



UPPSALA
UNIVERSITET

Uppsala Universitet

Beyond Informed Consent

Educating patients to empower them in the clinical trial process

Andrea Sandberg

Degree project in Biomedicine. Master's thesis (One year), 2010

Examensarbete Biomedicin, 30 hp magisterexamen, 2010

The Institute of Clinical Science, department of Pediatrics', Queen Silvia Children's hospital,
Sahlgrenska academy, University of Gothenburg

Supervisor: John Chaplin

TABLE OF CONTENTS

1	NOTE TO THE READER	3
2	ABBREVIATIONS	3
3	DEFINITIONS	4
4	ABSTRACT	5
5	INTRODUCTION	6
6	LITERATURE REVIEW	8
	Off-label prescribing in general paediatric practice	8
	Paediatric physiology	8
	Adverse drug reaction	11
	New paediatric research initiatives in the European Union	12
7	OUTLINE OF THE RESPECT PROJECT	16
	Thesis outline	17
	Potential outcome	18
8	METHOD AND INSTRUMENTS	19
	Part 1: Literature review	20
	Part 2: Development of educational material	21
	A: Identifying possible training needs in order to develop educational material	21
	B: Adapting and evaluation of educational material to panel groups – a pilot study	23
9	MAIN PROBLEM FOR THESIS OUTLINE	24
	The process of informed consent	24
	Recruitment of patients in paediatric clinical trials	27
10	RESULTS	28
	Part 1: Identifying possible training needs in order to develop educational material	28
	Part 2: Evaluation of the educational material in panel	36
11	DISCUSSION	42
	What might be considered in the future RESPECT project?	48
12	CONCLUSIONS	48
13	REFERENCES	49
14	APPENDICES	53
	Appendix 1: Short presentation of aspects explained in the educational material	53
	Appendix 2: Power point presentation used as educating material	54
	Appendix 3: Questions for interview	71

1 NOTE TO THE READER

The *RESPECT patient needs* project does not intend to find ways to convince parents to consent to their child's trial participation in a clinical trial, but rather to investigate the needs that underlie the informed consent process in order to empower them in their voluntary choice.

2 ABBREVIATIONS

Abbreviation, acronym or specialist term	Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
CRF	Case Report Form (paper)
EMA	European Medicines Agency
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
PIP	Paediatric investigation plan
PUL	Personuppgiftsagen
RESPECT	Relating Expectations and needS to the Participation and Empowerment of Children in clinical Trials
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
WHO	World Health Organization

3 DEFINITIONS

Clinical trial	The term clinical trial will be used here for the controlled evaluation of new medicines on humans. Medical devices will not be included.
Candidate drug	Used to denote the treatment that will be evaluated in the trial
Investigator	The term investigator will be used to denote the clinician in charge of the clinical trial
Off-label use	The practice of prescribing pharmaceuticals for an unapproved indication.
Standard treatment	The term standard treatment will be used to denote the established treatment in comparison to the candidate treatment
Patient	The term patient will be used here to denote an individual enrolled in a trial, whether or not they are being treated for a medical condition.

4 ABSTRACT

The purpose of this report is to identify the means by which medical researchers can improve their respect for the interest of their clinical trial participants and how they can motivate families in their participation in future clinical trials.

As a result of the European *paediatric regulation*, there is a growing need for paediatric trial participants. However, no statistics show any increase in numbers of paediatric clinical trials, which is why we need to explore new empowering methods to stimulate the development of drugs for use in children.

Issues related to the paediatric informed consent process in clinical research have reached professional attention. Taking needs and motivation of paediatric patients and their parents who will or have participated in a clinical trial as a study case, this report found some important factors that might contribute to the willingness to participate. The results also show that part of the information in the informed consent process is not always absorbed by the parents or has not been provided correctly during the process.

Finally, based on these findings, additional education to the informed consent process as an empowering method was developed and evaluated in pilot panels. It is my belief that, even though the informed consent process is strictly regulated to enable the consentor to make a voluntary decision, human factors such as the clinician's ability to provide information and the stress in taking a decision within limited time that concerns a child might complicate the consenting process. The conclusions are that some defined groups of parents might need or appreciate additional education about clinical trials and that it will be able to work as an empowering tool to be able to make an autonomous decision. However, substantial research in this area is needed in terms of defining which groups of parents may benefit from education as an empowering tool when considering consenting.

5 INTRODUCTION

It takes about 15 years and millions of dollars to evaluate a drug treatment and apply for market authorization for adults (Joseph, A DiMasi, Ronald, W. Hansen, Henry, G. Gabrovski, 2002). Today's requirements involve extensive human clinical research in order to gather the safety and efficacy data that is summarized on the product information leaflet. However, running clinical research trials in children is less common than in adults and as a result, drugs are frequently prescribed in the absence of specific recommendations for paediatric patients (MHRA, 2010).

The number of off-label drugs prescribed to children in Europe is today estimated to be ~50% of the total drug usage (Giovanni Tafuri et al, 2009). This means that every second drug that is offered to a child has no documented data that guarantees safety or efficacy and no user recommendations that suggest what dose would be the most beneficial and how often the drug should be administered. Because children are considered to be a vulnerable group, exposing them to the risk of clinical research has been thought to be ethically unjustifiable and dangerous and hence, efforts have been made to protect them from the possible harm of testing new medicines (Wagner, Martinez et al. 2006). It was not until the mid 1950's, when the discipline of paediatric research recognized several physiological differences between children and adults' susceptibility, that the strict attempts to limit paediatric clinical trials were brought into question (European Commission 2008). Treating children with drugs based on data derived from trials only performed in adults was now considered dangerous. The whole discussion reflected a moral dilemma between protecting children with clinical trials or from clinical trials (O'Lonergan and Milgrom 2005).

The strict ethical concerns heavily restricted clinical trials in children, this is why almost every child when hospitalized is using at least one off-label drug, which is the cause of increased adverse drug reactions, and a more frequent appearance of drug-related deaths (TEDDY 2010).

The history behind the special requirements of documentation over drugs in development has its roots in the catastrophe of Thalidomide, when newborn children were diagnosed with severe

irreversible peripheral neuropathy. Thalidomide used as a sedative drug, also effective against coughs, colds, headaches and morning sickness was found to be a teratogen drug, crossing the placenta barrier and harming the developing fetus. The American Food and Drug Administration (FDA) thereby introduced a new law in an attempt to protect people from severe unintended drug reactions and it was enacted in America in 1968, followed by several different countries. It required the drug manufacturers to prove quality, safety and efficacy in a clinical trial in order to obtain a license that grants a Marketing Authorization. It is now necessary to present all important information in a SPC that includes clinical indication, dose recommendations, age recommendations, method of administration and precautions (Powell and Gardner-Medwin 1994),

It was not until 1997 that a new regulation, introduced by FDA, came into force to support paediatric labeling. This established that all drugs, whether under development or already on the market, must be studied in paediatric patients if they could be prescribed to children. The clinical trial studies have to show the safety and efficacy data in order to receive a Marketing Authorization. European clinicians, who were reliant on the established documentation, frequently used the new recommendations that were developed from clinical trials in the U S. However, in January 2007, the European Union introduced the *paediatric regulation* requiring all applicants applying for Marketing Authorization to provide a paediatric investigation plan (PIP) describing how to clinically test the selected candidate drug in paediatric patients. The aim of the new regulation was to strengthen the health of European children and, since the plan is legally binding, having a PIP rejected will result in the new drug not reaching the market.

The gap between the number of drugs being marketed for paediatric patients and drugs in need of authorization has led to the situation where the clinicians need to extrapolate and experimentally decide dosages for children without having evidence for what effect it might have in children due to their organ development (John, Hope et al. 2008), (Neubert, Wong et al. 2008).

Today there is therefore an established need for new effective paediatric drugs, fully documented and authorized for paediatric use. The paediatric regulation promises to increase trials for children and to be able to meet these expectations, there is a demand for an increase in the number of paediatric trial participants.

6 LITERATURE REVIEW

Off-label prescribing in general paediatric practice

Drug usage without an approval will be defined in terms of either an *off-label* drug e.g., a drug with marketing authorization but used for a non-approved indication outside the terms of product licensing, or as an *unlicensed* drug without an authorization for paediatric use.

In Europe, no drug can be marketed for human use without a Marketing Authorization approved by a capable authority in a member state or by the European Commission. The Authorization guarantees that the drug has been tested in a clinical trial where the researchers document the safety and efficacy parameters and determine proper dose intervals (Raine 2009). The information is added to a label or leaflet accompanying the product summary of product characterization (SPC) describing appropriate drug dosages, how the drug will be administered, for what ages the product is intended, etc. (Läkemedelsverket 2010). This description aims to guide clinicians and patients to use the drug as effectively and safely as possible, offering the most adequate therapy.

Children represent 25% of the European population. Yet, a considerable proportion of paediatric drugs at the hospitals are prescribed off-label (Neubert, Wong et al. 2008) (FDA 2010), (Kimland 2006). Approximately every second drug used in paediatric therapy is not guaranteed to be safe or effective in use for the particular clinical indication.

Paediatric physiology

Paediatric medical healthcare differs from adult healthcare. When prescribing off-label drugs, clinicians have to consider that children, because of their stage of organ development, do not always respond to a drug in the same way as adults do. This is the reason why it is impossible to use information obtained from adult trials for paediatric labeling information and it leaves them no choice but to experimentally test the drug's suitability in order to develop an effective treatment.

The pharmacodynamic and pharmacokinetic properties are different in adults and children and, for a majority of drugs, a relationship between these factors exists. The pharmacokinetic properties

fluctuate during organ development and that is why it is of therapeutic value to understand and be aware of these changes when developing new drugs (Sumner Yaffe 2000).

Not only do adults differ from children, the paediatric population should not be considered as a homogenous group. These individuals are in various stages of development and do not have the same physiological prerequisites. They range from preterm to neonate, to infant to child and finally to adolescent. This may result in efficacy differences within the paediatric group, due to changes in organs and body tissue. In addition, drugs labeled for adults are applicable in almost any adult, which is not the case for children, for whom the effect of a drug dose might vary depending on the illness.

Drug absorption, drug distribution and protein binding

The absorption of a drug depends on different factors, such as gastric pH; gastric and intestinal transit time, the surface of the gastric compartments and the microorganisms and enzymes building the gastric flora (Sumner Yaffe 2000). In newborns (the first 24 hours) the gastric acid is generally lower than in slightly older children, as well as gastric emptying and intestinal transit time. In combination with gastric reflux, known to be frequent in neonates, administering drugs orally might result in irregular absorption. Both neonates and infants have an undeveloped peristalsis, which will increase the absorption of the drug. Considering the underdevelopment of their lungs, lack of anal sphincter muscles, decreased skin thickness, but also reduced muscle tissues, gastrointestinal enzymes and microorganisms, the pulmonary, rectal, percutaneous and subcutaneous administration of drugs needs to be clearly and carefully observed to avoid a decrease or increase in absorption (Sumner Yaffe 2000) (Virginia Poole Arcangelo 2006).

In a child's body, six different factors might interfere with the way the drug is distributed: the tissue mass, the blood flow, the membrane permeability, the body composition, the route of administration and the degree of binding to proteins all influence the distribution in different body components. Small children have a decreased fat mass while having a higher amount of water compared to adults. The water-fat ratio changes during development, altering the water-lipid ratio, changing the volume of distribution (Vd), which affects the pharmacokinetics of some drugs.

For instance, amino-glycosides require special administration because of a higher Vd and are therefore given in a larger dose to infants than to adults to get the same efficacy.

Tissue binding characteristics and physiochemical properties also alter the efficacy of a drug.

Most medicinal products are bound to intracellular components but distributed evenly into the whole body due to extra-cellular fluid. As is often seen, the variation of receptor affinity differs with age due to the differences in the amount of extra-cellular fluid. Infants seem to have more permeability in the blood-brain barrier, which allows a higher distribution of some medicinal products that can be dangerous when treated with antibacterial drugs. The plasma proteins' method of binding the extra-cellular components depends on the amount of the proteins and the affinity to the receptor, directly affected by the condition of pathophysiology as well as the different concomitant usage of drugs. In infants, the affinity to the albumin is lower than at any other age, consequently resulting in a lower drug affinity.

Metabolism and excretion

Clearance is a factor mainly dependent on the hepatic metabolizing system. The changes during development affect how drugs are broken down in the paediatric patient. The two metabolizing phases of the liver, oxidation, reeducation and hydrolysis (phase 1) and the conjugation reaction (phase 2), have a delayed function in children which can cause drug toxicity. Scientific studies show there might also be a difference in the cytochrome-p450 system as a part of the phase 1 metabolism. There might be an Iso-form developmental difference in both phase one and phase two drug-metabolizing enzymes (Sumner Yaffe 2000). The metabolism is affected by the size of the liver as it develops during childhood. The volume of the liver relative to the size of the body decreases from birth onwards, which explains why it is rapid during infancy and early childhood in comparison to adults. To eliminate the drug, the body often uses the kidneys or bile because the glomerular filtration and tubular secretion have not reached their full capacity until the child is around seven months old. To achieve safe paediatric health care, medical research must endeavor to keep in mind the development of children's organs, the short and long-term effects that might occur and the effects on chronic, underlying or concomitant diseases during treatment.

Apart from the fact that children develop during childhood, another factor supporting the requirement of trials in children is that formulations suitable for adults might need to be adapted for children. To administrate drugs to a child might not always be as easy considering their problems with swallowing big tablets. When you divide the tablet, it might result in decreased precision. Furthermore, crushing medicines makes them taste bad and the child ends up not taking his/her treatment (Edwards and Omar 2008), (Virginia Poole Arcangelo 2006).

Adverse drug reaction

One of the most important aspects when conducting a clinical trial on children is to determine whether the candidate drug is as effective as in adults without any major safety issues. When safety is compromised in a patient, expressed as an *adverse event* with or without association to the candidate drug (adverse drug reaction), the occurrence has to be reported to the Ethics committees and the Pharmacovigilance register, which records all reports, and to Regulatory Authorities (EMA 2007). There are different kinds of drug-reactions that will be defined depending on the type of reaction. The definition that is used to facilitate assessment of a possible adverse drug reaction, according to ICH guidelines (E2A) concerning the pre-approval clinical experiences with a new medicinal product or a new user (such as a child), is: “*all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions*”. The phrase refers to a medicinal product and means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

- For medicines with a marketing authorization, an adverse drug reaction is defined as “*a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function*”

- An unexpected drug reaction is defined as “*An adverse reaction, the nature or severity of which is not consistent with the applicable drug information (e.g. Investigators Brochure of an un-approved investigational medicinal product)*”.

The study drug might not cause an adverse event and it is therefore very important to examine the relationship. It is in the practice of a physician to judge the causality, (expected, unexpected) and the severity to explain the intensity of a reaction. When judging the adverse event, if it is suspected

to be caused by the candidate drug, this might become a reason to make significant changes in the drug development. This might be true in the case of a life-threatening situation or death. The level of seriousness of a drug reaction, serves as a guide for defining regulatory reporting obligations (EMEA 1994).

Adverse drug reactions due to off-label prescribing

Statistics show that adverse drug reactions in children are more often associated with the off-label prescription of drugs, typically at lower doses than in adults. A major concern dealing with adverse drug reactions in children is the effects on the growth and developmental process. Different conditions are associated with adverse drug reactions in children, such as: hepatotoxicity, increased risk for Reye's syndrome, tooth-discoloration and skin reactions, growth reactions and "grey baby syndrome" (McIntyre, Conroy et al. 2000).

When summarizing several different surveys, the use of off-label or un-licensed drugs tends to be associated with a more frequent incidence of adverse drug reactions than using drugs prescribed for the right indication (Sammons, Gray et al. 2008), (Ufer, Kimland et al. 2004). Adverse drug reactions are a major cause of hospitalization and have resulted in drug-related deaths in the paediatric hospital setting. Still, it is reported that every second adverse drug reaction might be preventable (Easton KL 1998; Samoy, Zed et al. 2006). The frequent appearance demands more careful risk-benefit analyses when prescribing a drug to a young person, facilitating the documentation of ADR and improve safety of medicines in pediatric health care by conducting adequate clinical trials adapted to children.

New paediatric research initiatives in the European Union

Great efforts have been made to protect children from participating in clinical trials. As vulnerable group they have always been considered as most entitled to protection and until the mid 1950s, exposing children to clinical research was considered as ethically unjustifiable. The idea of using children as "guinea pigs" in medical research created a wall of protection, which has led to the

situation today with an insufficient number of suitable medicines for the treatment of childhood illnesses.

It was not until the discipline of paediatric research found physiological differences between adults and children that an ethical discussion arose, recognizing differences between children and adults in terms of drug affinity. This called into question the idea of protecting children from clinical trials and suggested it was unethical to expose children to drugs only tested in adults. Since then, a moral dilemma surrounds protecting children from clinical trials versus protecting them through clinical trials (O'Lonergan and Milgrom 2005).

In 1994, an effort to increase medical research in the paediatric population was made. The Food and Drug Administration, FDA, was questioning whether data based from drugs tested in adults was applicable to guarantee the same safety and efficacy for children. The regulation required the drug manufactures, already producing marketed medicines for adults, to review the data that was collected from adult trials, in order to judge if it was adequate to permit the same recommendations in children and adolescents. If the data was judged as valid, the manufacturers were encouraged to modify the labeling to indicate that the product was applicable even for paediatric use. If, however, they judged that the data was not adequate for this assumption, the regulation required that the following supplementary information was added to the old label: *“safety and effectiveness in paediatric patients have not yet been established”*.

However, the review was voluntary and no notable labeling change was observed, which pushed the FDA to finalize *the Paediatric rule* in 1997. The *paediatric rule* made drug labeling mandatory by establishing that all not-yet-approved drugs must be studied in children and asserting the authority to require pediatric studies for currently marketed new drugs. *“However, manufacturers may obtain waivers from the paediatric studies requirement if the product (1) does not represent a meaningful therapeutic benefit over existing treatments for paediatric patients and (2) is not likely to be used in a substantial number of paediatric patients”* (BIO 2009).

The paediatric recommendations attained from clinical trials in the US were applied in European health care and used as standard recommendations by European clinicians since the European

Union had no mandatory requirements for pharmaceutical manufacturers to investigate new drugs for children (Neubert, Wong et al. 2008).

However, since 1997, the situation in Europe was that the use of drugs not applicable in US and the need to develop new drugs for children in Europe resulted in moves to strengthen the legislation on paediatric medicines in Europe. In 2002, the result was presented in a European guideline '*Note for guidance on clinical investigation of medicinal products in the paediatric population*' (ICH Topic E11).

New directives in good clinical practice regarding children's safety in clinical research were forced in 2004, followed by the release of a draft document "*Ethical considerations of clinical trials in children*" by the European Commission (EG Enterprise and Industry) in 2006. After a period of consultation, a regulation was proposed in 2000, and published in 2007: Regulation (EC) No 1901/2006 and the amending Regulation (EC) No 1902/2006 (EMEA 2007)(Agency 2008). The legislation requires that all new or existing drugs have to be tested in children in order to generate paediatric data that will be specified on the drug label. For drugs not appropriate for children, or for which no effect or serious adverse drug reactions are expected, the manufacturer may apply for a waiver.

The legislation for clinical trials in the paediatric population aims to improve children's health by:

- increasing high quality, ethical research into medicines for children
- increasing availability of authorized medicines for children
- increasing information on medicines and achieve the above without:
 - unnecessary studies in children
 - delaying authorization for adults

PIP: paediatric investigation plan

To assure that necessary data is obtained, a paediatric investigation plan, PIP, must be generated and accepted by the Paediatric Committee PDCO. The plan should follow the normal Marketing Authorization Application and, if not approved, the study drug will be rejected, leading to loss of profits and time. The PIP is a legally binding plan which should include information on how to clinically test the study drug in children (Consultancy 2007). In addition, the PIP should contain information about different formulations for children to facilitate treatment for children. The

paediatric investigation plan will preferably be applied in the end of phase I trials and submitted to the Paediatric Committee no later than after completion of the pharmacokinetic studies in adults. It should specify the measures that will be conducted to assess safety, quality and efficacy parameters in paediatric patients and all additions as mentioned in ICH E11 (EMA 2001).

If the plan does not fulfill the requirements for a valid application and qualify for the financial incentives provided by the regulation, a request is sent for re-examination.

Drugs that came on to the European market prior to the authorization requirements of the EC Pediatric Regulation of January 2007 have to demonstrate results from studies conducted in children in compliance with the pediatric investigational plan, unless a waiver has been granted.

Marketing authorization rewards

The regulation, Regulation (EC) No 1901/2006, also contains incentives for companies to develop medicines for use in children (EMA 2001). This functions as a stimulation to reward the industry to conduct paediatric research, giving the medicinal product a predetermined extension of its patent protection, as long as that the medicinal product is authorized in all Member States and relevant information from the studies is incorporated into the SPC. Whether or not the paediatric data is positive or not, the extension will be granted. The reward concerns medicines under development and authorized products irrespective of the existence of a supplementary protection certificate or patent. A new drug without Marketing Authorization and products covered by a patent will receive a six months patent protection if the PIP is approved.

7 OUTLINE OF THE RESPECT PROJECT

The scientific and ethical issues are complex, advanced trial designs offer poor profitability, and lack of motivation for children and their families to consent to the child's trial participation complicates the recruiting process. Therefore, new methods to recruit and keep young people in trials are essential.

To meet the needs of patients, the European research project RESPECT, led by the Institute of Clinical Sciences at Sahlgrenska Academy at Gothenburg University, Sweden, aims to identify the needs and motivations of children and their families who have participated or might participate in clinical trials. The project hopes to establish what factors empower children and their families to consent to participation.

The Project has two objectives;

- First, to clarify the expectations and needs of children and their families who have participated or who might participate in clinical trials for new drugs in Europe.
- Secondly, to identify methods by which the expectations and needs can be translated into empowering and motivating participants' in future clinical trials research

Stage 1: The project established a basis for coordination and harmonization. This involved a literature search and a preliminary workshop and the creation of a website for communication within the project and with a wider audience.

Stage 2: The project is grounding the diverse experience and knowledge through benchmarking good practice case studies and collecting opinions from patients' organizations in Europe. The result will be presented at an expert harmonization workshop composed of all partners of the project. This workshop will identify the operating procedures needed to encourage empowerment and increase motivation for participation in clinical trials.

Stage 3: The project will present its results in a series of European workshops and conferences. This will help to improve translational research, which depends upon the clinical trial process being undertaken with sufficiently large populations to ensure the safety and efficacy of new products.

The RESPECT project is exploring ethical issues raised by children's participation in clinical trials by gathering information, insights and suggestions from different groups such as support organizations, patients groups and families to young patients (RESPECT Project Outline, 2008).

Thesis outline

This Master's thesis will be a part of the RESPECT project. It will examine the means by which medical researchers can improve their respect for the interests of their clinical trial participants and can motivate families in their participation in future clinical trials.

As a background to this Master's thesis, the foundation of today's paediatric research has been examined and three questions have been identified:

- Why do we need paediatric research?
- What has caused the low frequency of paediatric trials in Europe?
- What has been the response to the current situation?

These questions are derived from the literature review of the Master's thesis.

The sub-project Beyond Informed Consent will run in parallel with work being carried out by German partners. One purpose of this thesis is to develop an educational material based on good clinical practice, with focus on understanding of randomization and equipoise. The idea is to empower potential paediatric clinical trial participants and their parents to make informed decisions about participation in a clinical trial. The educational material will consist of written materials, a short presentation and discussion topics. To be able to construct the material, identification of different needs will be explored in order to find a suitable method to empower the participants and their parents.

As a part of this EU-project, it has been decided to run pilot panels composed of teenagers, clinicians and nurses who will evaluate the material. The results from the pilot panels will be used to further develop panels in the future, collecting and establishing the means to help medical researchers to motivate, according to good clinical practice, paediatric trial participation. The results will also suggest improvements to the informed consent-process and thereby, the development of medicines labeled for the paediatric population.

Potential outcome

The potential outcome of this Master's thesis would be to consider educational material as an addition to the informed consent process in order to empower patients and their parents to be more meaningfully involved in the informed consent process in future trials.

8 METHOD AND INSTRUMENTS

In this Master's thesis work, comparative methods have been used to analyse by which means medical researchers can improve their respect for the interest of their clinical trial-patients, especially in terms of how to motivate the families of children, parents or legal guardians, in their child's future clinical trial participation. As proposed in the project outline, education implemented in the consent process is considered as a possible method to empower the parents, which was primarily evaluated in this thesis.

To be able to analyse the objectives, several questions were proposed from the RESPECT project:

- *Is standard informed consent enough?* The ethical implications, issues and needs when in a position to consent to paediatric trial participation was analysed from the literature and from interviews with parents and patients, as well as from clinicians and nurses.
- *Do people understand randomization and equipoise?* The understanding of equipoise in randomized clinical trials was analysed from publications and from interviews with parents of children in clinical trials and from the clinicians' and nurses' point of view.
- *What factors affect willingness to participate?* The evidence from the literature review was listed and clinicians, nurses and teenagers gave their thoughts on the subject.
- *What are the main concerns about participating in clinical trials?* This was discussed in teenager-groups after being educated about clinical trials. The issues and advantages were explored in group-discussions and an interactive questionnaire, together with available publications on what trial participation involves.

- *Can educational material be adapted in individual cases?* As a pilot study, adapting educational material for clinicians and nurses and teenager panels, explored whether educational material can be developed for individuals and if it is possible to include this in future clinical trials with the aim of establishing an adequate informed consent. The pilot

study needs to be further developed in studies including parents, but is beyond the scope of this thesis.

Part 1: Literature review

As the first step, theoretical material was used to understand the background behind the project, the ethical issues that are involved in the paediatric research and the foundation and details of clinical trials. The obtained knowledge has helped to focus on the objectives in the project.

The process of work has been mainly to read publications about clinical trials, investigating *informed consent, study participation, off-label and unlicensed drugs in combination with adverse events and empowerment of patients.*

The main considerations evaluating the sources were to:

- Find adequate, new information from established publications.
- Find articles that were in line with the objectives.
- No article should be older than 2004, except from publications regarding informed consent with a year limit of 1998 (to be compliant with the establishment of new regulations regarding children participating in research). Also, there was no year limit on articles about ethical issues and clinical trials and articles on physiology.

The keywords used when searching for publications on the process of consenting in paediatric trials in Pub Med were: *Informed consent, children* and *clinical trials*. However, more than 650 articles were found. Therefore the keyword: *parents* was added, resulting in 189 articles with publication dates no older than 1998 (because of the paediatric law that was introduced in the US in 1998). All articles that concerned specific diseases were dismissed after reading the abstract. Six articles were the main source.

Also a Google search was performed using the keywords: *Ethic, informed consent, paediatric* (in some searches paediatric *am* spelling), *parents, clinical trials*, which produced ten articles.

From the result, searching with the word “focus group” three articles were chosen, none older than 2004.

A couple of websites from children's hospitals emerged from using the Google function, searching for the most visited sites in order to find questions from parents whose children were planning to be in a clinical trial. The keywords for this research were *clinical trials*, *paediatric*, and *question*. Seven homepages with a high frequency of readers were used.

Using the keywords *Randomization* and *equipoise* at Pub Med produced twenty-one articles, of which three were chosen. The others were dismissed because of their specialist focus.

The keywords *Adverse event*, *clinical trials*, *child*, *off-label*, *un-licensed*, *safety* were used in Google and articles older than published in 2004 were dismissed.

Also, regulations from ICH judging causality of adverse events, the European commission regarding pharmacovigilance (EudraVigilance) and WHO guidelines and recommendations concerning children in clinical trials were used. Pharmaceutical books were consulted to describe the pharmacology of a child.

Part 2: Development of educational material

A: Identifying possible training needs in order to develop educational material

Information which concerned questions and worries from parents, regarding children participating in clinical trials was gathered and evaluated. The purpose was to find out what kind of information a parent might want to know before consenting and what fundamental aspects of a clinical trial seem to be hard to understand.

Literature-survey

Parents' understanding of clinical trials and their evaluation of the informed consent form was investigated. From the literature review, several articles exploring parents understanding of clinical trials and their point of view in the informed consent process were compiled as a foundation to the education, to find out what parts in the process might be further explained.

Interviews– patients and parents understanding of clinical trials

To be able to identify what concerns are associated with trial participation and what factors influence the willingness to participate/have one's child participate, a small interview survey was

performed. Five persons in total were questioned; two of them were children and the other three were parents, all of them with many years of experiences from clinical trials, either a diabetes trial or a growth hormone trial. The questions in the interviews were collected from earlier interview sessions from the QoLISSY project (appendix 3).

Both children and parents all consented to their responses in the interviews being summarized in this Master's thesis.

Interviews– how to conduct and educate panels

Interviews with people performing discussion panels in a medical context were conducted to get an idea what principles are of importance in educating people in rare situations, such as parents of hospitalized children. A nurse at the department of Cystic Fibrosis at the Östra hospital in Gothenburg and one doctor, Dr Carron Layfield at the centre of evidence based dermatology at the University of Nottingham were asked to explain how they conduct discussion panels and what educational form they used in their groups.

Video-interview – clinical trial participant; to education

A video interview with a paediatric trial participant was conducted, to be used as a part of the educational material. This was an idea proposed in the interviews on *how to conduct and educate discussion panels*. The interviewed girl was aged 14 years, highly motivated with several years of trial experience in a growth hormone study. She consented to the film potentially being used as education material. The questions that were asked were the same as those used in the parent and patients interviews (appendix 3).

Pre-evaluation of the educational material

The collected questions, the parents' worries and the evaluated interview questions were used as a base to develop educational material that could be used as an empowering method in addition to the informed consent process. The raw material was constructed from information from the literature survey and evaluated in two steps by different medical teams with years of clinical trial experience, according to content, degree of difficulty and effectiveness.

B: Adapting and evaluation of educational material to discussion panels – a pilot study

The finished presentation (educational material) was used in four groups. Two groups consisted of clinicians and nurses from two different departments, endocrinology and cystic fibrosis. All of them had several years of experience, working in different clinical trials at the Queen Silvia children's hospital in Gothenburg. The medical teams welcomed the opportunity to give their view of the education, evaluate the content and express their knowledge from clinical trials. The purpose was to understand what they felt was missing in the consent process, the parents' lack of knowledge when consenting to their child's participation and to encourage self-criticism.

The other two panels were composed of teenagers, 21 in each group and a total number of 42 teenagers. They were in the age category of 16-17 year old students who were all studying the natural sciences program. Approximately 50% were boys and 50% girls.

In the teenagers group a simple questionnaire was used, similar to the one adapted in part 1, evaluating adolescents' thoughts about issues in the informed consent process. The panels of teenagers were all free to discuss their thoughts among themselves before they answered the questions by raising an arm.

The two groups of separate knowledge were used as a foundation to evaluate if additional education is powerful as a method added to the informed consent process, to make the decision adequate.

9 MAIN PROBLEM FOR THESIS OUTLINE

The process of informed consent

The informed consent form is in its legal context a document that contains crucial information about the clinical trial the patient is being invited to join and is a requirement in order to recruit trial patients. The consenter shall not only be provided with trial information, he or she needs to truly understand what is provided. Furthermore, consenting to trial participation does not just start and end when the form is signed. As a trial participant you always have the option to withdraw at any time from the trial which makes the informed consent a *process* of consenting, starting with conveying the main points in a trial to the consenter in order to enable them to make the participation decision in the first place, and then the process will continue by providing information throughout the trial (Clinical Research Foundation, 2010).

All participants have to sign the agreement before any medical intervention can be undertaken, to establish their willingness to receive study treatment. It is the most important protection of a patient in clinical research to protect the person's autonomy. Young children are in most cases incapable of giving a legal informed consent but even though they are unable to consent to their participation by themselves, the consent made in proxy by the child's parents or legal guardian must represent the child's presumed will. Giving consent means that the patient/parent needs to make their own judgment based on personal beliefs, values and goals which enables the fully-informed patient to participate in the choice of his/her health care. It is “ *a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate*” (EMEA, 2002).

Why do we consent?

The concept of informed consent originates from ethical considerations in the process that concern the encouragement of autonomy and well-being, as well as to legally protect the integrity of a patient and the right to make their own decision given the issues of the relationship between the physician and the patient (Jessica W. Berg 2001). The consent has its roots in the history of medical experiments. The Nurnberg code (1947) was the first document to set out ethical regulations in human experimentation based on informed consent, followed by the declaration of Helsinki 1964 (Vollmann J 1996). It is the patient's right to receive sufficient information to make an adequate decision whether to participate or not. All patients have the right to decline a certain medicine, which is the core of individual autonomy. It was drafted in the European Convention of Human rights in 1950 (Wicks 2001).

Informed consent in paediatric trials

A patient might consent if he/she is competent to make his or her own decision. An infant will not be able to do so or understand the information, which makes the consent to clinical trials for children more complicated. There are also differences in mental development of children of the same age in their ability to understand and form an opinion. The main ethical question concerns what is best for the child rather than who has to decide and consent to study participation. A minor, defined as a person under 18 years old, is not legally allowed to sign consent. Instead, the parents or the guardian of the child will give their consent on the minor's behalf. According to pediatric ethical consultation:

“The parent(s)/legal representative should be given sufficient time and necessary information to consider the benefits and risks of involving the child in the clinical trial. Information should be given by an experienced investigator to each parent, or the legal representative, on the purpose of the trial and its nature, the potential benefits and risks, and the name of investigators(s) who are responsible for conducting the trial with background professional information (such as education, work experience) and direct contact details (telephone, address, e-mail). The investigator when seeking informed consent should not put undue pressure on the parent(s)/legal representative. For example:

“-According to Article 4(d) of the Clinical Trials Directive there must not be financial inducement to enroll the child in the trial; no financial incentive should be offered (other than compensation of expenses and time for job-loss),

- Parent(s)/legal representative should be informed of the possibility to revoke informed consent even though it was made in writing, in line with Article 4(d) of the Clinical Trials Directive.

- Parent(s)/legal representative should be reassured that the child's treatment will not be prejudiced by withdrawal from the trial, in line with Article 4(d) of the Clinical Trials Directive.

Page 10/34

- Consent should be obtained from the parent(s)/legal representative before assent is sought from the child, in line with Article 4 (a), (b) and (c) of the Clinical Trials Directive.” , (European Commission, 2008)

The investigator or a person with an adequate medical education has the responsibility of giving information both orally and on paper and the main goal is to give the patient enough information about the study, that he or she will be able to form questions in order to make a proper decision, such as discussing his/her decision, reasonable alternatives, risks, benefits and uncertainties as well as the acceptance of the intervention. The consent form is developed according templates (WHO, 2010), *the declaration of Helsinki* and reviewed by an ethics committee (Edwards, S. J, R. Omar , 2008)

Informed consent: an adequate decision in paediatric research?

The process of informed consent in paediatric research is a debated question. Is standard Informed consent sufficient to be able to make a proper choice? We can consider paediatric ethics as a triangle, with the clinical investigator at the base, the parents in the middle and the child at the top of the information cascade, how do the investigators empower the parents (and if possible the child) so the child's best interest is the first priority in the process of consenting? The knowledge that is passed between the clinician and the parent must be based on the patient's needs, not necessarily what the clinician has time or wants to explain. The question that needs to be answered is: How do we empower parents in order for them to make a decision for in proxy, completely voluntarily, to participate in clinical research?

The Nurnberg code states four characteristics of an informed consent that are required for the consent to be adequate: it has to be informed, competent, voluntary and comprehending. An informed consent will only be regarded as morally acceptable if it is genuinely voluntary. The treating physician has the major role in empowering patients. Problematically, the investigator also feels under pressure to enrol as many patients as possible and the parents are in many situations already in a state of stress and pressure, which might limit the process of making their own decisions in critical situations such as when the child is newly diagnosed.

This results in consent made from the clinician's perspective, contravening *the declaration of Helsinki* with a lack of respect to the family (Sumner Yaffe 2000).

Recruitment of patients in paediatric clinical trials

Recruitment to trials is often problematic. Most parents would not agree to their child's participation unless the trial implies an improvement in therapy. Another factor that is hard to implement is the placebo-controlled trial where parents, after being told about the circumstances, chose not to enroll their child. The distrust is often a question of fear of harming the child and parents are not comfortable with the thought of having their child treated as a "guinea pig" in a context with an extensive amount of complex information to consider in the informed consent (Clinical Research Foundation 2010).

Many parents might also withdraw their child because some aspects of the informed consent were not properly explained, which restricts a person's right to base their decision on personal beliefs, values and goals, and results in a distrustful environment. The involuntary decision might result in withdrawal or lack of trust in future trial participation.

The RESPECT project claims that participation might be a question of whether or not the family understands certain details of the principles of clinical trials before consenting. Is the patient aware of the ethical implications such as equipoise while randomized to an intervention? Is the patient sufficiently informed to withdraw for any reason? Or does the patient have the right information to ask questions and be aware of the possibility to report any adverse event?

10 RESULTS

Part 1: Identifying possible training needs in order to develop educational material

Literature survey

A literature-survey was conducted reviewing publications in the paediatric medical research field to find out what thoughts parents and in some cases children have about the informed consent process, their understanding of clinical trials and how they wish to improve the consent process in future. In addition, willingness to participate and concerns were examined and summarized according to different publications.

Issues related to clinical research in the paediatric informed consent process have reached professional attention (Harth, Johnstone et al. 1992), (Fell and Rylance 1991). Below are listed the categories of reactions to the informed consent process that have been found to concern parents with trial experience:

Time to consent

Several publications on the theme of parents' understanding and opinions of the informed consent process have discussed the amount of time given to consider consent. Results from interviews with parents about their own experience show that they need more time to be able to make an adequate decision. In one publication, 74% of the patients were invited to participate in a trial within 72 hours. The parents suggested that the investigator should plan the consent process in the most beneficial way to allow for as much time as possible to consider the consent, though within the limits of the child's medical condition (Eder, Yamokoski et al. 2007).

The level of knowledge regarding the information within the consent form

The outcome from the articles proposed a more qualified and also detailed informed consent process, including more information about the trial and the standard treatment, as well as time to

respond to different parts of the information. One article stated that one way to receive more adequate information is to explain the facts in different steps and confirm that the parents understand after every step. Another article showed that parents seem to think the amount of information was enough, but that it was too technical (Kupst, Patenaude et al. 2003), (Ferguson 2002).

Understanding of the fundamental aspects of conducting trials

Parents' perception of the information in the informed consent process has been a topic in many publications. Most of the parents thought they understood the overview of a clinical trial and that the information provided was adequate. However, some did not remember receiving any information from the investigator or experienced the information as too advanced; the leaflet contained medical terms not accessible for people without medical education (Ferguson 2002). One crucial principle of a trial that seems to be difficult to understand and also to accept is the randomization procedure in randomized controlled trials (Mills, Donovan et al. 2003).

A randomized controlled trial is a tool that brings power into the research. In a simple randomization the participants all have the same chance of being allocated to one of several study groups. The aim is to ensure that the characteristics of the participants are likely to be as similar as possible over all study groups at the baseline tests. This will decrease the risk of imbalance in serious unknown and known factors that might bias the clinical route of the participants.

The main reason to run a randomized clinical trial is to remove potential allocation bias that might compromise the outcome when allocating the patients to one of several interventions. There is no other method that ensures a balance of unknown prognostic factors at baseline. As a result of the randomization, the investigators have no possibility to allocate patients on their own to improve the outcome of the candidate drug in a trial to please the sponsor (Terrin 2003).

As seen in many surveys, both people inclined to accept to take part, as well as those who refuse to participate, usually understand the concept of randomization if they have been adequately

informed. The divergence is more related to belief in clinical equipoise (Mills, Donovan et al. 2003) (van Stuijvenberg, Suur et al. 1998).

Equipoise is the situation in which *it is thought equally likely that treatment A or treatment B will prove to be superior, a state that must remain as unrevealed*. A clinical trial must have an honest null hypothesis – the uncertainty of which treatment arm will prove to be superior. It is not ethical to run a trial with the answer known in advance (knowing one treatment arm is more beneficial than the other).

Randomization is a strong and significant approach and one might say it is excellent, though this is thought to be one of the main issues to take into consideration when deciding whether or not to participate, especially in paediatric trials. An informed patient is aware of the fact that he or she might get either of the treatments, which might conflict with the person's best interests.

The physician is in a position of convincing patients to consent to a trial only when they are in equipoise. Different surveys have found that parents willing to accept equipoise in connection with randomizing their child to one treatment arm tend to consent to participation and vice versa.

The points of information not clearly expressed and the questions parents wonder about when considering giving consent by proxy can be summarized as follows:

- The context of informed consent – how do I submit to a clinical trial?
- What are the benefits of clinical trials?
- What is a clinical trial? How is a clinical trial conducted?
- Standard treatment, randomization, equipoise

Factors that affect the willingness to participate according to the literature

The articles that were reviewed examined parents' thoughts about giving consent to their child's trial participation, all of them with similar outcome.

The negative aspects that might interfere with their willingness are:

- The time spent at the hospital. Participating in a clinical trial is commonly time-consuming, because of the visits that are additional to the normal treatment.
- Many parents consider the act of randomization as a major reason not to consent to a study, since the child might be allocated to the standard treatment. This factor is mainly true for the parents who consent only for their child's own benefit, and not for altruistic reasons.

The *positive aspects* are summarized to be;

- The extra medical examinations and that the child's condition will be monitored
- The investigator being on call 24 hours a day
- The contribution to medical research

Results of interviews with children participating in a clinical trial and their parents

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, a total of five patients and parents were interviewed.

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.

When they were asked to define the aims of the trial, all of them were able to identify the objectives of the clinical trial, 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. One mother stated; "I know they take blood tests and undertake some procedures and other examinations on my son, but I really don't know why they need to take them". The other two stated they were aware that their child was picked or randomized to the trials but were not able to define it (Table 1).

Most of the parents seemed to be aware of the term randomization 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. Two of them stated that they would not have allowed their child to participate if the trial included an arm of placebo injections. One mother explained that she consented to her son's trial participation because both the arms in the trial received the same medicine as he was using, but in fixed or individual doses. A parent of a 17-year old girl said she accepted the trial procedure on her daughter since it would not change her treatment.

Nonetheless, all of them were satisfied with the trials and would recommend others to participate and were inclined to include their children in future trials if it were to their benefit.

Almost all parents seemed to remember they signed a consent form, but did not remember the details. One mother told she did not remember signing a consent form or receive any additional information. Two parents described the information as "*too much*" and that it probably would have been better if all parts were described more clearly and in an easier way, since the information appeared to be hard to understand. None of them said they were reminded that they were in a trial.

The two children and the three parents were eager to see the outcome of the study in total, but were not aware if there was such opportunity or how they would receive the information. However, all claimed that it was of interest.

One parent (out of three) stated that she did not know what would happen if she decided to withdraw her child. The other two 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 when a major part of the participants did withdraw. One child did not like extra blood tests, but she was able to cope with it since she thought she would benefit from the study. She was aware of the potential adverse drug events but was still positive to participate in more trials in the future.

Table I
Questionnaire – The perception of clinical trials in families with children enrolled in a clinical trial - a selection of answers

Suggestion category	Interview examples Parents	
Do you know how to characterize the corner stones of a clinical trial?	<i>"No idea, my daughter was just picked as a participant", "Our child was just randomized"</i>	<i>"Yes, research to improve new therapies"</i>
Do you know if your child was randomized to an intervention?	<i>"I am aware of the fact that the study has two treatments"</i>	
Did you take your own decision when consenting?	<i>"Do not remember who took the decision in reality, but are aware I signed a consent form"</i>	<i>"I was the one who decided to say yes but my mom was very persistent that I should" "No I was too young I didn't have the choice"</i>
Are you aware what will happen if you choose to withdraw your child?	<i>"No"</i>	
On what premises did you consent?	<i>"It does not change the therapy"</i>	
Do you feel there are any advantages, participating as a minor in a clinical trial?	<i>"Better and more careful observations" "More time for questions, improving therapies" "Do not remember consenting"</i>	<i>To improve medicines for children</i>
Have you experienced that your child/you have been exposed for	<i>"Time consuming"</i>	<i>"I don't like taking extra injections, since I am afraid of them, but I do it because I feel better"</i>

The participants in the survey stated the following positive outcomes of being in a study:

- More time to examine every patient
- The clinicians and the nurses have the time to answer questions that might arise.

- The positive benefit of helping others and hopefully themselves (or their child) was a major reason for participating.
- 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.

How to conduct and educate discussion panels

As suggested in the work of the *RESPECT* project, to offer parents, in addition to the informed consent process, or parents with a potential interest to let their children participate in a trial, extra education may increase their motivation to allow their child's potential participation or empower them in the informed consent process.

Based on the fundamental elements of a clinical trial and to exploit the information obtained from the parents' assessment of what is important and what is difficult to understand in the process, education session was developed. This was then evaluated by pilot groups of physicians, nurses and teenagers. The idea behind the project was to find an additional group of parents of children with different diseases that might be interested about clinical trials, to evaluate the education. However, after several attempts, such a group could not be established.

In order to build and train pilot groups, two people with experience from similar projects were asked to give their views on how an adequate education is performed. From an interview with a nurse from the cystic fibrosis group at the Östra Hospital, the most effective way to educate and evaluate material in development for patients will be to empower discussion panels composed of a small number of people. The material developed should be presented in advance of the education session and in an easy and understandable way, without any difficult expressions and explanations. If using questionnaires to evaluate the material, it should be proposed in written form and the participants shall have a sufficient amount of time to consider their answers. To receive as much feedback as possible, the nurse proposed using problem-based questions from real situations to open up for discussions between the participants.

From an e-mail contact with Dr Carron Layfield at the centre of evidence based dermatology at the University of Nottingham who runs several patient educations about clinical trials:

“the best way to involve patients and parents in the disease of a child is to organize them in discussion panels around 4 – 6 patients or parents in each, where one of the major aims of the panel is to bring patients and carers together and give them the training and support that they need, to become involved in the development of the work. When designing surveys and questionnaires for children to be used in the development of studies (or throughout the course of a trial) the team ensures that appropriate language is used and use illustrations etc, to make the documents more interesting and relevant.”

As summarized from the literature, parents own evaluation of their level of understanding of an informed consent form, was estimated to be in a seventh to eight grade reading range, which implies that the educational material which aims to empower the patients needs to be at this level of knowledge (Davis, Mayeaux et al. 1994).

One study proposed that to evaluate semi-structured educational material, the use of clinician panels and a parental group would be the best way to reveal attitudes, opinions and feelings. According to one publication, the ability to use participant interaction to gain in-depth and rich data that would not be obtained through individual interviews is the most advantageous factor of using discussion panels.

The given proposal of a functioning program for evaluating material would be innovative, creative, enabling and responsive to individual needs, user-friendly for health educators, effective and efficient in design and based upon the evidence available, given the lack of research data on this matter. Evaluation of the impact of the program should be performed on parents, their children and the trial study staff (Dumas 2002).

A summary of how to conduct and educate discussion panels

- If possible, distribute the material in advance
- The material shall be user-friendly, conveyed on a simple level with no advanced expressions and explanations

- It shall be presented in groups and evaluated by both clinicians, nurses and parents and in this report also judged by teenager groups, evaluating the level of the material and giving opinions about the needs from a child's or adolescent's perspective.
- The evaluated material will be discussed in an interactive situation, meeting the participants' different and similar thoughts and concerns about the empowerment method.

Part 2: Evaluation of the educational material in panel

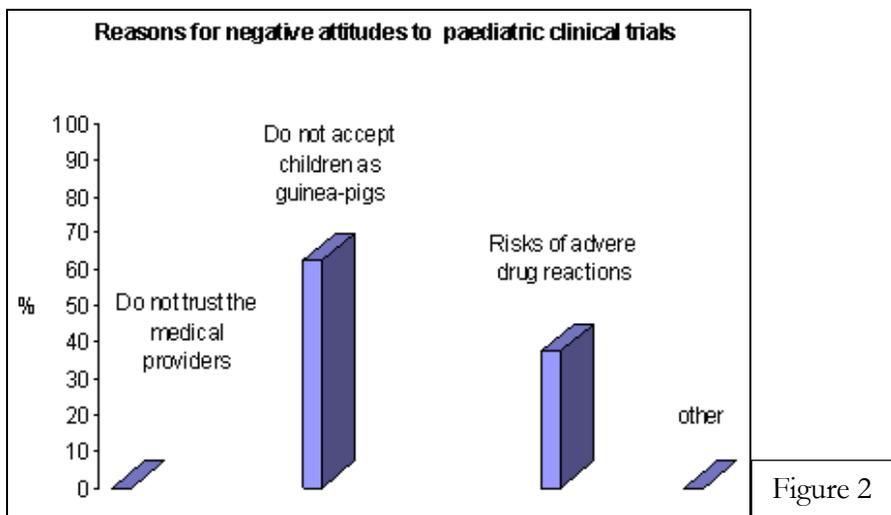
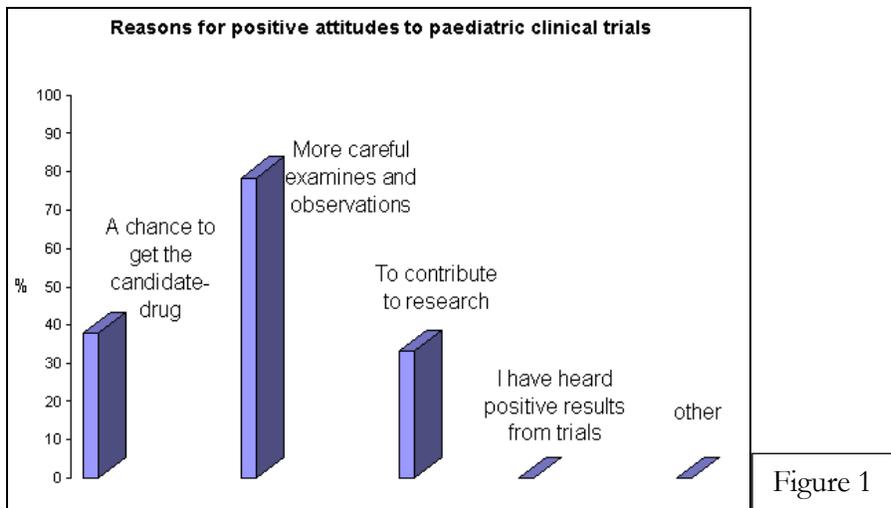
Teenager pilot discussion panels:

To establish the teenagers' knowledge about clinical trials, they all got to answer the question "*Do you know what a clinical trial is?*" One teenager in the first group was able to define some parts of what a trial is, but mixed it up with animal testing in the pre-clinical phase. No one in the second group had ever heard about the concept or the expression *clinical trial* and required a brief explanation of the subject.

In the second step, the educational material was presented in 25 minutes (See Appendix 1 for the education materials). After the presentation, the teenagers were asked again to explain the concept of a clinical trial. All 42 reported that they understood the basic principles of a clinical trial. To confirm if the presentation that was used was comprehensible, the groups had to define a trial in their own words. Both groups of participants were able to identify a clinical trial as a study to evaluate the efficacy and safety of a drug, to be able to develop a drug with good quality and adequate safety. The discussions continued to examine the teenagers' attitude towards children in clinical trials. In the first group, all 21 participants had a positive attitude towards paediatric medical research in comparison to the second group, where 16 of 21 agreed with this. The reasons for encouragement were prioritized in both groups as 1) the possibility to receive careful observation more frequently, the extra care and to be able to contact the trial clinician 24 hours a day. 2) A chance to be randomized to a candidate-treatment. 3) The significance for children to contribute to other children's medical health. This factor was actually voted as first priority in the second group. Even the ones not being positive to clinical trials were able to agree with this advantage (figure 1). Since no-one was able to recognize the concept of a clinical trial in the

beginning, no-one prioritized media or other resources as a factor affecting attitudes towards clinical trials. Also, no-one had other thoughts of why they were positive.

16 % had a negative attitude to clinical trials conducted in children. The reasons for this were discussed and prioritized according to the following: 1) the main-reason was that they did not think that children should be treated as a *guinea pig* in research. 2) They were not fond of the thought of children being placed at risk of adverse drug reactions (Figure 2).



The next test was for the teenagers to imagine themselves with a disease, getting a request to participate in a clinical trial of a new drug that in the best case would benefit them or other people with the same conditions. The groups were asked if they would say “*yes or “no”*” to this. The first group contained 9 teenagers willing to say “*yes*”. 1) The main reason was to contribute to the medical research, since there were no guarantees. 2) According to this group, an important motivation to participate was the extra care that a trial provides. 3) They considered hope to receive the candidate important but stated that this was just an extra advantage, since not all get the new drug being developed.

All participants agreed that altruism was the most important factor when considering consenting, regardless of whether or not they would say “*yes*”. 12 participants in the first group declined participation with the reasons: 1) having an illness would make them both physiologically and psychologically drained, and being exposed to additional tests with more visits would probably exhaust them and therefore they would be concerned about the illness worsening.

The second group was of another opinion. No one could decide if they would decline or participate. They were all compliant with the fact that it depends on the 1) severity of the disease, 2) the availability of adequate drugs, 3) the candidate drug’s proposed efficacy compared to the reference drug. However, they all agreed that the fear of adverse drug reactions and the extra visits were the reasons for not participating if they were hesitant. About half the group said that they would put their own interests first when participating in a clinical trial, hoping to get the candidate drug, and half the group stated they would do it for altruistic reasons.

Both the two groups agreed that educational material as an addition to informed consent would make it easier to decide about potential participation. Especially a brief and simple education was desirable in hurried situations, as some of the teenagers expressed their dislike of copious texts being an additional stress factor. Some of their proposals for desired additions to the information they got in the education session are presented below:

- Statistical frequency of severe adverse drug reactions.
- Actual number of paediatric drugs that are authorized after phase III.
- The opportunity to talk with other participants or to see an interview with a participant.

Clinicians and nurses pilot discussion panels:

The first group consisted of clinicians and nurses from the department of endocrinology. They were all experienced from running paediatric clinical trials such as growth hormone and diabetes trials and had extensive experience of recruiting patients; they were completely familiar with the information that is provided in the informed consent process.

The group was provided the same educational material that was developed in the teenagers groups (see Appendix 1).

After receiving the oral presentation, the material was openly evaluated without standard questions and the clinicians and nurses were also asked to speak freely from their own experience of the consent process and what parts in the process that might be hard to understand.

The clinicians and nurses described their way to inform the parents and patients as adequate and they explained that they encourage them to ask questions in connection to the information. They admitted that sometimes, if they are in a hurry or if the parents ask for more time, they let the parents take the consent form home to read properly. However, both the clinicians and nurses agreed to that in these cases, some of the information might not be considered thoroughly or even read, which means that some of the concepts are not fully appreciated by the parents. This might result in parents consenting with some parts not clearly explained and feeling taken by surprised.

The material was evaluated as understandable but that some information still might be too technical and the group agreed that education material in addition to the consent might increase the parents' and patients' knowledge about clinical trials, leading them to give a voluntary consent. Nonetheless, as stated by some of the nurses in the group, the drawbacks were that being aware of all investigations, details and aspects of a clinical trial might lower the ratio of trial participants, since the consenter has the possibility to re-think their decision and weigh their choice against the risks of possible adverse drug reactions or the extra time spent at the hospital. The clinicians and nurses did not however think that empowerment might slow the recruiting process, rather that it would increase the parents' and patients' autonomy to accept or decline trial participation. This might lead to a higher proportion of patients that decline participation, but instead fewer patients that withdraw because of insufficient knowledge about the importance of conducting paediatric

research. They also proposed that informed consent, given according to standard regulations, might be enough in the cases where the parents and patients have time to read the form are well informed and have sufficient time to answer.

The clinicians and nurses proposed information that from their own experience is not fully understood by parents and that might be of importance in the education material. They stated that one of the greatest factors to empower the patients is to clearly explain the advantages of being in a trial, such as benefiting research in order to produce quality drugs adjusted for children in different stages of physiological development and to explain the deficient knowledge about drug interactions that differ in children and adults.

Also educating parents and patients about adverse events and the adverse event reporting procedures is of importance. They seem to be unaware of why this is conducted and do not understand the importance. Also, the safety of a paediatric participant is a true component to be mentioned in the empowerment process that might not be totally explained in the consent form.

The group confirmed what the articles already stated, what the families in the interviews said and what the teenage groups felt was of absolute importance when participating: the benefits of being in a study; the chance to get a new medicine more rapidly and to be randomized to the candidate drug.

The second group consisted of clinicians and nurses at the department of cystic fibrosis. They were given the same education session as the first group.

The group was different from the endocrinology group since they have a close relationship to their patients during their lifetime, which makes it easier to empower them to participate in trials. They reported a low drop-out rate and attributed this to the close relationship between the patient and the medical team. The group stated that the verbal information that is given during the informed consent process is mostly understood by the parents who will ask the questions they need to ask to enable them to understand.

To show the differences in the recruitment-process, the situation of being a patient at the department of oncology was brought as an example of opposite characteristics. A family of a patient, with a newly diagnosed cancer who arrives at the hospital without being familiar to the medical research team, does not have the same ability to consider participation since this adds one more decision to their agenda and there is limited time for the clinicians to be able to inform the parents truly and to establish a sense of trust. This might limit the parent's ability to make that decision, which slows the oncology trial recruitment significantly.

Both these situations are extreme in both ways and therefore, the group stated that is not clear that any family in these predicaments is in a position to be helped by additional education.

They stated that the patients who have been in several trials get 'study-fatigue' and are thereby not always able to participate, but not because of fear of adverse drug reactions, which leaves the medical team to persuade them that it is necessary to participate in paediatric trials.

One study nurse reported that healthy children recruited to a trial performing gastrointestinal examinations had no regrets since they felt they were treated with a special status. To elevate the importance of being trial participants might be an empowering tool.

11 DISCUSSION

Limitations of the work

The intention of this report was partly to examine if the material developed for educational purposes corresponded to the needs and expectations that parents have in the informed consent process.

The time frame made it difficult to recruit the preferred number of people. A number of recruitment attempts with parents were made, but to no avail. There were also attempts to bring in young people for education but an insufficient number responded to the invitation. The ethical committees in Sweden were invited to comment on whether informed consent can be considered adequate when it comes to approving another person's participation but they all referred the questions to the limited information available on their websites. This work will therefore be considered a pilot study in an attempt to answer the objectives. Since the interviews in this report could only be implemented on a few people, their answers have to be considered preliminary, but they do highlight some concerns also seen in the literature.

Is standard informed consent enough?

As proposed from informed consent guidelines, it is *“a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate”* (EMEA 2002). By following the regulations, GCP and available templates, the informed consent process shall assure that the consenter is giving an adequate decision based on his or her personal beliefs.

In a quick overview of the result of the evaluated literature, it seems that most of the parents who signed a consent form are satisfied with the information given and do understand the primary

elements of a clinical trial. Also most of the interviewees felt that they had been insufficiently informed, nor were no one dissatisfied with the procedure in its entirety. Although the information process seems to work as a whole, there are many examples from the results that suggest the opposite. A mother from the interviews said she does not remember the moment she consented, or was informed and two other parents felt the information process was long and complex and would have preferred the information only verbally; a large amount of information presented as text was too heavy. Statements from parents from all of the articles that were used in this survey, suggest that some parents find the information to be too technically advanced and on a reading level above average which makes the text difficult to read, especially when in some trials there is a short time-limit that complicates the decision.

Further evidence that some elements of the informed consent are not perceived by parents was raised in the discussion of clinicians and nurses. Some physicians are under time-constraints during the information session and then they invited parents to take the information home and read carefully to understand it. This might cause a limitation in which parts of the form would be understood, when parents forget or do not have time to read the consent form carefully. In addition, parents who have a child with a severe disease to manage, rarely seem to cope with all the information, making the process more difficult.

Some parents experience this as stressful and chooses to decline, while others trust that the clinician recommends them the best choice when he or she proposes that their child should participate, which in unfortunate cases might lead to a withdrawal when the trial does not turn out as expected. This will contribute to the research in a negative way as a loss of trial data and loss of confidence and trust to the treating clinicians and nurses.

What are the main concerns about trial participation?

As collected from the results of all surveys, the main concerns about trial participation are the extra time required at the hospital and the additional tests and examinations that might be both physiologically and mentally draining. Also, there are results that indicate that people still considering having children as objects in clinical trials as unethical justifiable and many parents expresses their fear of adverse drug reactions.

Some parents dislike the randomization procedure, probably since their natural assumption is that their child will receive the candidate drug. The parents appear to understand the concept of randomization but it seems like they are not in every case in a state to accept the fact that their child will not have a hundred percent chance to be allocated to the candidate drug. This state of view might originate from not being informed, as the teenager groups were all aware of the randomization procedure and its real meaning and did not consider this a major concern. However, it might also be a question of parental protection, which the clinicians have to be aware of and respect during the process. As proposed in the result, the divergence is more related to belief in clinical equipoise. A clinical trial must have an honest null hypothesis – the uncertainty of which treatment arm will prove to be superior. An informed parent is aware of the fact that his/ her child might get either of the treatments, but it might still conflict with the person's best interests.

What factors affect willingness to participate?

As proposed in most of the literature, this thesis confirms that the most important factors when giving consent on a child's behalf is the possibility to in some cases receive the candidate drug before anyone else if it turns out to be effective, the hope of getting a better treatment or helping other children. Also, the extra care that is provided through extensive examinations and supervision of the child's disease and the opportunity having the clinicians and nurses being on call 24 hours a day are the most important positive factors.

Summed up, informed consent in its very true meaning, following the regulations, GCP and available templates shall be understood by the receiver and be based on a reading range appropriate to the normal population having no earlier experience of clinical trials. The chance to ask questions will ensure that the consenters will be informed enough to make an adequate consent. As this thesis shows, this is not always the way it turns out and the insecurity of certain information probably results in parents declining consent to their child's participation. Some people might find it hard to ask questions or end up withdrawing when the study does not turn out as they expected. Also, as proposed, in order to consent to a trial, additional information about certain trial procedures and results of the average safety of the drugs (as those mentioned in the result) might be of interest in

order to built up trust towards clinical trials. In some cases, improvement of the consent process might therefore be discussed in terms of:

- Statistics on drugs from phase III that are authorized
- The occurrence of adverse drug reactions
- The chance to follow a patient in a clinical trial, such as a film
- Maximizing the time made available to the decision maker as far as possible
- Lowering the reading age level
- Switching technical information to that of a more average level
- Checking that every part of the content of the informed consent form provided is understood

Education as a supplement in the informed consent process?

There are many issues to consider in the ongoing process in which parents or guardians must sign a consent for their child to take part as a research person in a clinical trial. Many factors affect a possible agreement. First, as mentioned in the discussion above, it should be emphasized that as a rule it requires a greater effort in time and that it may require a higher personal stress for the child. As seen in the results, there is fear of side effects and that the child is not capable of further samples without affecting their physical and mental health. These are major considerations that need to be evaluated. Since participation is not rewarded with any compensatory measures in the form of money, parents must have a good knowledge of what other benefits could derive from a trial. They must be aware of the risks that may arise and be well versed in what will be done during the time their children are participants in a study. In conclusion to what has been found in this study, there are several important aspects to emphasize to parents and it seems that these aspects do not always come over as clearly as they should. Giving parents a perspective on why there is a need for clinical trials in children - namely, to be able to develop drugs tailored to children's illnesses - in the education material seemed to be the overriding factor that would motivate their participation, maybe because it is almost the only factor that can be guaranteed, in addition to extra care and monitoring.

As a reflection of this Master's thesis is that if parents understand the whole concept, all events and building blocks in a clinical trial, it increases their ability to make a personal choice. The ethical issues as well as the concerns of clinical trials must be put in relation to the need to have scientifically proven efficacy and safety of medicines in paediatric healthcare. This might enable them to ask more questions to their clinicians and nurses and to achieve a totally autonomous informed consent. If they take on board all this information one should expect a reduction in the frequency of consenting to participation, but also a reduction in drop-outs during the trial. Looking soberly at this, one can look at the process of informing parents adequately as a business concept, which it is estimated would not result in a faster recruitment, but it does not lose as many patients already in the clinical trials since they knew what to expect. Therefore, we can expect a smaller loss of data overall, which enhances the significance of the results. Another positive effect is that when people know what they engaged in, they will be satisfied with the whole procedure, which makes them positively inclined to participate again in future or to recommend participation to other patients and parents, as the people interviewed in this report said they could consider doing.

To implement all the factors that make a consent totally autonomous might not be possible with only an informed consent form and verbal information since it requires a sufficient amount of time for the parents to think through their choice. It also requires the possibility for the clinician to answer to all questions and that he/she has the possibility to educate them well and inspire trust which is a situation rarely seen.

As a conclusion, there seems to be a need to expand the information in the informed consent process and further experiments are necessary. From all the results in the evaluation of the educational material one can safely say that the education could operate with positive effects in certain groups. It is important to point out all sides of a clinical trial and explain in additional depth why certain procedures are carried out, as it helps the parents to feel involved and engaged. Hopefully this will do a great deal to satisfy the participants and the families and empower them in the future.

The clinicians and nurses thought some parts needed to be further developed, since they were still too technical. However, as seen in the result, all the teenagers without any earlier experience of

clinical trials were able to understand the material and discuss the ethical dilemma that surrounds the consenting process without any problem. Also, a big part of them had positive attitudes towards paediatric research after being informed. This hints that education might work as an empowering tool to broaden the discussion and to be able to formulate questions that regards the consent process while understand the benefits of paediatric medical research in order to improve children's health.

Teenagers might comprise a suitable group to evaluate the educational material but, since there are obvious differences between the teenagers' perception of what is important when consenting to a trial in comparison to parents, it is necessary to obtain an evaluation of the parents'.

This part of the RESPECT project wanted to explore to whom and when education should be given. Personally, I have drawn the conclusion that it is mostly parents whose children have been approached to participate in a clinical trial who need the material. Expanding the education to include patients at health care centers or at regular clinics is a debatable approach and the educational medium that has developed in this work is probably not the most suitable. Therefore, there is a need for a clearer definition of what these groups are. By referring back to the results this group should not be parents of very seriously ill children, as they are under severe stress and already have a lot of information to manage. Nor should it be parents of children with chronic diseases who are already sufficiently familiar because of previous involvement in clinical trials. In these situations their unique needs should instead be met in other ways. The ideal group consists of parents whose children have a disease not characterized by too many difficult problems. There is a third group who would benefit from this education: parents whose children are not especially ill, as they may need a better understanding of the need for clinical trials before they would give consent based on altruistic rather than personal motives.

Can the materials be developed for individualized administration?

There might be further research needed to be able to judge if the material tested in pilot panels of non- parents can be used with parents on an individual basis. Before making any assumptions, a panel of parents should evaluate the material. However, as proposed in the chapter on educating panels, the most effective way to educate people is through interacting conversations with a certain

theme. On the other hand, one might consider that some parents may be unwilling to talk about their child's participation in front of other people.

What might be considered in the future RESPECT project?

During this study, several additional questions have emerged, and should be answered before continuing with the work of patient education. This is proposed without being aware of the parents' point of view and therefore is only speculations. Further work with parent's panels needs to be done in order to bring any adequate methods to reality.

- According to regulations, who will educate the patients?
- Depending on the child's condition, some parents might not be receptive to additional information education; how do we define who is in need of being empowered? And with what kind of methods and tools will this question be answered?
- When in the consent process shall the education be offered?
- According to the parents' wishes, would a standard education be applied or do we have to develop an individual education due to the trial design of a special indication?

12 CONCLUSIONS

Although this thesis shows that generally parents feel they receive information that most of them understand, there are a noteworthy proportion that feel uncertain about some parts of the information in the consent process. The clinicians and nurses stated that parents usually receive the proper amount of information that is needed to make an adequate consent, but this is not synonymous with finding that parents are confident in their decision. However, the staff's perception of the parents' knowledge might not be true in reality. This report claims that education in addition to the written consent form and the verbal information as discussed by clinicians, nurses and teenagers might empower the parents to ask questions and to get a wider perspective of how trial participation might be in practice. This will prepare the parents for what will come next if they choose to consent to their child's trial participation, which might decrease the frequency of

withdrawal and develop a positive attitude toward future trial participation. As mentioned in the discussion, further work on this theme is necessary to be able to implement empowering education as part of the information process.

13 REFERENCES

BIO. (2009). "History of Pediatric Studies, Rule, Legislation and Litigation."
<http://www.bio.org/reg/action/pedhist.asp>, (2010-03-12)

Clinical Research Foundation, (2010) "Paediatric." <http://crfound-eeu.org/special-populations/paediatric/>,(2010-04-13)

Davis, T. C., E. J. Mayeaux, et al. (1994). "Reading ability of parents compared with reading level of pediatric patient education materials." *Pediatrics* 93(3): 460-8.

Dumas, L. (2002). "Focus groups to reveal parents' needs for prenatal education." *J Perinat Educ* 11(3): 1-9.

Easton KL, P. B., Starr M, Brien JE (1998). "The incidence of drug-related problems as a cause of hospital admissions in children."

Eder, M. L., A. D. Yamokoski, et al. (2007). "Improving informed consent: suggestions from parents of children with leukemia." *Pediatrics* 119(4): e849-59.

Edwards, S. J. and R. Omar (2008). "Ethics review of research: in pursuit of proportionality." *J Med Ethics* 34(7): 568-72.

EMA (1994). "Clinical safety data management: definitions and standard for expedited reporting":12.

EMA (2001). ICH Topic E 11, "Clinical Investigation of Medicinal Products in the Paediatric Population":9-12

EMA (2002). ICH Topic E6, "Guideline for good clinical practise".EMA:8.

EMA (2007). "The European paediatric initiative: History of the Paediatric Regulation". EMA. London: 1-2.

European Commission. (2008). "Ethical considerations for clinical trials on medicinal products conducted with the paediatric population": *Eur J Health Law*. 15: 223-50.

FDA. (2010). "Should your child be in a clinical trial?",
<http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048699.htm>, (2010-03-12)

Fell, J. M. and G. W. Rylance (1991). "Parental permission, information, and consent." *Arch Dis Child* 66(8): 980-1.

Ferguson, P. R. (2002). "Patients' perceptions of information provided in clinical trials." *J Med Ethics* 28(1): 45-8.

Giovanni Tafuri, Francesco Trotta, Hubert G. M. Leufkens, Nello Martini, Luciano Sagliocca, Giuseppe Traversa, (2009), "Off-label use of medicines in children: can available evidence avoid useless paediatric trials?", *Eur J Clin Pharmacol* (2009) 65:209–216

Harth, S. C., R. R. Johnstone, et al. (1992). "The psychological profile of parents who volunteer their children for clinical research: a controlled study." *J Med Ethics* 18(2): 86-93.

Jessica W. Berg, P. S. A. (2001). "Informed consent: legal theory and clinical practice", Oxford University press, Inc.

John, T., T. Hope, et al. (2008). "Children's consent and paediatric research: is it appropriate for healthy children to be the decision-makers in clinical research?" *Arch Dis Child* 93(5): 379-83.

Joseph, A DiMasi, Ronald, W. Hansen, Henry, G. Gabrovski (2002) "The price of innovation: new estimates on drug development cost", *Journal of Health Economics* 22.(2003) 51-185

Kimland, E. (2006). "Off-label drug treatment and related problems in children", The department of Laboratory medicine, Division of clinical Pharmacology. Stockholm, Karolinska University. Licentiate 47. diss.kib.ki.se/2006/91-7140-684-0/thesis.pdf

Kupst, M. J., A. F. Patenaude, et al. (2003). "Clinical trials in pediatric cancer: parental perspectives on informed consent." *J Pediatr Hematol Oncol* 25(10): 787-90.

Läkemedelsverket (2007), "Kliniska prövningar", <http://www.lakemedelsverket.se/malgrupp/Foretag/Lakemedel/Kliniska-provningar/> Läkemedelsverket, (2010-02-25)

Läkemedelsverket. (2010). "Biverkningsrapportering vid klinisk läkemedelsprövning.", <http://www.lakemedelsverket.se/malgrupp/Foretag/Lakemedel/Kliniska-provningar/Biverkningsrapportering-vid-kliniska-provningar---efter-1-maj-2004/>, (2010-03-01)

McIntyre, J., S. Conroy, et al. (2000). "Unlicensed and off label prescribing of drugs in general practice" *Arch Dis Child* 83(6): 498-501.

MHRA (the Medicines and Healthcare products Regulatory Agency) (2008). "EU Paediatric Regulation", <http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesforchildren/index.htm>, (2010-02-15)

MHRA. (2010, 17 may 2010). "Medicine for children.", <http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesforchildren/index.htm>, (2010-01-27)

Mills, N., J. L. Donovan, et al. (2003). "Perceptions of equipoise are crucial to trial participation: a qualitative study of men in the ProtecT study", *Control Clin Trials* 24(3): 272-82.

- Neubert, A., I. C. Wong, et al. (2008). "Defining off-label and unlicensed use of medicines for children: results of a Delphi survey ", *Pharmacol Res* 58(5-6): 316-22.
- O'Lonegan, T. A. and H. Milgrom (2005). "Ethical considerations in research involving children." *Curr Allergy Asthma Rep* 5(6): 451-8.
- Paediatric research consultancy, p. r. (2007). "Paediatric Investigation Plans.", <http://www.child-medicines-research-info.com/paediatric-research-consultancy/paediatric-investigational-plans.asp> (2010-02-19)
- Powell, R. J. and J. M. Gardner-Medwin (1994). "Guideline for the clinical use and dispensing of thalidomide." *Postgrad Med J* 70(830): 901-4.
- Raine, J. M. (2009). "Off-Label Use of Medicines: Legal Aspects ", Springer Berlin Heidelberg.
- Regulation (EC) No 1901/2006 of the European Parliament and of the Council,(2006),” medicinal products for paediatric use”, *Official Journal of the European Union*
- RESPECT , (2008), “Project outline”,www.patientneeds.eu, (2010-02-12)
- Rylance, G. (1981). "Clinical pharmacology. Drugs in children", *Br Med J (Clin Res Ed)* 282(6257): 50-1.
- Sammons, H. M., C. Gray, et al. (2008). "Safety in paediatric clinical trials--a 7-year review" ,*Acta Paediatr* 97(4): 474-7.
- Samoy, L. J., P. J. Zed, et al. (2006). "Drug-related hospitalizations in a tertiary care internal medicine service of a Canadian hospital: a prospective study", *Pharmacotherapy* 26(11): 1578-86.
- Sumner Yaffe, M., Editor, Ronald W. Estabrook, Peter Boussein, Sarah Pitluck, Jonathan R. Davis (2000). "Rational Therapeutics for Infants and Children:Workshop Summary”, NATIONAL ACADEMY PRESS Washington, DC Washington, DC.
- TEDDY (2010). "TEDDY - Task-force in Europe for Drug Development for the Young “, <http://www.teddyoung.org>, (2010-03-01)
- Terrin, M. (2003). "Fundamentals of clinical trials for medical rehabilitation.", *Am J Phys Med Rehabil* 82(10 Suppl): S22-5.
- Ufer, M., E. Kimland, et al. (2004). "Adverse drug reactions and off-label prescribing for paediatric outpatients: a one-year survey of spontaneous reports in Sweden.", *Pharmacoepidemiol Drug Saf* 13(3): 147-52.
- Van Stuijvenberg, M., M. H. Suur, et al. (1998). "Informed consent, parental awareness, and reasons for participating in a randomised controlled study", *Arch Dis Child* 79(2): 120-5
- Virginia Poole Arcangelo, A. M. P. (2006). "Pharmacotherapeutics for advanced practice: a practical approach.”, Pa: Lippincott Williams & Wilkins.
- Vollmann J, W. R. (1996). "Informed consent in human experimentation before the Nuremberg code",*British medical Journal*.

Wagner, K. D., M. Martinez, et al. (2006). "Youths' and their parents' attitudes and experiences about participation in psychopharmacology treatment research.", *J Child Adolesc Psychopharmacol* 16(3): 298-307.

WHO,(2010), "Informed consent template for clinical studies",
http://www.who.int/rpc/research_ethics/InformedConsent-clinicalstudies.doc, (2010-05-28)

Wicks, E. (2001). "The right to refuse medical treatment under the European Convention on Human Rights." ,*Med Law Rev* 9(1): 17-40.

14 APPENDICES

Appendix 1: Short presentation of aspects explained in the educational material

Below, aspects used in the educational material in the pilot panels are presented. The presentations were used as a Power point presentation with a short film as an introduction in which a young study participant explains her thoughts about clinical trials. The content shown below of the presentation was developed in different steps and evaluated by clinicians:

- The background of medical research in children and the great value of paediatric trials to produce safe and effective drugs on-label.
- The ethical resistance to research including children resulting in deficient drugs.
- Inconvenient drug formulations as a price to pay when prescribing drugs off-label.
- The physiological reasons for requiring extensive drug testing in children.
- The Paediatric Regulation and its aim to improve children's health.
- A summary of the recruiting process and how it will work out.
- The concept of a clinical trial
- How a new substance or already existing drug is evaluated in comparison to a reference drug or placebo.
- Informed consent – how it is conducted, what it contains and the process of consenting.
- The voluntary nature of participation and the possibility to withdraw; the drawbacks of patient recruitment when patients withdraw during the trial. Important considerations before consenting.
- Randomization and equipoise and the reasons for blinding a trial.
- How a patient's safety is secured in a trial
- How patient data will be connected with one person and who is able to break the “code” of integrity.
- What happens after the trial.

Appendix 2: Power point presentation used as educating material





Medicinska kliniska prövningar på barn

Bättre läkemedel-säkrare vård



Mer än hälften av de läkemedel som ges till barn idag är inte godkända för ändamålet.

Läkare använder medicin anpassade för vuxna och experimenterar sig fram till nya lösningar genom att spä ut doser eller ändra administreringsväg.

Lite mer än hälften av alla de läkemedel som ges till barn är bara godkända att använda till vuxna människor. Eftersom det inte finns någon läkemedelsbeskrivning om hur medicinen skall administreras till barn måste läkaren själv "testa" sig fram till en behandling som fungerar. Det kan innebära att man spär ut en redan befintlig dos eller att man utnyttjar en ny administreringsväg. Att inte veta hur man skall ge läkemedel till barn ökar därför risken att fler biverkningar uppkommer



Anledningen till att det finns så få godkända läkemedel till barn har att göra med att det ansetts oetiskt att låta barn vara objekt för att utvärdera läkemedelseffekter. De hårda motsättningarna som skyddat barn från att delta i prövningarna har lett till att läkemedelsforskningen till barn näst intill uteblivit och därmed gjort det svårare för läkare att få tillgång till användarrekommendationer.



Att använda sig av icke godkända läkemedel medför också att dem inte är anpassade efter små barn vilket gör det svårt för barnen att inta sin medicin. Exempelvis kan det vara problematiskt att svälja en stor tablett och om man istället delar den kan den minska i effekt. Krossade tabletter spottas oftast ut eftersom de smaka illa.

Varför måste man pröva läkemedel på barn?

*Organ inte helt utvecklade – annan ämnesomsättning

*Användning av läkemedel som inte är anpassade för barn leder till fler biverkningar



*Kan resultera i störningar i njurutveckling, kroppsutveckling, tillväxt, tandmissfärgningar och hudallergier

Varför kan man inte använda data från läkemedelsprövningar i vuxna? Att betrakta ett barn som en liten vuxen är inte möjligt. Eftersom barn fortfarande växer är deras organ inte färdigutvecklade vilket medför att deras ämnesomsättning är annorlunda än hos en vuxen individ.

Idag doseras icke godkända läkemedel utefter vikten, vilket medför att man inte tar hänsyn till att barn inte har samma mottaglighet för läkemedel. Detta har lett till en ökning av biverkningar i allt lägre doser så som störning i njurutveckling, kroppsutveckling, tillväxt, tandmissfärgningar och hudallergier.

2007 – Europa – the "Paediatric regulation"

*Syfte av främja barns hälsa

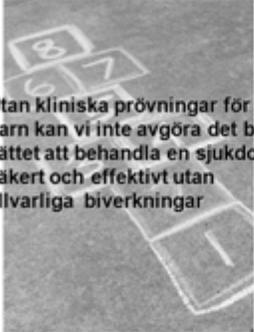
- Öka tillgänglighet och forskning på läkemedel till barn och ungdomar

- Läkemedel till barn- och ungdomar måste vara högkvalitativ och byggas på etik och säkerhet

- Utläsa användarinformationen för läkemedel



År 2007 infördes en ny lag i EU, likt den som finns i USA, i syfte att främja barns hälsa genom att kräva att alla nya läkemedel måste ha en plan för att pröva läkemedel i en klinisk prövning även för barn. Med detta förväntas man att uppnå en ökad tillgänglighet på forskning av läkemedel till barn och ungdomar som skall vara högkvalitativ, byggd på etik och säkerhet för att på så sätt möjliggöra för utökad användarinformation av läkemedel i samma population.



Utan kliniska prövningar för barn kan vi inte avgöra det bästa sättet att behandla en sjukdom säkert och effektivt utan allvarliga biverkningar



Att delta i en klinisk prövning

Noggrann utredd

Engagerat sjukvårdsteam

Behandlingsfördel kan förekomma

Extra besök

Bieffekt kan uppstå – noggrann uppsikt

Att delta i en klinisk prövning är alltid frivilligt och är i regel tidskrävande. Det ställer dessutom krav på att patienten inleder sig vid de besök han/hon kallats till och följer prövningsläkarens ordination. Som deltagare i en prövning får man i gengäld mycket noggranna kontroller och man följs upp i sin sjukdom oftast även efter prövningens slut av engagerade och intresserade specialister.

Ibland kan det förekomma att man som patient har en viss behandlingsfördel om man får det nya studieläkemedlet. Att vara med i en prövning innebär dock inte alltid att man får just studieläkemedlet och det garanterar inte heller att detta fungerar bättre än ett gammalt eller att biverkningar inte skulle kunna uppstå.

Förhoppningen med en prövning är att patienter kommer att kunna dra nytta av deltagarnas insats. I flera studier har man funnit att barn som deltagit just hoppas på att man lyckas utveckla en ny och bättre behandling som kan hjälpa antingen dem eller andra barn i liknande situation, men man bör vara medveten om att det inte behöver vara fallet. Andra barn ställer upp för att de visstats mycket på sjukhus och hjälper till i läkemedelsutvecklingen genom att delta och får ta del av intressant forskning.

Att bli förfrågad...



**Anna remmitteras från
barnvårdcentralen för utredning
av sin längd**



Anna har varit på kontroll på barnvårdcentralen och blivit remitterad till tillväxtenheten på barnsjukhuset för undersökning då man sett att hennes tillväxtkurva ligger långt under nomalkurvan.



Hon utreds på barnkliniken genom en mängd olika tester som bekräftar att Anna har tillväxthormonbrist!

Inne på kliniken utreds hon genom olika tester och tillslut bekräftar man att Anna är kort pg .a tillväxthormonbrist.



Anna återkommer till barnsjukhuset för att få veta hur hon skall bli behandlad...

Läkemedel under utveckling?

Gammalt läkemedel?

När Anna och hennes föräldrar kommer på återbesök för att få veta hur hennes behandling skall gå till och hur hon skall ta sina hormonsprutor berättar läkaren att man håller på att utveckla ett nytt läkemedel som man hoppas skall vara ännu bättre än det läkemedlet ges idag. Läkaren frågar Anna och hennes föräldrar om man kan tänka sig låta Anna delta i något som kallas för en klinisk prövning.

Men vad är en klinisk prövning?

En klinisk prövning görs för att få fram så säkra och kvalitativa läkemedel som möjligt

Undersöker exempelvis hur säkert ett läkemedel är och vilken effekt den har, eller utvärderar hur effektiv en behandling är

En klinisk prövning är en vetenskaplig studie som genomförs för att svara på frågor om hur exempelvis ett läkemedel fungerar jämfört med ett gammalt läkemedel. Det kan också vara en utvärdering av en produkt eller hur man bäst bör behandla patienter.

När ett läkemedel utreds i en prövning är det inte godkänt, man vet inte exakt effekt eller om det är utan biverkningar. Som deltagare i en prövning kan det hända att man slumpas till just den nya test-behandlingen. Då vet varken deltagare eller sjukvårdspersonalen hur läkemedlet kommer att fungera.

En prövning följer en strikt plan- ett protokoll

• Protokoll innehåller information om:

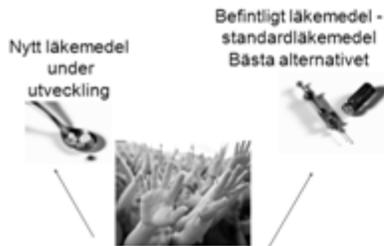
• Alla studieprocedurer; hur de skall utföras

• Vilka patienter som skall ingå i studien, vilka sjukdomar och egenskaper de inte får ha resp. får ha.

• Vilka lagar och regler som finns m.m.

Protokollet är det styrande dokumentet vilket man går tillbaka till flera gånger under studien för att se till att allting sköts enligt riktlinjer. Det är information som innehåller strikta riktlinjer för alla studieprocedurer. Man kan hämta förklaringar för hur många gånger ett prov skall tas och under vilka beting, man kan också inhämta information om vilka patienter som skall vara med, dvs. vilka symptom och sjukdomar de inte får ha resp. får ha. Här finns också noggrant beskrivet vilka lagar som styr försöken och information så som hur läkemedelstemperaturen skall förhålla sig

VILKET FUNGERAR BÄST?



I en klinisk prövning vet man därför inte precis hur läkemedlet fungerar och det är därför man måste testa det först, innan det blir godkänt, under väldigt kontrollerade förhållningar. I just den här prövningen kommer det nya läkemedlet att jämföras med det redan godkända läkemedlet, den idag bästa standardbehandlingen, vilket innebär att studien kommer att delas in i två grupper som får varsin medicin. Anna och ca: hälften av de andra barnen som också kommer att ingå i prövningen får en av behandlingarna; medan resterande halvan får den andra. Så här fungerar de flesta prövningar. Ibland kan det också innebära att barnet får båda behandlingarna efter varandra. Viktigt att poängtera är att oavsett vilken grupp man som prövningspatient hamnar i får man alltid behandling om det finns behov. I vissa studier finns ingen standardbehandling. Då använder man sig av en placebo. Det är en överksam substans, ett sockerpiller som bara får användas när man kan garantera patienters säkerhet.

Innan man får lov att utföra någon studierelaterad procedur måste ett informerat samtycke skrivas under. Ett informerat samtycke innebär att man genom att informeras om studien och alla relevanta aspekter därefter kan ta ett beslut om att delta. Informerat samtycke kan bara hämtas från de patienter som har kapacitet att besluta och laglig rätt (dvs. 18) att göra det. I en prövning som inkluderar unga måste föräldrar eller vårdnadshavare signera det informerade samtyckes- formuläret samtidigt som, om möjligt, barnet godkänner att delta.

Informationen skall enkelt beskriva läkemedlets funktion, hur planen för prövningen ser ut, syftet, de metoder, prov och antal besök som skall göras. Risker och fördelar och möjligheten att alltid avbryta sitt deltagande. Man beskriver kort om de lagar man följer och vilka försäkringar personen som medverkar skyddas genom. Om placebo finns skall detta förklaras.

Man har alltid möjlighet att i förtid avbryta sitt deltagande, utan att förklara orsak. Att avbryta innebär endast att man återgår till den behandling som normalt finns, alltså standardbehandlingen. Man skall dock betänka sitt deltagande innan och samla ihop frågor innan man ger ett medgivande. En klinisk prövning har ett förutbestämt antal deltagare för att kunna avgöra om och se mönster i hur läkemedelseffekt och biverkningar uttrycks. Desto färre som avbryter deltagandet ju säkrare blir det slutgiltiga effekt – och säkerhetsmättet.

Informerat samtycke

- Läkemedlets funktion
- Forsöksplanen
- Syfte med prövningen
- Metoder, prover och besök
- Risker och fördelar
- Frivilligt, får avbryta
- Regler och lagar , försäkringar
- Placebo om det används



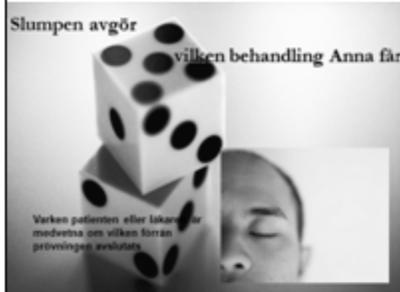
Anna och hennes familj tackar ja...vad händer nu?



- Anna uppfyller de kriterier prövningen kräver!
- Anna kommer att gå på besök under hela studien. Läkare och sjuksköterskor följer henne noggrant och antecknar hennes data i ett formulär som kallas CRF.

I Annas fall väljer man att tacka ja och Annas föräldrar skriver under samtyckesformuläret. Prövningspersonalen undersöker Anna för andra sjukdomar, symptom eller annan medicinering som kan störa den nuvarande behandlingen, exklusionskriterier. Det visar sig att Anna inte uppfyller någon av exklusionskriterierna och det visar sig också att hennes tillväxthormon- mängd i kroppen och hennes ålder är värden som passar för att kunna testa det nya läkemedlet, inklusionskriterier. Om Annas värden inte skulle instämma med de krav prövningen har, skulle hon inte få vara deltagare.

Anna kommer att få komma till sjukhuset fler gånger än om hon skulle ta det vanliga läkemedlet och genomgå mer noggranna undersökningar. Alla hennes resultat kommer att nedtecknas i ett formulär som man kallar CRF. Dessa samlas, när prövningen är avslutad, in från alla deltagare och resultatet kommer att sammanställas för att slutsatser skall dras. Utifrån prövningens generella resultat tillsammans med de biverkningar som eventuellt uppstår kan man då avgöra om tillväxthormonet fungerar.



För att den behandlade läkaren inte själv skall få möjlighet att avgöra vem som skall få vilken behandling, slumpas varje patient till en av behandlingsgrupperna. Vanligtvis slumpas man till det nya läkemedlet under utveckling, en standardbehandling och ibland en placebobehandling. Att slumpa, eller randomisera som det heter i en prövning är en vanlig metod och man utelämnar risken att de personer som har en bättre sjukdomsprognos skall få det nya läkemedlet och därmed ge ett bättre resultat av det nya läkemedlet än vad det egentligen har. Ingen skall ha större chans/risk att få läkemedlet som är under utveckling.

Många prövningar är dubbelblinda. Det innebär att varken patient eller läkare vet vilken behandling patienten får. Att utföra en dubbel-blindad prövning innebär att man säkert kan säga att det är effekten av läkemedlet som man bedömer och inte effekten av läkaren eller patienternas förväntningar.

Hur skyddas Anna i prövningen?

- Protokoll godkänt av en etik-kommitté
- GCP- good clinical practise
- Biverkningsrapportering
- Läkemedelsförsäkringen och patientskadeförsäkringen



För att en prövning skall utföras måste en etikkommitté granska protokollet och godkänna. Alla studieprocedurer måste följa good clinical practise ett regelverk som skall utesluta att det sker diskriminering av rättigheter, välfärd och säkerhet.

Under studien noteras alla avvikelser och biverkningar och om en allvarlig sidoreaktion uppstår skall detta rapporteras till myndigheter och i vissa fall avbryter man prövningen.

Den information som kommer sparas från Anna är behandlingsdata, sjukdomsdetaljer, biverkningsrapportering och ibland blodprov och annat organiskt material så som biopsier. Vissa prövningar utvärderar deltagarnas livskvalité i formulär. Man skall dock vara medveten om att dessa prov och uppgifter skyddas genom Personuppgiftslagen, biobankslagen, arkivlagen och sekretess och tystnadsplikt.



Den ansvariga läkaren har tillgång till Annas uppgifter.
Representant från läkemedelsbolaget.
Följer Personuppgiftslagen – utan påskrift av det informerade samtycket kan ditt barn inte medverka



När prövningen avslutats får man ofta vänta på att resultatet skall presenteras. Deltagare som varit med i en blindad klinisk prövning får nu reda på vilken behandling d fick och i vissa fall kan man få tillgång till de nya läkemedlet om det är i förväg godkänt av läkemedelstillverkaren.

Att fundera kring innan samtycke!



- Förstår mitt barn och jag som förälder/vårdnadshavare vad studien går ut på, har vi fått tillräcklig information?
- Är vi tillräckligt informerade att avbryta i förtid?
- Accepterar vi alla delar av det informerade samtycket?
- Finns det något i förväg som talar för att mitt barn inte kommer att kunna delta i hela prövningen?
- Kommer jag och mitt barn ha tid att vara med på alla besök?

Sätt dig in i situationen...

- Förstår du vad en klinisk prövning är?
- Om du förstår har du en positiv/negativ inställning av kliniska prövningar för barn?
- Om negativ, varför?
 - 1.) Vet ej
 - 2.) Massmedia
 - 3.) Jag känner någon som deltagit som råkat illa ut
 - 4.) Jag tror att det kan skada mer än göra nytta
 - 5.) Annat



- Om ja till positiv inställning, varför?

- 1.) Finns chans till bättre behandling snabbare om man deltar
- 2.) Man blir undersökt noggrant, det finns mer tid och man följs upp långt efter studien
- 3.) Det gynnar forskningen och i förlängningen många barn och ungdomar
- 4.) Jag eller någon jag känner har deltagit och är mycket nöjd
- 5.) Annat



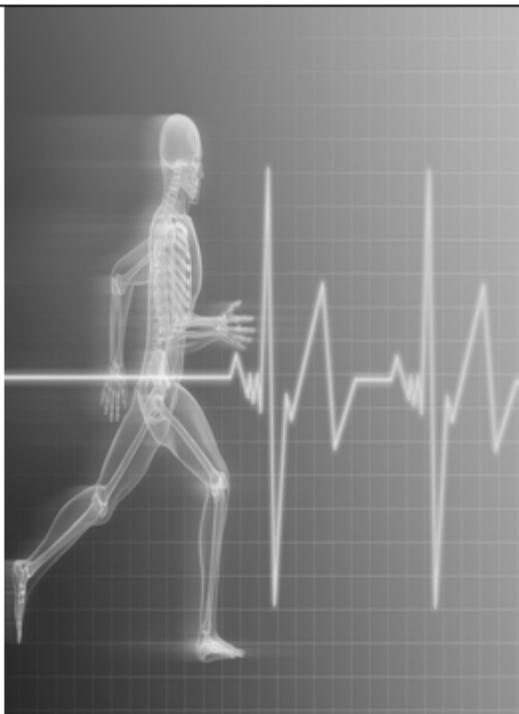
Tänk dig in i situationen

att du har en sjukdom och går på behandling och blir tillfrågad att ställa upp i en klinisk prövning av ett nytt studieläkemedel.

Detta skulle eventuellt gynna dig mer än det gamla läkemedlet.

Det finns inga garantier, men förhoppningen är att andra patienter kommer att kunna dra nytta av resultatet oavsett om du gynnas eller inte.

Skulle du ställa upp?



- Nej
- Jag vill inte känna mig som ett objekt att testa produkter på
- Jag tror inte jag skulle orka/ ha tid jag skulle inte vilja göra fler provtagningar än vad jag redan skulle göra
- Jag vill inte riskera onödiga biverkningar
- Jag vill inte bli skrämmd av sjukvården
- Annat _____

- Ja
- Jag hoppas att studieläkemedlet skall hjälpa mig
- Jag vill få extra kontroll av min sjukdom och veta att man har uppsikt om något sker
- Även om jag ställer upp och inte blir hjälpt finns det många andra som kommer att gynnas av det
- Andra åsikter _____

Om jag fick mer information, varför skulle jag ändra inställning?

Jag vet för lite och det är svårt och tar tid att ta reda på informationen själv.

Många delar av en klinisk prövning är svåra att förstå, jag behöver få det enklare förklarad

Övrigt _____

- Rangordna alternativen efter vad som är viktigast för dig att veta mer om , i de fall du skulle kunna tänka dig att ställa upp i en klinisk prövning:
- Vill veta mer om regelverk, försäkringar och Good Clinical practice
- Vill veta mer om utförandet på kliniken
- Vart och vem kommer att se mitt material, hur kommer det till användning för andra?
- Mer fakta om det redan testade läkemedlet?
- Hur kommer jag att kunna se mina data och uppgifter?
- Kommer jag att kunna använda läkemedlet efter studien?
- Annat?

- Tror du att information som denna är en bra att ge till föräldrar och barn innan man tackar ja att medverka?
- Ja
- Nej
- Vet ej

Appendix 3: Questions for interview

Bakgrund Respect- projektet och syftet med studien?

Vem är jag – vad gör jag här?

De flesta mediciner som används på barn i Europa idag är bara testade på vuxna, vilket innebär att ingen vet med säkerhet den lämpligaste doseringen för ett barn, så att inga biverkningar uppkommer och så att man får max effekt.

I USA har det i över 10 år funnits en lag som kräver att varje nytt läkemedel som ska användas på barn skall först ha testats på barn i kontrollerade kliniska prövningar. Man införde den då man insåg att det var få läkemedel som var godkända vid användande till barn under arton. Läkare i Sverige och andra europeiska länder har tidigare varit hänvisade till amerikanska studier för att ta reda på den rätta dosen för barn. När det gäller läkemedel som inte används på barn i USA måste de europeiska läkarna helt enkelt göra en egen bedömning om huruvida medicinen är lämplig för barn och i så fall i vilken dos.

I januari 2007 instiftades en ny EU-lag (Regulation EC No 1901/2006 on Medicinal- Products for Paediatric Use) som motsvarar den amerikanska lagen och kräver kliniska studier på barn innan läkemedel kan godkännas för användning på barn. Detta innebär ett ökande behov av barn som ställer upp för kliniska studier framöver.

Det europeiska forskningsprojektet RESPECT, som leds av Sahlgrenska akademins institution för kliniska vetenskaper vid Göteborgs universitet, undersöker vilka faktorer som är viktiga för att familjer med barn skall delta i kliniska studier. Vi vill ta reda på vilket stöd de behöver för att vilja delta i kliniska prövningar. Utifrån de resultat som forskningsprojektet RESPECT genererar skall man kunna sammanställa riktlinjer för hur man på bästa sätt tillgodoser familjer och barns behov vid deltagande i kliniska prövningar.

Därför vänder vi oss till dig, med ett barn i en studie för att få reda på dina tankar om denna slags forskning. Du behöver inte svara på alla frågor och ingen av den information du delger kommer att kopplas till dig utan kommer vara ett resultat i en sammanställd rapport.

- Hur gammalt är ert barn?
- Varför kommer Ni/ert barn till kliniken?
- Vet Ni om att ert barn deltar i en studie?
- Vad är syftet med studien? (förklara med egna ord)
- Vad sade läkaren/sjuksköterskorna?

- Vad är en klinisk prövning?
- Blev ert barn randomiserad inom studien? (till en behandling eller en annan)
- Tror Ni att det är någon skillnad mellan det ert barn får och andra i studien?
- Blir ni påmind om att ert barn är med i en studie när ni kommer på undersökningar och besök?
- På vilka villkor tog Ni beslut om att delta?
- Fick Ni skriva under ert godkännande för att ert barn skulle delta?
- Vilka frågor ställde Ni innan Ni gav ert medgivande att låta ert barn delta? Om du inte kan komma ihåg, vad skulle du fråga om nu?
- Är ni intresserade av att få resultatet av studien?
- Om ja, sade läkare att Ni skulle få se resultatet?
- Av vilken anledning skulle Ni plocka ut ert barn ur studien?
- Känner Ni att Ni upplever fördelar med att Ert barn deltar i en studie?
- Vilka?
- Finns det något Ni känner är till nackdel för Ert barn när Han/hon ställer upp?
- Finns det någonting du känner man skulle vilja ändra på för att få Ert barns deltagande att kännas bättre?
- Har Ni en uppfattning av vad som skulle hända om ni valde att låta ert barn avsluta studien?
- Skulle Ni i något avseende rekommendera andra föräldrar att låta sina barn delta i en studie?
- Varför då?
- Upplever Ni att ert barn vet om att han/hon deltar i en studie?

Frågeformulär barn

- Vet du vad forskning är?
- Varför tror du de gör de forskning på barn?
- Vet du varför man gör det?

- Vad har varit bra med att delta i den här prövningen?
- Vad gillade du ej att vara med?
- Vad går att göra bättre för att de ska kännas tryggt för dig att vara med?
- Hur känns det att vara med?
- Fick du bestämma om du skulle medverka, fick du skriva på någonting?
- Vad gjorde att du ville vara med mest, var det en doktor, en sjuksköterska, mamma och pappa eller en tidning som spelade roll
- Känner du att du någon gång inte har velat vara med mer?
- Har du fått reda på dina testsvar från proverna som tas?
- Vad tror du doktorerna får veta och kan använda dina svar till?
- Vill du vara med en gång till? Och varför?
- Tror du forskning hjälper barn?
- Tror du de kan skada dem?

