDY European Network of Excellence.
- Azienda Ospedaliera di Padova - Dept of Pediatrics, University of Padova. A clinical partner conducing clinical trials with children with a focus on HIV. Co-odinator of the PENTA clinical trials network.

The RESPECT consortium responded to a call from the EU Seventh Framework programme for a coordination study concerning Identifying patients' needs in the clinical trials context (HEALTH-2007-4.1-4). This call requested that three questions be answered:

- How can patients be better mobilised and empowered?
- How can patients get the clinical outcomes that really matter to them?
- How can the patients' needs be integrated into clinical trials?

The RESPECT project investigated children's participation in clinical trials. The objective was to determine if there are opportunities to improve recruitment through empowering the children and their parents. The reasons for participation and a model of empowerment were investigated. The reason behind this was the then recent implementation of the European Paediatric Regulation in 2007.

The Paediatric Regulation aims to improve the health of children in Europe by:

- facilitating the development and availability of medicines for children aged 0 to 17 years;
- ensuring that medicines for use in children are of high quality, ethically researched, and authorised appropriately; and
- improving the availability of information on the use of medicines for children, without:
- subjecting children to unnecessary trials or
- delaying the authorisation of medicines for use in adults.

The anticipated benefit has been estimated by the European Academy of Paediatricians to be a social savings of up to 250 million Euros per year through improved healthcare (excluding any quality of life benefit and the value of lives saved)

The aims of the RESPECT project

The RESPECT consortium aimed to identify:

1. the needs of children and their families as related to clinical trials of new drugs in Europe.
2. methods by which the needs can be translated into empowering and motivating participants in future clinical trials research.

The aims of the RESPECT project were realised though three objectives, of which the first was to construct a common basis for understanding. The second objective was to collect and analyse various approaches and practices for recruiting patients into clinical trials in different medical areas and conditions. The third objective was to disseminate these outcomes in order to widen the debate to encourage the adoption of better empowerment and recruitment methodologies for patients in clinical trials. The RESPECT consortium consisted of experts from the fields of clinical research, patient representation, and European paediatric research ethics and regulation. In addition, a wide consultation was conducted by the consortium among other European research projects in this area as well as European academic, industry, and regulatory experts. Further consultation and research was also included from the global clinical trials community.

By drawing together different actors, the project opens the debate on how Europe can improve the participation of children in clinical trials. Together with the partners in the project, who represent both the research side and the patients' perspective on involvement in paediatric clinical trials, a stronger, more integrated, and more fruitful coordination with different actors can be realised.

Through the dissemination activities of the project, it is intended to contribute to the empowerment of European paediatric patients and their organisations in clinical trials as well as to assist researchers in defining improved and more appropriate recruitment strategies for paediatric clinical trials. The project also intends to contribute to the further development of European paediatric research ethics and regulation policy.

Methods used and clinical areas

The project employed a variety of methodologies for analysing current European patient perspectives on clinical trials. These methods were chosen and adapted according to the specific groups studied and the needs of the project.

Case study interviews and surveys were employed for child participants and potential participants in clinical trials, including at times the parents of such children; focus groups were used to evaluate clinical staff views on children in clinical trials; interviews were employed to understand industry views on children in clinical trials;, group exercises in schools were conducted among children in schools;, and surveys were undertaken among members of ethics committees and of patient organisations.

The disease areas focused on were epilepsy, growth problems, diabetes, mitochondrial disease, HIV, Thalassaemia, and cancer.

The main emphasis was on obtaining qualitatively rich data that includes the families' own stories of why they agreed to participate and why they continued to participate. All centres were also strongly encouraged to consult with local and national research groups and companies involved in clinical trial research.

Interviews

* Case study interviews: CT participants (63 responses)
* Focus groups: CT participants (5 responses)
* Paediatrician interviews (4 responses)
* Focus groups: CT staff (16 responses)
* Pharma interviews (4 responses)

Surveys

* Child-Parent survey (110 responses)
* Healthy Child survey (38 responses)
* Patient organisation surveys (30 responses)
* Paediatrician survey (10 responses)
* CT networks survey (7 responses)
* Ethics committee survey (77 responses)

Workshops

Workshops were held in each participating partners' countries. These helped us to establish a 'common knowledge' with a wider audience and to identify the operating procedures needed to encourage empowerment and increase motivation for participation in clinical trials. The project workshops were open to other participants invited to contribute to the topics discussed, thus providing another means by which networking can be progressed.

* Methodology workshop (October 2008)
* Trust seminar (November 2009)
* Paediatricians seminar (January 2010)
* Patient organisation workshop (April 2010)
* Pharma industry seminar (May 2010)
* Ethics workshop (June 2010)
* Harmonisation workshop (June 2010)
* Decision aids workshop (December 2010)
* Dissemination meeting (May 2011)

The initial project meeting took place in Gothenburg and this was followed by two workshops which took place in Hamburg and focused on developing the methodology for the project and training in case study description (WP1). The of the studies study plans, interview questions, case study manual, questionnaires were developed. Here the survey instruments were discussed and the case studies work-plan finalised. The second workshop was a knowledge base workshop to present the information collected and identify the issues for further consideration in the harmonization stage. This workshop gave the partners an opportunity to discuss the emerging issues and raise further areas for consideration by the project. As part of this initial stage a literature review was undertaken. The overall project management was provided by the Project Coordinator (PC) and the administrative and financial control resources required to oversee the project as a whole. The PC will responsible for the overall planning and monitoring of the work of the project including tracking the deliverables for the half yearly and final reports. The initial work of the project was to develop a platform for cooperation between the partners. This was achieved through a web-based coordination tool developed (WP2).

The first qualitative data collection was undertaken in WP3 where the objective was to explore the normal procedures for identifying and satisfying patient needs in clinical trials research. The aim of WP3 was to deepen and extend the knowledge of patient needs, attitudes, expectations, motivations and perceived barriers to participation in clinical trials. The first source of information was case studies of normal and benchmark best practice in the participating clinical trials centres. Information was also collected on how families get involved in clinical trials research and what their 'non-articulated' wishes were for outcomes of the research.

Focus groups with CT staff were arranged with a standard schedule. Following approval by the local ethics committee interviews with families and children currently participating in clinical trials

research was undertaken. The lead partner also undertook to solicit and collate opinions drawn from the internet discussion list and from the web-based questionnaire. Telephone interviews were undertaken with representatives from the pharmaceutical industry and ethics committees.

A web-based survey of patient organisations and groups throughout Europe (WP4). In addition a workshop held in Brussels was undertaken in order to identify the concerns and needs of their members and their recommendations as to how empowerment of their members in the clinical trials landscape could be achieved.

The data and opinions generated from the earlier work-packages were then brought together in a harmonisation workshop (WP6). From the integrated sequence of approaches the RESPECT project was able to obtain improved understanding of children and their families' needs concerning clinical trials. In WP6 the survey findings were categorised and described in order to draw conclusions that can contribute to recommendations for the future development of patient focused clinical trials research. On the basis of the information gathered it was possible to outline a decision tree for children and their families who are thinking about participation. This aid to decision making outlines the structure for the patient and also for the clinical trials researcher and was developed into a decision aid tool (presented in this report).

The harmonisation workshop also included a presentation of the education package based on case study data. The objective of the education package was to pilot test a procedure for school education that would describe the needs for clinical trial research and discuss the ethical issues concerning research with children (presented in this report).

The final work-package involved dissemination of the RESPECT findings in order to facilitate collaboration and information exchange between different elements of the clinical trials landscape and to ensure that the results of the project influence the research community and exist in the public domain. Education and outreach formed a major theme of this WP; in addition to a dissemination conference held in Brussels, supporting materials were also developed and distributed. Our public website is one of the main channels for wider public information dissemination and will continue to be maintained in the years that follow the project.

Project Results:

Process of ethics review

The RESPECT project was not designed as a data collection study and as such not all partners were required to interact with patients or gather information directly from individuals. Appropriate ethics review was sought in the cases where data collection was carried out which occurred in mostly in the first period of the project. In the second period the treatment of this data became the main ethical consideration. The RESPECT project exercised its responsibility to ensure that the physical, social and psychological well-being of research participants was not affected by participation in the research. The RESPECT project has sought to protect the rights of those included in the study, taken consideration of their interests, sensitivities and privacy. Our objective has been that the research relationships would be characterised, by trust and integrity. Participation in the research was based on freely given informed consent of those studied. The studies purpose and how the data would be used were explained in appropriate detail, and in terms meaningful to children. The participants were made aware of their right to refuse participation whenever and that they did not need to give reasons for refusal. Anonymity and confidentiality were assured and identification of participants was not required and not transmitted between partners.

The main S & T results of the RESPECT project

The experience of paediatric patients and their parents

The RESPECT project is not a quantitative study but rather a 'coordinating action' exploring the issues surrounding clinical trials on children. As part of this process, we conducted about sixty structured interviews and some small-scale surveys of parents and children in hospital outpatient settings in Slovenia, Sweden, Italy and Germany.

Various groups of clinical trial participants were interviewed: diabetes, HIV, epilepsy, mitochondrial disease. The majority of participants who participated in clinical trials were families who were being treated for their health care needs at the trial site. In the majority of cases, the participant was asked directly by their health care physician.

Slovenian parents of children with epilepsy & mitochondrial disease

Case study interviews were conducted with 30 parents of epilepsy patients and 14 parents of mitochondrial disease patients participating in clinical trials in Slovenia in May 2009. A general pattern was that parents of children in the mitochondrial disease trial gave more positive responses than those in the epilepsy trial. They saw the study in a more positive light: more worthwhile and more likely to help their child or others like them, which compensates for the extra discomfort the child incurred in this trial. It is possible that this reflects the severity of this condition and the limited treatment options currently available, compared to epilepsy treatment.

Themes that emerged

- Benefit to the child personally: Many of the parents talked about the trial as an opportunity to get more information on their child's condition. They referred both to the

chance of a more precise diagnosis from the additional MRI scan involved in one of the two trials but also to the fact that they learned more about their child's condition and wanted to do anything that could improve the child's chances of improvement, even if the benefit was only in small increments or not until a more distant future. This was also their motivation to participate in other trials, if asked in the future.

- Altruism: Apart from wanting the best for their child, the parents spoke of a duty towards all children with a similar condition. Some considered their own child unlikely to benefit but believed that other children may do.

- Increased knowledge: The vast majority of the parents were (or became) interested in the research and wanted to learn more. Some parents searched the internet for information on the disorder; the majority wanted to know the outcomes of the study.

- Pain & discomfort: Many parents observed that the procedures were unpleasant for the child, particularly in the mitochondrial disease trial because it involved general anaesthesia and an MRI. Some drew the line at accepting general anaesthetic or an additional MRI that was being conducted for research purposes rather than for the child's therapy, seeing what discomfort it caused the child. They also found it hard to watch their child's distress when giving blood samples.

- Inconvenience: Some reported long journeys to the hospital and long waiting times once there. It could be hard to get the time off work for this. Nonetheless, the vast majority expressed the feeling that the study warranted the amount of their time it demanded. Some felt that it was no more inconvenient than a normal visit to the hospital paediatrician.

- Informed consent: The parents did not always understand what the study was about. The specialist language (including Latin terminology) in the informed consent material made it harder for them and they wanted the information to be presented in layman's terms. It was notable that they did not consider the use of their personal information by the researchers to be an issue; this relates to the hope to get personal benefit for their child if possible.

- Trust in the child's doctor: Despite not being sure of what the study was about, these parents usually consented to the full procedure and did not feel under pressure to consent. The vast majority liked the clinical staff and felt that they were serious and responsible people. This suggests that they could put their trust in these individuals without having to understand all of the facts.

Swedish diabetes vaccine trial - children and parents

Case study interviews with fifteen paediatric patients and their parents participating in a Swedish diabetes vaccine trial were conducted during 2009.

Themes that emerged

- Trust: Parents often assume there are no risks involved in a trial. They trust the doctors and rarely refuse to participate. ("It's good that it's the same doctor at the same hospital. It feels safer here.")

- Altruism vs. personal benefit: Parents say it is worth the time and trouble as long as somebody's child stands to benefit. In practice, they hope for direct benefit to their own child. They don't want their child to get the placebo or miss out on the latest treatment. ("We only participated because there was a 60% chance of getting the vaccine.")

- Understanding: For both the parents and the child, it is not clear what the trial will involve. It often comes as a surprise that it is time-consuming or painful or that there may be side effects.

- Pain & distress: No-one wants their child to suffer. Needles are particularly distressing. ("I wouldn't let my son be used as a 'guinea pig' in an experiment that could harm him.")

- Assent: Parents vary in the degree of autonomy they give the child to make the decision. Most often, the child does not have much say in the decision and trusts that the parents have understood what the research involves. ("It's easy to agree to something if you don't know what it actually involves.") The child often wants to stop at first but is persuaded to continue. Some of the children say they have now adjusted to the discomfort while others say they would refuse if asked again.

- Information-seeking: Some parents sought information independently (often reading journal articles) before deciding to participate. Parents repeatedly express an interest in receiving feedback on the study findings but rarely get any. ("We definitely want some report of the results: we want to know which group he was in [placebo/vaccine], but also what this study found.")

Italian HIV paediatric patients and their parents

The case study questions were presented to children with HIV and their parents: Only one of the families had been involved in a clinical trial. Those who had not participated in clinical trials were asked questions on their conception of whether it would be important, what would affect their participation, and so on.

Themes that emerged

- In general, having seen enormous progress in HIV treatment, all are willing to participate in clinical trials and have good knowledge of how things work. This could

be taken to signify that distribution of results and progress made through trials, particularly to relevant patient groups, might encourage participation.

- They would want all info available but would feel free to ask if they had questions.
- They did not think anybody would feel forced to participate.
- They were not concerned about time lost (off school, work, etc).
- They appreciated it might be for a collective good rather than necessarily the good of the individual.
- They thought the doctor-patient rapport is very important, but if a study were proposed by a new doctor a rapport can be created.
- A few stated they had an interest in medicine which had arisen out of the illness and frequenting the hospital environment.

Swedish interviews exploring understanding of clinical trials

In order to survey the needs that may exist for a child to participate in a clinical trial, what level of knowledge parents and patients have about their child's trial and the principles it is built on, we interviewed five children and their parents participating in a growth hormone clinical trial in Sweden, with the particular focus on their understanding of clinical trials

The parents were all aware that their child was a participant in a trial but some of them, having young children, admitted that their child was probably not conscious of the research part, since they were minors when enrolled.

Themes that emerged

When they were asked to define the aims of the clinical trial, all of them were able to identify the objectives but hesitated when asked to explain, in their own words, what is a clinical trial?

All of the interviewed people expressed their lack of knowledge about the fundamental aspects of a clinical trial, particularly the way it is conducted.

All parents seemed to remember signing a consent form, but did not remember the details. They described the information as "too much" and hard to understand. They said that it probably would have been better if all parts were described more clearly and in an easier way. None of them said they were reminded that they were in a trial.

Most of the parents seemed to be aware of the term randomisation and what arm their child belonged to and they accepted the procedure. However, it was not clear for everyone that this is used to compare groups against each other. They consented to participation because both arms in the trial received the same medicine, but in fixed or individual doses. All of them were satisfied with the trial and would recommend others to participate; they were inclined to include their children in future trials if it were to their personal benefit.

The extra blood tests were unpleasant but the children were able to cope because they thought they would benefit from the study.

They stated the following positive outcomes of being in a clinical trial:

- the clinicians and the nurses give more time to examining each patient and answering questions that might arise;
- the positive benefit of helping others and hopefully themselves (or their child);
- the trust that they placed in the clinicians and the candidate drug, due to the safety requirements, the careful observations that will be conducted and the adverse event reporting.

They knew that their child would receive their standard treatment if they decided to withdraw, but they were not aware of the negative outcome of the study that would arise if a major part of the participants did withdraw.

They were eager to see the outcome of the study in total, but were not aware if there was such an opportunity or how they would receive the information.

Child-Parent survey (Italian thalassaemia patients)

RESPECT received responses to the online survey from Italians with thalassaemia, who were undergoing progressive replacement of the intravenously administered iron chelation agent deferoxamine with the orally administered iron chelation drugs deferiprone and deferasirox.

These results were interesting because there was a mix of responses from children and parents. Most (8 of 12) had participated in a trial.

Themes that emerged

- These patients were attending hospital regularly for blood transfusions and thus did not experience the clinical trial as an extra burden when they had to come for appointments anyway.
- It was thus like a continuation of their treatment and they saw a definite benefit for the child. They also noted the potential benefit to other children but this may have been of secondary importance to them.
- They understood that this was a CT and felt it had been clearly explained to them and that it was a worthwhile study.
- They wanted to receive a report on the results after the CT.
- They expressed trust in the clinical staff and most felt appreciated and would participate again if asked.

Child-Parent survey (German parents of asthma and eczema patients)

The German responses to the online survey gave a different perspective because eight of the nine parents who responded had never been asked to participate in research at a hospital, so they gave an outsider's point of view.

Themes that emerged:

- These patients were more hesitant at the prospect of participating in a clinical trial.
- It would be a burden to them because they would not otherwise come to the hospital regularly; most indicated that this inconvenience would not be great but they would expect some kind of payment and practical help. (This may refer to travel expenses.)
- They did not feel any obligation to the clinical staff and indicated that there would have to be a positive relationship for them to agree to participate.
- They were not totally against the risks involved in a CT and were not particularly interested in having this explained to them, but they were against the child being used as a 'guinea pig' for research. They wanted to know how the results would be used.
- They were unwilling to have their child assigned to a control group and did not want to be tied to one treatment and miss other options because of the trial. This indicates that they did not appreciate the basic principles of clinical research and the importance of randomisation; they expected more personal benefit.

Child-Parent survey (Slovenian parents, PHIME study)

Half of these parents completing the online survey gave responses concerning participation in this study (not actually a trial of a new medicine), while the other half indicated their opinions on potential participation in a clinical trial.

Themes that emerged (participating in this study):

- This was a long-term study and the parents were aware that they were participating in research and volunteered freely without feeling any pressure. There was no immediate advantage to the child (such as better treatment) and the families would not have been coming to the hospital anyway; they had to make special trips for the study but did not find this a problem.
- They were motivated by interest in worthwhile research that could help all children, including their own, as well as showing a desire to 'pay back' to the medical profession for help already received.
- They indicated respect and trust in the staff but did not feel especially valued for their contribution.
- They wanted to receive the results at the end of the study.
- They would participate in other studies if asked.

Themes that emerged (potential participation in clinical trials):

- Altruism, gratitude and an interest in research featured in these responses too.
- The parents would want a lot of information when considering participation. They wanted to see whether it was a worthwhile study and to know exactly what would be expected of the child, as well as the risks and benefits.
- The parents would not expect a direct benefit to their child but, on the other hand, they did not want their child to end up in the control group and thus effectively be a 'guinea pig' in the research.
- They would want a report of the results at the end of the study.

Child-Parent survey (Slovenian parents, HIE study)

A shorter version of the child-parent questionnaire was filled in manually by 52 Slovenian parents (mostly mothers) of control group adolescents who have been included many times in longitudinal follow-ups in a neonatal hypoxic-ischaemic encephalopathy (HIE) outcome study. These children were born in 1987-1989 and were included at birth in the research study on HIE, especially on biochemical markers. Later on they were included in two different follow-up studies, around age 4 and age 7 years (mainly clinical and neurological follow-up), then some of them were included in magnetic resonance study (MRI) done at the age of around 15 years, and finally at the ages of 16 years and 20 years respectively in two neuropsychological studies.

The questionnaire was distributed to parents by the adolescents included in the study.

Themes that emerged:

- The parents indicated that participating was of no personal benefit but that they felt a duty to participate for a worthwhile cause. One quarter of the respondents felt that they could not refuse to participate.
- They did not find it painful or difficult and, although it was time-consuming, they were willing to volunteer the time necessary for the research.
- One-third indicated that it was fun to take part in the research and most respondents were interested to see what the research was about.

Healthy adolescent survey (Swedish)

The Swedish version of the healthy child survey was sent by email in Oct 2009 to healthy 19-year-olds who had previously given their email address after having their height and weight measured in a study of normal growth curves run by the children's hospital in Gothenburg.

The majority (30 of 38) had not even heard of the concept of a clinical trial, so their views were interesting to us to get a snapshot of adolescents' potential reactions to being invited to participate in a trial.

Themes that emerged:

- The response that surprised us most was that they were generally comfortable with the idea of being a 'guinea pig' for medical research, as long as the risks were minimised. This suggests a trust in the medical profession.
- They could see the benefits for the progress of medical knowledge, showing an altruistic attitude to societal benefits. (As healthy adolescents, they had no personal need of new medicines, which is often the motivating factor in our other groups studied.)
- They were not motivated by payment or other rewards, apart from some token gesture of appreciation.
- Altruism was a stronger motivation than personal benefit.
- There was striking agreement that they would only participate if they were given a lot of information about the trial.

German follow-up study: the 'willingness to participate' construct

In the RESPECT project, one aspect of the different approaches to understanding participation in clinical trial was a closer investigation into the "willingness to participate" construct. In a pilot study, questions specifically regarding willingness to participate were extracted from the RESPECT online survey for parents and children; these were then presented to a convenience sample of medical students, health sciences students and hospital outpatients. In total, 215 questionnaires were returned and psychometric analysis of these responses was carried out to identify the largest explanatory factors for willingness to participate in clinical trials.

Interpretation of the identified factors

The identified factors were interpreted in terms of factor one (control), factor two (general concerns about participation), factor three (general interest in clinical research) and factor four (personal benefits of participation).

The first factor is mainly about a sense of control for the trial participants. These respondents are not only interested in basic information about the clinical research, but also in a precise description of the smallest details of the study and its implementation. We also note that the anonymity of the participants is very important to these respondents; they do not want to be identifiable, thus removing fear of uncontrolled dissemination of the results.

Factor two describes more general concerns that lead to participation or non-participation in a clinical trial. The corresponding items concern fears and anxieties of the respondents. This factor also describes the aspect of the time required for participation in a trial, including easy accessibility of the research site.

The third factor is a general interest in clinical research, with an altruistic attitude being linked to participation. This depends on the person's own experience with clinical research projects, or at least

general knowledge about clinical research. The more points of contact there are in this respect, the more likely is a commitment to participate.

The fourth factor identifies the personal benefits to be crucial for a commitment to participate in a clinical trial.

Conclusions

This analysis suggests that the general willingness to participate in clinical research is influenced by the patient's interest and the effort involved to participate. The positive decision to participate in a study depends upon the patient having a basic general knowledge of clinical research and a certain interest in such projects.

The prospect of benefit to others is of great importance but, at the same time, the degree of willingness to participate depends greatly on the extent of personal gain the respondent can derive from participation.

If these respondents were given access to all the information on the use of the data and the results, it would affect their willingness to participate. Apparently, they want to have a say in the study as part of their participation. However, this expectation may reflect the fact that 80% of the respondents were medical or health science students. It would be valuable to follow up this analysis by analysing responses from children and parents.

In planning a clinical trial, the responses indicate that it is important even before the implementation of the study to provide information about possible risks and side effects of the drug to be tested or potential negative consequences from participating in the study. This could be in the form of a brochure or a personal interview.

Trust in doctors: discussion with an expert on the trust concept

During the RESPECT project, doctor-patient trust emerged as an important factor in why people participate or refuse to participate in clinical trials. Therefore, RESPECT carried out a workshop on trust with an invited expert in this area.

Doctor-patient trust is a crucial element for participation in clinical trials. In the absence of an established relationship between the doctor and patient, willingness to participate is markedly lower according to our observations. So how can we increase the level of trust so that, if there is only a weak relationship between the doctor and patient (or the parent making the decision), the patient might still feel safe in agreeing to participate? Should we generate more trust or ensure that the family can make a truly informed decision that is not so dependent on the doctor's influence?

Themes that emerged:

Trust is a multidimensional concept. Important aspects established in the literature are summarised below.

Trust judgements take into account honesty (telling the truth), reliability (promise fulfilment) and emotional respect (avoiding criticism, not causing embarrassment). These elements are independent:

you may for example trust someone to be honest but not that the same person will keep their promises.

Trust is dependent on beliefs (gut feeling), trusting behaviour (tendency to trust others) and trustworthiness (demonstrating honesty, reliability and emotional respect).

Trust is reciprocal (mutual) - the patient needs to trust their doctor but the doctor also has to trust the patient (to be honest, to adhere to the treatment regime/protocol, come for check-ups, etc.). Even children of 5 or 6 yrs appreciate reciprocal trust.

Trust is dynamic - it may build up gradually or initial trust may be weakened over time, as it is reassessed based on experience.

We show trust in all levels of society, from trust in family members, to trust in doctors, to trust in the government, and our trust may be directed at a specific person, a group or a generalised other. We need to trust others in all walks of life to be able to function.

Most research on trust focuses on interpersonal relationships, but in our case it is also interesting to consider obedience to authority and the power imbalance of doctor-patient and adult-child relationships. (A paediatric patient is weaker on both scores.)

Rotter (1980) showed that higher-trusting people are not gullible. These high trusters are good at judging trustworthiness and will look for reliable information to help them make a decision. Low trusters won't even look at the information - their mind is already set to be cynical.

Model of Trust in Paediatric Clinical Trials

Three bases of trust according to different levels of generality/familiarity can be identified:

- trust beliefs between the parent and child;
- trust beliefs in physicians; and
- trust beliefs in medical treatment

Bad publicity about trials reduces willingness to participate, although this subsides over time. There is no research yet on how to promote trust or shift entrenched attitudes. Predicting trust beliefs is the first research step.

'Promise reliability' should be part of the informed consent process - and the entire trial - to build and maintain the patient's trust. Probabilistic statements ("We expect fewer seizures") are more honest than absolute ones ("You will be cured"). Honesty is more crucial when the discussion is about the patient's health than when it concerns a more neutral situation. Note that fear is a separate dimension: you might be afraid of needles, just as some people are afraid of the dentist, but you still trust the clinician to be subjecting you to this pain for a good reason.

In the majority of cases, the RESPECT project found that the patients in CTs were happy with their participation but there were examples given that in health care they felt they had not been treated with the same level of respect that they would wish for and not what they had found in CTs. This would appear to come down to a question of trust. The trust has been broken. The feeling of being treated unjustly leads to the demand for greater control over the health and CT process.

Being empowered to decide (or not) seems strongly related to how much information the family has. Trust fills a gap when the doctor knows more than the patient does. If you are confident that you have received enough information, you feel empowered to make the decision for yourself, either for or against. If you do not have enough information, you make a judgement (maybe a gut feeling) about whether you trust the doctor enough to participate. This trust may be violated over time and the Swedish case study reports indicated that some children in our diabetes vaccine trial reacted this way. In the light of their experience they were more knowledgeable about what is involved in a clinical trial and whether they could trust the doctors to be honest with them about it. They felt empowered to say no if they should be asked later to participate in another trial.

Conclusions on the experience of children and parents

We gathered the comments of families who agreed to participate in clinical trials and individuals who had never been asked, but it should be noted that we did not get any responses from those who refused when invited to participate or those who withdrew from an ongoing trial. Thus, some of our material sheds light on how people think they would respond to a hypothetical invitation to participate, while those who were in a trial could reflect on why they consented and how they experienced it.

Many of the parents we interviewed saw the trial as a way to get the latest and best medicine for their child (thus misunderstanding the principle of equipoise that is fundamental to clinical trials). They are disappointed that their child might get the placebo and thus miss out on the latest treatment. A child placed in the control group was seen as a 'guinea pig' in the research, whereas testing the experimental drug was not seen in this light. This indicates that they did not appreciate the importance of randomisation; expecting more personal benefit (which is the normal role of the medical profession). Only the healthy adolescents we surveyed were comfortable with the idea of being a 'guinea pig' for medical research, on the assumption that the risks would be minimised.

Families generally reported that participating in the clinical trial was inconvenient, apart from those who had to come for appointments anyway. Parents said it was worth the time and trouble as long as somebody's child stands to benefit, but we saw repeatedly that the greatest altruism came from those who had not actually been in a trial or whose participation had not been painful or unpleasant. There was clearly a 'tipping point' if this altruism involved subjecting the child to extra pain or distress and the parents in this situation did not always feel that their sacrifices were appreciated sufficiently. They wanted more gratitude and token gestures of appreciation.

When faced with the (real or hypothetical) decision to participate, there was an almost universal desire to get as much information as possible, but those who were in a trial often complained that the information they had received was not easy to understand. Thus, they had to trust the doctors and nurses to guide them in their decision and it was common for parents who had entered their child in a trial to say that they had confidence in the staff and felt that it was a worthwhile study. They were often motivated by a desire to 'pay back' to the medical profession for help already received.

When we surveyed outpatients who had never been in a clinical trial, we found that they were more hesitant at the prospect of participating. They did not feel any obligation to the clinical staff and indicated that there would have to be a positive relationship for them to agree to participate.

Most often, the child does not have much say in the decision and trusts that the parents have understood what the research involves. Thus, trust is a pivotal aspect of consent and it is important

that families do not feel that this trust has been broken if the trial was not as they were led to expect. For both the parents and the child, it was not always clear what the trial will involve and it often comes as a surprise that it was time-consuming or painful or that there were side effects. The child is at particular risk of understanding the least while suffering the most distress, and some of the older children reflected this when they said they would refuse if asked again.

Parents often saw the trial as an opportunity to get more information on their child's condition. They were eager to see the outcome of the study in total, but were not sure if there was such an opportunity or how they would receive the information. Other parents saw themselves as research partners in making medical progress and wanted to feel that their input was valued. This interest in the research was clearly a motivation for participating in further trials if asked again.

It is important to ensure that families understand the need for research and are respected for their valuable contribution to the improved safety of medicines for children.

The experience of patient organisations

Email survey: Patient organisations

Introduction

The RESPECT project conducted an email survey to identify patient organisations' views and perspectives on the level of participation in pediatric clinical trials and the reasons why children participate in CTs, why they do not participate and what can be done by patient organisations (POs) to answer their needs and increase participation in and quality of paediatric CTs.

Thirty-six patient organisations (POs) and 48 further organisations were contacted; 11 organisations responded to the questionnaire. Among the respondents, six POs reported having experience in paediatric clinical trials while five POs did not have this specific experience.

The survey aimed to explore critical aspects of the levels of participation in clinical trials (CT) and to highlight positive examples and best practices. These are the specific aspects investigated:

- the extent of paediatric clinical trial participation per disease;
- the reasons why paediatric patients and families decide to take part in clinical trials;
- the specific barriers to participation;
- good practices and motivating factors;
- informing potential participants;
- the role of patient organisations.

Results

Extent of paediatric clinical trial participation:

The results showed lack of knowledge of specific figures of paediatric CT per disease.

Patients' needs: WHY patients DO participate in CTs

According to the experience of the POs responding to the survey, participants in CTs are mainly motivated by their direct interest in receiving new treatments. Sometimes the idea of helping other children with similar diseases is also a motivator. In certain cases, they also feel more confident in taking drugs that are being tested than existing drugs that have not been tested on children. The decision made by parents to improve the condition of their child is also one of the reasons that contribute to the participation of children in CTs.

Patients' fears: WHY patients DO NOT participate in CTs:

The analysis of the answers provided by POs, sometimes citing direct responses from parents and children involved in CTs, indicate four main types of barriers to participation:

- emotional barriers;
- ethics and transparency of information;
- practical barriers;
- the relationship with physicians and other entities.

The emotional barriers concern fears of the parents. Parents are afraid that their child might not understand the process. They also fear that the treatment might not provide any direct benefit or that it could even worsen the situation. Finally, they are concerned with the invasiveness of the treatment and of health checks. These fears translate into a perception of risk and into safety concerns related to CTs.

Ethics and lack of transparent information constitute another group of barriers to participation in CTs. Parents are especially concerned with the possibility of complicated 'informed consent' procedures for children whenever communication is not implemented at the right level for the child to understand. According to POs, the lack of knowledge from the parents about the existence or on the importance of CTs is also an obstacle to participation.

The third group of barriers relates to practical aspects of CTs. Time-consuming treatments, extra visits to hospitals and an excessive waiting time before having results are considered reasons that reduce participation in CTs.

The fourth group of barriers is in the realm of the relationship with physicians and concerns the role played by institutions and POs. Parents are afraid that they will not receive adequate support from physicians and that the legal system lacks regulations to ensure trials are safe. Among the POs surveyed, the absence of training for patient organisations might also constitute a barrier to participation.

Good practices and what should be done

Informing potential participants

The results of the survey highlight a need for a more transparent and structured flow of information by involving in the process physicians, nurses and patients' organisations.

Two key concepts emerged from the survey: cooperation and trust. Better cooperation among stakeholders involved in clinical trials will provide tools to parents and children to be actively involved, informed and supported. To know will trigger mechanisms of trust. It is helpful if the person informing parents and children or introducing them to the 'informant' is somebody they know or somebody they consider reliable, such as their GP. To reinforce the feeling of trust in parents and children, the involvement of medical associations, national health authorities (but not of the industry according to some interviewed) can also be relevant.

Strengthening the role of patient organisations

A guiding principle is that patients must be treated as partners in knowledge rather than recipient only of health care treatments, therefore the role of POs needs to be shaped accordingly.

POs should be sources of unbiased and reliable information to guarantee transparency in the CT process to parents and children. In particular, they need to stand on the side of children and design their work as intermediaries, facilitating children's input as well.

POs should also be responsible in promoting ethics and principles through formal guidelines at the international level. To safeguard that the conduct of the CT is in line with these principles and that it is beneficial to the patient, POs can be involved in pre-study meetings.

They should also be in charge of disseminating available information about existing trials, the value of participating in it and sharing information with other POs when the trials are in their same disease area.

On the quality of the information disseminated, POs must opt for a 'family-friendly' language and methods. Focus groups, studies of child and parent attitudes are useful tools in ensuring that their input is included in CT design and implementation and to ensure that parents and children can truly provide informed consent.

Finally, POs should provide emotional support to parents and practical help. POs should play a role in facilitating logistic problems and reducing obstacles (e.g. by guaranteeing access to transportation when the child is requested to go often to hospital, or by helping to fill in forms).

Responsible role of Institutions:

A solid legislation framework is needed. Regulations and legislation will provide a more organised structure to rely on and will allow the development of a family-friendly CT system. Below are some aspects from the survey that emerged as 'future landscapes' to be promoted:

- Work to develop a system in which true informed consent by families - including by the children themselves - becomes possible;
- Parents' opinions must be integrated during the trial;
- The creation of an internationally agreed principles charter must be designed and implemented. The Eurordis Charter on CTS for rare diseases can be used as a model;

Conclusions

Parent- and child-friendly clinical trials are the solution to increase participation and transparency. Patient organisations are the key group to produce the change by organising themselves to empower patients involved in CTs and adopt a child-input perspective.

For this to happen, better cooperation, education and training need to be further developed at all stakeholder levels. The final expected result will concern the involvement of patients in CTS as partners in knowledge and in the development of true informed consent by families, including by the children themselves where possible.

Physicians and nurses need to develop a family-friendly language and communication strategy, while GPs - who already have a trust-based relationship with their patients - are also expected to play a major role by being the first contact among patients and doctors involved in the CT.

A solid and reliable legal framework that prescribes international standards and guidelines will provide the political tools for all stakeholders to cooperate better but especially for patient organisations to take the lead in empowering children and motivating them to take part in clinical trials, by reducing their fears and concerns.

Online survey: Patient organisations

Introduction

This online survey focused more on the way patient organisations (POs) operate in the field of paediatric clinical trials (CTs). The results of the survey provide information on three main points: firstly, the type of questions parents of children involved in CT ask to POs, when asked at all; secondly, why patients DO and why DO NOT participate in CTs and thirdly, what kind of good practices are already being done and the role of POs at present and for the future.

This survey is based on a questionnaire translated into all languages of the project consortium and conducted online. Nineteen responses were collected; below are the figures according to language/country:

- English: 2 replies
- Swedish: 7 replies
- German: 5 replies
- French: 1 reply

- Slovenian: 1 reply
- Greek: 1 reply
- Polish: 2 replies

The questionnaire targeted patient organisations involved in different areas of diseases, among the respondents there were organisations involved in pathologies such as asthma, diabetes, kidney issues, lupus, allergies, Thalassaemia, AMD, haemophilia, cystic fibrosis, Addison, child heart diseases, young rheumatic, Ehlers-Danlos syndrome, epilepsy, mitochondrial disorders, adrenoleukodystrophy, Duchenne muscular dystrophy and some unspecified self-help organisations.

The POs that participated in the survey were asked to provide information on their experience of paediatric clinical trials (CT) and specifically to address the issues mentioned above-.

Results

Questions to POs

The survey aimed to establish what kind of questions parents ask POs to better evaluate what role they (the parents) can play. The results showed that parents do not usually ask questions about CTs directly to POs, but it is more likely that parents tend to enquire with doctors or healthcare professionals involved in the CT. In case of questions asked directly to POs, these helped to understand parents' concerns and limits to participation in CTs.

Parents' queries about CTs

Several POs received questions about which studies are ongoing in their specific disease area in order to find out whether there are specific treatments being tested for children. This is seen especially with parents of children with severe and usually debilitating diseases or heart disease. In this last case, more information is often requested by parents about cardiac research, in the treatment of pulmonary arterial hypertension, research on anticoagulant medicines or on artificial pacemakers. Some POs registered questions linked with safety and efficacy concerns about the risks involved

Why patients DO participate in CTs

According to the experience of the POs that participated in the survey, parents agree to their child being involved in a CT mainly because they would like immediate benefits from a new treatment, access to new generation of drugs or if they want to ask for an early introduction to these. In some cases parents feel a sense of 'gratitude' for the possibility of accessing new treatments and they are keener in having their child participate.

Why patients DO NOT participate in CTs

On the other hand, parents who are not willing to let their children participate in CTs are mainly concerned about risks and side effects. In certain disease areas, parents are more worried for girls because of possible fertility issues in the future. In some cases, logistical problems such as lack of time can be a barrier to participation, especially if the CT requires more visits to hospital to receive the treatments. Parents might be less in favour of invasive CTs but more prone when the trials are part of routine examinations.

These barriers to participation might be the consequence of a general lack of trust in physicians or in the scientific sector. According to one of the respondents, a major role is played by public media, which tend to create a dichotomy between the 'good' (alternative medicines, new-age, free-chemicals) and the 'bad' (conventional medicine, drugs). At the same time, scientific magazines that could provide more scientifically reliable articles are not read and not so accessible to the general public on a wide scale, creating a gap in knowledge.

Good practices

What should be/ is being done

The aim of good practices is to increase children's participation in CTs and ensure that this is a safe and empowering experience for the child.

Convincing parents of the usefulness/need of the CT, to better inform them, and to increase their interest to cooperate are the objectives of good practices. This can be achieved by educational activities, individually and in groups, such as by organizing regular meetings. POs should provide a good level of expertise and structure during these meetings, which can be also organized in order to target children directly. A risk factor in focus groups may be the influence of one parent over the group. Indeed, among the respondents to the survey one PO gave as an example the case in which a parent who was especially negative about a CT could undermine their trust-building programme or, on the other hand when the good approach of one parent can enhance positive emulation.

Role of patient organisations

Participants in the survey were asked to describe what is being done already in their POs and what can be improved.

Among the responding POs, some are already quite dynamic in activating mechanisms to increase participation in paediatric CTs. The majority consistently disseminate information through their internal newsletters or magazines to members in letters or articles. The second choice is to liaise with clinical trials projects, while the third choice is to get involved directly in campaigning and lobbying activities, sometimes at the EU level as well.

One of the respondents described in detail its own strategy, which consists of regular meetings, a specific phone line to share problems at national level, lectures and support groups, publication of pamphlets to target practical and daily needs. This organisation also works with universities by mentoring and co-mentoring graduate and postgraduate papers, financing research, promoting

postgraduate courses ad hoc. Finally, this PO is also active in providing logistical support to patients who need to travel abroad to get surgical treatments.

Among proposals to improve the role of patient organisations, what emerged is that POs ask for a more active and recognized position as an intermediary in CTs between patients and professionals.

POs especially ask to be involved from the beginning in a CT, by helping to recruit participants and presenting them the information as first interlocutor; in this way they can act as a resource both for families and researchers. They further ask to be responsible for developing ethical guidelines and to advocate and campaign for regulations.

POs want to play their role of intermediaries among the researchers and patients through platforms that involve all stakeholders in CTs and they want to be the first to disseminate information to other organisations and to patients.

Finally, POs were asked to highlight critical aspects or their specific needs according to their area of research. These are the main findings:

- Research into a rare disease area is less profitable, therefore some diseases are neglected
- To improve education of staff participating in clinical research provides an important source of income
- There is a risk of sponsors and investigators having vested interests in recruiting a patient for a CT of a new drug when it is not necessarily in that patient's best interest to switch from their current treatment, if it is relatively effective. There should be an independent assessment of such decisions, and the trial drug should be compared against the existing treatment, not just against a placebo.

Conclusions

Patient organisations are ready to be active players in managing the relationship between paediatric patients and the research sector to improve participation in CTs and to make the experience more empowering for children.

To achieve results through good practices, POs ask to be formally recognized as the intermediary among patients and professionals and to act within a common legal framework. They want to be involved all along the process of CTs, starting from recruiting the participant, though information activities and disseminating the results.

Reinforcing the role of POs will increase the level of trust towards the research sector. Indeed, both of the surveys conducted by EPF highlighted that parents tend to mistrust based on their lack of - or limited access to - information.

This second survey stressed an additional aspect: the role of the media in creating fallacious perceptions. General media tends to emphasize the importance of natural remedies, creating a negative perception of traditional medicine. This can bias the approach of parents considering involving their children in CTs . At the same time, scientific magazines with more accurate information are not so accessible at the public level.

POs can thus be expected to reduce information gaps at the level of parents involved in CTs through education and training, but also at public media level, by pursuing and reinforcing their activities of information dissemination.

The experience of clinical trials staff

Focus group with German clinical research staff

RESPECT conducted a focus group with German researchers and clinicians to explore their concerns about the difficulty of recruiting children to studies that imply some risk for the child.

Themes that emerged:

GCP

- Everybody gives information about the study to the parents and children, but the whole process is not standardised. They also explain the risks and benefits of participating
- Standardized consent documents (often provided by the sponsor) are used.
- To protect participants, the study group makes clear that the participants have the right to withdraw from the study at any time.
- They offer no special legal or psychological advice.
- The participants get information about their health status, but not about the global research results of the trial: the sponsor will not disclose the results

Consent/assent

- The age of the child who is asked to participate (assent) is a problem: sometimes the children are so well informed that even a 5-year-old is capable of stating if he or she wants to participate or not. It is difficult to say where to draw this line.

On the other hand, everybody from the study group agreed that if the child has a life-threatening disease any refusal from the children should be ignored even if the assent is very important.

Motives for the child to participate

The study groups agreed in saying that, for the older children, the money they receive is the most important motive. The parents they identified a mixture of getting the latest medical care and the feeling that they wanted to do everything possible to help the child

- clinical trials with children do need more time than clinical trials with adults

- Concerning the level of knowledge parents and children do have about medical research, they agree that most people they spoke with fear being treated as a 'guinea pig' - they stressed that this is an outdated idea of medical research. On the other hand it depends strongly on the diagnosis: parents and children with serious diagnosis know better about medical research because of personal research about the diagnosis.

Barriers to clinical trials with children

- The clinicians expressed problems with participating by design - parents are more likely to refuse participation in studies with a placebo wing.
- They sometimes think that panel research will be better than clinical trials

Focus group with Swedish clinical research staff (diabetes)

RESPECT ran a focus group with Swedish nurses involved in a diabetes vaccine clinical trial. The discussion material consisted of patient statements drawn from our earlier literature search and case studies indicating why they had participated in a clinical trial, as well as additional statements suggested from the literature review indicating why a patient might refuse to participate.

Themes that emerged:

General

We explored which of the statements they believed their patients had expressed and whether there were additional opinions reported by patients.

It was much easier for the nurses to remember patients' reasons for participation in a clinical trial than reasons against participation, largely because it is extremely rare for patients attending this clinic to refuse to participate. (The patients and parents we have interviewed in our case studies are full of praise for these nurses and seem happy to get more attention from them by being in a trial.)

Motives the children and/or their parents have expressed for participating

The nurses confirmed that the following reasons were sometimes or often given:

- The study could lead to improving other children's health.
- The research could help me/my child personally.
- It isn't painful or unpleasant.
- I/we don't mind the time it takes.
- I/we have no problems travelling to the hospital.
- It is better than being at school / at home / at work.

This suggests that the families consider their participation to have no real disadvantages while having the advantages of potential benefit to their child's health and that of other children. Of course, we cannot rule out that they only make positive comments to the nurses and privately have some worries but, nevertheless, we know that they willingly agree to participate and continue for the duration of the trial.

The nurses also commonly heard the following comments:

- I want to receive a report on the research results at the end of the study.
- I/my child would be willing to participate in further research.
- I would like to be a researcher / doctor / nurse.

This suggests that the families also consider themselves active participants in the research (not just passive patients) and feel entitled to know the findings at the end of the study. It is not clear whether any of the families are given a study report of any kind.

Motives the children and/or their parents have expressed for refusing

As stated above, this is a rare scenario, so there was not much to say. However, the nurses did recognize the following statements from parents:

- I don't want to put my child through unnecessary procedures.
- It would be painful or unpleasant.
- I was worried that my child would be put in a control group that doesn't get any treatment.
- It would involve too much of our time.
- It is inconvenient to travel to the testing location.

They reported that pain and distress to the child do get mentioned frequently by both parents and children in connection with having to undergo blood tests and injections. The children are often afraid of needles and complain that it hurts. Several parents have said that they do not want their child to participate in future trials if it involves more needles. If they are coming to the hospital anyway for tests then it might be acceptable.

Focus group with Swedish clinical research staff (cystic fibrosis)

The clinical staff reported that, because CF is a chronic disorder, they build up a strong relationship with their patients over many years, which makes it easier to encourage them to be in a clinical trial. The team staff reported low dropout rates in their trials, probably because of this strong relationship. They discussed how much harder this would be if they were dealing with, for example, cancer patients who would have recently got a diagnosis and be coming to a clinic where the staff didn't know them. It would be hard to establish trust quickly and their acute condition would make them less willing. Parents would find it tough to make such a decision in this situation.

The doctors present stated that they want what is best for their patients and would not enter them in a trial unless they felt it would help them.

The staff members explain what the trial is about verbally, in addition to the written information, and answer any questions the family may have. Parents are quite knowledgeable, especially when they have been in several trials, and it is not clear if specific education would help them. The children are not so aware.

The only risk is that families get 'study fatigue' and don't want to be in yet another trial. Then it is the staff's job to explain how important it is to take part and contribute to research.

They also reported that children themselves may not want to participate in a trial because of the blood tests (fear of needles), but that the staff then encourage them to be 'brave and strong'.

One nurse reported that some healthy children were recruited to a trial involving bowel investigations (which she would have refused to volunteer for herself). Surprisingly, they were keen to participate and did not regret their decision once the trial was underway. They felt that they had a special status. (It has been mentioned by Slovenian and Swedish doctors that it helps to make the patient feel that they have 'VIP' status if they are in a trial, even though this would not really be true.)

When asked if they had any patients spontaneously asking to be in a trial, most did not think that this happens, but one nurse said that she had one such patient. It is more usual that patients respond to a request from the doctor. (It may be that most patients here are already in a trial.)

Interviews and survey with paediatricians

Background

This part of the RESPECT project aimed to explore how paediatricians approach the task of recruiting children and their parents to clinical trials.

Data collection took place in Nov-Dec 2009. There were four interviews with professors of paediatrics in Sweden, Italy, Germany, and the Netherlands. The same questions in the form of a survey were distributed to paediatricians in Slovenia and we received ten responses. These respondents had considerable experience of clinical trials, recruiting on average 85 participants each (ranging from 10 to 300).

Themes that emerged:

Barriers to participation

When asked about the timing and their general approach, several of the respondents commented that it is particularly hard to raise the issue of participation while the family is stressed. Often this is because of the shock of just having received a severe diagnosis or because they only have a short time to think about the request to participate. One paediatrician reported that he sleeps badly when he knows he will have to approach a parent for consent in an acute situation (such as taking a blood sample before and after bypass surgery); they need more time to decide and a good relationship of trust with the staff.

Parents do not want any extra distress for their child, particularly when the child is very small, or has a devastating disease or even mental or motor disabilities, and the CT protocol includes invasive or semi-invasive procedures. They are also afraid of infection or side-effects,

They do not like to think of their child as 'guinea pig' and dislike being assigned to different treatment arms (especially in double blind randomisation). This is because they assume there is a personal disadvantage if they miss out on the experimental drug. It is thus important to explain to the family the novelty of the new treatment and the fact that they will be able to receive the new treatment after the trial if it proves to be effective (regardless of which arm of the study the child was in). They considered the ideal situation to be when a separate appointment is made with the family, meeting in a more comfortable room (not behind a desk).

A common problem that families report to them is the inconvenience of participation (time lost and the logistics of getting to the trial site). The paediatricians were often frustrated that they could not offer more logistical support.

Doctors themselves feel less motivated to join a CT when the workload will be high with too many complicated, formal procedures.

In some cases, families are reluctant to make the long-term commitment that participation involves. If they have participated in many trials, they may show 'CT fatigue' and a loss of hope in the promise of new treatments.

Families' motivations to accept

The expectation of better treatment motivates both the families and the paediatrician. Indeed, the paediatricians commonly reported that they emphasise the extra monitoring and potentially better treatment when encouraging families to participate.

As a consequence, a comment was made that some parents may feel that they will not get full and appropriate treatment unless they agree to participate in the CT.

The personal relationship with the doctor was considered to have an impact, with the child and the parents wanting to follow the doctor's wishes. In return, the paediatricians were concerned to reduce inconvenience & pain as far as possible and wanted protocols to minimise the number of blood tests the child would undergo.

Explaining clinical trials

When asked about what families understand about clinical research and whether it is hard to explain about the CT, many of the paediatricians reported that the parents' level of knowledge varies and that children understand even less and can be inattentive. These paediatricians gave vastly different responses when asked how old a child needs to be to give their assent (ranging from 4 to 18 years of age).

Particularly problematic are situations where the parent will consent, but the child will not give assent (especially if he or she is rather small); children do not see the necessity for the study.

On the question of explaining risks & benefits, they stressed the importance of being honest, as you would with your own child, with explanations appropriate to the child's age. Listening and responding to the family's questions was considered important. These subtle skills are not available in the ethics committee guidelines.

Payback to participants

More than half of the respondents reported that they give the family information on the results of the study, but in several cases this was only on request. One paediatrician suggested that knowledge is something they could offer when encouraging participation, because the interested parents and children will learn about the research by participating.

Interestingly, some of the respondents mentioned that patients would like to see more gratitude from the staff or the sponsor, probably reinforced by token gestures (gifts or treats, such as a meal) for the children.

Recruiting patients: discussion with experienced paediatricians

In January 2010, we held a seminar with the senior paediatricians among the RESPECT project partners, to find out more about their experience in relation to the interview and survey responses we had gathered from other paediatricians. They gave us the following insights.

Barriers to participation

The parents who are most resistant to invitations to enter their child in clinical trials are the ones for whom the existing treatment is working well and the clinical trial concerns testing different doses or oral versus intravenous administration. They do not want to change anything, so recruitment will be a problem and the clinical trials will probably have to reduce the sample size required for significance (as they do now for orphan diseases). It may even be necessary to recruit from more countries. Often around half of those asked to participate will refuse. One suggestion was that there should be campaigns (appeals) to the public to raise awareness of clinical trials and increase the likelihood of participation.

If the parents have no established relationship with the doctor (for example, a mother approached when she has just delivered), only about 20% will agree to let their child participate. They are usually the more educated mothers who feel research is important and personal benefit to the child is likely. The other 80% do often come round to the idea later and it is very rare for families to withdraw once they are in a trial.. If their child has a chronic disease, they are more likely to participate for altruistic reasons; they feel that they will see reciprocal benefit in the long run.

In the case of chronic diseases, the clinicians already know the patients and may ask them to be in many trials. Indeed, they avoid inviting new patients to participate and wait until they know them better. In any case they would always contact the patient's primary care physician for background information (medical history and also previous compliance to their medical regime). The patient's physician may have little experience of randomised clinical trials or alternatively have been involved

in many trials before. He or she may be asked to join someone else's clinical trial as a satellite trial centre but an alternative is to send the patient(s) to the main trial centre instead. This may be better for the patient in terms of expert monitoring. It means that the patient effectively receives a second opinion on their diagnosis and prognosis, which the primary physician may see as a benefit or (possibly) a threat.

Exclusion

Immigrants tend not to get included in clinical trials. There is an assumption they will not understand the instructions because of low education, but this may be an assumption by medical staff. We need to be more inclusive and provide cultural mediation, not just translation. There is a European Commission project called European Standards on Confidentiality and Privacy in Healthcare among Vulnerable Patient Populations (EuroSOCAP) that is producing guidelines on addressing patients in their strengths instead of focusing on their weaknesses.

In the case of HIV (in which the child contracts their condition from their mother), it has been observed that some mothers refuse to let their child participate because they themselves had a bad experience (such as a rash) with the drug and don't want the child to risk this. Since adherence is important, the clinician will not enter these patients in a clinical trial of a drug they are unlikely to take.

Spontaneous requests

If the patient is on a standard drug and it is not helping, the parents are glad to try something new. In fact, they consistently ask spontaneously to be included in any trials that may be started, especially if their child has a fatal disease. Many parents spontaneously seek information about their child's condition on the internet.

Patients who are more empowered will want to find a clinical trial that suits them. It is possible - at least in USA and Sweden - to respond to an advert in the press or radio recruiting clinical trial participants, but in other countries, these spontaneous applications by patients may not be allowed.

Conclusions from survey and interviews

These responses raise the question of whether the existing Good Clinical Practice guidelines are enough. Just ticking informed consent checklists may not be a guarantee of true informed consent. We cannot be sure whether parents and children have really understood what they are being asked to do or whether they consent instead because they trust the doctor, the nurse or the researcher to do what is in their best interests. This leaves families in a vulnerable position.

There is a risk that some adults (among both clinicians and parents) do not consider the child's opinion to be valid and do not communicate directly with the child. It is important to gain the family's respect and trust by being honest - as one would with one's own child; the clinical staff must give and take feedback before, during and after the trial;

The responses highlight the importance of clinical staff respecting their patients' needs in order to increase willingness and motivation to participate in a clinical trial. It is important to listen to the family's concerns; wherever possible, the clinical staff should strive to reduce distress for the child and keep inconvenience for the family to a minimum

Physicians are in a unique position to inform trial sponsors about the child's unmet medical needs and to influence which trials are conducted, but it was not clear whether they use this influence; however, they do sometimes emphasise to sponsors that they prefer to avoid too many blood tests on their young patients.

It is important to ensure that families understand the need for research and are respected for their valuable contribution to CTs; randomisation must be clearly explained and the clinical staff must show appreciation, acknowledging that the child is a 'medical hero'.

The experience of clinical trial networks

Clinical trial networks: involvement of paediatric patients and their parents

Survey findings

Our consultation shows that only three out of the eight paediatric clinical trial (PCT) networks participating in the survey systematically involve patients and/or patient organisations (POs) in their clinical research. Two of these networks are "disease oriented" and fall in a very specific 'rare diseases' category, while the third (MCRN) is a "generic" network facilitating the development of medicines that are both safe and effective in the treatment of children.

CVBF-TEDDY highlights the fact that the direct participation of patients in the planning stage of the clinical research depends on the type of study, and in particular on the investigated disease: if there is a strong patient organisation (as in the case of thalassaemia and cystic fibrosis), it is more likely that their input is sought from the early stages of the research.

Recruitment is usually carried out within the network's members and/or participating centres; if the number of patients recruited through the network is not sufficient, specialists and/or POs (in the case of rare diseases) are contacted; only occasionally the clinical trial is publicised through advertisements.

Feedback is systematically given only by PENTA, while usually it is encouraged, but not always attainable. The amount of information given to patients depends on the Sponsor, but usually data relate only to the general outcome of the trials, while personal information are typically not given.

Examples of best practice are provided by FINPEDMED, PENTA and MCRN.

- FINPEDMED developed a national template for providing information on a clinical trial to paediatric patients of all age groups and templates for informed consent in all age groups. They have also developed picture cards to use when providing information on a clinical trial for children.

- PENTA established youth groups that providing feedback on their HIV infectious status and their medical and social care.

- MCRN encourages the active involvement of young people and families in the design and delivery of clinical trials via the MCRN young person's advisory group, or topic specific focus groups.

Conclusions

The following conclusions can be drawn from the results of our survey: direct involvement of patients and patient organisation still is not in the current practice of PCT Networks, and it is necessary to increase awareness on the subject.

It might be useful to draft and circulate recommendations targeted to families and patients to encourage their involvement in clinical trials.

Clinical trial networks: involvement of public stakeholders

Background: The European network of paediatric research (Enpr-EMA)

The European Paediatric Regulation posed the legal basis for the development of the "European network of existing national and European networks, investigators and centres with specific expertise in the performance of studies in the paediatric population".

The European Medicines Agency (EMA) was appointed the responsibility to set up such a network and in May 2010, the recognition criteria requirements to become member of the Network were agreed on by participants from 38 national research networks and clinical trial centres and the European Medicines Agency.

CT networks interested in joining the network were invited to complete a self-assessment form (to be updated annually). A total of 33 networks submitted self-assessment forms to the European Medicines Agency: eighteen are now officially members of the European network of paediatric research (Enpr-EMA); one is, at the time of writing, undergoing clarification and fourteen do not qualify for membership.

Recognition criteria for self-assessment

The self-assessment form contained the following six criteria that networks should fulfil to be recognised as a member of the Enpr-EMA:

- Criterion 1: Research experience and ability.
- Criterion 2: Network organisation and processes.
- Criterion 3: Scientific competencies and capacity to provide expert advice.
- Criterion 4: Quality management.
- Criterion 5: Training and educational capacity to build competences.

- Criterion 6: Public involvement.

The RESPECT partner CVBF analysed the responses to Criterion 6 to find best practice examples of patient/parent or patient organisation involvement.

Within Criterion 6, the minimum requirement was involvement of the public in at least one of the following three component items:

6.1 Involvement of patients, parents or their organisations in the protocol design.

6.2 Involvement of patients, parents or their organisations in creating the protocol information package.

6.3 Involvement of patients, parents or their organisations in the prioritisation of needs for clinical trials in children.

Results: Involvement of families or their organisations

Almost 85% of the applying CT Networks involve patients, parents or their organisations in at least one of the activities included in Criterion 6 (Public involvement).

In particular, 54.5% include the public in protocol design, 51.5% in the creation of protocol information packages, and 57.6% in the prioritisation of needs for clinical trials in children.

Moreover, 27.3% of these Network involve patients, parents or their organisations in all three criteria, 24.2% in two of the three criteria, 33.3% in just one criterion and 15.2% do not involve the public at all.

When taking into account the two most represented categories separately, it results that more almost 67% of member Networks involve patients, parents or their organisations in protocol design and in the creation of protocol information packages, while 72.2% include them in the prioritisation of needs for clinical trials in children.

Moreover, around 35.7% of Networks currently not qualifying for membership at Enpr-EMA declared to involve the public in the protocol design and the creation of protocol information packages, while almost 43% involve them in the prioritisation of needs.

Conclusions

It is sometimes assumed that involving families in making the informed consent material clearer is the closest patients, families and/or Patients Organisations (POs) can get to involvement in the design of clinical trials, but this report shows that much greater involvement is possible and is already practised by these organisations to some extent.

Public involvement is required by European Authorities.

The inclusion of patients, parents or their organisations in the Networks' activities as one of the qualifying criteria for membership in Enpr-EMA is just one of many examples within the European Medicines Agency, that includes POs representatives in their various Committees and working groups.

The fact that those Networks not qualifying as members of Enpr-EMA are also those that apparently have weaker links with patients is a fact that should not be taken lightly, especially if compared with the very different approach employed by Enpr-EMA member Networks that on the other hand more systematically involve patients and their representatives.

Making patients able to have a direct input in the design and execution of the trial, as well as in the prioritisation of needs, will motivate their participation.

In addition, a closer cooperation between researchers and children and/or their representatives as active research partners enriches the understanding of the medical condition and the outcomes.

There are many initiatives aimed at promoting and encouraging patient and public involvement in clinical research and many examples on how to make these initiatives successful: PENTA, MCRN UK, ECFS-CTN. These Networks prove that the involvement of the public does work.

The experience of ethics committees

Survey on the involvement of European ethics committees in paediatric research

The CT-Directive introduced a number of measures to harmonize the ethical review of clinical trials and facilitate clinical research. It required Member States (MS) to legally establish ethics committees, including obligations and specifications, formal procedures and timelines, composition and competencies. Specific provisions were also adopted for reviewing clinical trial protocols including children. However, due to the nature and legal force of a Directive, MS had some flexibility in implementing its provisions in their national legislation. Thus, ethical review procedures and the amount and quality of publicly available information vary significantly among European countries.

To evaluate the impact of the new European paediatric regulatory framework on the activities of ethics committees charged with reviewing paediatric research protocols, the TEDDY Network of Excellence and RESPECT set up an inventory of ethics committees existing in Europe and conducted a survey among them on their approach to paediatric trials. Replies were gathered from a total of 154 ECs (18.2%) operating in 22 countries; with a response rate below 10%, in 4 countries (Spain, Finland, Germany, UK) but exceeding 30% in 12 countries.

Themes that emerged:

ECs' knowledge of the European paediatric regulatory framework

Our results demonstrate that a gap exists between the current regulatory framework and ethics committees' awareness, knowledge and understanding of the major issues related to paediatric clinical research; only 14% of 139 ECs had discussed and analysed the most important European legal

instruments devoted to paediatric research. That could explain the lower response rate (73 ECs) answering the optional questions related to more specific issues.

Impact of the European Paediatric Regulation and European Ethical Recommendations

Overall, ECs recognized, as possible effects of the new European paediatric regulatory framework, the increased involvement of children in clinical research and, thus, an increase in the number of medicines tailored for children, as well as better-designed paediatric trials and more multicentre paediatric clinical studies.

When asked about the influences of the new regulatory framework on their work, around two-thirds of the 73 responding ECs reported no impact or low impact from the Paediatric Regulation or the European Ethical Recommendations and under 10% acknowledged a high impact.

This low impact was particularly true of ECs operating in EU-15 Member States (Belgium, France, Germany, Ireland, Italy, Luxembourg, Portugal, Spain, Sweden, and The Netherlands). In contrast, one-third of ECs in new EU MS (Cyprus, Czech Republic, Estonia, Latvia, Malta, Poland) declared a high impact of the Paediatric Regulation and most acknowledged either high or sufficient impact of the European Ethical Recommendations. These data suggest that ECs in the new EU MS are more actively involved in efforts for integration and harmonization towards EU research and health norms and systems than EU-15 ethics committees.

The major influences recognised by ECs were: the creation of new rules for reviewing paediatric protocols and sometimes changes in the EC organisation; increased quality and number of paediatric protocols and especially the increased time needed to review these protocols. Lesser effects included increased attention to paediatric protocols; increased facility to carry out paediatric trials; and the necessity to specify ethical requirements. It was also underlined that it is difficult to adapt information to parents and children in accordance with the new requirements.

Main issues to be dealt with by ECs

Looking at the opinions of ECs on the major issues to be dealt with under the regulatory framework, about half of our sample identified the increased need for additional expertise to evaluate paediatric protocols and for measures to minimize pain, distress and fear of children. It was stressed that there is still a lack of knowledge regarding the risks and burdens that are acceptable for children in different age groups.Complexity in evaluating inclusion/exclusion criteria, risk/benefit balance and consent/assent procedures were also highlighted as main concerns.

Training and networking for ECs

Only 30% percent of the 73 respondents indicated that they had participated in initiatives in the field of paediatric research and those who did mainly took part in conferences and, to a lesser extent, training activities. Moreover, a significant number of ethics committees operating in Europe showed interest in initiatives related to paediatric research, preferring means such as training at national and local level and networking among ECs. Debates and conferences (at the national level) and

educational initiatives supported by European institutions were also of interest. Three-quarters of those ethics committees interested in networking belong to the EU-15, while the remainder are established in new Member States (Cyprus, Czech Republic, Estonia, Latvia, Malta, Poland).

Conclusions

This survey demonstrated that there is a lack of knowledge of the European paediatric regulatory framework among ethics committees, and that their awareness of ethical issues related to paediatric research is limited, reflecting their low level of involvement in paediatric research, especially in terms of training, education and other similar activities.

Given that ECs are one of the most important actors in guaranteeing the safety, rights and well-being of children involved in clinical research, it is of primary importance to increase their competence and their involvement in paediatric research, and to promote the implementation of the European Ethical Recommendations at the local level. In this context, training and education in the field of ethics of paediatric clinical research should be an important objective.

Networking may be a fundamental tool to enhance collaboration and experiences and information exchange. It should be particularly important to promote these initiatives in the new Member States, where the number of clinical trials is increasing.

One possible relevant result of networking could be the development of a comprehensive guide practically addressing paediatric ethical issues in accordance with all the relevant international and European ethical and legal sources. This guide, chaired at the EMA level, should address all those specific ethical issues related to paediatrics: information/authorisation-assent process, paediatric expertise of ethics committees in charge of reviewing paediatric protocols (including training and education of the members of the ECs), use of placebo, compensation for damage, as well as other specific aspects to be considered in reviewing paediatric protocols.

Swedish Central Ethical Review Board interview

Background: the structure of Swedish ethics committees

In Sweden there is one Central Ethical Review Board, which was founded in 2004, and six regional boards, which are situated at the Universities of Gothenburg, Linköping, Lund, Umeå and Uppsala and at the Karolinska Institute in Stockholm.

These are independent authorities, divided into two or more sections that make decisions on behalf of the regional board. Each section is headed by a chairperson who is a judge or has been one. The sections have ten members with scientific qualifications and five members representing the general public. It is important that every application should be processed by members who have sufficient expert knowledge. The scientific members are therefore highly qualified. All members and their substitutes are appointed by the government. Each of the sections is expected to have 10-12 meetings annually.

Within each section, a scientific secretary is appointed from among the scientific members. Together with the chairperson of the sections, the scientific secretaries are responsible for processing cases and dealing with them.

Interview responses

In 2009, RESPECT interviewed the scientific secretary of the Central Ethical Review Board.

The respondent reported that the regional boards reviewed a combined total of 1125 applications for clinical trials in the period 2005-2007, but these figures are not divided into paediatric applications versus other applications.

The respondent confirmed that a paediatrician is a member of the committee and is always involved in paediatric application decisions, and also that the ethical review of paediatric research is preceded by a scientific review.

When asked which documents the Central Ethical Review Board refers to in its review of paediatric research, the respondent cited four statutes concerning the ethical vetting of research on humans but did not refer to the European Paediatric Regulation (Regulation (EC 1901/2006) or the 2008 European Ethical Recommendations (Ethical considerations for clinical trials on medicinal products conducted with the paediatric population).

The respondent could confirm that the committees never consulted an external patient organisation on an application for paediatric research.

Conclusions

This interview confirmed the picture of a lack of knowledge among ethics committees of the European paediatric regulatory framework. It also reflects the closed structure of ethics committees and their reluctance to include parties who could contribute to their work.

The experience of the pharmaceutical industry

Pharmaceutical industry interviews

RESPECT conducted four phone interviews with senior managers in the area of protocol feasibility and patient enrolment within both small and large multinational pharmaceutical companies.

Themes that emerged:

Transparency

The current moves towards increased transparency throughout the biotechnology and pharmaceutical industries regarding drug-development information are increasingly being accepted but companies vary in how they interpret this.

The two larger companies who responded represented best practice by posting information about ongoing and completed clinical trials on their website. They do not give patients the results about the

CT while it is still in progress but, when the trial is completed, a detailed report of the results is published on their website.

Information to participants

Since the fear of something unknown is the most frequent reason the parents express when they refuse to enter their child in a clinical trial, some sponsors attempt to expand parents' knowledge by providing in-depth information material about the products they are developing and what the CT will involve, for the investigator to give to the parents of participating - or prospectively recruited - paediatric patients. They want to ensure that physicians and patients have access to all relevant information.

One interviewee stressed that they strive to find the best-qualified and fully engaged investigators with a broad spectrum of knowledge and strong commitment. They consider these qualities in a physician to be extremely important in order to assure the patients' and their parents' best interests.

Willingness to participate

Several of the companies we contacted develop drugs targeting rare diseases. They acknowledged that, because of this, they do not usually have problems recruiting paediatric patients. In the case of rare diseases, there might be no existing medicines, or only 'good but not great' medicines that the parents assume could be substituted by new, more beneficial drugs provided through clinical trials. Furthermore, the interviewees indicated that many of these families, after the child has participated in a trial, report that they would do it again if asked; the inconvenience (such as time off school and work) is not a major problem to them, since they will gladly go to great lengths to help towards finding a cure for their child's disease.

In the event that these companies do not get enough recruits to continue the clinical trial, they try to make the reluctant parents understand the beneficial input they would make by entering their child in the study.

Education

The improvement of public awareness about clinical research was stressed by one interviewee. This large, multinational company works with non-profit organisations and the media to broadcast a positive message about clinical research. They support events such as the AWARE for All Clinical Research Education Days, live webcasts run by the Center for Information and Study on Clinical Research Participation (CISCRP), USA. The aim is to educate the public and widen knowledge about clinical trials and the positive aim of clinical research.

Patient organisation involvement

Patient organisations (usually for orphan diseases) provide pharma companies with lists of their members' unmet needs for treatment. One respondent confirmed that the company's R&D department consults such lists.

One company reported actively consulting patient organisations when designing clinical trials, for example to seek their opinions in candidate drug selection, whereas other companies merely expressed an 'open attitude' to strengthening their relationship with patient organisations. One respondent representing a larger company had not considered this possibility and was hesitant, as it would imply creating policies for guidance and an understanding of what the company's role should be. They have never had any suggestions or other involvement of patient organisations.

A company providing regulatory advice on Paediatric Investigation Plan (PIP) submissions reported that there has never been a situation in which a patient organisation requested access or input into a PIP; if that should happen, they would have to get approval from the pharmaceutical company.

At the other extreme, a respondent representing another large pharma company had an interesting case study illustrating the attitude of the company in general to relationships with patients groups:

A few years ago they acquired two smaller pharma companies with a lot of experience of oncology trials, which this company lacked. Thus, they decided to consult with all the different stakeholders, from top leaders in oncology, economists to patient groups for both common and rare cancers. They wanted to find out what are the current big issues in cancer research and standards of care. The patient groups gave feedback about their wishes, which was new and unexpected for the company:

1. a desire to get more information about what research is in the pipeline of pharma companies;
2. hopes for improvements in the experience of patients participating in clinical trials;
3. interest in involvement in protocol design

This company has now created a board to look at a way forward to address such issues and it includes a patient group representative. The board recognises there is a role for patient involvement but that it needs to be carefully designed. It requires that the people who are given this role be knowledgeable, and it requires there to be assurances to researchers that there will not be too much interference or multi-source input delaying the research process (which, the interviewee felt, is already painfully slow).

Regulatory issues

The Paediatric Regulation (EC 1902-2006) brings the obligation to conduct a paediatric clinical trial unless a waiver is obtained. A Paediatric investigation plan (PIP) has to be submitted to the Paediatric Committee once adult pharmacokinetic (pk) data are available.

The paediatric needs assessment lists compiled by the EMA-PEG group did not actually address unmet needs for treatment but rather a 'top-down' assessment of which existing drugs urgently need efficacy/safety studies for paediatric authorisation and labelling. The assessment procedure explicitly excluded the identification of priorities with these lists. One interviewee pointed out that the increased

number of clinical trials required by the Paediatric Regulation also diverts resources from adult clinical trials, which is unfortunate if some of these paediatric trials would otherwise qualify as low priority.

Inclusion of patient-reported outcome measures in the protocol

Many pharma companies include quality of life as an endpoint (outcome measure) in their clinical trials; indeed, this is necessary in many EU Member States in order to get reimbursement from their customers. For example, the UK National Health Service is more likely to buy a company's medicinal product if they can show that they have followed the NICE guidelines on health technology appraisal, which includes a criterion of documented improved health-related quality of life (HRQoL) for patients using the candidate drug. This requires the development of patient-reported outcome measures.

Reducing the burden on paediatric participants

Although equipoise is the basis for all clinical trials, one interviewee commented that the sponsor would generally be relatively confident already that their new drug is likely to be an improvement on the standard care, based on the results of trials in adults, and the fact that in many cases there are no tested paediatric medicines already available for the condition in question (in which case, an increased burden is acceptable in relation to the burden of taking drugs not tested on children).

One interviewee mentioned the emerging use of adaptive design methodologies, in which patients can be switched to another arm in the course of the clinical trial if they were assigned to an arm (e.g. a particular dose) that is proving ineffective. This involves the intervention of a data monitoring committee to unblind the study. The clinical trial may include interim analysis, whereby early assessment may be made, although some health authorities and ethics committees are not in favour of this.

The interviewees were asked about pharmacokinetic/ pharmacodynamic (pk/pd) modelling and simulation and they indicated that their companies increasingly use these techniques. If this type of simulation is run, the number of patients entered in a pk/pd clinical trial could often be reduced to around 50 children, relieving the burden on individual sick children and on the CT team recruiting participants to the trial.

Conclusions

It should be pointed out that pharma companies lacking a strong patient focus were less likely to agree to be interviewed and it was generally difficult to make contact even with companies who appeared to have admirable practices, judging from the materials they made available in the public domain, because of standard corporate policies about protecting company-confidential information.

Our interviews gave a snapshot of pharma companies with a commitment to facilitating patients' participation in paediatric clinical trials. They are aware of the importance of keeping families informed and reducing the burden for the child, but they still have to improve their contacts with patient organisations, for example in allowing them to contribute by reviewing the CT protocols.

Main conclusions from the RESPECT findings

Many of the parents we interviewed saw the trial as a way to get the latest and best medicine for their child (thus misunderstanding the principle of equipoise that is fundamental to clinical trials). Both children and parents were surprised to find that some of the procedures were painful.

Paediatricians reported that parents did not always understand the difference between clinical trials and regular treatment. They felt that many parents did not see the importance of medical research and did not always have an altruistic attitude. Longer-term participants are no longer able to identify differences between their normal treatment and the clinical trial.

When faced with the decision to participate, families identified a need to trust the doctors and nurses as a motivation for participation.

However, other parents saw themselves as research partners in the trial and wanted to feel that their input was valued, although they did not always feel that their contribution was appreciated sufficiently. They wanted to receive the study results but several paediatricians confirmed that they do not inform parents about the results unless specifically asked.

Several patient organisations reported that they were ill equipped to give input on which trials and which outcomes have the highest priority for their members. This is something that could be improved through surveys of their members as a basis for contact with pharma companies.

We found good examples of trials where patients felt empowered to make valuable contributions. We also found patient organisations giving input into trial design and protocols, helping to define outcome measures and to recruit trial participants, as well as pharma companies making their trial results accessible to all via their website.

It is important to ensure that families understand the need for research and are respected for their valuable contribution to the improved safety of medicines for children.

Potential Impact:

The project has contributed towards the impacts listed in the original work programme. The major impact of this project has been on the promotion of clinical trials for the development of innovative medicines to improve child health and treat paediatric diseases. We have identified areas of cooperation between different partners in the clinical trials landscape which will help to make clinical trials more effective and thus encourage greater innovation and industry development.

This project has created the possibility of cooperation wherein greater participation in clinical trials will be achieved through identifying the RESPECT tools and mechanisms required to empower patients and promote a debate on the benefits of biotechnology.

The project has advanced our understanding of how to more efficiently promote good clinical practice in clinical trials research through various debates between different actors within this field.

The lack of participants in clinical trials research, especially children, has been a major bottleneck to the development of new medicines. Improved competitiveness of the European-based pharmaceutical industry through releasing this bottleneck has been addressed at various meetings.

The project has lead to the development of a set of norms and standards for clinical trials, which in its turn will lead to the accelerated development of new or improved medicines for child diseases.

The project has had an impact on improving links between research organisations, patient representatives and industry.

Account has been taken of other national or international research activities in this field through the broad networking with the partners. The RESPECT partnership has been able to take advantage of the close link to other networks within the European framework and this has ensured that all our discussions have been included in the debate on needs of the paediatric clinical trials participants. Working closely with other network projects and with our approach to a broad membership of the dissemination workshop in Brussels which was held at the end of the project has ensured the high impact of the project.

Through close contacts with patient organisations and through the projects web page the project has encouraged an informed societal debate on the benefits and risk of participation and the eventual benefits of an improved biotechnology industry.

The educational packages and decision aid which have been developed are made available through our dissemination activities and through the web site. These will encourage further research and development in this area and ultimately greater participation of people in clinical trials research. The project has taken a European (rather than a national or local) approach which has made it possible for the project to address the concerns of patient needs in a research are that is increasingly European. It is only at the European level that legislation can be effective in changing the way that clinical trials will be carried out. It is only at the European level that requirements can be set for industry and we can develop a broad based strong clinical trials landscape which will promote innovative medicine development in Europe. This will form the basis upon which the industry will grow. This is particularly true for the small to medium sized businesses who will, due to the need to minimise risk capital, want to stay within the European framework.

The positive impact of information sharing.

According to the recent Eurobarometer survey in 2006, one in two Europeans believe that biotechnology will improve their quality of life. The survey showed widespread support for medical and industrial applications of biotechnology therefore the situation has been ripe for the promotion of increased participation in clinical trials. The positive impact of the RESPECT project will be seen as the debate on the benefits and risks of participation between different stakeholders will identify the benefits and risk of clinical trials participation.

All centres have been strongly encouraged to work in partnership with local and national research groups and companies involved in clinical trial research. This liaison has enhanced an important consultative role for several partners.

The methodology and requirements for generating empowerment have been identified and the RESPECT project has developed professional materials such as a book, decision aid and training packages that will ensure that individuals and those professionals who work with clinical trials have the opportunity to utilise the projects findings.

A European dissemination conference was hosted by the project to ensure dissemination to policy makers, service providers and service users. In addition, the production of training packages, together with the RESPECT website has provide a wider dissemination of the issues.

The results of the RESPECT project has been published in the literature and will continue to be the basis of further publications. RESPECT will maintain a website after the project has ended so that it acts as a reference database for others working in the same field.

Maximum use has been made of Community/International Clinical Congresses to discuss the outcomes of the study and to disseminate the results as widely as possible to all within the European clinical trials landscape.

All partners have contributed throughout Europe to the dissemination information about the project and its results at conferences and seminars.

Contribution to standards

The aim of the project has been that the results will contribute to international standards of good clinical practice in clinical trials with children. This will be further encouraged through our publications.

Contributions to policy development

The project results have, via the dissemination activities, fed into the development of policy in this area. As the impact of the new regulations of the testing of medicines for children takes effect policy will also need to be developed. The project has been timely in that the results are able to inform and influence the development of those policies throughout Europe. Comments were sent to the rapporteur at the Commission concerning the concept paper for public consultation on the revision of the clinical trials directive 2001/20/EC.

This project has contributed to the coordination of high quality research by going beyond the current state of knowledge and identifying the needs and motivations of children and their families when participating in clinical trials. The project has drawn together different actors in an open debate on the how Europe can be more encouraging to the participation of children in clinical trials. The project workshops have been open to everyone in the field and this has meant that greater networking could be possible. Together with the partners in the project who represent both the research side and the patients side of the debate a stronger and more fruitful coordination with different actors having an equal role has been realised. We believe that the project will continue to benefit the work programme by being able to support the health theme across a number of areas. The results will be directly implemented by the clinical partners. This will have a snowball effect as the benefits of the approach become evident. The results will be applicable to all medications and all medical conditions. The results will also be transferable to adult clinical trials as the relevance of the needs approach and empowerment of the patient will be applicable to the adult patient groups.

List of Websites:

http://www.patientneeds.eu

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