

40. Instituto Nacional de Salud del Niño del Peru, Instituto de Investigación Nutricional del Peru, Hospital Nacional Edgardo Rebagliatti Martins, US Naval Medical Research Unit No. 6, NAMRU-6 311013

Response to the Nuffield Council Call on Research with Pediatric Populations

Working Group - Peru

Participants:

Dr. Luis Huicho, Instituto Nacional de Salud del Niño (National Children's Institute)
Dr. Miguel Oliveros, Instituto Nacional de Salud del Niño (National Children's Institute)
Dr. Mary Penny, Instituto de Investigación Nutricional (Nutritional Research Institute)
Dr. Teresa Andrade, Instituto de Investigación Nutricional (Nutritional Research Institute)
Dr. Teobaldo Herrera, Instituto de Investigación Nutricional (Nutritional Research Institute)
Dr. Julio Cesar Alfaro, CEI Hospital Edgardo Rebagliatti (National E. Rebagliatti Social Security Hospital)
Dr. Juan Garcia, Instituto Nacional de Enfermedades Neoplásicas (National Cancer Institute)
Dr. Claudio Lanata, Instituto de Investigación Nutricional (Nutritional Research Institute)

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

In Peru, there are two different research settings: Clinical Trials and Observational research.

Clinical trials are regulated by the Peruvian Regulation of Clinical Trials and its corresponding manual of policies and procedures, <http://www.ins.gob.pe/portal/jerarquia/2/990/reglamento-de-ensayos-clinicos/jer.990> and <http://www.ins.gob.pe/portal/jerarquia/2/991/manual-de-procedimientos-de-ec/jer.991>.

The current Peruvian regulation states that "the consent form requires the signature of both parents." At the Peruvian National Cancer Institute, almost 50% of the patients come from the provinces and are accompanied only by one single parent. Because of this, these minors cannot participate in the clinical research studies being conducted. In general, the rate of households run by a single parent in Peru is between 25% and 27% in urban areas. Children are excluded from clinical research because they only have one parent present to sign the informed consent.

There are also clinical trials with minimal risk, such as the community-based trials of food supplements. These studies generally present with the prospective of direct benefit for the pediatric population, however, the requirement for the signature of both parents in the informed consent remains. This requirement is in place for both, minimal risk and greater than minimal risk studies.

Observational studies are reviewed by some Research Ethics Committees (RECs) as clinical trials, and thus, subject to the same regulations.

One way to overcome this problem would be that the phrase “material impossibility (imposibilidad fehaciente)” be interpreted as the responsibility of the investigator to locate and inform the parent, and to accept the will of the parent who is present in cases where the other parent cannot be present. Not doing so is a restriction of the autonomy of the parent who is present as the sole care-giver. In the case of parental absence due to travel, the assenting minor may be enrolled in the study with the signature of the parent who is present and the missing signature may be obtained when the other parent returns.

The need for the signature of both parents in the consent form is also an obstacle for research studies on sexually transmitted infections in 15-17 year-olds at risk and who no longer live with their parents. In cases such as these, the consent of a parent, as a step prior to the assent of the minor, could not be requested from the parents without placing the minor’s well being at risk.

Many research studies with pediatric populations will be restricted if new observational research regulations are implemented under the same current restrictions for clinical trials.

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.)

The following aspects should be taken into consideration:

- a. The degree of risk involved in the study: in cases of greater than minimal risk, parents will need to make the decision regardless of the age of the minor.
- b. The availability of a direct benefit to the health of the minor, such as, a diagnosis or the possibility of treatment or others to which the minor may not have access outside the study. In these cases, parents will make the decision.
- c. Minor’s age: if a minor is 16 or 17 and states that he/she is not willing to participate, this will prevail. However, if the minor were 0 to 8, then it is the opinion of the parent because children are not requested to assent at such an early age.
- d. The family’s cultural characteristics: there are cases where the father has the final word, and other cases where both parents make the decision.
- e. Therapeutic misconception by parents: this will lead parents to consent for their child to participate. Information needs to be reinforced in the process of informed consent to avoid this mistaken perception on behalf of parents.

In Chile, Argentina and Colombia, the legal stand of a ‘mature minor’ allows a 16- or 17-year old to assent to research studies of, for instance, sexual behavior, without the consent of their parents. In Peru, the legal stand of a “mature minor” does not exist. In Peru, even mothers who are under 18 years old cannot consent for their children to be

enrolled in a clinical trial. The parents of the underage mother need to consent for their grandchild to participate and this, in many circumstances, impedes their participation in research.

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

We find this distinction between assent and consent useful. Assent is for minors and as such, it uses simple, easy to understand language. A minor's assent is required for his/her participation in a research trial and thus, his/her cooperation with the study procedures. As it occurs with the consent, a thorough assent form ensures good participation of minor subjects in the study.

If the name changes from "consent for minors", it may lead to documents that are harder to understand and this would deny the true purpose of the assent form.

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?

It depends on the family and their cultural habits.

Sometimes the 'collaborative' decision-making model is somewhat difficult logistically speaking. Its feasibility varies with each situation, and it should not be a requirement. It is good to promote communication between parents, children and researchers, and the latter should be available for any additional information.

In community-based research studies, the informed consent process ideally should start at the prospective subject's home and end with the signed form. In that process, all the family members are progressively informed, and if there is an important member, such as the grandmother or the mother-in-law, whose opinions weigh heavily in the decision making process of the family, these members should be involved in the process, even though they may not sign the consent form. This may also involve their attending the research center on the day of the signature, so they can hear and ask whatever questions they need to.

It is critical for the investigators to understand how far they can go so as not to cross the line and unduly influence the parents' decision, and to ensure that the investigators' input is objective. A good informed consent process is crucial in the enrollment phase, not only because it is the investigator's obligation, but also to ensure that participants are committed to the study and guarantee transparency of the research process. Participants must enter the study trusting the investigator and the study, based on the information they have received.

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?

It is hard to generalize and laws and regulations do not always consider the cultural differences among families. Parental decision making is oftentimes based on the availability of treatment at no cost their children will receive if they participate in the research study. Professionals and the law must keep this approach in mind, in addition to the cultural differences, and allow for a flexible informed consent process that is respectful to each family's idiosyncrasy and cultural patterns.

The role of the local research ethics committees is essential at this point in order to provide guidance to what is most appropriate with the local population, and if feasible, to conduct a community consultation and/or to talk to the community leaders.

6. Rewards (such as vouchers) for children participating in research may be welcomed as an appropriate way of saying 'thank you', or criticized as a form of undue incentive (to either child or parent). What forms of compensation/reward/expression of gratitude for research involvement do you think acceptable, and why?

Some of the researchers who contributed to this discussion believe that there should be some form of expression of gratitude for the participant, whether this is a reimbursement of expenses incurred or the time invested, or a monetary or in-kind compensation as a thank-you gesture. There is no consensus on what the best moment is to announce this compensation. Some investigators believe that the compensation should not be announced at the start of the study so as not to influence what should be a voluntary decision to participate. Others believe that it should be disclosed at the very beginning of the study so that participants may not think that compensation is provided because something has gone wrong in the study.

It is important to assess that incentives should be commensurable to the research context, that is, an observational study versus a clinical trial; a study that involves one single visit and a study that involves several follow-up visits.

Other researchers of our working group do not agree with compensations of any type for research volunteers, they believe that these compensations distort the voluntary nature of the informed consent process, placing a focus on the economic interest, which may include gifts. Even if there is no mention of compensation, all potential participants eventually find out and this changes their perception of the study. This group of investigators is in favor of reimbursement for expenses incurred while attending the research.

Finally, they recommend that if there is an appreciation gift, that this may be a photo or a diploma, and not something with an economic value.

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

It is a very ambiguous concept. The best interests of the child participant must be defined as what is best for the child but always keeping in mind his/her dignity. The best interests of the child refer to the quality of the medication, the quality of the treatment and proper care of the participant.

The question may be extended to “best interests of the pediatric patient” since there is little evidence in pediatric medicine. For example, in Pediatric Oncology, many children participating in research receive the benefits of brand-name medications, close follow-up during the study phase, and proper transportation and care when bringing them to study visits.

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 balance between the children’s rights and protection is achieved through the various review levels that a research study goes through.

Several issues need to be taken into consideration:

- a. Few children are enrolled in research studies and face their risks for the benefit of others in other countries and without a direct benefit. This is not a fair distribution of burdens and benefits. Adequate distribution of burden and benefits deals with no discrimination when selecting study populations. For example, investigators must not select study groups based on their condition of vulnerability. Studies that discriminate will not be approved. However, a point to consider in this particular aspect is that when the medications or vaccines tested become effective, the benefits may reach the whole world.
- b. When study results are not provided to the communities where studies were conducted, there will be less and less communities who are willing to participate in research, precisely because they do not see the product or fruit of their participation and they develop a distrust to the research process. There is very little experience available of clinical trials that provide results to the family members of pediatric patients. Additionally, for this delivery of results to the community to work, dissemination activities must be included within the original protocol plan and budget. Result dissemination activities help create a culture of solidarity to participate in research. It is also very important to spread the word

when the benefits of research finally reach the communities and the way in which they do. For example, in case of vaccines, their inclusion in national vaccination plans needs to be widely disseminated, particularly in the communities where studies were conducted, to ensure they enjoy the benefit, as well. In cases of new medications, wide dissemination is needed when these new medications are part of the national plan and become available to the population at large. The Ministry of Health is responsible to discuss with the sponsors appropriate terms to facilitate the introduction of these new medications, resulting from clinical research, to the public sector, particularly when they respond to a public health need.

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

We believe that said situations do exist. For example: a phase I trial which could be conducted in healthy pediatric population would be done in the population affected by the disease to which the drug is directed. To resolve the conflict, the study population would receive some benefit, even when the study is only testing safety or pharmacokinetics of the drug. In Pediatric Oncology, the participation of minors with an advanced stage of disease and no prospect of cure in phase I trials, whose results would benefit other children.

Some of the members of our working group believe that there are always benefits when participating in clinical research, and these may be indirect, such as a more detailed test, or easier access to medical care. The study would be acceptable if risk is lower than minimal and there is prospect of benefit to other children.

There is no agreement on the provision of compensation to minors participating in research as an incentive in the absence of direct benefit to the minor.

On the other hand, we must emphasize the need for strict and close monitoring of the safety and well-being of the child participant throughout the study process.

10. Are there any circumstances where it would be right for a research ethics committee to approve research involving risks they would usually regard as too high, if parents and young people had clearly expressed their willingness to accept these?

We believe that it is very unlikely for a REC to approve a high-risk study in the circumstances presented in this question. Clinical research is first approved by the REC and then presented to the parents and high-risk studies would most likely not be approved by RECs. There is always the chance that high risks may occur in the course

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of the study, and in that case, the REC must assess continuation or termination of the study in question.

The practice of open community consultation to discuss potential research studies before the review process is not frequent in our country.

If parents were willing to accept the participation of their children in high risk studies, an assessment of the real motives and interests of the parents would be in order.

11. Do you think the current regulations strike the right balance between promoting clinical research in children, protecting child participants, and involving children in decisions about their own participation? What (if anything) would you like to change?

In Peru, the current Regulation of Clinical Trials is extremely protective of research subjects, which leads to selection bias in the case of the requirement of the signature of both parents in the consent form. This also leads to the exclusion of minors due to their inability to meet the parental signature requirement. Another requirement that precludes pediatric research due to the Regulation is the mandate to have a hospital infrastructure at the study site, which greatly limits the conduction of community based, low risk studies. The current Regulation of Clinical Trials requires the same conditions from clinical trials and community based trials, thus hurting the progress of community-based trials.

What (if anything) would you like to change?

Clinical trials with minimal risk should be authorized to be conducted at study sites, such as medical consultation offices or the community. Clinical trials of greater than minimal risk should be conducted at greater complexity medical

As stated in Item 1, the phrase 'material impossibility' should be made more flexible and the definition of 'mature minor' should be added to the regulation in Peru.

12. With limited resources, how would you decide which childhood conditions should be the priorities for research? Who should be involved in making these decisions?

Pediatric diseases, to include diseases that affect teen agers, should be included in the research priority list, depending on the epidemiological profile of each country and of each region within the country. A study that assesses the disease burden based on disability-adjusted life years attributed to each condition, should be conducted. This type of assessment must be the guide toward disease priorities in the countries.

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In Pediatric oncology, not considered a research priority in Peru, the burden has profound impact on the sensitivity of the people, particularly now that there are greater treatment expectations for children. Pediatric oncology should receive special attention also given the high cost of treatment and burden, as well as its limited numbers.

Priority should be given to the disease that are more prevalent, more severe, and that affect the development of pediatric populations and have a high cost. The list of research priorities should not be restrictive nor impede research in other topics that are novel and promising, but not well known yet. Decisions on research priorities should be made by the local, regional and central governments in conjunction with the scientific community, this is a shared responsibility. Efforts should be made to ensure that decision makers do not have conflicts of interest.

13. What responsibilities do funders, researchers and stakeholder groups have to encourage the coordination of children's clinical research?

It is morally unacceptable to have such little pediatric research and to use drugs testing in adults to treat children without producing data in children. Funders and investigators are responsible to include pediatric populations in their study designs for new drugs, vaccines, devices and others. A professional panel, with the participation of all groups involved, should discuss, prioritize and encourage pediatric research as befitting the needs of the country.

14. What responsibilities do researchers have towards child participants and parents when the study is over?

The following are among some of the researcher responsibilities:

- Provide study results to each patient or to those who may be interested in them.
- Publish study results in collaboration with the sponsors.
- If it is a Phase III study and the final results indicate its benefit, researchers should discuss with sponsors a preferential Access to the experimental medication or product evaluated when it reaches the market, as appropriate.