Monographs of the Víctor Grífols i Lucas Foundation 40

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Ethical aspects of research with children

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Ethical aspects of research with children

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INTRODUCTION

This is not the first time that the Víctor Grífols i Lucas Foundation has considered the topic of clinical research, but it has never before focused on research with children and adolescents. In the context of cooperation with the prestigious UK-based Nuffield Council on Bioethics, and to mark the publication of its detailed study "Children and clinical research: ethical issues", we thought it would be interesting to create a space to enable researchers in Catalonia to discuss the issues with British researchers, and to compare perspectives and experiences.

This publication gives readers access to the contents of the Seminar, which brought together speakers from the Nuffield Council and specialists in the field of paediatrics and offered some interesting insights into the ethical questions to be addressed when considering the involvement of minors and their families in the research process, from the identification of criteria for prioritizing research to the direct participation of minors in a clinical trial.

The Víctor Grífols i Lucas Foundation has also sponsored the Spanish translation of the Nuffield report, and the accompanying magazine and animated video produced for young people. All of this material is available via the Foundation's website (www.fundaciogrifols.org).

Núria Terribas
Director

Presentation of the Nuffield Document. Children and clinical research: ethical issues

Bobbie Farsides

Chair of the Working Party and Professor of Clinical and Biomedical Ethics at Brighton and Sussex Medical School

The Nuffield Council on Bioethics was established in 1991 with the aim of exploring ethical issues arising out of developments in biology and medicine. The council is funded by the Nuffield Foundation, Wellcome Trust and Medical Research Council but it operates independently of these bodies in terms of the work it undertakes and the positons it holds. Since its establishment the Council has overseen the production of over 30 specialist reports addressing important topics in science and biomedicine. The reports have been influential nationally and internationally, and have a reputation for combining robust scholarship with a detailed understanding of the context within which related ethical and social issues arise.

In 2013 the Council decided to produce a report looking at issues related to the involvement of children and young people in clinical research. It has been acknowledged for some time that many children and young people are being given drugs and other therapies that have never been tested for paediatric use. Indeed it is widely quoted that up to 50 percent of drugs are prescribed off label, with clinicians being left to adjust dosages etc. to suit their young patients. Therefore the report would also need to consider the implications of *not* involving children in research, given that the potential benefits of doing so seem to be trumped by our moral and practical concerns.

I was invited to chair the working party and work began in June 2013 under the magnificent guidance of Katharine Wright, Assistant Director of Nuffield Council on Bioethics. Our starting position was this – maintaining the status quo was not a morally neutral position to adopt. Children and young people were being put at risk every day, and some would die for want of appropriate medical treatment. More research was needed to ensure the safe and appropriate use of existing therapies and to introduce new treatments designed specifically to meet the needs of children and young people where those differed in any way from adults. Given that this was so, we needed to understand the barriers to this happening and where possible suggest ethically sound ways in which these barriers might be removed. However, before being able to do this we needed to understand exactly what we meant by children, what we can say about their distinctiveness, and importantly how we tend to characterize and respond to them in the context of medicine and research.

An early meeting of the working party focused on what was meant by a child or young person in the UK in the twenty-first century, and we asked whether practice and policy were utilizing appropriate concepts of childhood when deciding how to conduct medical research. After hearing from child development experts, sociologists, lawyers and paediatricians we felt able to challenge the old-fashioned view of children as necessarily vulnerable individuals unable to make important decisions. Instead we chose to emphasize the developing personhood and capacity of children, their interest in the world and how it impacts upon them, and their commitment to making a difference for themselves and others. For us childhood as a morally relevant factor had little to do with chronological age. We were much more interested in the characteristics and experiences of particular children when they found themselves confronted by illness and the possibility of research. We realized early on that the route to improving the experience of children in this area was to engage with them to understand them better and involve them in bringing about change.

This early recognition of the importance of children and young people's voices meant that the final report adopted by Council in May 2015 came about in a rather different way to previous reports. At no point was scholarship or conceptual analysis forfeited, but alongside the carefully argued and fully referenced academic/policy-focused report there was a series of activities and outputs co-produced with children and young people and often addressing them directly rather than through adult mediators. Young people helped us to decide what to think about, how to think about it and most importantly how to present those thoughts back to their peers.

Like us they were dismayed by the reluctance to ask them to participate, and again, like us, they saw part of the problem residing in the persisting representation of children as vulnerable beings who need to be protected and who are at risk of being 'experimented on'. The children we worked with gave us the confidence to think about children and young people as partners to work with and they challenged us to find ways of allowing this to happen safely and ethically.

By speaking to young people and their parents we were able to urge those charged with designing, approving and carrying out research to become more courageous, but this was only the first step. Clearly we wanted more

children to be invited to participate in research, but having said this we were also clear that children and their families should not be overburdened, particularly at times of acute illness and distress. We also knew that some children would find themselves in situations where they would be vulnerable. In common with any human being who is invited to participate in research, and particularly research which holds no promise of direct benefit, some level of protection is important. We therefore developed the idea of a 'fair offer' wherein lies an extra level of protection.

The idea of the fair offer works to ensure that children are not asked to agree to anything that should strike them as unreasonable when considered against their primary interests. It is also designed to protect those who may be made vulnerable by the situation they find themselves in when asked to participate in research. Consider the following possibility. If I were to ask you to participate in something that is ill thought out, risky and ultimately doomed to failure it is probably not going to be a good idea for you to agree to join in. However, there may be various pressures upon you to do so – I am your friend, I get cross when people don't do what I want, and you depend upon me heavily in your social life so you don't want to upset me.

In a medical setting any patient may be subject to analogous pressures. Your doctor has cared for you for a long time, you want to do something that they appear to endorse, and you worry about the consequences of not agreeing. Hopefully, scientific review will ensure that a project is worthwhile, and ethical review will protect all participants from inappropriate treatment, but participating in a particular piece of research may still not be the best option for a particular child.

The idea of a fair offer protects children and their families from the possibility of being asked to do something unreasonable by placing a responsibility upon researchers to demonstrate that the offer they are presenting is something that it would be appropriate for the child and their family to consider because it is scientifically sound and ethically robust. It is then for the child and their family to consider whether or not it is in line with the fundamental interests of *this* child and this family – it is important to recognize that a fair offer can be turned down without its validity being called into question.

Much of the report speaks to how best to ensure that offers are fair and who to look to for support in doing this – hence our interest in methodology, the analysis of risk, our detailed discussion of the role of research ethics committees and the emphasis we place upon the moral duties of individual researchers, the importance of trust and open communication.

There is much to take away from the report in terms of moving forward, and clearly progress will be made by working together to ensure that educational, regulatory and participatory practices are all pulling in the same direction. Until this happens more children will remain at risk from untested therapies than will ever be harmed by scientifically excellent and ethically robust research.

Balancing risk and benefits in research with children: how can they be protected?

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Statement of principle

The best and only way (that I know) to protect children is to have them actively participate in research and provide them with the best (potentially) available opportunities to access health. In my opinion, research with children is: 1) not accepting vulnerability as a fatal condition; 2) caring; 3) exploring the future with courage; and 4) a human mode of existing.

In this article I try to illustrate with exemplifying stories, from our own experience, each of the above mentioned meanings for children's research.

Why research *with/for* children?

Recognizing children as a biological entity that poses specific and unique problems is the necessary first step to face the problem. Children are a well characterized biological entity and as such it should be reviewed here before addressing ethical questions.

Human beings are complex biological systems, in motion. It all begins at the moment of fertilization which is followed by an amazing expansive force that generates growth and development. Growth and development is thus a physiological process that, from a pluripotential and undifferentiated cell, makes possible the differentiation, maturation, organization, and function of tissues, organs, and apparatuses that, as a whole, make up the human body[1]. As multifactorial and complex as the process of growth is, normal growth is remarkably predictable and established in three stages: 1) cellular hyperplasia during organogenesis and the foetal period characterized by cellular division and cellular proliferation; 2) Hyperplasia-hypertrophy, when the organ or tissue is reaching the predetermined cellular content; 3) Hypertrophy, when the adult cellular content is reached, cellular division stops and cellular growth depends exclusively on the size of the existing cells.

A mathematical method modeling human growth composed by three additive and partly superimposed components was proposed in 1989 by Karlberg – the infancy–childhood–puberty (ICP) model[2]. Each subcomponent reflects the different hormonal phases of the growth process. The pattern of human linear growth is very well documented and shows a sigmoid morphology, with a peak prenatal velocity of growth and a rapid deceleration for the first two postnatal years, followed by a period with lower and slowly decreasing velocity from the third year until puberty. The infancy component expands from the second half of pregnancy until two to three years of postnatal life. This period is mainly dependent on maternal nutrition, independent of hormones. The childhood component lasts from the end of infancy until the beginning of puberty. During this long period, the intense deceleration of the first two to three years becomes a stable slow growth rate. The beginning of this component is marked by the initial progressive influence of growth hormone (GH) upon linear growth. The puberty component is the result of the synergy of the two hormonal systems, one dependent on GH and the other on sexual steroids.

Normal growth (cellular proliferation), balanced with appropriate development (differentiation of tissues), gives rise to normal organs and systems providing normal physiology and conforming normal children. Growth and development stops sometime after age 20 years, finalizing a really long and complex process of developing a normal adult body. The stepwise process of generating tissues correctly in time and space is very precise and requires highly orchestrated cellular functions. It is perhaps not surprising that the error rate is substantial – most human embryos fail to implant or subsequently die. This is the reason why paediatrics exists as a branch of medicine, the fundamental recognition that the growth period of developing an adult human being is critical and has unique properties of its own. A clear example is developmental – paediatric – cancer.

An embryonic theory of cancer was proposed in 1875 and is now supported by an increasing number of experimental studies[3-5]. Briefly, the theory is based upon the relationship between ontogeny and oncogenesis and implies an impaired cellular maturation that would result in the overproduction of undifferentiated (stem-like) cells, which then accumulate. In support of the theory is the connection between congenital anomalies and childhood cancer. Studies show an almost threefold overall increased risk of malignancies like leukaemia and lymphoma with congenital anomalies[6]. Embryonic

tumors, because they originate from immature tissue, resemble tissues in the developing embryo and foetus. Furthermore, some tumor cells not only look like embryonic cells, but they functionally mimic their behavior. For example, cells of hepatoblastoma and germ cell tumors can secrete α-fetoprotein – a serum protein that is produced by normal foetal cells only during pregnancy. In general, the biology of embryonic cancer cells largely recapitulates the behavior of cells that are found in developing tissues. For instance, gene expression profiles of developmental tumors have been compared with those of various stages of normal tissue development. This has demonstrated the close relationship between these cancer cells and the immature cells of the developing organs from which these tumors arise: Wilms tumors and the metanephric mesenchyme[7], neuroblastoma and the sympathoadrenal progenitors of the neural crest[8], retinoblastoma and cone precursor cells of the retina[9], foetal skeletal muscle and rhabdomyosarcoma[10], hemangiomas and foetal endothelial cells[11], medulloblastoma and cerebellar precursor cells[12], and gliomas and neural precursor cells[13].

Story 1: I (Infancy) tumors

Not accepting vulnerability as a fatal condition

Neuroblastoma in the infant has a more favourable prognosis than in older children. One reason for this is the peculiar behaviour of stage 4S disease (where "S" stands for special), which frequently undergoes spontaneous regression. In 1971, this special and rare subgroup of metastatic neuroblastoma affecting very young infants, characterized by a unique pattern of dissemination and a high incidence of spontaneous regression, was described by Giulio d'Angio and Audrey Evans[14]. Stage 4S has been recognized as a distinct clinical entity in all subsequent classifications of neuroblastoma. Research performed over the last decade has demonstrated that stage 4S neuroblastoma is a clonal expansion of mutated (specific pattern of mutations) precursor cells (neuroblasts) able to escape growth control initially and grow as large tumors until they stop proliferating at the end of the infancy period[15]. Stage 4S neuroblastoma is able to respond to differentiation signals and regress on its own. Research from our group and others has described distinct chromosomal aberrations reflected in specific gene expression profiles associated with spontaneously regressing or aggressive infant neuroblastoma[16]. Therefore, very young infants early in life, really vulnerable and sick, have benefitted from basic research performed on their tissues and clinical cases so now they can be managed much more precisely and securely. Preventing research on these very young children would not help to advance better management and cures. It is therefore imperative that all actors involved in protecting children should encourage and promote research as the best way to protect them.

Story 2: C (Childhood) tumors

Research to understand why we fail and to guide the future

Diffuse intrinsic pontine glioma (DIPG) is the most common and malignant form of children brainstem tumor[17]. DIPG is generally a disease of middle childhood, with the majority of children diagnosed between five and ten years of age. The median survival for children with DIPG is less than one year from diagnosis, and no improvement in survival has occurred in more than three decades[18]. The pons contains cranial nerve nuclei and nuclei critical for life-sustaining function, so damage by the tumor or its treatment has tremendous repercussions. Resection is not an option and the tumors have shown resistance to essentially all therapeutic measures. Without radiation, median survival is approximately four months. Radiation is effective as a palliative intervention in a majority of cases, providing transient symptomatic improvement. Subsequent tumor progression is almost universal, with median overall survival between 8 and 11 months, and overall survival of approximately 30 percent at one year and less than 10 percent at two years. Over 200 clinical trials have investigated various medical interventions in addition to radiation, either as initial therapy or at recurrence; none have demonstrated benefit[19].

The reasons why as a community we have failed repeatedly are many, including, in my opinion, 1) following the wrong (adult) models; 2) not recognizing the disease as a developmental tumor; 3) a lack of courage to face the challenge; and 4) not involving the parents and patients in the critical decision-making.

The diagnosis of DIPG is based on characteristic imaging (MRI) findings in the face of a typical clinical presentation[20]. The uniquely characteristic MRI features of DIPG were initially described in 1985 and reflect a tumor that appear as a large brainstem mass as opposed to an extrinsic mass compressing the pons, meaning that the epicenter of DIPG lies within the pons, and the lesion involves the majority of the pons. Prior to the routine use of MRI, up to 15 percent of patients diagnosed with DIPG actually had a non-glial tumor and biopsy procedures were frequently undertaken for histological confirmation. Consequently, in the early 1990s when MRI became widely available, it was proposed that obtaining tissue for histology confirmation was not necessary in children with typical clinical presentation and distinctive radiographic findings on MRI. This recommendation was rapidly incorporated as standard practice given the perceived surgical risk in this delicate area. Since available therapies were primarily non-specific cytotoxic agents, the initial repercussions of diagnosis without tissue appeared to be of little consequence. Therefore, until very recently, the knowledge of DIPG came primarily from evaluation of autopsy specimens, small biopsy samples obtained from patients with atypical radiographic findings, and biopsy samples obtained from a small number of institutions such as the Necker Institute where biopsy has been routinely performed on children with suspected DIPG since 2003[21]. Because of limited tissue availability, very little information on the pathophysiology of DIPG has been available in the literature until recently. The importance of understanding the biology of DIPG has been brought to the forefront with the development of molecularly targeted agents. The use of molecularly targeted agents has not shown any improvement in survival in clinical trials for children with DIPG. The main reason of this probably relates to the fact that only therapeutic agents aimed at targets defined in adult high-grade gliomas have been evaluated.

In 2009 the first international DIPG meeting was celebrated at our institution, sponsored by the Alicia Pueyo Foundation. We all recognized that after 50 years of making no progress in the outcome of DIPG, the expertise existed to obtain tumor tissue for molecular analyses that could be used to determine treatment. The ethical issues of accessing the brainstem of a child for whom no therapeutic benefit could be anticipated were the major barriers raised. Different institutions and countries took the difficult journey of overcoming such barriers. In our institution answers came from the parents of children with DIPG who reminded us all of the principle by the philosopher and theologian Saint Thomas Aquinas: "*there are a number of human goods to which every human person is naturally inclined: the knowledge of truth. All men by nature desire to know and knowing is a mode of existing.*" Following our recommendations, parents took their children to Paris for biopsy and to obtain the molecular diagnosis of their child's tumor. They wanted to know. Furthermore, the tissue obtained from those initial biopsies allowed the establishment of our DIPG translational research programme, initiated in 2010. After two years, in April 2013, the first DIPG biopsy was performed at HSJD and thereafter all patients have been systematically biopsied. Since then considerable coordinated and collaborative international efforts have been made and more has been published on the biology and pathophysiology of DIPG in the past five years than in all prior years combined[22]. These studies have provided insight as to the possible cell of origin, genetic profiling, driver mutations, and oncogenic alterations. In February 2015 the third Alicia Pueyo international DIPG meeting took place at HSJD. Major strikes were presented including the two international biopsy-oriented clinical trials already ongoing and the preclinical translational consortium of DIPG laboratories. While the etiology and exact pathophysiology of DIPG remain to be determined, critical pathways and potential treatment targets have been identified, and critical conclusions can be drawn: (1) DIPG differ from adult high-grade gliomas, (2) DIPG differ from paediatric supratentorial high-grade gliomas, (3) genomic studies of DIPG demonstrate aberrations in druggable targets, (4) significant interpatient and intrapatient variability exists, and (5) the tumor microenvironment appears to play a key role in DIPG tumorigenesis. In our institution the first clinically, genotyped, functionally validated orthotopic animal model of DIPG has been developed, and cooperation between institutions to use the tool for advancing knowledge and therapeutics on a valid DIPG model is ongoing[23]. Preclinical pharmacol-

ogy is now available and better and more directed clinical trials could be designed increasing the chances of clinical success in the near future. The design of an immunotherapy based trial using the cell lines grown from DIPG patients biopsied at HSJD was presented at the 2015 DIPG meeting with accrual expected to start in October 2015. The elevated costs of the trial will also be covered by philanthropic donations of DIPG families, the same unconditional support for advancing knowledge they showed when ethical issues were raised for biopsy. In our experience, only when the families and patients were engaged in the decision-making process with regard to the enormous difficulties posed by the disease have advances occurred.

How do we protect children's research?

The numerous hurdles on the way of approving drugs for children

Neuroblastoma (NB), the most common extra cranial tumor of childhood, constitutes 7 percent of all cancers in children less than 15 years of age, 90 percent of patients being less than 5 years old at diagnosis[24]. About 60 percent of NB patients greater than one year of age at diagnosis present with distant metastases and most of these patients will achieve remission with dose intensive chemotherapy and surgery. However, despite aggressive multimodality therapy, most patients relapse and survival remains poor with a three-year event free survival of <30 percent[25]. Eradication of minimal residual disease (MRD) remains the major challenge in improving prognosis. Immunotherapy, with its potential for target specificity, is a promising approach to eliminate chemotherapy-resistant NB cells. Most of the clinical experience in immunotherapy of NB has focused primarily on monoclonal antibodies (MoAb) against cell membrane antigens like the gangliosides GD2, GD3, and GM3.

Gangliosides are complex, acidic glycolipids found on the outer cell membrane. They are found mostly in nervous tissues, and serve as membrane receptors for viruses and are important for cell adhesion. GD2 is a ganglioside normally expressed during foetal development and highly restricted to the central nervous system in healthy adults, with low levels of expression on peripheral nerves and skin melanocytes[26]. GD2 has been found to be expressed in neuroectoderm-derived tumors and sarcomas, including neuroblastoma, retinoblastoma, melanoma, small-cell lung cancer, brain tumors and sarcomas. Because of its surface expression on tumor cells and restricted normal expression in the brain and low levels in the periphery, GD2 has been an ideal target for the development of MoAbs, which cannot cross the blood–brain barrier[27].

The murine IgG3 MoAb 3F8 was initially developed in 1985 by Nai-Kong V. Cheung. It has undergone extensive preclinical testing and was the first MoAb to be studied in patients with NB[28]. To date, more than 500 patients with NB have been treated with 3F8 therapy. MoAb 3F8 is a murine IgG3 with the highest reported affinity for GD2. Phase II clinical data have demonstrated that 3F8 when combined with the cytokine GM-CSF can significantly improve the survival of children with metastatic NB. Concerns about the development of human anti-murine antibodies in a majority of patients treated with 3F8 led to the development of chimeric MoAb ch14.18. Ch14.18 (Dinutuximab) consists of the variable heavy- and light-chain regions of the murine anti-GD2 mAb 14.18 and the constant regions of human IgG1 heavy-chain and κ light-chain. Dinutuximab is produced in the murine myeloma cell line SP2/O. In vitro, dinutuximab binds to neuroblastoma tumor cells and is more effective than its murine counterpart (14.G2a) in mediating the lysis of tumor cells with human effector cells. Immunotherapy with dinutuximab in combination with GM-CSF, IL-2 and RA, relative to standard therapy with RA, significantly improved outcomes in patients with high-risk neuroblastoma who had a response to induction therapy, autologous stem cell transplantation and radiotherapy. At a median follow-up of 2.1 years, dinutuximab recipients had significantly higher EFS rates (66 vs. 46%; $p = 0.01$) and overall survival (OS) rates (86 vs. 75%; $p = 0.02$) compared with standard therapy recipients in a randomized, open-label, phase III study[29].

In 2010 the United Therapeutics Corporation and the National Cancer Institute (NCI) signed a Cooperative Research and Development Agreement to develop dinutuximab (Unituxin™; ch14.18). In June 2011 the EU recognized the status of dinutuximab as an orphan drug and in December 2013 the

EMA accepted the marketing authorization application. In June 2014 the US FDA accepted the biologic license application and on 10 March 2015, the US FDA approved intravenous dinutuximab, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2) and 13-cis retinoic acid (RA), for the treatment of paediatric patients with high-risk NB who achieve at least partial response with prior first-line multiagent, multimodality therapy. The marketing authorization application for dinutuximab for the treatment of high-risk NB in the EU was approved on 21 May 2015, 30 years after the report by Nai-Kong V. Cheung describing the first MoAb against GD2.

Dinutuximab is the first and only drug approved for the treatment of neuroblastoma and has been developed integrally by academic research sponsored by public and philanthropic funding. More than one million dollars have been invested in its development. Now the price negotiation is pending but the prospects are €100,000 per treatment, a huge expense that will be certainly limiting its use in most parts of the world. This is a huge ethical burden that will keep our children worldwide as far from increasing their chances of cure from NB than before marketing approval for this new drug.

Legal barriers and wrong models

1. Traditional oncology drug development

For more than 40 years, the development of new cancer drugs has followed a linear pathway, beginning with phase 1 single-agent assessment in adults. Single-group phase 2 trials in adults generally follow with the proportion of patients achieving an objective response (complete or partial responses) as the primary endpoint to establish efficacy. Only after phase 2 trials in adults are completed then phase 1 in paediatrics are implemented only if registration for adult indications is made worthwhile according to the previous phase 2 trials. In the USA and Europe, a major delay in the initiation of early-phase clinical trials by companies occurs. Paediatric investigation plans require review and approval of a complete development plan for adults before any paediatric clinical data are available. As a result, companies delay initiation of phase 1 investigation while trying to develop complex phase 3 development plans for adults and waiting for paediatric investigation plans to be approved. Overall, in the past 20 years, this approach in paediatric oncology trials has not yielded many new drugs, and the few novel agents discovered have had little effect on children with cancer.

Early-phase development of paediatric cancer drugs differs substantially between the USA and Europe, in terms of regulatory requirements, structures and governance. The US National Cancer Institute, through its Cancer Therapy Evaluation Program, funds a consortium focused on paediatric phase 1 cancer trials that has supported trials directly, and also trials by industry collaborators. In Europe, an integrated research network was created in 2003 to run early-phase trials sponsored by industry and academia and a target evaluation programme. The Innovative Therapies for Children with Cancer consortium (ITCC) runs new drug trials through project funding from industry, national grants, and philanthropic organizations, but no sustainable European funding for infrastructure is available. This difference in public funding largely explains why almost ten times more early-phase trials are done in children in the USA than in Europe. As a result, outside the USA, most children and adolescents with relapsed or refractory cancer do not have access to early clinical trials (like the Dinutuximab example) investigating innovative compounds.

As in DIPG, investing in biology and preclinical research to more comprehensively understand the biology of paediatric cancers is essential to identify key drivers of tumor progression and dissemination. The results of whole-genome sequencing of paediatric tumors have shown that, contrary to adult cancers, mutations are not frequent in paediatric tumors. Other mechanisms, such as epigenetic modifications, might be more important. Therefore, pursuing the path led by the pharmaceutical industry in adult cancer will likely yield very few advances on drug development for children´s tumors. Therefore, specific initiatives like the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program, funded by the US National Cancer Institute, to facilitate the identification of potential treatment targets for childhood cancers, will be a great resource for biology-driven drug development in the future.

Improved preclinical models of childhood cancers are needed to prioritize agents in the clinical development pipeline. The Pediatric Preclinical Testing Program (PPTP) funded by the US National Cancer Institute provides one approach, and allows the study of new drugs in well characterized in-vitro cell lines and in-vivo xenografts. New patient-derived orthotopic models, transgenic, and ex-vivo three-dimensional models need further investment and investigation. The reinforcement of basic science and predictive, innovative, preclinical pharmacology should be the major force driving new drug development for children.

2. Orphan diseases and drugs: new models of partnership

Most parents of a child with a life-threatening disease demand innovative treatments. As the biopharmaceutical industry copes with changing regulations and incentives, an improved approach is needed to coordinate research efforts. One difficulty is the small number of children who are potentially eligible to participate in research for any particular disease, and research cannot be prioritized solely by the biopharmaceutical industry or the regulatory agencies. Instead, the academic community, with the support of patients' and parents' advocates, need to lead the way.

In the USA, key legislative changes in 1997 have now become The Best Pharmaceutical for Children Act and the Pediatric Research Equity Act[30]. The 2007 Paediatric Medicine Regulation in Europe combined some elements of the US approach, resulting in paediatric investigation plans, which are based on incentives and requirements for the pharmaceutical industry[31]. The consideration of childhood cancer in the development of new drugs for adult indications is increasingly being integrated into industry drug development strategies. However, these legislative initiatives have limitations. First, the legislation only addresses how cancer drugs developed for adults should be studied in children. Industry does not pursue first-in-children indications because of a lack of incentive. To address that, in 2012, the Creating Hope Act was enacted in the USA, creating an incentive that is transferable to other drugs developed and submitted to the administration by the same company.

Second, drugs are labeled for cancer on the basis of a nosological indication, even though the drug for a common adult cancer might be highly relevant to a nosologically distinct paediatric cancer[32].

Conclusions

According to our experience and in my opinion, if we want to protect our children, the best way is not to have them 'safely' excluded from (potentially harmful) research but to have them actively participate in research. Children's research should be a required activity and part of the objectives for all practicing clinicians at the leading institutions. Children's research should be reinforced and promoted by the governors and sponsored by the public health authorities. Importantly, children's research should be exempted from the abusive wages of current clinical trial infrastructures.

Initiatives like "kids and families impacting disease through science" (KIDS health) are generating novel areas of interaction between regulatory bodies within institutions and professionals. The goal of such initiatives is to generate interest among kids for innovation and research so they can help in the design of new research projects and clinical trials. In those interactions parents and children are given the adequate voice to be part of research teams, a key factor that has proved successful in our experience. Furthermore, it is our firm belief that parents and children should also be part or regulatory agencies and ethical committees, as experts. This way, the balance of risks and benefits from research can be openly discussed by all parties involved, including children.

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Assessing the degree of maturity of the child for his/her involvement in the decision making process

Introduction

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Evaluating a child's level of maturity is very difficult, and is a task that involves a huge level of responsibility (both in moral and professional terms). The granting of *informed consent* by a participant in clinical research is not just a task to be ticked off a "to do" list by completing a questionnaire or holding a short interview. Informed consent is based primarily on the consideration of three aspects:

- The *information* provided: this must be appropriate to the child's age, and capable of being understood by the child, given their level of maturity.
- The *capacity* to understand the information provided, the consequences, and any potential alternatives.
- The *freedom* to take part in the research or not, and to withdraw from it after it has begun.

The minor's decision should be based on their own, personal values (which may or may not be the same as those of their parents or of the medical staff).

In addition, evaluating the minor's *level of maturity* requires us to identify other factors, including:

- *Cognitive development* and reasoning capacity.
- *Comprehension* of the proposal, based on the child's accumulated experience (which in turn depends on their education, family values and previous medical contact).
- *Autonomy* of the decision: this can be influenced (both positively and negatively) by parents and medical staff.
- *Nature* of the decision: this is very important because the child's decision may vary depending on the seriousness of the illness, the time required to take the decision, and whether or not the consequences are irreversible (remember that up until seven years of age, children consider many irreversible situations in daily life to be reversible).

When considering these factors, it is also important to bear in mind that values may change over time (as is the case in adults) and that children may experience time differently (children live in the present and find it hard to envisage the future). It is also important not to be misled by physical appearances (the physical maturation that comes with adolescence is not necessarily accompanied by emotional maturity), and to remember to consider factors such as stress, and the influence of the medical condition itself.

In bioethics it is important to remember that the paediatric population is particularly *vulnerable:* it is easy to under-estimate their cognitive capacity (based solely on physical appearance), but it is also important to be aware that the stress of being ill can cause emotional regression. The development of decision-making capacity is a gradual process, and unfortunately there is no standardized way of testing it. In conclusion, it is necessary to combine three parameters to evaluate maturity:

- The level of *maturity*: what is involved in understanding the decision.
- The *seriousness* of the decision: there is a useful tool for this, Drane's sliding scale competency model.
- *Contextual* factors: such as stress, the chronic nature of the illness and family pressure.

In seeking to answer this series of challenging questions, I had the honour of introducing two exceptional speakers: Mark Sheehan of the University of Oxford, who drew on the document "The participation of children and young people in clinical research," focusing on the core issues addressed in it. And Montserrat Esquerda of the Hospital Sant Joan de Deu, Lleida, who presented a range of instruments to evaluate cognitive maturity in children, distinguishing between instruments to evaluate their decision-making capacity in clinical processes and those used in research processes.

In the question and answer session, issues raised included at what age a child is considered to be a mature minor, the differences between legislation in different European countries with regard to recognizing the capacity of minors, and whether minors experience the placebo effect. There was agreement that the document published by the Nuffield Council on Bioethics and the Víctor Grífols i Lucas Foundation provides a good starting point from which to identify criteria for evaluating the child population.

The child: the focus of protection and the holder of rights

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Childhood has its ways of seeing, thinking, and feeling that are proper to it.

Nothing is less sensible than to try and substitute our ways.

Jean Jacques Rousseau

One of the basic principles of the current research paradigm is the requirement that individuals consent to their participation in the project. This has created a paradoxical situation with respect to patients who are minors. On the one hand, children are protected and are thus excluded from clinical trials because they lack the capacity to grant full consent.

On the other hand, this very fact means that children are exposed to risk, because the lack of prior studies means that up to 50 percent of prescribed drugs lack studies of safety and efficacy in a specific pathology or age group[1].

As a result, we are seeing a gradual shift towards including minors in the decision-making process, viewing them not just as the focus of protection but also as the holders of rights[2,3]. This change in our attitudes towards minors reflects not only ethical considerations but also a clear trend in the legal sphere towards considering the minor as possessing rights, even if the law varies from country to country[4].

The rights of minors include the right to develop their own personality and the right to take decisions in a way that is proportionate to the individual's capacity and maturity. This recognition requires a delicate balancing act because the minor is immersed in a family and cultural context in which the child is both entitled and, to some extent, obliged to develop the capacity to take decisions[5].

It is against this background that the document developed by the Nuffield Council of Bioethics on "Children and clinical research"[6] describes three possible scenarios.

- Scenario one: the child who is *incompetent* to decide (babies or small children, and children whose illness or clinical situation renders them incapable of making a decision).
- Scenario two: *children who are capable of developing points of view and expressing their opinion*, but are not yet competent to take a decision on a fully autonomous basis.
- Scenario three: children or adolescents *who are capable of deciding for themselves*, but who are still minors as far as the law is concerned.

It is important to remember that maturity develops gradually, as the minor's abilities and skills increase over time. In this context of gradual maturation, we need to be able to decide which of the three scenarios above applies to the minor in any specific situation.

However, there are no standardized procedures or instruments to evaluate the maturity of the minor, and instead we are forced to depend on the subjective assessment of the researcher. This subjective assessment carries two risks: the risk that incompetent minors are required to take decisions when they do not yet have the capacity to do so; and the risk that competent minors are excluded from the decision-making process.

Recently, Irma Hein et al.[7] published an article in which they asked why it is so hard to make progress in assessing children's decision-making competence. And there is no question that it is a real challenge. In the 1990s, Rutter[8] described it as follows: "Often there is a wish, by courts and by researchers, that there be a suitable simple criterion or measure of competence. Unfortunately, not only is no such test available but … it is highly unlikely that such a test could be devised. Rather, the question is of a child's compe-

tence in a particular context, for a particular type of decision, given particular circumstances."

As a result, when assessing competence to take decisions with regard to research, it is important to consider the following[9]:

1. The actual *maturity* of the individual minor
2. The specific *type* of decision:
   - What decision has to be taken?
   - Risk/benefit of the decision
3. Specific *context and circumstances*:
   - Family, social and cultural context
   - Emotional state (stress, anxiety), presence of pain, etc.

This text focuses on the first point – assessing the maturity of the individual minor – in order to determine which of the scenarios described above is applicable.

The maturity of the minor to take decisions relating to research

The first challenge when assessing a minor relates to how we define the concept of maturity itself[10], and what type of maturity we are referring to. Maturity can be defined in terms of cognitive development, ethical-moral criteria or values, applied capacities or even socio-emotional development.

Cognitive development

The cognitive development of the minor must be sufficient for them to be able to understand concepts relating to the proposed research or clinical trial, and to the concept of illness. In particular, they must have sufficient cognitive capacity to understand information, evaluate alternatives and consequences, and be able to take decisions in a reasoned and reasonable manner.

Children's cognitive development follows a sequential pattern in which they acquire key concepts such as time, space, causality, permanence and order. These concepts are acquired gradually and enable the child to understand other, more complex phenomena such as illness or death.

The acquisition of cognitive maturity is a sequential, systematic and fairly predictable process in the majority of children, although not all children have the same level of development at the same age.

It is important to know what stage of cognitive development the individual child is at, to adapt to what the child can understand and what explanations they are capable of comprehending, such as how the body functions, and the causes of illness.

In his classic work on cognitive development, Piaget[11] describes the development and organization of intelligence in the child at different stages:

- Sensorimotor functioning during infancy (from birth to 2 years).
- Pre-operational thinking, primarily egocentric (from 2 to 7 years).
- Logical thinking based on concrete operations (from 7–8 years until adolescence).
- Logical thinking based on formal operations (from adolescence until adulthood).

This sequence may provide a basis for distinguishing between children in scenarios one and two, separating pre-operational thinking from logical thinking The appearance of concrete, logical reasoning would enable the child to express opinions and participate in decision-making, but formal operational thinking would be the minimum standard required to take health-related decisions, to understand the concept of illness, treatment, causality, the role of symptoms, of side effects, consequences, and the operation of the human body and of treatment mechanisms[12].

Another benefit of assessing cognitive development is the possibility of detecting children or adolescents with low IQ. There is a long psychometric tradition that has developed a number of instruments to measure intellectual development. Although many of these instruments are time-consuming to administer, there are sufficient rapid instruments that provide an approx-

imate assessment of the minor's cognitive level with a high degree of validity and reliability.

Ethical and moral maturity

Moral maturity, according to Kohlberg's definition[13], is the ability to take decisions based on internal principles that govern a person's life, in accordance with a scale of values, and with the capacity to act in accordance with these principles. Moral development is key to the development of values, preferences and options.

There are various theories of moral development, of which the most complete and widely accepted is Kohlberg's theory of the development of ethical-moral conduct. This author, a follower of Piaget, developed a theory of the development of maturity based on Kant's notion of justice.

Kohlberg starts from the position that individual moral development does not consist simply of internalizing social rules, but rather that the individual constructs new structures on the basis of interaction with the environment. This interaction goes through a number of stages which, like cognitive development, appear in all children and in all cultures.

1. Pre-conventional level: based on obedience of norms and authority, avoiding punishment (from 7 to 11–12 years).
2. Conventional level: based on gaining approval of others and maintaining good relationships with others, at the group or social level (from 12 to 18 years).
3. Post-conventional level: based on generalized ethical principles (adult).

Although this model was initially heavily criticized from a gender perspective, subsequent work has consolidated it as the most extensive and complete theory of moral development, with several longitudinal studies and numerous cultural comparisons (in up to 45 separate studies)[14].

The empirical basis that underpins this paradigm means there are a number of validated instruments to measure the level and specific stage of development of children and adolescents. However, these instruments were designed for studies related to the development of moral thinking, and this means that almost all of them are time-consuming to administer and correct, a process that requires a lot of experience, rendering them of little use in the consent process for clinical trials.

Applied decision-making capacity

To help answer the question of whether a person is competent to take decisions, whether clinical or research-related, a number of instruments have been developed to evaluate this competency in adults[15,16].

In the research field, there is the MacCAT-CR (MacArthur competence assessment tool for clinical research)[17]: this is a semi-structured interview, which takes 15 to 20 minutes to administer and a further 10 minutes to correct, and explores the four principal areas of decision-making: comprehension, reasoning, appreciation and expressing a choice. This has been translated into Spanish and validated[18].

Studies of the use of MacCAT-CR in children and adolescents are now being published. The most extensive, by the group led by Dr Hein[19], involved 160 children who had been proposed for inclusion in clinical trials. Of these, 54 (33.5%) were deemed competent based on the standard reference (subjective criterion of investigator) and 66 (37.9%) were deemed competent according to MacCAT-CR. No children were found to be competent below the age of 9.6 years.

However, the study that concluded that MacCAT-CR is useful in children also found that the problem of validation remains unresolved given the lack of external validation or a gold standard. Other studies propose the term "assent"[20] or seek to establish validation criteria[21,22].

However, establishing criteria, procedures and instruments to validate the maturity of minors remains unfinished business. One route would be to use instruments that have already been validated (for cognitive development or moral development) to validate instruments to measure applied capacity.

In addition to the question of maturity, it is also important to promote the minor's participation in the process of consenting to research. It is important to remember that, in individuals, the process of developing human capacities does not derive solely from genetic inheritance but depends also on interaction with the environment and with society. In other words, attaining maturity is not a milestone that is reached at a given age but depends, rather, on a multitude of complex factors, and thus involves a learning process.

The Royal College of Paediatrician and Child Health[23] in the UK offers a set of guidelines with respect to the active participation of minors:

1. Inform the minor in a manner that is appropriate to their level of understanding, helping the minor to feel that they have a leading role in any discussions of their own health.
2. Listen to the minor from as early an age as possible, promoting their participation and encouraging them to express an opinion.
3. Include the minor's opinions in the decision-making process, wherever possible, so that they assume responsibility for the decision to a proportionate degree.
4. Consider the competent minor as the principle decision-maker.

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Decision making in research[a]

Mark Sheehan

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What I am going to talk about in the next few minutes is the way in which the report constructs the ethical issues associated with decision-making research, and then a little bit at the end more specifically directed to these sort of questions about maturity. The idea of the report is to construct a particular picture of the problem, and to be clear about what ethical issues are at stake. It won't necessarily solve all the problems but what it will do is make those problems clear, and hopefully more manageable and negotiable.

So the first thing, as emphasized in earlier presentations, is the importance of *context*. The ways in which children and researchers and parents will respond to participation in research, the ways in which they will all be engaged or able to be engaged, will really depend on the context. It will depend on the nature of the research (whether it's interventional or the extent to which it's interventional); it will depend on the sort of practical aspects, such as how much time will it involve, how much trouble in missing school, those sorts of inconveniences; and it will depend on the child's own medical history and on the relationship between the person (the child, the young person) their parents and the researchers.

So here the kind of thing we might imagine is a child being involved in research in a medicalized setting for the first time, compared to a child who has spent the last portion of their life in medical settings. And so the idea of the medicalization of the child's life is really quite significant. They ways in which they are going to relate both to their parents in this situation, and to the idea of research, and what they understand are all going to be very different. And these differences are very important in how we think about the context of the decision and their involvement.

One of the things that follows from this is that there is not a straightforward linear progression for children. It's not as though their ability to be involved in decision-making, the way in which they interact, just goes from A to B in a straight line. Children develop in different sorts of ways. All those contextual factors will make a difference. As well as the context of the research itself, the context *outside* of the research will make a big difference: for example how their education is going, and how they are being brought up by their parents, will make a difference to the way they feel and respond.

The way in which the Working Party approached this was to identify three distinct paradigm cases to describe the situation, to pick out different elements of that variation and development. The idea here was that these three cases point to ethical issues. They don't attempt to categorize children and their development; rather, they pick up particular kinds of ethical issues that arise in different circumstances.

So I'll just go through these three cases briefly now. **Case One** is children who are not able to contribute their own view about participation. So here, as the paradigm example, we think about very young children or babies who are really not in a position to help decide whether they want to be in research, or have a view of what research is. However, the case is not necessarily restricted to very young children: it may also include children or young people who are very ill or unconscious. In this case, really what we are concerned about is working out that the children can't contribute their own view about participation. Obviously, the kind of issue that is then going to come up here is that of children's interests and their welfare, and that's going to be the correlative ethical issue.

Case Two is children who *are* able to form views and express them, but who aren't able to make independent decisions. I tend to think, I guess in my own mind, of a five or six-year-old: they very clearly have views, but you wouldn't in any sense put too much weight on that as determining their involvement. There might be some things – for example choice of breakfast cereal or television programme – that they will have a view about and you might want to re-

a This text is an edited transcription of a lecture.

spect that, but in other kinds of issues such as research you might think, "No, they're not…" This is not the kind of situation where the child is going to be given, as it were, a robust role in the decision-making. And it's not just five and six-year-olds. You might also include 'decision-naïve' twelve-year-olds – children who really haven't been faced with making these kinds of decisions at all and who don't quite have the sort of capacity to be able to express a strong view in that kind of case. Or again you might think of an older child who has a life-limiting condition, and again is not quite in the position of being able to understand and take it all in.

So the ethical questions that arise in this case are questions like: how should we treat these children; how should we involve them in decision-making; and *why* should we involve them in decision-making? They clearly don't have the capacity to make an independent decision, but they do have views. So there's a question about how those views enter into our consideration of their involvement. This is the question about assent, and the *process* of assent.

Case Three is where the child looks like they *do* have the intellectual capacity and maturity to make their own decisions. Now that the child has reached that level, we have to try to decide, to understand ethically, what role their decision should play in our understanding of their participation. Again the spectrum of ages comes in: we might have a very knowledgeable ten-year-old, or we might have a thirteen-year-old who has been involved in some non-interventional study, perhaps a questionnaire, the sorts of things that we might think the thirteen-year-old is capable of. Or we might have a fourteen or fifteen-year-old who is used to taking responsibility for decisions, and really does grasp these things.

So the ethical question that this case picks out is the question of when is the child competent to make a decision? And then how determinative will their decision be? So it's going to be those borderline cases that we need to be clear about but there are also going to be questions about what kind of *normative* or ethical power we give to the decision that they want to make.

Now, what you see very clearly, I think, is that these cases really focus on context – they pick out the variations in context, rather than picking out age groups. Given this variation in context, the question of whether or not a particular case applies, and how it applies, will be determined by lots of other things, and age is perhaps not a really good marker of that. So, as I said earlier, factors to do with the context and nature of the research, and the context of the relationship between the parents and the child, for instance, will make a difference to how we understand the situation in front of us with a particular child. And then we have to work out which set of ethical issues or which ethical issue applies most in this kind of case.

Each of these cases brings with them certain kinds of ethical issues, and these are linked with the principles mentioned by earlier speakers: respect for children as individuals regardless of age and capacity; recognition of children's developing capacity to make decisions; and concern for immediate and longer term welfare. Let's start with concern for the child's **immediate and longer term welfare**. We might think this one comes out of Case One – we can see that most clearly in cases where the child can't make a decision, where the child isn't able to express a view. And here the stark reality for the parents and the researcher is: how do we understand the child's welfare in terms of their participation in the research? Importantly, this principle doesn't disappear as the child gets older; welfare will always be a concern. But in Case One that concern is very much to the fore.

Then there is the **recognition of the child's developing capacity to make decisions**, to take on responsibilities. This, of course, is central to Case Three, where we have a child with decision-making capacity or something that looks very like it. How does that capacity feature in the decision, how does it feature alongside the parent's ability to consent, and the researcher's role in the decision to participate?

And then finally the first bold point there, this idea of **respect for children as individuals, regardless of age and capacity**. This is the idea that really comes out of Case Two, of trying to understand ethically *why* we should take notice or involve a child who has a view but doesn't have the ability to decide for themselves. And the thought here is that the child is not just a decision-maker, or a growing decision-maker: the child is also an individual. And individuals are due respect, irrespective of whether or not they are able to make their own decisions. And this recognition of each child as an indi-

vidual provides ethical justification for involving the child in the decision-making process.

Of course, *how* these things get balanced is going to depend on lots of different things, all of that context, and the principles are going to overlap. But we can use the three paradigm cases, and the principles that come out of them, to try to unpack how in the standard kinds of cases parents might go on to make a decision. And we can also understand their role in the decision-making.

So Case One again is the clearest kind of case: parents in this case need to think about welfare and wellbeing and the interests of their child – in short what is best for their child. And this is in a full sense of what is 'best' – allowing an account of learning about the value of helping others and the value of social participation, those sort of things, as well as just their own individual, physical or emotional wellbeing. The role of parents here is not just about protecting the child's welfare but also about being responsible for actions determining that welfare – determining what's going to count as the interest of the child by helping to shape who the child is. And so you might certainly say that part of their welfare is going to involve some of these kinds of things as well.

In Case Two, the idea here is that parents support their child as they gradually start to be involved in making decisions. So this is understanding one important parental role as a pedagogical role, teaching the child, bringing the child into a community of decision makers. And that's going to happen in different ways and to different extents. But in Case Two, the child is starting to express an opinion, starting to express a view, and that needs to be managed by the parents and encouraged in various kinds of ways. So it's important that the parents are responsive to the ways in which the child is starting to come up with views, and so understands the way the child is involved in these things.

And in Case Three, there is a shift because the child – the young person – now has capacity, and in these kind of cases a child's decision is really going to be the central thing. The child's view comes to the fore, and the role of parents in this kind of case is going to be more supportive and more advisory. Part of that advice is going to be to do with welfare, but you might see the parents' input in a slightly different light from in the previous sets of cases.

So what about the role of the professionals, the researchers, in all this, given our account of the role of parents? In Case One, the primary responsibility of the professional is going to be to help the parents to understand and make a decision about what is best for their child: to try to get a sense of the way in which they think about the welfare of their child, and to help them to understand how this particular piece of research and this potential participation might fit in. That support, of course, is not necessarily always right. So there might also be cases where the researcher will disagree with the parents.

In Case Two, the professional has a responsibility to involve the child, again treating the child as an individual, respecting the individual that the child is, making sure that the child is involved to the extent that they want to be, or making sure the child is involved to the extent that they're used to being involved. Again this ties back to our understanding of the parent's role of teaching the child how to be a decider. The responsibility of the researcher here is to be *part* of that process, not moving against it, neither forcing a kind of involvement on the child for which the child is not ready, nor denying the child the kind of involvement that they are capable of having. The aim is to involve the child at the right level and to the right extent.

Importantly, this is about a *process* of involvement. It's not about whether or not the outcome of that involvement is recorded and how it's recorded, though ideally that's important. But the focus here is really on the process of involving the child appropriately, rather than on achieving a particular outcome, whether assent or dissent or neither. What matters is the process.

In Case Three, the researcher really needs to respect the child's or young person's ability to make their own decision by asking for their *consent* and not just assent, as well as asking the parents to consent. So in Case Three we have a dual element of consent.

Importantly, one of the things that matters in all this, and that fits with the ethos of the report, is this idea of the **shared decision**. Certainly in Cases Two and Three this seems clear, that the emphasis on involvement and the ethical principles that I've been talking about push towards decisions being made together, both where the child is able to consent for themselves, and where the focus instead is on the process of involvement and assent.

And the question we might expect the researchers to want to ask about involvement of a particular child is whether inviting *this* child to take part in *this* research constitutes a 'fair offer'. Is it the kind of research where the risks and burdens to the child are adequately balanced in the light of the benefits of the research? Is the way in which they are being involved appropriate, and not exploitative? Does it fit with the ways in which the parents have been teaching the child to make decisions? Is there a possible benefit from participating? Is it compatible with their welfare? These are all going to be questions that the researcher will be asking. And then there is the question of how best to show respect for the child or the young person as an individual. This might be just at the level of an assent, of giving a view and listening to the view; or it might be at the level of respecting the decision that they make. And even prioritising that in particular kinds of ways perhaps over the parent's view or in conjunction with the parent's view.

Finally, a couple of points here to make about the cases of disagreement, because these principles are not going to make all the problems go away: there may still be conflict and disagreement. The parent's views don't always cancel out other things: the other obligations that researchers have are still in play, and parental consent makes their child's participation in research legally permissible but not mandatory. So just for example, if the parents are prepared to give their consent, the researcher still has the responsibility to think about welfare, to think about the way in which welfare is applied in this particular case and to think about the process that is involving the child. Has the child been involved in the right kinds of ways? These are the obligations that just don't fall away. And we can still imagine cases where each of the three parties to this decision are in disagreement. We can imagine the parents and the child wanting to participate but the researcher feeling uneasy. We can imagine the child and the researcher wanting the child to participate but the parents feeling uneasy. And we can imagine the child feeling uneasy and the parents and the researcher being interested in the child's participation.

And in each of those kinds of disagreement, there are going to be different circumstances, and it can go either way. So we can imagine cases where the parents and the child want the child to participate but the researcher is uneasy, for example because they're not convinced that research participation in this particular case is a 'fair offer'. And the other kind of case, perhaps the most obvious kind of case we think of, is where there's parental consent but the child is a bit uneasy. So in these kinds of cases, one of the things that we thought as a Working Party was that the child's views and preferences are always important. They are not always going to be the only thing to take into account (for example, because of parents' responsibilities to take account of their child's welfare), but they are never going to be unimportant. So the researcher really needs to use their discretion in particular cases in understanding the context in coming to some kind of understanding about how this is going to work.

Assisting research ethics committees in their consideration of research involving children

Ethics in paediatric research: the role of the Research Ethics Committees

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The role of Research Ethics Committees (RECs) in the evaluation of paediatric research studies involves both an understanding of and a commitment to all the ethical obligations of research in adults, with additional obligations and protections. Children are an especially vulnerable population, and respect for children is the fundamental principle for research in this population. In the European Union, the rights of children involved in clinical research are ensured by Directive 2001/20/EC. In this regulation, a specific article (Article 4) ensures the protection of minors considering the emotional, psychological and physiological peculiarities of this population[1]. In January 2007 the European Paediatric Regulation[2] came into force with the aim of increasing the availability of drugs specifically studied in children and stimulating the implementation of high-quality clinical research in paediatrics. In February 2008, the European Commission issued the ethical guidelines for clinical trials in the paediatric population in an attempt to develop safe and effective medicines for children, defining the rules related to the balance between risk and benefit, consent and assent, the evaluation process and the ethical review of paediatric protocols[3]. This legislation provides recommendations on the ethical aspects of clinical trials involving children and constitutes a reference document for RECs.

Paediatric Research and Ethics Committees

1. The need for paediatric experts in RECs

The primary responsibility of the REC is to protect the rights of the person who enters a study. This requires and obliges the members to know the laws and regulations and to determine whether the study has been designed according to the ethical and legal standards applicable in the community and the country where the study is to be conducted. RECs reviewing paediatric research proposals must have experts in paediatrics with appropriate knowledge of the special medical, psychological, ethical and social needs of children[4]. It is expected that members of RECs are individuals acting for the best interest and welfare of the subjects under study. In practice, at least one member of the REC should be a paediatrician with expertise in bioethics and law, although in many paediatric studies it is necessary to use external experts to act as advisors, as in the case of studies involving special populations such as newborns, cancer patients or critically ill children.

2. Evaluation of informed consent

All the principles that should be met in the informed consent process in adults are applicable to parental permission to include a child in an investigation. The information provided must be written in a language understandable to the parents and the minor whose assent is requested. The REC, as well as ensuring that the text is understandable and appropriate for parents, must ensure that the assent of the minor implies an adequate understanding of the study by the child[5,6,7,8]. The child's age does not excuse the researcher from providing information. Maturity and ability to understand the research by the child is very variable and depends not only on their biological age or health condition. For example, young children with a chronic disease such as cystic fibrosis may understand the purpose of a study better than older children who have been previously healthy. From age of four, in general, the researcher must make an effort to explain the study to the child, and at six to eight years, in many cases, children will be in a position to agree if given explanations appropriate to their level of understanding.

The majority of the informed consent forms (ICF) for clinical trials in adult patients includes exhaustive information of the characteristics of the drug under investigation, the described side effects, the regulatory aspects of insurance and responsibilities of the patient and treating physicians that

are elaborated more for the sponsor's protection than for patient's information. This is particularly important for children participating in clinical trials. Most of the ICFs delivered to minors that have the age and maturity to assent are simple adaptations of the forms written for adults involving more colloquial language. Moreover, no effort is made to use more appropriate language for small children. The ICF should consider using cartoons or other simple ways of communicating with children. One way to achieve this objective would be including parents or young people as advisors in the elaboration of ICFs in all studies where children participate. In addition to providing better information to children and parents, this would help researchers to better understand the needs of the patients and their families.

It is beyond the scope of this review to explore in depth the final decision of minors participating in clinical trials, but RECs should emphasize that, when possible, the child assents to participate in the research by stimulating his/her participation in the decision and ensuring that the final decision is taken by the whole family.

3. Risk assessment in paediatrics

For an investigation to be acceptable in children[9,10] it must meet one of the following requirements:

1. Clinical research involving no more than minimal risk for the participant.
2. Clinical research that implies more than minimal risk but offers the possibility of obtaining a clinical benefit to study subjects.
3. Clinical research that implies more than minimal risk with no prospect of benefit to be gained individually, but which will generate a better knowledge about the disease.

If the study does not meet one of these three conditions, there is a fourth condition, which includes research that can help to prevent, alleviate or cure a serious disease that affects children. In this case, despite not fulfilling the three conditions, a paediatric study may be approved.

All protocols that include drugs that are going to be administered to children should be carefully evaluated and consider the same potential risks that are assessed in adults, with a number of additional risks for children.

These include, for example, the feelings of fear and anxiety of separation from parents, family or friends. Moreover, the number of invasive procedures should be minimized. Examples to minimize the risk include: limiting research in certain circumstances, such as pharmacokinetic and safety studies; combining these with (or replacing them by) pharmacodynamic studies; and minimizing the drawing of blood using micro-punctures and micro-methods.

Minimizing risk also requires that those who perform research studies in children are properly trained and that paediatric studies are designed with special care. In general, new drugs should be tested on adults for safety, pharmacokinetics and efficacy before being tested in children. For this reason it may be appropriate to delay the analysis in paediatric patients until Phase 3 of drug development in adults. However, the severity of the disease and the availability of alternative treatments may influence the decision to advance research in paediatrics. Also, when a paediatric disease has no equivalent in adults, as with certain congenital errors of metabolism, efficacy data in adults may not be available. However, even if there is no equivalent in adults, it is reasonable to obtain initial safety data before initiating any paediatric studies.

4. Monitoring and safety committees

Given that children are a potentially fragile population, we should provide more stringent safety control standards during an investigation. It is not possible to foresee all the risks associated with study drugs in children, and unexpected events can and do occur. Therefore, there must be an independent data analysis and safety monitoring committee for all Phase 3 trials conducted in children[11]. A committee of independent external security for some phase 1 and 2 trials, especially in the case of blind studies, may also be necessary. It is also essential to include a monitoring committee in all paediatric studies to ensure that the study is suspended immediately should an

unexpected problem be detected[12]. For Phase 1 and 2 trials that do not have an external committee, a strict monitoring plan must be ensured.

5. Paediatric research plans

The 2007 EU legislation on medicines for paediatric use marked a radical change in the European Union regarding the stimulus to develop medicines for paediatric patients and improve the information available on the use of medicines in children[13,14]. For the first time, pharmaceutical companies were required to study drugs in the paediatric population and develop appropriate formulations for the child's age. As a reward or incentive for this effort, pharmaceutical companies have an extension of patent protection and market exclusivity. In addition, the regulation establishes a network and a program of paediatric clinical trials for off-patent drugs funded by the Framework Programmes and a Paediatric Committee based on the European Medicines Agency (EMA), responsible for the approval of paediatric investigation plans (PIPs), was created. All drugs approved for paediatric use will be identified with a new symbol on the packaging. Since 2007, there has been an improvement in the number of pharma-sponsored trials for new medicines in children, mainly in paediatric cancer. However, attempts to have many off-label drugs commonly used in children approved were less successful and advances in this setting have been minimal in recent years.

6. Special considerations: research in newborns and critically-ill children

The difficulties identified so far in assessing the ethical aspects of research in paediatrics produce a greater paucity of studies in particularly vulnerable populations, such as newborns and critically-ill children. In contrast, the use of medications without approved indication is even greater in these children, as are the use of treatments or application of techniques without proper knowledge of their efficacy and safety. In a report published by the Ethics Group of the Newborn Drug Development Initiative[15], the main conclusion were the additional difficulties in the design and performance of clinical trials in critically-ill newborns, emphasizing the point that both doctors and parents must be convinced that clinical studies in neonates are scientifically necessary and ethically appropriate. The report makes the complexity of obtaining parental consent for research in critical neonates very clear. In some cases, parents may consent before a critical event occurs, such as in the treatment of cardiac arrest, inotropic support in the postoperative period of cardiac surgery or the treatment of subclinical seizures. However, in other cases, parents may be under considerable pressure, as occurs at the unexpected birth of an extremely premature infant or term newborn with perinatal suffering. These circumstances force researchers to be especially careful in assessing the ability of parents to freely decide to participate in a clinical trial. Therefore, there should be a very careful assessment by the ethics committees of the adequacy of clinical trials in these highly vulnerable patients and they should be limited to centres where the staff have specific training, experience and competence.

7. Adapting RECs to European regulations on research studies in paediatrics

In 2012 an initiative funded by the Seventh Framework Programme called Task Force for European Development of Drugs for the Young (TEDDY) conducted a survey of RECs in the European Union as to whether the European rules for conducting paediatric studies were known[16]. The survey consisted of 12 questions in two sections:

1. RECs and paediatric research under European legislation: the degree of knowledge of it and its impact on the activity of the committees.
2. The interest and involvement of RECs in paediatric research.

The survey was sent to a thousand RECs identified among EU members, and answered by 18 percent of committees. The level of knowledge of European legislation was very limited and a substantial number of RECs had no experts in paediatrics. In addition, most RECs belonging to the initial 15 members of the EU (EU-15), which includes Spain, stated that the paediatric regulation was generally unknown and therefore did not influence their decisions. By

contrast, among the new EU members, knowledge of these regulations and their impact on decision-making was significantly higher. These results suggest that the new EU members are more committed to the integration and harmonization of ethical standards for research. On the second set of questions, most expressed interest in updating knowledge about studies in this age group. The main conclusion is that there is a lack of understanding of the risks and burdens acceptable in clinical research in children of different ages. As a result of this, the authors proposed to develop a practical guide to ethical issues in paediatrics for RECs. This guide should emphasize ethical aspects of paediatric care, the authorization process, consent and assent, the need for paediatrics expert members for review paediatric studies, the training and education of members of the RECs, the use of placebo, compensation for damage and other relevant aspects of studies in children.

In conclusion, the ethical aspects of paediatric research pose a challenge to the RECs, which should ensure the adequacy of the studies conducted in the paediatric population. Children subject to clinical research should be specially protected as vulnerable but this vulnerability should not be an excuse for not doing research that should directly benefit children. Only institutions with experts in paediatric research must perform paediatric trials. These should ideally have a paediatric investigation plan approved by a committee of experts and their ethical aspects carefully evaluated by an ethics committee. RECs evaluating paediatric studies should have at least one member who is a specialist in paediatrics and the European regulation that applies to paediatric studies should be known.

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Assisting research ethics committees in their consideration of research involving children

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This lecture will give an insight into the routine work carried out as member of a paediatric Research Ethics Committee (REC) at Hospital Universitario Niño Jesús. REC is an independent body made up of health care professionals and other non-health specialist members responsible for ensuring the protection of the rights, safety and welfare of human subjects involved in a clinical trial and to provide public assurance, by an opinion on the trial protocol, about the suitability of the investigators and the adequacy of facilities, and the methods and documents to be used to inform trial subjects in order to obtain their informed consent. Most of what we do at RECs is legally regulated: aspects such as composition of the committee, timing of work, interactions with trial promoters, researchers, the national medicines agency, etc.

In order to comply with the above requirement to "protect the rights, the safety and the welfare of the humans that participate in a clinical experiment", REC members:

- assess the methodological, ethical and legal aspects of the clinical trials protocols
- consider the balance of risks and benefits for subjects and society
- check that the conduct of clinical trials is in accordance with the protocol
- evaluate experimental, observational or any other type of studies affecting humans

- assess (scientifically and ethically) and eventually approve, paediatric investigation plans (PIPs)
- make sure that the sponsor informs the public prosecutor about authorizations for clinical trials whose population includes children.

At Hospital Niño Jesús, an exclusively paediatric hospital, the list of members of the REC is as follows:

- two persons outside the health professions, one of whom must be graduated in law
- one pharmacist working in a hospital
- one pharmacist working in primary care
- one clinical pharmacologist
- two pediatricians involved in clinical work
- one nurse (university graduate)
- one member of the healthcare ethics committee
- one member of the hospital research commission.

The presence of an expert in legal aspects is mandatory, and he or she must be always be present during deliberations, otherwise the conclusions have no legal value. The other members represent the different departments involved in the care of children in the health system. Nine is the minimum number of members. At least one of them must be not related to the centres leading the trials or the projects. All members must act freely and voluntarily from the very beginning, and they must apply for membership not to the REC but to the hospital authorities. All members must sign a confidentiality agreement before starting to participate in the deliberations, since the information we deal with is confidential.

When evaluating each and every project, either a clinical trial promoted by big pharma companies or a small clinical study proposed by an independent researcher, we follow four basic principles of bioethics: no maleficience (do no harm), justice (give each his own), autonomy (self-governance) and beneficence (do good). We evaluate the projects in terms of their scientific validity, and also the competence of the people behind the investigation. We need to see that the study has no unacceptable bias towards any population, that possible harm has been anticipated and compensations are prepared,

and we need to estimate the impact of the study beyond the cohort of patients that will be recruited.

The principle of autonomy is probably the most important for us. We need to be sure that the research project does not interfere with the right of the children and their families (or legal guardians) to take a decision about themselves. We will take some time talking about how the information in the trial is passed to the patients, when the patient is a child. Finally, the principle of beneficence deals with the risks the patients bear if they choose to participate and the benefits they may receive, knowing the risks will always be the minimum, otherwise the study is not ethically acceptable. This is important: participation in a trial will not prevent the participant from receiving the best therapy representing the state of the art.

Autonomy in bioethics recognizes the ability of the individual to decide what can be done with his or her body. All potential participants must be consulted for their willingness to participate after comprehensible information has been provided. This information is collected in a very important document, which is the Informed Consent that the participant will sign before entering the trial. Another aspect related to this principle is the confidentiality that must cover participation in the study. Surrogate decisions are an everyday feature of the work of paediatric RECs. When trials are performed on minors or incapacitated persons, it is necessary that parents or legal guardians give their consent to participate in the study (presumed to want the best for the participant). If the children are 12 years or older their assent to participate in the study is also needed, and there is a moral obligation to respect their decision.

When the subject is a child:

- Parental or legal representative informed consent must be obtained prior inclusion in the trial; consent must represent the minor's presumed will and may be revoked at any time without any harm to him.
- When the child is 12 or older, he/she must also give consent (assent) to participate in the trial.
- The minor will receive information about the trial from staff with experience in dealing with minors, appropriate to his/her capacity of understanding.

- The researcher will accept the expressed desire of the child to refuse to participate in the trial or withdraw at any time, when he/she is able to form an opinion based on the information received.

The informed consent (IC) is a major issue, as noted before. It is mandatory that the patient gives his consent and signs the form before he is recruited into the trial. To be valid the IC should be given freely, without external constraints and having received and understood all the information about objectives, benefits, alternatives, risks, etc. of the study. It must be clear that there is always the possibility of repealing/revoking the IC without explanation. There is no standard document that may be used in every case, but there are guidelines. It is very difficult to define the minimum information to be given, but the most widely criterion used by RECs is that it must contain everything a *reasonable person* should know before giving permission to participate in a clinical trial.

University Research Ethics Committees in the UK

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Introduction

This paper explores how University Research Ethics Committees in the UK are supported in their consideration of research involving children. The paper is largely informed by my role at the University of Sussex and the Nuffield Council for Bioethics report *Children and clinical research: ethical issues* (2015). My role, at the University of Sussex, is to manage and provide guidance, advice and support on research governance, ethics and integrity and to advise research ethics committees. In the Times Higher Education World University Rankings 201415, Sussex is ranked amongst the top 15 universities in the UK and is 34th globally for research influence, meaning that research is at the heart of academic activity at the University of Sussex.

In the UK we've observed increasing endorsement from organizations of the value and benefits of patient and public involvement in the design and review of research studies. This has also been the case in relation to children and young people with the Department of Health, the Royal College of Paediatrics and Child Health and the Health Research Authority making clear statements on the importance of the involvement of children and young people in research, in order to build evidence base, and to involve children and young people in the design and conduct of research.

Since 2010 the Department of Health and the National Health Service in the UK have increased the involvement of patients in choices about their care and treatment, and sought to increase patient and public involvement in research (Department of Health, 2010). A draft policy, currently out for consultation, will replace the Department of Health Research Governance Framework (2005), includes not just a steer towards the importance of involving care users, especially those from hard to reach groups "not only by their participation in research, but also through their involvement in the design and conduct of research, or as members of research approval bodies such as research ethics committees." (Health Research Authority, 2015).

Research ethics committees and research involving children

Many Universities in the UK are working towards greater transparency of ethical review and research standards, the University of Sussex' research standards are published on this website so that if members of the public or external stakeholders are interested this information is freely available[1]. The University of Sussex currently has patient and public involvement in research studies predominantly where it is a funder requirement, which tends to be for large clinical research grants or if there is an established patient or special interest group available[1] and willing to be involved.

In the wake of the 2104 Nuffield Council on Bioethics report Children and Clinical Research the University of Sussex decided to address its research governance structures in relation to research involving children and young people. The University has a considerable amount of research being undertaken involving the participation of children, young people and babies, some of it quite challenging in nature. An example of a research group undertaking research involving children as participants is the Child Anxiety Theory and Treatment laboratory which explores for example children's fear of the dark or of spiders, as examples of recent studies.

In 2013 I had the privilege to be part of the mock Research Ethics Committee in the films used in the Nuffield Council for Bioethics' research activity to ask children, young people and their parents[2] what they felt about the research ethics committee process and thoughts on the study being reviewed. As an exercise, I realized that how I review a study, or the views I have of children

and young people participating in research, had never been under public scrutiny before. The report's findings became more valuable for me because the report opened up the ethical review process for scrutiny.

The Nuffield Council for Bioethics' report demonstrates two years of investigation and consultation and provides evidence which reinforces the importance of the involvement of children and young people in research, in terms of study design, review of materials, seeking their expertise and supporting their participation in research. It has both recommendations for virtues research ethics committees (RECs)[3] should demonstrate and specific recommendations.

"A shift to acknowledge that children and young people have expertise in their own lives." (Nuffield 2014 p41). There are significant benefits to involving children and young people in research projects. The involvement of children and young people holds both intrinsic and extrinsic value to research projects. Being able to demonstrate that children and young people have been involved in the study design or review of materials increases the trustworthiness and integrity of a study. Seeking understanding of how a study can impact on a young person's life may help with compliance. By understanding and factoring in what is important to the children and young people in how the study is designed may lead to fewer drop-outs from studies. Developing recruitment materials that children and young people approve of and endorse will lead to an increase in recruitment numbers. Their involvement also promotes the benefits of participating in research and supporting it, which encourages wider public confidence in research.

The University of Sussex hopes for a positive impact from the Nuffield Council for Bioethics report on the ethical review system and standards in place. Some of the recommendations require cultural shifts of the understandings RECs apply to reviewing projects involving children and young people and explore deeply how RECs operate. The next chapter will explore the specific recommendations.

Recommendations from the Nuffield Council for Bioethics Report (May 2015)

The University of Sussex considers the following specific recommendations to be particularly helpful to support RECs, support researchers and to build internal, and external, trust in University research governance procedures.

Actively support research involving children and young people

a. "RECs should have a balanced approach between protective and facilitative. Ultimately RECs should support research involving children and young people and should not shy away from it because of the perception that this is riskier research with a more vulnerable cohort.[4] Paragraph 5.34 (p. 140) suggests that being overprotective may be as damaging as being insufficiently protective.

b. RECs should expect children and young people to have involvement[5] in study design and should encourage researchers to disseminate study findings to participants and through their institution's website." INVOLVE, funded by the National Institute for Health Research to provide advice and support on public involvement, defines public involvement in research as research being carried out *'with'* or *'by'* members of the public rather than *'to'*, *'about'* or *'for'* them. There are distinct differences between participation, engagement and involvement: *Participation* is defined as participating in research activities as a research participant; *Engagement* is outreach, stakeholder activities, activities to support the dissemination and engagement with outputs or outcomes of research; *Involvement* is undertaking the research: e.g., being in the role of researcher, seeking and obtaining research funding or being involved in designing a research project or reviewing recruitment materials or materials used to seek consent.

    i. The report suggests that RECs can be overprotective, which may be as damaging as being insufficiently protective. The perception

from RECs appears to be that children and young people are a more vulnerable cohort[6] and in turn that research is too risky. This has manifested in researchers shying away from undertaking research with children and young people and RECs preventing this. RECs need to balance their approach and ensure truly proportionate review. They should welcome studies involving children and young people and should have the expectation, especially in larger studies where there are interventional, impactful or longitudinal characteristics, to see evidence of consultation with children and young people.

ii. Across UK higher education institutions, research involving children (individuals under 18 years of age) is perceived to be high risk and therefore warrants a more stringent ethical review. The report challenges RECs to re-think vulnerability as an 'alert' rather than a reason to 'block' research. It is important for researchers and RECs to safeguard by checking that researchers are working to mitigate against risks or burdens for research participants. There needs to be an understanding of developmental context rather than a direct association with vulnerability in the context of clinical research. The report encourages a professional response to concerns about vulnerability by ensuring partnership with children and young in research and seeking the right professional expertise.

iii. Nuffield present the idea of a 'fair offer' to be what RECs should be looking for when reviewing projects ethically and suggest that researchers and RECs should be asking is it a fair offer: e.g., is participation compatible with welfare? "The fundamental role of ethical review is to ensure that an invitation to participate in research would constitute a 'fair offer' to children, young people and their parents, where the value of the research and its likely risks, burdens, and benefits have been carefully weighed up." (Nuffield 2015, p. 28).

iv. Understanding or having the capacity to review a fair offer as a potential participant raises questions around capacity and competence in decision-making. Hein et al. (2015) reflect on children's decision-making competence and question how regulatory models and RECs currently perceive maturity. They state that regulations concerning competency are established on a strong presumption that persons older than a certain age are competent, whereas younger persons are not and that age limits are practical but ineffective and arbitrary (2015, p. 3). "Children's competence to consent, however is currently not assessed in a standardized way. Moreover, neither the correlation between competence to give confirmed consent and age in children, nor which factors exactly contribute to children's competence, have ever been systematically researched" (2015, p. 2). Hein et al. reflect accurately that RECs lack empirical evidence to understand standardized and validated assessment tools and therefore RECs should not only encourage the involvement of children and young people but the participation of children and young people in research around maturity, competence to consent and decision-making skills. This empirical research is required in order for RECs to understand validated methods and to have reassurance which will avoid disproportionate concerns around competence and maturity.

v. In addition to the challenge the report makes against ideas of vulnerability the outcome of the work with children and young people could also challenge ideas around financial reward and reasons for participating in research. The comments of the children and young people in the films around financial incentives brought to the fore that altruism, seeing the wider benefits and societal responsibilities, may override any interest in receiving a reward for participating in research.

vi. **A recommendation for research involving other groups**: The learning from these recommendations has value which I suggest can be more far-reaching, beyond children and young people, to research involving other groups, for example marginalized, vulnerable or hard to reach groups, who are also regarded as too vulnerable and too risky to research with. Without information and evidence from research, the lack of knowledge, evidence-base and uncertainties will continue in the care and treatment these groups are provided. Making similar recommendations for

research with these other groups may also have the impact of balancing the approach from overly protective to facilitative and may help to build more evidence around the care of these groups and reduce complexities around facilitating research involving them.

Support for RECs and access to expertise

a. RECs need access to expertise. The report strongly recommends seeking access from external advisers with appropriate clinical expertise and from children, young people and parents. The report suggests to National Research Ethics System and Royal Medical Colleges that a database of experts is set up for RECs to have access to. The report also suggests the RECs form links with clinical research networks.
b. Recommendation 7 (2014, p. xxvi) suggests that organizations with individuals who are REC members are supported to do so by being provided with protected time.

    i. RECs, and researchers too, need access to appropriate expertise. The report strongly recommends seeking access to external advisers with appropriate clinical expertise and from children, young people and parents.
    ii. If RECs have access to this expertise the perception of risk may become more balanced and less overprotective because they have been reassured by appropriate information and expertise. Ethics applications will, I hope, also improve in quality and will take into consideration the personal needs and impact on the everyday lives of children, young people and their families. At the University of Sussex there is an intention to build on and encourage accessing relevant professional expertise and scoping access to established groups of children and young people who may review study design and materials.
    iii. The report recommends to the National Research Ethics System (run by the Health Research Authority) and Royal Medical Colleges that a database of experts is set up for RECs to have access to. The report also suggests the RECs form links with clinical research networks. Although at the University of Sussex there is access to academic expertise from specialists in neonatal medicine or paediatrics, for example, access to a database developed by NRES or medical colleges would be extremely valuable to universities and I hope would reassure researchers that the right expertise is being sought to review their study.
    iv. Seeking expertise from children, young people and their parents will depend on access to pre-established groups and their availability and willingness to review our studies. Setting up a young people's advisory group for a university would have cost and resource implications, which is important to take into consideration. I aim to develop stronger links with clinical research networks in the UK (CRNs provide the infrastructure that allows high-quality clinical research to take place, and help researchers to set up clinical studies quickly and effectively and provide health professionals with research training) and hope that this can key the university in to established groups who may be able to review some of our studies.
    v. The report also suggests that organizations with individuals who are REC members are supported to do so by being provided with protected time, this is an insightful recommendation as most RECs, in universities in the UK, are composed of volunteer members of faculty, who are time limited due to research and teaching and are not provided with protected time.

Virtues held by RECs

a. Paragraph 5.35 (p. 141) recommends that the way in which a REC conducts its business should be in accordance with the following professional virtues; and, secondly, that these virtues should be at the heart of what is expected of researchers whose protocols are under scrutiny. The report suggests that the features of ethical review processes, and ethical research practices, that demonstrate these virtues could include:

    i. Open and constructive communication between researchers and RECs, based on a shared understanding that any invitation to take

part in research must constitute a 'fair offer' in which children, young people, and their parents can reasonably place their trust.

ii. Openness with respect to communicating the outcomes of research, whether positive or negative, both to participants and to the wider public.

iii. Recognition by RECs of the role of professional judgment by the researcher, and the need at times to allow for professional discretion in the field: for example, through requirements describing guiding values and outcomes, rather than highly specified procedures from which no deviation is permitted (see paragraphs 6.10–6.14).

iv. Recognition by researchers of the role of RECs in scrutinizing their capacity to exercise that discretion.

b. An overarching virtue for researchers and those that manage or govern research is trustworthiness. The report states that children and young people and their parents will only take part in research if they can trust both the researchers and the way the research is organized. Equally, potential research participants and their parents must also be able to trust governance systems to trust the researchers who are subject to that governance. The report suggests that trustworthiness and confidence can be cultivated through openness and clear communication between the researcher(s) and potential research participants and their parents.

c. Research Ethics Committees need to be transparent about their processes around ethical review, for institutions, like universities, to be clear about the robustness of their ethical review system. As the ultimate beneficiaries of research, it is important that the public trust our methods of ethical review in order to trust the outcome of the research. It was significant that the virtue of trust, honesty and openness was reflected in the outcome of Nuffield's work.

d. My view is that RECs need to be self-reflexive around our demonstration of these virtues and to reflect on the approach we have, whether we have the balance right between identifying risks, having a truly proportionate risk perception and encouraging studies through support and facilitation. RECs can increase their trustworthiness through being open in how they review, sharing their processes, standards and systems externally. It is important that external stakeholders trust our methods in order to trust the outcomes of our research. We publish our research standards and expectations clearly on our website so that if members of the public are interested in the standards we uphold this information is freely available[7].

e. Recommendation 3 encourages allowing space for professional discretion in the field, and researchers in turn respecting RECs' ability to assess their capacity to exercise that discretion. A hypothetical example may be a researcher applying to a REC to use ethnographic methodology during their fieldwork, a circumstance where not all risks or research opportunities can be anticipated, the researcher can demonstrate their expertise and experience by considering how they can mitigate against certain likely risks and the protocols they will follow to seek informed consent e.g. in the event of a potential interview.

f. The REC must review the researcher's application in the knowledge that it is impossible to predict what will happen in the field. There can be a difference in expectation depending on the research field in terms of how much discretion is provided to researcher. For example, in clinical research there isn't much space for uncertainty in protocols, whereas there is more space provided to applications where there are ethnographic methods where every opportunity cannot be anticipated. An overarching virtue for researchers and those that manage or govern research is trustworthiness; my view is that, as well as increasing external stakeholder trust, there needs to be more trust given to researchers to exercise their professional discretion (providing their track record allows this). This raises the delicate issue of colleagues judging one another's records.

Building trust in research governance procedures

The report states that children and young people and their parents will only take part in research if they can trust both the researchers and the way the

research is organized. Equally, potential research participants and their parents must also be able to trust governance systems in order to trust the researchers who are subject to those governance systems and mechanisms. The report suggests that trustworthiness and confidence in systems, methods and research outcomes can be cultivated through openness and clear communication between the researcher(s) and potential research participants and their parents.

The University of Sussex seeks to foster a culture of professional integrity, not a culture of box-ticking and disproportionate risk perception, and the evidence provided by the Nuffield report supports our work in research integrity which encourages openness and honesty.

As the ultimate beneficiaries of our research, it is important that the public trust our methods of ethical review in order to trust the outcome of the research and I found it significant that the virtues of trust, honesty and openness were reflected in the outcome of Nuffield's work. These virtues have been a driving force in the research integrity requirements in the UK for research councils, and research suggests that it is customary practices which build research cultures demonstrating these virtues.

My hope is that evaluating how a university meets these virtues and being transparent about process and upholding of standards may renew public confidence in participating in research. No institution is immune from incidences of research misconduct or questionable research practices, considering the evidence demonstrated by the Nuffield report on the culture of scientific research in the UK (Nuffield, 2014) which summarizes that the pressurized research culture in the UK encourages the cutting of corners and a reduction in standards, how can institutions support their researchers to demonstrate the virtues of research integrity and those stated in the Nuffield report for children in research in the current research culture context?

A great deal of research and investigation has been undertaken by the UK Research Integrity Office, the US Office of Research Integrity and individuals like Dr Andrew Rawnsley at Teeside and Professor Nick Steneck at Michigan, around how to change a research culture and customary practices, habits and assumptions in order to foster these virtues in research practice. It will be important to learn from the research integrity[8] movement how to install such values of openness, rigour, transparency and self-reflexivity.

Conclusion

To summarize, the main recommendations from the report, which the University of Sussex will find useful in reflecting upon and developing its own practice, are that RECs need to have a balanced and facilitative approach, they should welcome studies to review which involve children and should not be too protective or restrictive in their review:

- RECs need to have access to expertise like professionals and children, young people and parents. Having access to this expertise, and with the involvement of children and young people in developing research design or reviewing materials, may assist RECs in being more facilitative because they are more reassured and therefore less protective. This is speculative but it is hoped this will hold added benefit.
- RECs need to be self-reflexive to consider the virtues demonstrated in their operation and in order to encourage and foster openness, honesty and a more balanced and facilitative approach. RECs can increase their trustworthiness through being open in how they review, sharing their processes, standards and systems externally and within their own institution to researchers.
- The learning from the Nuffield report on vulnerability as an alert not a reason to obstruct has potential value for research involving other groups: e.g., hard to reach or other groups who are also regarded as too vulnerable or too risky to research with e.g. in mental health issues, learning disabilities, marginalized groups. As Modi et al (2014) state, without information and evidence from research, lack of knowledge and uncertainties will continue in these groups care.

The University of Sussex has agreed to bring together a working group looking at involving children and young people in research and encouraging studies where children and young people are participating. This will be chaired by Professor Bobbie Farsides, and will include members of the medical school

faculty and members of faculty from other schools and departments who regularly have children and young people participating in their research.

At the University of Sussex I look forward to being a part of the working group looking at how we can implement Nuffield's recommendations into our processes, systems and mechanisms but also into our approach and into our research culture and virtues demonstrated by our RECs. I hope that we can identify how we can begin to involve children, young people and parents in designing studies, being consulted and reviewing materials and to working with the RECs at the University of Sussex to encourage, support and facilitate research involving children and young people as participants.

Although the University of Sussex aims to be transparent and open around research governance and integrity I think we could benefit more from looking at our approach and reflecting on what virtues we demonstrate and those we do not. My initial aim for the working group was to develop guidance for researchers to undertake consultation with children, young people and their parents around research design and reviewing materials. My aims now, after reflecting more fully on the recommendations of the report, will also be to undertake a review of the approach the RECs demonstrate with regard to applications involving children and young people participating and of the virtues recommended and how they are demonstrated in the activities of the RECs. I am also keen to see how this can improve the approach of facilitating and not shying away from research with other groups who are deemed too risky or vulnerable to research so that the benefits and impact of the learning form the Nuffield report can be much wider felt.

I look forward to undertaking this work and hope to have the opportunity to report the outcomes and learning with other institutions.

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Notes

1. http://www.sussex.ac.uk/research/standards/
2. I have used the term 'Parents' in the same way as the Nuffield report as the term which encompasses anyone with parental responsibilities and duties for a child or young person. The report uses the term parent(s) as an umbrella term which encompasses anyone with the responsibility of a parent e.g. parent, carer, legal guardian.
3. The scope of the report includes review of clinical research and social or psychology research and therefore Research Ethics committees (RECs) in the report includes RECs managed by the National Research Ethics Service (NRES)/Health Research Authority (HRA) and University RECs. Please note that some recommendations are for NRES led committees only.
4. Paragraph 5.18 states "it is particularly important to emphasise this two-fold (protective/facilitative) responsibility in the context of research with children and young people because of the nervousness with which many REC members may approach the question of involving children (particularly younger children) as study participants. Elsewhere in this report we have discussed and challenged the commonly-held idea that children and young people are automatically vulnerable in research, and also the associated assumption that the governance of research involving children should be one in which additional protections are heaped on top of those thought to apply to adults (see paragraphs 4.53–4.62). These assumptions about children's vulnerability may lead to the sense that it is always 'safer' to prevent research going ahead because of concern about an aspect of the study". (Nuffield, 2015 p. 134).
5. INVOLVE, funded by the National Institute for Health Research, to provide advice and support on public involvement http://www.invo.org.uk/posttyperesource/what-is-public-involvement-in-research/. INVOLVE defines public involvement in research as research being carried out '*with*' or '*by*' members of the public rather than '*to*', '*about*' or '*for*' them. There are distinct differences between participation, engagement and involvement: *Participation* is defined as participating in research activities as a

research participant. *Engagement* is outreach, stakeholder activities, activities to support the dissemination and engagement with outputs or outcomes of research. *Involvement* is undertaking the research e.g. being in the role of researcher, seeking and obtaining research funding or being involved in designing a research project or reviewing recruitment materials or materials used to seek consent.

6. Paragraph 5.18 states "it is particularly important to emphasise this two-fold (protective/facilitative) responsibility in the context of research with children and young people because of the nervousness with which many REC members may approach the question of involving children (particularly younger children) as study participants. Elsewhere in this report we have discussed and challenged the commonly-held idea that children and young people are automatically vulnerable in research, and also the associated assumption that the governance of research involving children should be one in which additional protections are heaped on top of those thought to apply to adults (see paragraphs 4.53–4.62). These assumptions about children's vulnerability may lead to the sense that it is always 'safer' to prevent research going ahead because of concern about an aspect of the study". (Nuffield, 2015 p. 134).
7. http://www.sussex.ac.uk/research/standards/
8. Research integrity, or responsible research conduct, is best defined in the Singapore Statement as;
   i. Honesty in all aspects of research
   ii. Accountability in the conduct of research
   iii. Professional courtesy and fairness in working with others
   iv. Good stewardship of research on behalf of others

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List of participants

Speakers

- Victoria Camps, President of the Víctor Grífols i Lucas Foundation.
- Montserrat Esquerda, Director of the Institut Borja de Bioètica. Paediatrician. CSMIJ Sant Joan de Déu (Lleida).
- Bobbie Farsides, Chair of the Working Party and Professor of Clinical and Biomedical Ethics at Brighton and Sussex Medical School.
- Soledad Gallego, Chair-Elect Ethical Research Committee and Head of the Paediatric Oncology Unit, Hospital Vall d' Hebron.
- Kate Harvey, Senior Research Officer, Nuffield Council on Bioethics.
- Jaume Mora, Scientific Director, Department of Paediatric Haematology and Oncology. Hospital Sant Joan de Déu (HSJD), Barcelona. Affiliated Member of Institut de Recerca de Barcelona (IRB).
- Isla Morris, Research Governance Officer, University of Sussex.
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- Mark Sheehan, Member of the Working Party and Oxford NIHR Biomedical Research Centre Ethics Fellow at the Ethox Centre at the University of Oxford.
- Katharine Wright, Assistant Director, Nuffield Council on Bioethics.

Chairs

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- Gareth Tudor-Williams, Chair-Elect, Clinical Ethics Committee and Consultant in Paediatric Infectious Diseases, Imperial College Healthcare NHS

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- Júlia Martín, Completing Ph.D. in bioethics and applied ethics, University of Barcelona.
- Concepción Martín, Department for Research into Cell Therapy and Regenerative Medicine, Carlos III Health Institute.
- Daniel Morgenstern, Consultant and Honorary Senior Lecturer in Paediatric Oncology, Great Ormond Street Hospital.
- M. Dolors Petitbo, Head of Psychology Section, Sant Joan de Déu Hospital.
- Joan M.V. Pons, Health Quality and Evaluation Agency (AQuAS).
- Javier Revuelta, Vice President, Business Development, Premier Research.
- Bernabé Robles, CREC, Parc Sanitari Sant Joan de Déu.
- Emília Sánchez, Assistant Dean for Postgraduate, Research and International Relations, Faculty of Health Sciences, Blanquerna Ramon Llull University.
- Núria Terribas, executive director of the Víctor Grífols i Lucas Foundation.

Publications

Bioethics monographs

40. *Ethical aspects of research with children*
39. *La incapacitación, reflexiones sobre la posición de Naciones Unidas* (Disability: some reflections on the position of the United Nations)
38. *Ética, salud y dispendio del conocimiento* (Ethics, health and waste of knowledge)
37. *Determinantes personales y colectivos de los problemas de la salud* (Individual and collective determinants of health problems)
36. *Ética y altruismo* (Ethics and Altruism)
35. *Treinta años de técnicas de reproducción asistida* (Thirty years of assisted reproductive technology)
34. *Ética de la comunicación corporativa e institucional en el sector de la salud*
33. *Alcance y límites de la solidaridad en tiempos de crisis* (The scope and limits of solidarity in times of crisis)
32. *Ethics and public health in times of crisis*
31. *Transparencia en el sistema sanitario público* (Transparency in the public health system)
30. *The ethic of care*
29. *Case studies in ethics and public health*
28. *Ethics in health institutions: the logic of care and the logic of management*
27. *Ethics and public health*
26. *The three ages of medicine and the doctor–patient relationship*
25. *Ethics: an essential element of scientific and medical communication*
24. *Maleficence in prevention programmes*
23. *Ethics and clinical research*
22. *Consent by representation*
21. *Ethics in care services for people with severe mental disability*
20. *Ethical challenges of e-health*
19. *The person as the subject of medicine*
18. *Waiting lists: can we improve them?*
17. *Individual good and common good in bioethics*
16. *Autonomy and dependency in old age*
15. *Informed consent and cultural diversity*
14. *Addressing the problem of patient competency*
13. *Health information and the active participation of users*
12. *The management of nursing care*
11. *Los fines de la medicina* (Spanish translation of *The goals of medicine*)
10. *Corresponsabilidad empresarial en el desarrollo sostenible* (Corporate responsibility in sustainable development)
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8. *The rational use of medication: ethical aspects*
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6. *The ethics of medical communication*
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Reports

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