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Clinical trials in practice: how to achieve the best protection of the study subjects?

The challenge of achieving appropriate protection of patients participating in clinical trials carried out in resource-constrained settings

Chairs

- Professor Asrat Hailu, University of Addis Ababa
- Professor Umberto D'Alessandro, Institute of Tropical Medicine Antwerp (Belgium) and Medical Research Council, the Gambia

Topics and presenters

- Informed consent and decision-making in vulnerable populations. The findings of a multi-methods study carried out in Burkina Faso. *Lea Paré Toé, IRSS/Centre Muraz, Ouagadougou, Burkina Faso*
- The research and the challenges for the community: the point of view of Community Advisory Boards. *John Mutsambi, International Partnership for Microbicides, South Africa*
- The role of clinical trial insurance in protecting health research subjects: is it possible? Is it sufficient? *Francis P. Crawley, Good Clinical Practice Alliance–Europe, Brussels, Belgium*
- The quality assurance of *investigational* medicinal products: challenges for the patient and for the research. *Christophe Luyckx, Quamed (Quality Medicines for All), Institute of Tropical Medicine Antwerp, Belgium*

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¹ European Developing Countries Clinical Trials Partnership

Introduction

The “Switching the Poles Clinical Research Network” brings together researchers from Belgium, Benin, Burkina Faso, Cambodia, Cuba, the Democratic Republic of Congo, Ethiopia, Indonesia, Nepal, Peru, Uganda, Vietnam and Zambia. It aims at jointly developing capacity, tools and procedures to apply universal standards for clinical research in resource-poor settings.

The Network was officially launched in 2008, as part of a programme for institutional capacity strengthening, funded by the Belgian Development Cooperation and coordinated by the Antwerp Institute of Tropical Medicine. Its motto is “Switching the Poles”, and its explicit aim is to transfer not only expertise but also resources and decision-making to the South.

Several network partners participate in EDCTP-funded projects, and this was the second Workshop organized by the Network at an EDCTP Forum (the first one took place in Arusha, in 2009).

The objective of the 2011 Workshop was to analyze the real-life challenges related to some major determinants of the protection of the individual and communities taking part in clinical trials, namely: the informed consent, the community engagement, the trial insurance and the quality of investigational medicines.



Panel 1: the research, the informed consent, the community

The decision to participate in clinical trials precedes the informed consent process Léa Paré Toé presented unpublished results of a social science project recently carried out in Bobo Dioulasso (Burkina Faso), to investigate the place the informed consent has in deciding to participate or not in a trial. This was an ancillary study of Malactres, a non-commercial trial conducted in Bobo-Dioulasso, Burkina Faso and comparing *in vivo* and *in vitro* efficacy of the national first-line antimalarial treatments. Overall, 440 children <15 years old were randomised to either Artemether-Lumefantrine or Artesunate+Amodiaquine and followed-up for 42 days.

The research consisted of a mixed methods study, based on the triangulation of qualitative data (interviews, focus groups, participants' observation and informal conversation) collected in health centres and at community level, and of quantitative data collected at different time points: an "entry questionnaire" was administered to the parent of potential trial's participants at the health centre before they met the trial team, an "exit questionnaire" was administered after they met the trial team, and a "follow-up survey" was conducted at community level two months after the inclusion in the trial. The surveyed population consisted mainly of women. Most of them had no formal schooling, worked in the informal sector (street vendors, small scale subsistence farmers etc.) and lived in temporary housing and informal settlements, with difficult access to health care.

A manuscript with the detailed results is in preparation. Nevertheless, preliminary analysis shows that more than half of people arriving at the health centre were already aware of the trial, based on information obtained through relatives, neighbors or health staff, and that almost all of them had already decided to agree to their child's participation. Most of those who did not know about the trial, stated that they would participate (again, before meeting the research team). Many even insisted to meet the trial team rather than the health centre doctors; nonetheless, only 1% of interviewed people had understood the research nature of the study, while many perceived the researchers as people providing free care, malaria experts or just as "people helping our children". The trial itself was often perceived as free care, aid or as the possibility to get better quality of care compared to the health centre standard of care. Strategies were developed by the potential study participants to be included, by attending the health centre very early in the morning, trying to negotiate inclusion, and even deliberately giving wrong information to the study team (e.g., hiding previous medication or medical symptoms, if it was known that these led to exclusion), which may be very risky for the patients and for the quality of the study data.

In a context characterized by socio-economical vulnerability and poor access to free health care, the *process* of informed consent does not always reach the goal of informing people and leading them to a free and informed decision. The "information role" is somehow anticipated by the community, and the decision-making process is guided by the desire to have access to free quality health care rather than by the information provided in the consent interview. It is

unclear how these findings are representative, as the Centre Muraz is well established in the surrounding communities. Therefore, additional information should be collected in research-naïve communities, though some results were substantiated by the comments from the audience, e.g. the negligible rate of refusals to consent in resource-constrained settings is seen by many as a serious matter of concern.

To make informed consent fulfill its “information role“, a better involvement of communities and its representatives is needed, for accurately spreading the content of the informed consent before and throughout the study. In addition, study-specific information forms should explicitly mention the difference between “research” and “aid”. The problem represented by fully free decision-making, however, remains an open challenge in communities that lack free access to essential health care. Hopefully, more insights will come from an EDCTP-funded research looking at the impact of clinical trials on communities and health systems, which will be carried out in Burkina Faso, Ghana and Zambia



Lea Paré Toé



John Mutsambi

Role of Community Advisory Boards in improving the ethical and scientific integrity of clinical research John Mutsambi addressed one of the questions posed by Lea: if and how the community engagement can improve the quality of a research and of the informed consent process.

“Community-engaged” clinical research should be grounded on solid formative research. Critical contextual information should be gathered, firstly on general aspects such as the community’ cultural beliefs, values and norms, its socio-economic status, levels of education and health services, the general decision-making processes and the gender and power relations; then, on how the community perceives “research”. This is a vast subject, which includes the reasons for participating in a trial, the understanding of research vs. treatment, the reasons of therapeutic misconceptions, the positive and negative myths about research, the language and comprehension challenges, the sources of information and the possible sources of indirect inducements (e.g. better standard of care provided to study participants).

Community Advisory Boards (CABs) may be operationally defined as “a volunteer group of interested community members representing a diversity of constituencies and sectors in the

larger community". Their roles often involve (but are not limited to) providing input to research centre staff, investigators and study sponsors on study design, protocols, informed consents, enrolment, recruitment strategies and community education.

CABs may play an important role for helping researchers to better understand the community and vice versa, so they should ideally be involved in all the phases of a research. In the pre-trial phase, they can provide accurate information on the community and on its perception of research, and may help to identify those factors that predispose a population to vulnerability. In the protocol development phase, they can provide inputs for the design of appropriate recruitment and retention strategies, for the translation of study materials into local languages and for the development of lexicon of research terms. In the implementation phase, they can help to channel accurate information to the community and educate it about research, while bringing community needs and concerns to researchers and eventually recommending adapted study results dissemination strategies. In short, CABs can provide bi-directional feedback between researchers and community. This view was echoed by various comments from the audience, who also reminded that CAB can collaborate with Ethics Committees (ECs), counteracting any biased statements of sponsors/researchers and helping them to get a balanced information.

However, CABs' contribution could be weak or even counterproductive, if the several challenges they face are not timely overcome: the risk of not being inclusive and diverse enough to represent the interests of the target population (resulting in lack of ownership by the community, and in the potential for conflict of interest); the risk of lacking autonomy to make fully independent decisions; the difficulties in understanding and communicating complex scientific concepts. Other concerns came from the audience: that CABs may put an additional bureaucratic layer to the already complex process of protocol's approval; that they are used as a shortcut for getting more easily the local ECs' approval, or as an easy way for outsiders to "enter" the community and get its trust. It was also noticed that the notion of "community entry" could dangerously overlap with the process of individual consent, which should never be replaced or "coerced" by a community endorsement to the research.

Various solutions were suggested to ensure that CABs are effective in providing bi-directional feedback and guaranteeing a *balanced relation* between the researchers and community (in particular, by educating the community and the individuals to critical appraisal of the research, including the possibility of refusal). CAB's composition should take into account the nature of the research; its members should receive adequate training on research literacy, protocols' and informed consents' review and research ethics. Logistical support is needed (meeting space, materials) as well as acknowledgement to CAB members for their role.

However, the operational and supportive link between a specific protocol/sponsor and the CAB should never create any kind of conflict of interest; in this sense, it was suggested by some participants that CABs should be operationally and financially de-linked from specific studies, for being fully autonomous and independent in their choices.

Panel II: insurance, quality of medicines, sponsorship

The role of clinical trial insurance in protecting health research subjects: is it possible? Is it sufficient? Francis Crawley reminded that the insurance for the trial's subjects (as well as the indemnity for the researcher) often arises as a major ethical and operational challenge in North-South/South-North collaborative clinical research.

The ethics of health research is characterized by a sort of polarity: on one side, the need to promote health research, because of its recognized contribution to public health; on the other side, the need to protect research participants and communities, based on the recognition of vulnerability and the fear of exploitation. Ethical review and informed consent are the two pillars of human subjects' protection in health research, but insurance is also part of the "protection package". It may be seen as a sort of back-up plan, to be used for providing compensation if things go wrong in a clinical trial (compensation can never be waived!). Nonetheless, according to the EDCTP¹, "clinical trial insurance is not addressed or is under-addressed in the applications. It is recognisably difficult to have insurance for clinical trials in some African countries, but it is unacceptable that no indication is provided in the applications as to how clinical trial participants will be compensated and supported if they are injured in a clinical trial. The EDCTP should develop guidance on clinical trial insurance and perhaps assist applicants in finding insurance brokers specialised in clinical trials".

How does regulation help research teams to address this topic? According to the ICH Good Clinical Practices (GCP)², "if required by the applicable regulatory requirements, the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence. The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirements...". The European Directive of 2001³ states that "a clinical trial may be undertaken only if [...] provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor", and that "insurance or indemnity must be considered by the EC". Thus, the burden of verifying the appropriateness of insurance is put on the members of ethics committee, in the European Directive as well as in the Helsinki Declaration⁴ ("...the EC must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards"). From a Southern perspective, the Ugandan regulation⁵ clearly states that "injury related to research participation may be physical, social or psychological", and that it may be classified as definitely, probably or possibly related, unlikely to be related or not related². In this framework, "... research participants shall be entitled to compensation when the injury is classified as *probably* or *definitively* related ... Sponsors shall ensure that research participants who suffer injury as a result of their participation in the

² Definitions are given for each of these terms

research project are entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap. In the case of death as a result of their participation, their next of kin are entitled to compensation". Also the guidelines of the Democratic Republic of Congo⁶ explicitly requires that "a copy of the insurance policy taken by the sponsor for covering the research participants [...] to be reviewed by the EC".

Thus, there is general consensus that insurance is mandatory in clinical trials, that it is the responsibility of the sponsor, and that ECs should ensure that it is present and appropriate. Nonetheless, academic sponsors and North-South collaborative consortia face a number of challenges (and there is indeed traditionally resistance to insurance from academics, irrespective of whether from the North or the South): a general poor awareness of insurance's requirements, difficulties in defining who is the sponsor and in funding the insurance and, in many resource-poor countries, the scarce availability of insurance companies and brokers for clinical trials. Other concerns were raised by the audience: how to ensure that patients in vulnerable communities are aware of their right to compensation? How can ECs get the expertise needed to assess not only the availability, but the appropriateness of the insurance? What to do in contexts where the personal liability of medical staff (malpractices or negligence) is not covered by a separate assurance? How to define a risk assessment to decide when an insurance is needed, and how to help researchers and sponsors to read and understand an insurance contract?

The right to compensation to an individual who suffered injuries in relation to a clinical trial can never be waived. Non-commercial sponsors and North-South research consortia, which share the same public health-oriented objectives and the same shortage of strong managerial and financial background, should look for joint solutions, e.g. by setting an insurance fund at national level or at EDCTP level, and by jointly developing guidance (e.g., on the risk-assessment for trials and on how to negotiate and read a policy insurance contract). Patients' awareness could be improved through the measures suggested by Panel 1, while the challenge of strengthening the capacity of ECs to adequately assess the insurance and follow up on its actual implementation remains open.



Francis Crawley



Christophe Luyckx

The quality assurance of investigational medicinal products: challenges for the patient

and for the research Christophe Luyckx started his presentation by giving an overview of the quality problems on the globalized pharmaceutical market. The current situation of “multiple standard” is sadly described by the example of deaths due to contamination with diethyleneglycol (DEG): in rich countries, the last case was documented in 1937, while an increasing number of cases continue to be reported in resource-poor countries⁷. The international attention has been focusing during the last years on *counterfeit medicines*, which are defined by the World Health Organization (WHO) as “medicines deliberately and fraudulently mislabelled with respect to identity and/or source”⁸; thus, they are always illegally manufactured and distributed. Conversely, *substandard medicines* are “genuine medicines produced by manufacturers authorized by the national drug regulatory authorities (DRA), which do not meet quality specifications set for them”⁹. Failure to comply with appropriate standard and specifications is due to inappropriate practices at different stages in the life of a medicine: poor adherence to Good Manufacturing Practices (GMP)¹⁰, poor quality of active pharmaceutical ingredients (APIs), lack of compliance with the specifications stated for the final products (e.g., content in API, dissolution or sterility tests etc.), poor stability, lack of therapeutic equivalence to the innovator (for generics), poor packaging, labeling and product information, poor compliance with Good Distribution and Storage Practices. Such failures have deleterious consequences for individual health, e.g. under-dosing, poor or irregular bio-availability, unexpected toxic impurities, decreased efficacy, cross-contamination with highly active molecules, decreased shelf-life, lack of sterility, accelerated deterioration due to poor packaging, etc. They may also negatively affect public health, for instance when underdosing and poor bio-availability trigger the development of resistances to antimicrobials¹¹. Eventually, non-compliance with appropriate standards will also negatively affect the reliability and validity of the results of clinical trials: defaults such as poor/irregular therapeutic equivalence, poor stability or impurities can seriously bias the efficacy or safety evaluation of a product, or the comparison between a trial’s arms.

Thus, the source of the investigational medicinal product (IMP)³ and of the comparator⁴ should always be selected among products that have been subjected to a rigorous and complete quality assessment, so as to ensure that the rights and the safety of trial subjects are protected, and that the trial itself will bring useful, scientifically valid results. The WHO GCP¹² says that they should comply with the “current GMP Guidelines published by WHO”⁵, and add that the sponsor is responsible of the quality of the IMP and comparator.

³ A pharmaceutical form of an active ingredient or placebo, being tested in a clinical trial. It may be a product not yet registered, or a product with a marketing authorization but used in a way different from the approved form, or for an unapproved indication, or to gain further information on an approved use.

⁴ An investigational or marketed product, or placebo, used as a reference in a clinical trial.

⁵ WHO Technical Report Series 957: WHO Expert Committee on Specifications for Pharmaceutical Preparations. 44th report, 2010

However, while commercial sponsors are mainly manufacturers and they may directly control the quality of medicines used in trials, most academic and non-commercial sponsors cannot directly control it, despite being accountable for it. Thus, how can they select them? Since it is the role of the national DRA to assess the quality of medicines tested or marketed in their own country, non commercial sponsors must firstly check that the investigational products and comparators have been authorized (for the trial or for marketing) by the national DRA in the study country; but unfortunately this is often not sufficient. In fact, according to the WHO only 20% of its member states have fully functional DRAs, while 50% have DRAs with variable capacity, and up to 30% have DRAs with limited or no capacity¹³. This weakness, due to the lack of sufficient resources, negatively impacts on the DRAs' capacity to verify rigorously the safety, efficacy and quality of medicines tested or marketed on their territories.

Therefore, non commercial sponsors should establish internal policies to comply with this responsibility. The Switching the Poles Network, for instance, applies the following policy:

IMPs in phase I-III trials (by definition, not registered yet)	IMP in phase IV trials, and comparators in all phases
Selected if manufactured at a site which is:	Selected if the product is:
a) Approved by a stringent DRA: ICH member ⁶ or observer ⁷	1) Registered by a stringent DR: (ICH member or observer)
b) Approved by WHO pre-qualification programme ⁸	2) Approved by the WHO pre-qualification programme
- It is also suggested to check if it is planned to submit the product dossier to WHO PQ or a stringent DRA (including <i>ad hoc</i> mechanisms: EMA Art. 58 ⁹ , FDA tentative approvals ...)	3) Received the scientific opinion of EMEA under article 58.
	- If no products qualify, seek technical advice of an independent Expert Group

Sponsors have the responsibility to ensure that the quality of medicines evaluated or used as comparator in clinical trials have been verified according to rigorous criteria, in order to avoid risks for the patients and serious bias for the study result. This responsibility is especially challenging for non commercial sponsors, who cannot directly control the quality of the investigational medicines and who cannot always rely on the judgment of resource-constrained national DRAs. Thus, they should put special care in selecting only medicines which have been approved by a stringent regulatory body.

Meanwhile, an authoritative forum like the EDCTP could provide a platform for guidance, taking into account the multiplicity of standards in the global pharmaceutical market.

⁶⁶ The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities of Europe, Japan and the United States (<http://www.ich.org/cache/compo/276-254-1.html>).

⁷ They include the European Free Trade Association (EFTA), currently represented by Swissmedic (Swiss Agency for Therapeutic Products), Health Canada and WHO, and some countries which are associated with an ICH member : Australia, Norway, Iceland and Lichtenstein.

⁸ <http://apps.who.int/prequal/>

⁹ European Medicines Agency Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the WHO for the evaluation of medicinal products intended exclusively for markets outside the community. EMEA/CHMP/5579/04. Rev.1 7th November 2005

Some inputs and suggestions for the way forward

- Supportive **social science research** is currently neglected or underfunded in clinical research, but it may greatly help to improve communication between the research team and the community, as well as to design and implement the consent as an efficient and fair process, adapted to the specific context of a research site.
- Similarly, **Community Advisory Boards** can improve communication and reduce the power imbalance between the researchers and the community, while informing the community about their rights (e.g., the right to refuse and the right to compensation for trial-related harm). However, they should have fair representativeness and appropriate skills, and they should work in coordination with other local actors, like ECs. To ensure full autonomy and independence (e.g., from sponsors), they should also be operationally and financially “delinked” from a specific study; for instance, the local research institution could earmark a percentage of overheads from different projects, for creating a fund to support the local CAB.
- In socio-economically vulnerable communities, the **lack of free access to care** may impair the capacity of free decision on informed consent, pushing the patients to consent for the sake of free care. This remains an open challenge, especially for non-commercial sponsors which depend on external funds and have less budgetary flexibility (e.g., to ensure free treatment to all screened patients, for reducing the gap between the study care and the routine care).
- Some measures, needed to fulfill **sponsorship’s responsibilities** by protecting trials’ participants, are especially challenging for academic and non commercial sponsors. These include:
 - The moral and legal obligation to provide adequate compensation to those who suffered harm due to a clinical trial: this should be achieved through **insurance**, but it is difficult to find companies and brokers in developing countries, as well as to fund and negotiate the insurance (there are no contract templates’ models, nor risk assessment scales to guide the sponsors). Non-commercial sponsors and North-South research consortia should join forces for developing guidance documents and for exploring innovative solutions: e.g., an insurance fund could be constituted at national level or under EDCTP.
 - The responsibility to ensure that medicines tested or used as comparator in clinical trials are quality-assured: generally, non commercial sponsors cannot directly control the **quality of the investigational medicines** (sponsor and manufacturer being two different entities) and they cannot always rely on the judgment of resource-constrained national DRAs. Using medicines whose quality has not been rigorously verified is dangerous for the patients, and it can seriously bias the reliability of the study result. Non commercial sponsors should develop internal policies for the selection of medicines to be used in trials, while an authoritative forum like the EDCTP could provide a platform for guidance, taking into account the multiplicity of standards in the global pharmaceutical market.

- The presence and appropriateness of trial's insurance must be verified, according to most national and international Guidelines, by the **Ethics Committees**. However, ECs members often lack the expertise to assess the appropriateness of these complex legal documents; specific training modules should be developed for strengthening the ECs in relation to this aspect, and mechanisms to monitor their performance after the training should be developed.

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