

45. University College London and the European Network for Cancer research in Children and Adolescents 041113

1. What do you consider to be the main obstacles to recruiting children to research? How might these be overcome?

In the field of paediatric oncology, two kinds of obstacles shall be distinguished, obstacles to recruiting children efficiently (to recruiting enough children in CTs) and obstacles to recruiting children appropriately (to recruiting children in the proper ethical way) ([26]¹).

The proportion of children with cancer participating in clinical trial(s) during their treatment pathway is high. Obstacles to recruiting children efficiently are mainly related to:

- low incidence and therefore numbers even in cancer centers (rare diseases);
- regulatory requirements inadequate to cancer children needs;
- international cooperation is necessary but sensitive to localisms and time-consuming.

Although parents and patients are supportive of paediatric cancer research, to secure well-informed consent remains a critical issue in paediatric oncology. Obstacles to appropriate recruitment are mainly due to:

- psychological distress, especially if inclusion occurs near the time of diagnosis or relapse;
- inaccurate assessment of a child's chances to benefit from research (risk of misconception) and to what extent (risk of misestimation) ([23], [8], [9]);
- when treatments fail, research participation still has to be carefully balanced against alternatives (risk of futile inclusion – overmotivation) ([10]).

Without optimising recruitment in both respects, “experimentation would not stop. [It] would increase in the medical care setting”; in paediatric life-threatening diseases (especially in paediatric cancer), experimentation would develop in a non-scientific way and/or on unfair bases ([17]). Main answers to aforementioned obstacles are:

- to adapt innovative scientific designs of clinical trials, in order to maximize the statistical power on small populations (Bayesian designs) and to reduce the interval between two research studies (use adaptive designs, multi arm multi stages studies);
- to improve incentives for pharmaceutical industry to conduct trials in children and adolescents;
- to harmonize review procedures of protocols by ethics committees, locally as well as in Europe, in a view of maximizing both children's protection and consistency (thus predictability) of decisions ([2], [12]);
- to improve general public's information about clinical research, especially in paediatric conditions, by which people may feel more comfortable once in the situation themselves to make a decision about enrolling a child (example of

¹ References are detailed in Annex 2.

organ donation can be mentioned as an analogous setting in which early public information is a key factor in optimising accrual rates);

- to develop consent procedures which are not primarily oriented towards meeting formal legal requirements but towards fitting the needs and realities of overwhelmed parents facing high-risk situations for their child (need for careful communication and for therapeutic alliance) ([11], [6]).

As an illustration of such a situation-adapted consent procedure, when the inclusion in a clinical trial is required at the time of diagnosis (or at the time of disclosing a relapse), a two-step parental consent might be offered to parents, by which they could provisionally agree to start with the experimental therapy and then would be left with enough time to fully assess information properly and to provide (or to deny) appropriate informed consent to the entire procedure.

2. **Who should make the final decision as to whether a child participates, or continues to participate, in clinical research when parent and child disagree? What responsibilities do health professionals or researchers have in such cases? (You may wish to distinguish between children at different stages of development and/or the different ways in which disagreement may arise or be expressed.)**

It is to be noted that, in Europe, legal requirements can explicitly preclude to overriding a child's refusal to participate in research. French law states this way that: "In any event, their refusal or revocation of acceptance cannot be ignored" (« En toute hypothèse, il ne peut être passé outre à leur refus ou à la révocation de leur acceptation. » Code de la santé publique, art. L. 1122-2). Obviously, such legal dispositions are open to interpretation, at least according to a child's age and maturity; moreover it does not prevent intra-familial disputes about research participation to occur.

To arbitrate in intra-familial disputes on research participation relies on a definition of the nature of parental representation. Willard Gaylin early on distinguished between a Burkean (to do what is best for the individual) and a Millean (to do what the individual would do could he consent) definition of representation. He then concluded that he would be Millean with adults while being "dogmatically Burkean with the child" ([19], ch. 1). This echoes today's view that "pediatric ethics generally gives priority to beneficence over autonomy" ([14], ch. 1).

The prevalence of beneficence over autonomy in paediatrics actually has two meaningful consequences on the reply to the above question. First, decision should be made following objective (such as the "best interests" standard) rather than subjective (such as the "substitute judgment" standard) rules. Second, the rights of the child must be central in the decision about research participation; to disregard a

parental preference (if ever appropriate in child's interest) does not violate any parental right. Yet, this should never be interpreted in a way of marginalising the role of the parents and of leaving the child unprotected. This merely means that parents share responsibilities with professionals towards the individual child or adolescent, namely ([19], ch. 4):

- to avoid any conflict of interests (they are only agents of the interests of the child);
- to avoid any decision detrimental to the health or well-being of the child;
- to behave with diligence and competence (which means to comply with objective standards such as the reasonable person standard, for instance).

Accordingly, several variables and related intra-familial disputes about research participation may be distinguished in a view of suggesting principled replies to the above question. These variables and situations are summarised in a tentative table in Annex 1. Grey boxes designate topical situations where it is highly problematical to disrespect the views of the child or of the adolescent (i.e. to coerce the patient to undergo or to forego the intervention, being assumed here that patients are paediatric cancer patients). In a view of simplifying, situations where parents disagree are to be considered alike the corresponding situation where parents are like-minded and disagree with the patient (parental disagreement should never obfuscate child's interests). While it is desirable not to arbitrate intra-familial disputes solely on a case-by-case basis, it is of paramount importance to take the specifics of each situation into consideration and to maintain good communication, or "shuttle diplomacy" ([14], ch. 18), with patients and parents. For professionals, to elicit a disagreement with parental (or patient's) views should have as a primary objective to give the parents (or the patient's) an opportunity to reconsider their initial position and thus to restore a successful intra-familial dialogue in child's best interest.

3. How useful is the concept of assent? Is it helpful to distinguish between consent and assent for young people?

Only adult patients "are allowed to define their own concept of "best interests", even if their views [...] are very different from those of the rest of the society" ([5]). Accordingly, assent is not legally binding (by contrast with consent, where the law acknowledges to minors a capacity to decide for themselves like for adults).

To seek young people's assent is crucial, yet. Indeed, assent can be seen as playing three key functions in the care pathway of children and adolescents with cancer when they are involved in clinical investigations, namely:

- a function is both deontological and consequential: as children grow in autonomy and in maturity, to fully respect their dignity involves to take their assent into consideration in a correlatively increasing degree. Arguably, it also allows to better secure their adherence to research protocols;

- another function is educational: it is another basic need (in addition to healing) of sick children and adolescents to keep on developing and getting ready to make autonomous decisions. To involve them in medical decisions (including research participation) is a powerful mean towards that end;
- last but not least, assent has a documentary function: it is the only one way to get a direct access to a child's will. The appropriateness of a minor's wishes elicited during the assent procedure can be brought into question, but the accuracy of these preferences cannot (or at least, there is no better approximate).

4. **A 'shared' or 'collaborative' decision-making model is often advocated for decisions about a child's research involvement, involving the child, relevant family members and professionals. Is this a helpful approach? How might any problems arising in this model be overcome?**

In research on life-threatening paediatric diseases, there is no relevant way to think about any kind of "conscriptio" (or mandatory enrolment) in research. To think about a "moral duty" to participate in clinical research would even induce a slippery slope towards using children as "guinea pigs" for the sake of patients to come. As it is an alternative offered to patients, research participation has to be free and consensual between parents, patients and professionals. Shared decision-making in such settings is unavoidable; there is a matter of rights and of principled thinking, much more than a matter of utility and of consequential thinking.

Since professionals are free whether or not to offer this alternative, there can hardly be seen a situation in which a dispute may arise with the family on the opportunity to participate in research. Following the principle of equipoise, professionals must be uncertain enough about the appropriate way to proceed (without such uncertainty, either the experimental procedure would set a new medical standard or the offer to enter the clinical trial would be unethical). As surrogate decision-makers, parents are entirely free towards the professionals to consent to, or to deny, research participation, without having to justify their decision.

Claims for access to clinical trials or to experimental drugs outside clinical trials present a slightly different setting where professionals do not offer inclusion, but have either to accept or to reject it based on a request of the family. A shared decision-making in such setting can occur only if professionals are entitled to sufficient professional autonomy to deny inclusion or access to expected experimental drugs. The main issue in this respect is whether acknowledging to professionals an ability to open access only to "reasonable" therapeutic options (based on clinical evidence) impinges in terminally-ill patients' right to "self-

preservation” or “self-defense” ([3]). This latter view, rooted in a libertarian account of patient’s rights is at the very least debatable in ethics’ standpoint and its ethical plausibility is even more dubious in paediatric environment given the priority which is widely acknowledged to beneficence over autonomy.

Obviously, the issue of intra-familial disputes also remains especially relevant in the paediatric environment. In case of disagreement between both parents, a conservative principle should apply, namely that the child should not be enrolled in research. This principle would hold that it is a responsibility of the parents to agree in the first place and neither professionals nor the society can have any clue as about a proper resolution of such a dispute. Intra-familial disputes between child and parent(s) offer a different setting. Where only the child denies, or desires, research participation, objective standards about legal ability to consent and maturity to assess relevant information properly should apply; it is on society to set up the boundaries of parental authority.

Shared decision-making about research participation has three additional merits that deserve to be mentioned here:

- first, the need for a consensus between all parties recalls the nature of the medical encounter between doctors and families: consent is not a matter of contract (under the assumption that contract is based in distrust between partners), it is a matter of “alliance” or “covenant” (involving trust, “oath” and shared-commitment) ([20]);
- second, it offers a firm ethical background for professionals to tell the parents not to exclude the child in the decision-making, according to his or her age and maturity, provided that, based on his/her right not to know (as acknowledged in the *Oviedo Convention*), the child can elect not to participate in the decision;
- thirdly, it recalls the necessity and the value of maintaining a good communication between all parties. Here it can be referred to Myra Bluebond-Langner and colleagues’ model of a “shuttle diplomacy framework [where] there is room for dissent, and there is room for negotiation” ([14], ch. 18; quoted above). The main aspect in this respect lies in the distinction between agreeing with a decision and agreeing with the underlying decisional process; while, in the end of a dispute, a decision can be made with which some party can keep disagreeing, it is essential in paediatric healthcare environment that all agents (patients, parents and professionals) will agree on the underlying decisional process.

5. Parents’ views on whether (and how) children should be involved in decisions vary enormously both within and beyond the UK. How

should the law and professionals take account of such different parenting approaches?

To respect parenting styles is a liberal concern, a matter of the State, or the society, not intruding into the family sphere unduly ([30], ch. 3). While it is essential to respect the right to private and family life, it is also relevant to recognise the intra-familial conflicts that can arise between child and parents.

The first role of the law and of professionals in this respect should be not to preclude the possibility for the child to grow in autonomy, by deferring too much to parental preferences. Indeed, it is an equally strong liberal principle to acknowledge that children are “born to” the full state of equality with others, including gaining full autonomy. This principle carries a powerful limitation of parental authority, namely that it is temporary and goal-oriented, the goal being here to “leave a man at his own free disposal” ([18], §55).

Accordingly, the concern to benefit the child and to foster his or her interests should always prevail over the concern to respect parenting styles and parental preferences. Often however, not to intrude in the family sphere is a child’s paramount interest.

Clear and objective standards should always be applied first, and subjective standards (such as deferring to parental authority because of the age or immaturity of the child or such as respecting family values) should be called in only secondarily. This is not to say that parental idiosyncrasies (such as parenting styles) have to be marginalised against society’s concept of a child’s best interests; rather, this means that it is on the Law and professionals to design the choices left to parents in clinical research environment, so that these are “confined within the bounds of objective reasonableness” ([19], ch. 4). Deviations from principles (e.g. surrogate instead of autonomous decision-making) may be consequential in a given situation (e.g. in infants), but always constitute exceptions that are called incrementally to lose their justification as and when the child grows up. Two objective standards offer clear guidance, despite the need to further qualify it according to the specifics of the cases:

- *no double-agency*: professionals are the agents of the interests of the child (the patient). Both doctrines of the “best interests” and of the “basic needs” to be fulfilled offer additional objective rules for acting with paediatric populations;
- *no double standard*: following European human rights instruments, fundamental rights are the rights of any person regardless of age, gender or condition. For instance, the right to be informed about his or her health and the right to participate in medical decisions according to age and maturity is a right of “anyone”, thus of children as well as of adults.

**7. How helpful is the notion of the best interests of the child participant?
How would you define 'best interests'?**

The notion of the “best interests” is helpful for it elicits an objective standard for the fair handling of sick children and adolescents.

It allows setting up the respective roles and responsibilities of professionals and of parents towards children and adolescents. It also prevents paediatric research ethics discussion being obfuscated by secondary considerations concerning practicability (e.g. research facilitation) or convenience (e.g. parental preferences). Finally, it recalls that research participation is primarily about benefiting all children, including the actual patients involved in the clinical investigations (see below question 9).

Only a broad definition of “best interests” can be proposed, as including everything that is susceptible to promote a child’s health and self-realisation in a given situation. “Health” is to be held in its comprehensive definition by the WHO and “self-realisation” can be defined in the sense of allowing the child to live the most valuable life possible in his or her view.

Accordingly, a child’s best interest in participating in clinical research can be determined using two criteria, namely whether participation could benefit the child’s health directly or indirectly, and whether it could constitute a valuable achievement in his/her life. Latter criterion is developed by David S. Wendler as a new justification for children’s participation in research; it involves respecting the views of the child (if he/she is old and mature enough) but it is also meaningful in the view of younger children, since participating in valuable research projects can become “part of the narrative of the individual’s life” and make “that narrative a better [...] one” ([34], p. 150).

8. How can the rights and interests of individual children (potential participants in research) be balanced against the rights and interests of all children (potential beneficiaries of the knowledge gained by the research)?

The principle of a “balance” or of “proportionality” involves safeguarding the rights and interests of *both* parties. No balance can be struck where the rights or interests of one party are merely negated.

This approach involves avoiding “brave sinner”-like or supererogatory approaches of paediatric research ethics. Latter approaches would be prompt to acknowledge hard case situations (e.g. early phase non-beneficial research) as moral dilemma

situations where colliding interests are irreconcilable, thus calling for heroic resolutions. Paul Ramsey developed such a deontological approach to paediatric research in the early 1970s. According to him, no research involving children could be morally justified except in direct relation with their own healing ([29], p. 12sq.) while to stop making paediatric research would lead to deprive children from appropriate treatments; therefore, researchers are committed to behave on the edge of morality, to “sin bravely” ([27]). Such approaches do not fit empirical evidence about paediatric cancer research, showing that participating in research or at least being treated in a research cancer centre has a demonstrable positive effect on overall survival and quality of life. In addition, such approaches are outdated since they do not reflect contemporary claims about accessing new drugs through clinical trials.

Accordingly, the rights and interests of individual children can be balanced against the rights and interests of all children (or against society’s interest in the development of science) insofar as the rights of the former come first, it means inasmuch the rights and interests of those children currently in treatment and involved in clinical investigations remain in the forefront of ethical reasoning. Such a principled balance or proportionality approach avoids any notion of “interpersonal utility” or “interpersonal trade-off” where the benefits for future (potential) patients might outweigh the rights and interests of present (actual) patients inasmuch as the overall utility function would remain positive.

9. **Are there any situations in which you think it would be acceptable for a child to be invited to participate in clinical research when there will not be *any* personal benefit to them? If so, please give examples.**

This question is an invitation to further specify the former (proportionality-based) approach to paediatric research ethics.

This calls for a brief caveat. To motivate paediatric research on personal benefits is equally ethically problematical than to justify paediatric non-beneficial research. Indeed, it might pave the way for therapeutic misconception, therapeutic misestimation ([23], [32]) and/or for coerced participation (or “conscriptio”). Moreover, retrospective reviews show that, in phase 3 clinical trials, the prospect of individual benefit is slightly lower than 50% (and the amount of effect is generally small) while, in early phase clinical trials, it is highly unlikely to happen ([16], [24]). If these results were reversed, it might suggest that paediatric research violates ethical and methodological principles (e.g. “equipoise” or clinical indifference between both standard and experimental alternatives). Although research must satisfy obligations to participants ([1]), it does not primarily intent to benefit the individual patient.

The rather clear notion of “basic needs” helps in specifying the aforementioned approach consisting in prioritising the rights and interests of actual sick children and adolescents without precluding research developments. To care for children and adolescents with cancer means to make best possible efforts to fulfil two such basic needs, namely:

- to health, it means for paediatric patients to heal wherever possible and always to receive best possible care;
- to education and self-realisation, it means for paediatric patients to keep on developing and flourishing independently of their illness.

Ethical debates about the moral justification of non-beneficial paediatric research developed significantly over two different periods of time (in the 1970s and much more recently in the 2010s).

In the 1970s, three basic positions could be contrasted: 1° non-beneficial research can be justified based on reciprocity and sociality (it is rational to presume that children would volunteer could they consent, since this is the very condition for developing treatments) ([21], [22]), 2° non-beneficial research cannot be justified on moral, but only on consequential, grounds (thus researchers, alike the Machiavellian statesmen, are “brave-sinners” acting without moral justification out of necessity) ([27], [28]), 3° non-beneficial research can be justified based on a moral argument tied to education (it learns children to be altruistic) ([4]).

In 2012, the debate evolved following a novel proposal by David Wendler ([35]; [7], [13], [15], [17], [25], [31], [33]). Wendler suggests justifying non-beneficial paediatric research based on its value for the life of the child-participant: to participate in research is a valuable achievement the child can be proud of and thus is better off participating even if he or she had any personal benefit ([35]). Along this plausible moral justification of non-beneficial paediatric research, the reciprocity-sociality justification remains sound (future patients will benefit as actual patients benefit from past research) ([25], [17]). Finally, justification based on education (learning altruism) can also be relevant in older children and in adolescents, while former justifications are plausible whatever the age of the patient. A variant of the “brave sinner” doctrine today may be seen in the argument that should non-beneficial research be disqualified, “experimentation would not stop”, thus creating an (at least) equally unethical situation ([17], [15]).

Consequently, there are different – but sound – justifications of non-beneficial paediatric research. No one is compelling, yet. Accordingly, it would be fallacious to infer a “moral duty” to participate from any of these arguments. Participation in non-beneficial paediatric research is irreducibly a matter of individual choice (mostly mediated by parental consent), but not a matter of supererogatory behaviour or self-sacrifice (since participation can concur to fulfil some identifiable basic needs of

young patients and since it is subjected to objective risk-ceiling and public order measures to prevent unethical agreements – [35], [17], [7]).

Accordingly, the two conditions for non-beneficial paediatric research to be acceptable are:

- *subjective*, based on the basic needs of sick children and adolescents involved in the clinical investigations, and based on informed consent (most often parental consent);
- *objective*, based on the scientific value of the research (futile research is unethical) and on the level of risk tied to participation (see question 10).

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Annex 1: Table related to question n°2

SHOULD THE CHILD BE INCLUDED IN THE INVESTIGATION?		Patient is incompetent (ex. below age 7): she cannot understand fully what is involved in the intervention.		Patient is immature (ex. below age 14): must be established that she did understand fully what is involved in the intervention.		Patient is mature (ex. above age 14): she can understand fully what is involved in the intervention (otherwise, akin immature patients).		Relevant examples
		Parents want & child doesn't	Child wants & parents don't	Parents want & child doesn't	Child wants & parents don't	Parents want & child doesn't	Child wants & parents don't	
Does inclusion involve significant risks to child's health?	Yes	YES	*	YES ²	NO ³	NO	? ⁴	Phase 1 clinical trial.
	No	YES	*	YES	NO	NO	YES	Retrospective study.
Does inclusion involve a reasonable prospect of benefit?	Yes	YES	*	YES	NO	NO	NO ⁵	Phase 3 clinical trial.
	No	YES	*	NO ⁶	? ⁷	NO	YES	Blood sample collection.
Does non-inclusion have the potential to impact child's future life?	Yes	YES	*	YES	YES ⁸	? ⁹	YES	Experimental fertility preservation procedure.
	No	YES	*	? ¹⁰	? ¹¹	NO	YES	Accrual of residual samples in a biobank.

² Risk of parental over-motivation (heroic measures).

³ Personal value of participation (why patient wants to participate?).

⁴ Personal value of participation (why patient wants to participate?).

⁵ Standard therapy available, patient can be unduly risk-taking or undervalue inconveniences.

⁶ Would imply unnecessary coercion.

⁷ May depend on the social value of the research.

⁸ Parental preferences should not obfuscate a child's future.

⁹ Patient may come to regret her decision (preferences are not fixed).

¹⁰ Sound reasons justifying the inclusion, so the patient can come to value it later.

¹¹ May depend on the social value of the research.

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Key:

* = not relevant

? = situational (Manichean answer may disregard major interests at stake in individual cases)

Annex 2: References

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