

Editorial

Challenges of non-commercial multicentre North-South collaborative clinical trials

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Abstract

The last decade has witnessed a substantial increase of multi-centre, public health-oriented clinical trials in poor countries. However, non-commercial research groups have less staff and financial resources than traditional commercial sponsors, so the trial teams have to be creative to comply with Good Clinical Practices (GCP) requirements. According to the recent experience of a large multicentre trial on antimalarials, major challenges result from the complexity of multiple ethical review, the costs of in-depth monitoring at several sites, setting up an adequate Good Clinical Laboratory Practices (GCLP) framework, lack of insurers in host countries, and lack of adequate non-commercial data management software. Public research funding agencies need to consider these challenges in their funding policies. They also could support common spaces where North-South collaborative research groups may share critical information, such as on research insurance and open-source, GCP-compliant software. WHO should update its GCP guidelines, which date back to 1995, to incorporate the perspectives and needs of non-commercial clinical research.

keywords Malaria, multicentre clinical trial, sub-Saharan Africa, good clinical practice

Introduction

The last decade has witnessed a substantial increase in the number of clinical studies in poor countries. These include commercial trials for marketing authorisation applications

in other countries/continents (Department of Health & Human Services 2010; European Medicines Agency 2012) and non-commercial trials addressing relevant public health questions. In particular, the number of multicentre studies by independent North-South research consortia

Table 1 Study treatment to be tested by country

Country	Sites	Study treatments		
Burkina Faso	Nanoro	ASAQ	DHAPQ	AL
Gabon	Fougamou, Lambarené	ASAQ	DHAPQ	AL
Nigeria	Afokang, Pamol	ASAQ	DHAPQ	AL
Zambia	Ndola	ASAQ	DHAPQ	AL
Rwanda	Rukara	DHAPQ	CD + A	AL
Rwanda	Mashesha	DHAPQ	CD + A	AL
Uganda	Jinja	DHAPQ	CD + A	AL
Uganda	Tororo	DHAPQ	CD + A	AL
Mozambique	Manhiça	ASAQ	CD + A	DHAPQ
Uganda	Mbarara	ASAQ	CD + A	DHAPQ

has increased, also thanks to new and innovative product development partnerships and funding mechanisms. Here, we illustrate the challenges faced by these new actors from the experience of a trial we have recently completed.

The 4-ABC trial (The Four Artemisinin-Based Combinations (4ABC) Study Group 2011) was a head-to-head comparison of four antimalarial treatments conducted at 12 sites in seven sub-Saharan countries (Burkina Faso, Gabon, Mozambique, Nigeria, Rwanda, Uganda and Zambia) (Table 1). The trial was funded by the European and Developing Countries Clinical Trials Partnership (ED-CTP). Overall, 4116 children with uncomplicated *P. falciparum* malaria were recruited and followed up for 7 months. The trial was steered by a Co-ordination Committee of representatives of all partners, but the day-to-day scientific coordination was delegated to the coordinating investigator and the field coordinator. The Institute of Tropical Medicine Antwerp (ITM) took responsibility for the legal sponsorship and hosted the Trial Management Group (TMG), which brought together all the 'central' operational staff: scientific coordinators, project manager, data manager, clinical trial assistant, financial administrator, laboratory coordinator and study monitor. The TMG ensured the coordinated execution of all activities and the documentation of key decisions, including integrating the inputs from the study sites. The preparatory phase began in December 2005 when the contract with EDCTP was signed; recruitment started in July 2007 and the clinical follow-up was completed by mid-2009. The database was locked in June 2010.

Organisational and contractual aspects

The long duration of the pre-study period (December 2005–July 2007) was due to the complexity of preparatory

activities, ranging from the finalisation of the organisational and contractual aspects to the full set-up of the study sites and procedures. Although such organisational and contractual aspects are common to any multicountry clinical research programme, they may present a major challenge for an academic sponsor with a small staff, particularly when compared with most commercial sponsors. For instance, when the preparation for the 4ABC trial started, the Clinical Trials Unit at the ITM comprised the equivalent of 3.5 full time staff, that is, a project manager, a data manager, a biostatistician and an administrative assistant, who were also dealing with other ongoing projects. In commercial multicentre trials, the range of activities is spread across different specialised units such as planning, regulatory affairs, monitoring, database development and validation, data review and data cleaning, pharmacovigilance. In non-commercial multicentre trials with an academic sponsor, these are often concentrated in a small unit and sometimes on a single person.

The procurement of investigational medicinal products (IMPs) is a good example of additional difficulties met by non-commercial sponsors. While in commercial trials, the sponsor and the manufacturer of the IMP are often the same organisation, in non-commercial trials, the sponsor is not the owner of the products, which must either be bought or be provided by their respective manufacturers. In the case of the 4ABC trial, the IMPs came from four manufacturers, requiring individual contractual and procurement agreements and parallel arrangements for the shipment to the sites, which increased the administrative workload and often caused unplanned delays. Notably, a double blind study design had to be ruled out because of the difficulties and the costs of a double-dummy – a relatively common problem for non-commercial studies (Christensen & Knop 2012), for which it is difficult to foresee concrete solutions.

Multidisciplinary expertise, efficient prioritization and communication among the study partners and the sites are therefore required to fill in the gap and to comply with all good clinical practices (GCP) requirements. Noteworthy, these requirements were defined in the early 1990s (World Health Organization 1995; International Conference of Harmonization 1996) in relation to the capacities of the traditional commercial sponsors and to date they have not been updated.

Study insurance

The sponsor provided a no-fault insurance policy to cover any harm caused by participation in the trial. The lack of public guidance on trials' insurance made it difficult to negotiate the contract, for example, aspects related to the

R. M. Ravinetto *et al.* **Editorial**

maximum amount per patient and total compensation. Due to the difficulty to find insurance companies in the study countries, insurance was contracted in Belgium (the sponsor's country) rather than in sub-Saharan Africa, where patients were recruited, treated and followed up. As no compensation for trial-related harm was claimed during the study, it remains unclear (and should be further investigated) whether an insurance policy stipulated by a company located outside Africa, with significant language and legal differences to the study countries, may work efficiently.

As proper compensation mechanisms are essential to fulfil the ethical obligation of protecting patients, particularly in vulnerable populations, we also suggest that non-commercial consortia should create spaces to share critical information, such as contract templates, examples of how fees are calculated and a database of experienced insurance companies in low-income countries to provide study specific insurance or 'umbrella insurances'.

Multiple ethical reviews

The length of the ethical review process was particularly unpredictable. The initial clinical protocol and the subsequent amendments were sequentially submitted to the ITM Institutional Review Board (IRB), to the competent Ethics Committee (EC) in the country of the sponsor and to the IRBs/ECs and competent authorities (CA) in the study countries, a total of 20 bodies. Multiple ethical review was undoubtedly beneficial because of the clear North-South complementarities. Ethical aspects related to indemnification for harm, insurance and confidentiality were highlighted by the Northern ECs, while the comments of ECs in the South focused on the need to ensure the co-ownership of the study data, the study sites' qualification/capacity, the transfer of biological samples abroad and the appropriateness of patients' travel reimbursement (Ravinetto *et al.* 2011). But, the large number of bodies, the multiplicity of procedural requirements (including different policies on the ethical fees) and the unpredictable timelines for some committees caused delays in achieving the expected milestones.

For North-South collaborative research, we believe that a common process is needed in which different ECs reviewing the same protocol communicate, build on common practices and jointly address conflicting opinions. Such harmonisation of procedures would be beneficial for any other commercial and non-commercial multicentre study.

Monitoring

Monitoring the study conduct, including laboratory activities, presented significant challenges. It soon became evi-

dent that the external budget provided for monitoring was not sufficient to meet expectations, particularly during the early months of recruitment, when frequent visits can detect systematic mistakes and anticipate structural problems in a timely manner. Similarly, early visits from the laboratory coordinator are critical to harmonise quality assurance in multicentre trials and to build a comprehensive good clinical laboratory practices (GCLP) (WHO Good Clinical Laboratory Practices 2009) framework for laboratories with less research experience. Unfortunately, no specific budget was available for these activities.

Research groups and donors need to appreciate the relevance of early and timely monitoring of the clinical and laboratory aspects of multicentre trials. They should plan adequate human and financial resources to meet these tasks, based on the complexity and inherent risk of each study, on the relevance of laboratory results for the efficacy and safety outcomes and on the sites' specific context. Research consortia could, in parallel, set up alternative or complementary measures, allowing the verification of the completeness, accuracy and coherence of the study data, even when resources for external monitoring are very small. This may include mechanisms for internal quality control and for reciprocal monitoring schemes. In the first case (often called 'internal monitoring'), data entered in the case report form by an investigator are formally double checked against source documents by a second investigator or a study nurse. This system has the advantage of working continuously, allowing timely detection of problems and mistakes, though it should not substantially raise the workload of the study staff, as this would in turn lower the quality of the data collected. In reciprocal monitoring schemes, institutions in a research partnership could agree on common monitoring standards and procedures. Interested qualified staff could be offered training in clinical and laboratory monitoring, and exchange monitoring visits between different sites could take place (Chilengi *et al.* 2010). Such a system would be more expensive than internal monitoring, but still cheaper than external monitoring by commercial contract research organisations (CROs); in addition, it would allow mutual learning. The two systems are not mutually exclusive and could be used in parallel.

Data management

The main challenges during clinical follow-up until database lock were related to collecting and managing the trial data. Given the size of the database (overall 4 000 000 data points), data entry was performed at the

R. M. Ravinetto *et al.* **Editorial**

sites by *ad hoc* trained clerks, and data were then transferred to the ITM server. As most sites lacked a sufficiently stable Internet connection, commercial software (Macro[®]; Inferred) was used as it offered the possibility of entering off-line the data in the electronic case report form (eCRF). This set-up worked satisfactorily, and its efficiency improved when some training and data review activities could be delegated to skilled data managers in the South, as in Burkina Faso (task decentralization allows earlier queries and timely data cleaning).

Therefore, we strongly encourage North-South collaboration in clinical data management (van Loen *et al.* 2011). However, depending on the commercial software, full capacity transfer to the South cannot be achieved; an open-source GCP-compliant software that can work off-line is urgently needed.

Perspectives for the future

In conclusion, a multicentre clinical trial is a challenging undertaking, particularly for independent research groups, which have fewer human and infrastructural resources than commercial sponsors and have to concentrate a variety of specialised tasks on a handful of people. The low flexibility of the funding obtained from public donors for this purpose makes the task even more difficult. Nevertheless, it is important that non-commercial trials are carried out in compliance with the appropriate ethical principles (World Medical Association Declaration of Helsinki 2008; Nuremberg Code 1947; CIOMS 2002; The Belmont Report, 1979) and methodological standards, to ensure protection of trial subjects and their communities and to guarantee the quality of data and results. Different actors may facilitate this process, firstly by ensuring that sufficient resources are mobilised and secondly by allowing the adoption of appropriate, cost-effective quality assurance tools. In particular:

- Public research agencies should be sensitised about the inherent difficulties of non-commercial trials, and their policy of granting funds adapted accordingly.
- These agencies could support or facilitate the development of common spaces where North-South collaborative research groups can share key information such as on insurance and on open-source GCP-compliant software.
- Non-commercial research institutions and sponsors could develop mechanisms to improve the long-term efficacy and quality of independent clinical research, for example, facilitating the dialogue among ECs in collaborative ethical review, adopting internal as well as reciprocal monitoring schemes and encouraging task shifting within the teams.

- WHO needs to update its good clinical practice guidelines, which were issued in 1995 (Lang *et al.* 2011) and consequently do not address most of the contemporary challenges faced by the noncommercial sponsors. The updated guidelines could, among others, allow new cost-effective quality control mechanisms such as internal monitoring, delegating tasks from the sponsor to the sites and double ethical review, to improve the protection of patients and communities.

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R. M. Ravinetto *et al.* **Editorial**

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