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Perspective Piece: Good Clinical Practice in Resource-Limited Settings: Translating Theory into Practice

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Abstract. A Good Clinical Practices (GCPs) course, based on the combination of theoretical modules with a practical training in real-life conditions, was held in 2010 in Burkina Faso. It was attended by 15 trainees from nine African, Asian, and Latin American countries. There were some discrepancies between the average good results at the end of the theoretical phase and the GCP application during the first days of the practical phase, underlying the difficulties of translating theoretical knowledge into good practices. Most of the findings were not unexpected and reflected the challenges commonly faced by clinical investigators in resource-poor contexts (i.e., the high workload at peripheral health facilities, the need to conciliate routine clinical activities with clinical research, and the risk of creating a double standard among patients attending the same health facility [free care for recruited patients versus user fees for non-recruited patients with the same medical condition]). Even if limited in number and time, these observations suggest that a theoretical training alone may not be sufficient to prepare trainees for the challenges of medical research in real-life settings. Conversely, when a practical phase immediately follows a theoretical one, trainees can immediately experience what the research methodology implicates in terms of work organization and relationship with recruited and non-recruited patients. This initial experience shows the complexity of translating GCP into practice and suggests the need to rethink the current conception of GCP training.

BACKGROUND

Medical research has produced substantial increase in life expectancy as well as quality of life but more so in the developed countries. Progressively, there has been resizing of the world maps in terms of population, burden of diseases, medical training, and size of medical work force, with collective dynamics less in favor of the developing world.[1] Meanwhile, globalization of clinical trials has resulted in an unprecedented shift of activities from Western Europe and North America to newer sites in Asia and Africa.[2] The number of clinical studies carried out in developing countries has significantly increased,[3–5] partly thanks to new non-commercial research programs addressing the health problems of vulnerable populations.[6,7]

In clinical research, compliance with universal ethical principles[8–11] and appropriate methodological standards[12–14] is fundamental for avoiding exploitation of individuals or groups, ensuring data reliability, creating a research-friendly environment, and increasing the effectiveness of public health-oriented research. However, clinical research programs in developing countries have to overcome context-specific difficulties related to the logistical constraints, the socioeconomical vulnerability of the study populations, and the weakness of the regulatory framework and ethical review system[15–20]; non-commercial research groups face additional challenges linked to the limitations of the research budgets. In recent years, a number of initiatives have been launched to create and strengthen the capacity for clinical research and research ethics in resource-poor settings (e.g., CANTAM [African Network of Excellence for clinical trials; http://www.cantam.org/] and WANETAM [West African network against AIDS, TB and Malaria; http://www.wanetam.org/]). However, other than some international partnerships aiming at training individual investigators,[21] capacity-building activities are often characterized by a strong regional approach, with little or no South–South communication between researchers from different geographical areas.

To build capacity on common grounds, the Switching the Poles Clinical Research Strategic Network was created under the Framework Agreement between the Institute of Tropical Medicine (ITM), Antwerp (Belgium) and the Belgian Directorate-General for Development Cooperation; it brings together research institutions from Southeast Asia, sub-Saharan Africa, and Latin America, with the objective of developing clinical research policies that are compliant with appropriate ethical and methodological standards and feasible in resource-constrained settings and programs.[22,23] Even if a formal needs assessment was not carried out, the Network develops its activities based on the priorities identified by the partners on a stepwise basis. This approach allows the inclusion of the contributions of newcomers (the group gradually grew from 7 partner institutions in 2008 to 13 partner institutions at the beginning of 2012). Based on such exercise, we have carried out several initiatives for conducting research in resource-constrained settings, such as social sciences research for improving the informed consent process,[24] development of a common platform for clinical data managers,[25,26] and development of a common platform for the staff responsible for the laboratory component of clinical trials. Such platforms include training sessions and workshops, where participants share experience and develop solutions relevant to challenges not addressed by the international guidelines, because they are either context-related (e.g., poor internet connection compromising remote data entry) or linked to structural resources' limitations (e.g., internal and external quality control for laboratories operating in remote locations). Within this context, it was agreed in 2009 to develop a course in Good Clinical Practices (GCPs) enabling

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future investigators, sponsor-investigators, and research project leaders to set up a research site fulfilling the essential GCP requirements, despite context and budget constraints. We conceived a course based on the combination of theoretical modules and practical training in real-life conditions. We report here the lessons learned from this first experience.

METHODOLOGY

The course was organized by the Clinical Research Unit of Nanoro (CRUN) in Burkina Faso in collaboration with the Clinical Trials Unit of the ITM. Key support was provided by QGates, a start-up African clinical research organization based in Tanzania, and the African Malaria Network Trust (AMANET), an African non-governmental organization (NGO) that offered web-based training on GCPs, trial management, health research ethics, and Good Laboratory Practice (GLP). The maximum number of participants was restricted at 15 to allow for individual tutorship during the theoretical modules and feasibility of the practical exercise. The trainees came from nine countries: Benin (two participants), Burkina Faso (three participants), Cambodia (one participant), Cuba (one participant), Democratic Republic of Congo (two participants), Ethiopia (two participants), Peru (one participant),

TABLE 1
Good Clinical Practices (GCPs) course theoretical modules administered to participants

Number	Topic/event	Practicals/case studies
Session 1: opening session		
01	Pre-course test	
02	GCP: a historical perspective	
03	From the test tube to the person: current requirements in a clinical development plan	Sample clinical development plan
04	Implications of GCP in developing countries: experiences from African countries	Cases from participants, discussion
05	Who is an investigator and what does (s)he do? Including issues on delegation of tasks	
06	Who/what is a sponsor?	
07	Ethics committees and their role	
08	Source documents and essential documents (ED) (before, during, and after the trial)	Exercise on identifying the ED for pre-trial, initiation, during trial, and post-trial periods
09	Maintaining the investigator's file	
Session 2: trial preparations		
10	Standard operating procedures (SOPs)	Presentation and group exercise: developing list of SOPs and develop one
11	Informed consent process; informed consent form	Presentation and discussions, informed consent movie, case studies
12	Quality assurance/quality control	
13	Laboratory organization and safety	
14	Organization and personnel	
15	Setting up of cohorts for clinical research: experiences from Nanoro	Presentation and discussion
16	The Trovan Trial in Nigeria	Case study and group presentations
Session 3: conduct of the trial 1		
17	Selection of the source of the investigational product; handling of the study product and accountability	
18	Adverse events/serious adverse events; suspected unexpected serious adverse reactions	AE/SAE, SUSARs exercises
19	Role of regulatory authorities	Presentation and discussion
20	Role of the clinical monitor	Presentation and discussion
21	Clinical trial insurance	Presentation and discussion
22	Trials audits and inspections	Presentation and discussion
Session 4: conduct of the trial 2		
23	Randomization and keeping the blind	
24	Data Safety Monitoring Boards (DSMBs)	
25	Clinical data management and dealing with data queries	
26	Pre-mature termination of the trial and study closeout issues	
27	Reports: investigator obligations	
29	Making it happen presentations (from theory to practices: challenges for a clinical investigator)	
Session 5: trial end		
30	The participants and research community	
31	An overview of clinical trial methodology: the example of malaria	
32	Capacity building in clinical trials: the example of the Institute of Tropical Medicine (Belgium) and the IRSS/Center Muraz (Burkina Faso)	
33	Post-course test	

Uganda (two participants), and Zambia (one participant). Most participants were medical doctors. In addition, there was one pharmacist, one biologist, and one laboratory technician, all of whom were interested in project management or laboratory management of clinical trials. The course lasted 10 days: the theoretical modules were administered in Ouagadougou from the 4th to the 9th of October of 2010, whereas the practical session in Nanoro was carried out between October 11th and 15th of 2010.

Theoretical phase. To ensure a minimal common basis of knowledge among trainees from different backgrounds and contexts, the participants were asked to complete in advance the free web-based course provided by AMANET consisting of modules in Basic Health Research Ethics, Advanced Health Research Ethics, and Good Clinical Practice. Trainees were followed through the web to continuously assess their performance, and individual assistance was given when required. The theoretical training in Ouagadougou consisted of a pre-course test and interactive adult-learning presentations on different aspects of GCPs, with a focus on exercises, cases studies, and discussions (Table 1). Participants were then re-evaluated (post-course test) to assess their performance before starting the field practical session.

Practical phase in the field. The practical session was held in Nanoro (Figure 1). The trainees joined a local research team conducting a phase IV study on the effectiveness of the new national policy for uncomplicated malaria (amodiaquine + artesunate; given parasitological diagnosis by a rapid diagnostic test) implemented in rural health centers. The study was sponsored by the Institut de Recherche en Science de la Santé (IRSS), Bobo Dioulasso, Burkina Faso. It was approved by the Institutional Ethics Committee of the Center Muraz, and it was registered at ClinicalTrials.gov (ID: NCT01213433). The local research staff comprised the Principal Investigator (PI) and for each participating health center, a study nurse and a field worker.

The participants were divided in five groups of three participants, and each group was allocated to one of the peripheral health facilities where the study was conducted. Groups had to be balanced in terms of professional background (i.e., no more than one non-medical doctor per group) and language (i.e., at least one native French-speaking trainee per group). Each group collaborated with the local research staff during the enrollment and initial follow-up of 50 patients. Trainees had to prove to have a full knowledge of the protocol and provide a signed curriculum vitae (CV) showing that they had adequate professional skills and qualification for participating as coinvestigators or—for those participants without a medical degree—other research staff in a clinical trial. In addition to the direct supervision by the study PI, each group was closely supervised by the course facilitators, with a daily wrap-up session dedicated to feedback and comments on the challenges experienced in the field.

OUTCOMES AND DISCUSSION

Most participants (14) completed the pre-course web-based Basic Health Research Ethics modules with high scores (the lowest was 84.5%). However, only five participants completed the Advanced Health Research Ethics modules, and only five participants completed the GCP modules. Eight participants started the modules, but they did not undertake the tests, and two participants did not enroll for one or more topics because of late registration. Among the reasons for low compliance, the lack of good internet connectivity in some countries played a major role, particularly in Africa. In some cases, this problem was so important that it challenged the continuity and effectiveness of the web-based individual assistance. Therefore, establishing a good and reliable internet connection should be an essential component of capacity strengthening for Southern institutions, both for training purposes and fast-track communication (e.g., reporting of serious adverse events in clinical trials).

The theoretical course in Ouagadougou was conducted according to the modules scheduled (Table 1). The pre-course

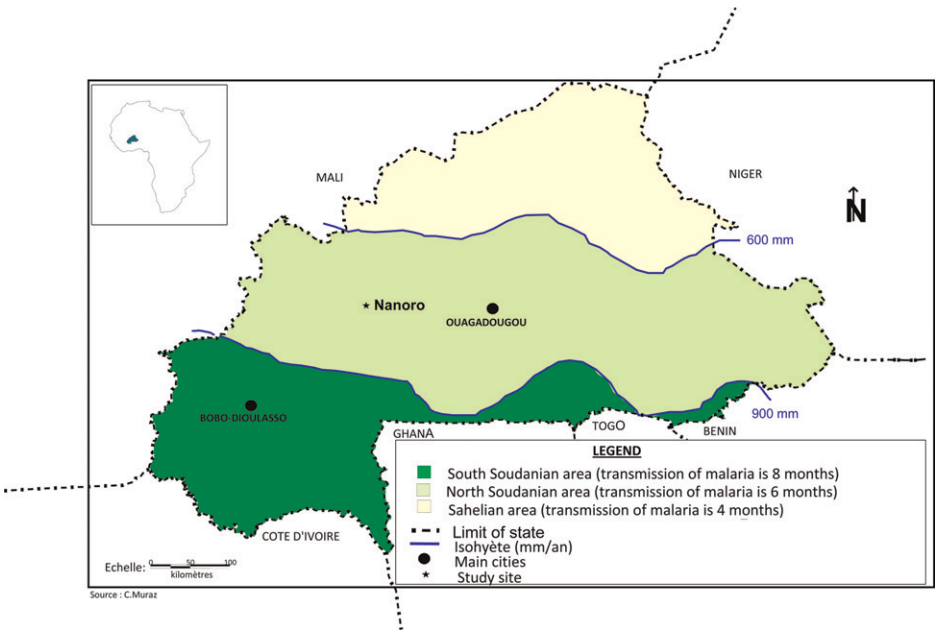

FIGURE 1. Map of Burkina Faso with Nanoro position.

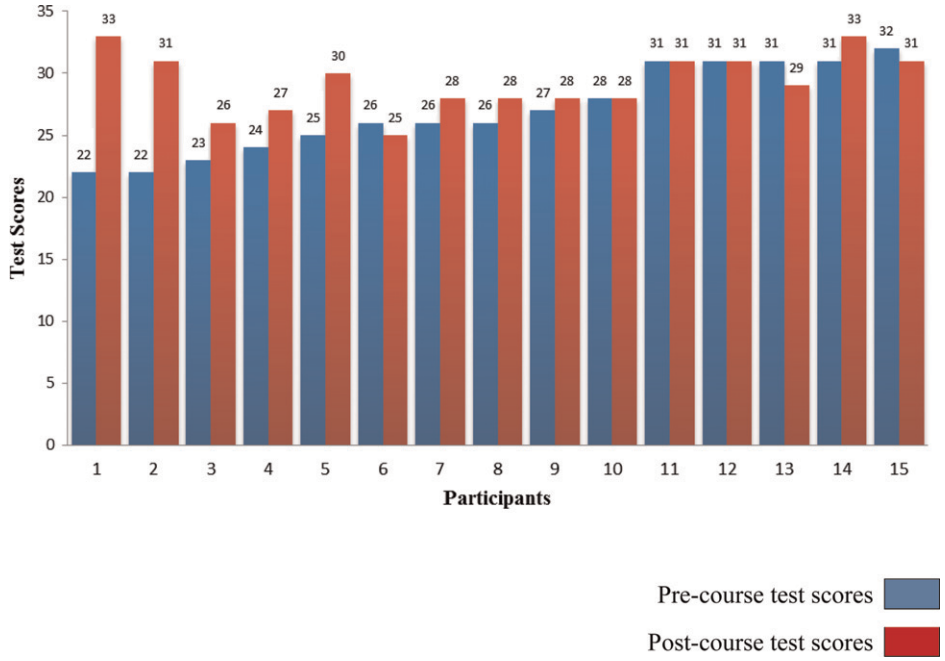

FIGURE 2. Pre- and post-course scores of participants at the beginning and end of the theoretical session.

test showed varying degrees of knowledge (Figure 2), with scores ranging from 62% to 91% (average = 77%), possibly reflecting the differences in time allocated to the pre-course web training, past clinical research experience, or a mix of both. When comparing the scores of the pre-course test with those scores of the post-course test (Figure 2), it appears that the average score increased to 83% (range = 71–94%), even if among those participants with higher initial scores, three participants did not improve, and two participants dropped by a small margin.

Despite the relatively good results of the post-course test, the first 2 days of the practical phase revealed some difficulties when translating the acquired theoretical knowledge into good practices. For instance, some Informed Consent Forms (ICFs) were not immediately signed by the investigators; in a few cases, it was not indicated if the name registered was the name of the patient, parent, or tutor, although there was a tick box for this purpose, or the name of the witness was written under the sentence "I accept to participate in the trial" instead of the name of the illiterate patient/parent. The concerned investigators explained that the time pressure did not allow them to fill or sign all ICFs immediately; after the consent interview was completed and formal consent was obtained from the participant, they went straight to other study procedures to shorten the patients' waiting time. The latter is a positive behavior in terms of respect of persons as per fundamental medical ethical requirements. Nonetheless, this method may create problems (e.g., inability to match the ICF with the investigator who took it as well as the risk of omitting the signature on the ICF copy given to the patient). These specific issues were immediately addressed by the PI, and these shortcomings were not observed during the next days. The lesson learned here is that, especially in health facilities with a great catchment area and thus, a large number of patients in the waiting room, revising in advance the consent documents may facilitate their completion and the signature flow.

Similarly, the PI initially noted that some essential documents (e.g., the drug dispensing log or the subject identification log) were not timely filled in, whereas others, such as the new investigators' curricula vitae, even if available at the site, had not been timely placed in the Investigator File. Beyond the purely formal aspects, the late completion or filing of essential documents may cause inaccuracies, loss of information, or even reporting mistakes. These poor practices were reportedly because of time constraints; however, they may be avoided by anticipating the daily workload and self-organizing accordingly, such as it happened after the first supervision. When we looked at the correctness and completeness of data recorded in the Case Record Form (CRF), we found a negligible percentage of mistakes, but a certain number of fields (e.g., medical history, symptoms, vomiting or not after taking the study medications) were left blank to be completed later. Again, this procedure—adopted because of the time pressure—obviously increases the likelihood of mistakes, and it could be avoided by better planning and organizing the work schedule.

In one case, the study drug was administered to a patient screened but not enrolled in the study. The investigators made this decision, because the patient could not afford to pay for malaria treatment; also, the medicine was registered and used routinely as first-line antimalarial treatment in the country (conversely, this decision would represent a serious problem in a phase II or III trial). In making this decision, they put the wellbeing of the person above the requirements of the research.[11] Similar situations are not infrequent when medical research is combined with medical care in contexts where non-eligible patients have to pay a user fee for accessing essential treatment. Such issues could be anticipated and properly addressed. For instance, planning an extra stock of medicine for patients screened but not enrolled may help overcome the ethical dilemmas: no one would be left untreated, there would be a transparent accountability of the study drug stock,

and the patient's freedom to refuse participation in the trial would be enhanced.[24]

None of the observed shortcomings can be considered as unexpected, because similar findings are often highlighted by clinical monitors in their visit reports. To some extent, they reflect the challenges commonly faced by many clinical investigators in resource-poor contexts: the great catchment area of peripheral health facilities, the need to combine routine clinical activities with clinical research, and the risk of creating a double standard among patients attending the same health facility (e.g., free care for recruited patients versus user fees for non-recruited patients with the same medical condition). Even if limited in number and time, these observations seem to suggest that a theoretical training alone may not be sufficient to prepare investigators for the challenges of real-life settings. Conversely, those participants who are confronted with field reality just after the theoretical course will immediately experience what the research methodology implicates in terms of work organization and relationship with recruited and non-recruited patients. This process would help them to bring GCPs into practice, going beyond the formal knowledge of rules and regulations, and develop self-engagement and self-organization, which are essential for the good conduct of a study.

Our findings have obviously several limitations, mostly related to the small size and limited representativeness of the trainees' group; in addition, we need to further develop the evaluation methods for incorporating not only the theoretical training but also practical and/or qualitative skills gained through the stage in the field. The next course of this kind will, therefore, shed more light on the validity of our present findings. Another major limitation of the proposed methodology is represented by the language barrier, which in this case, applies to non-French–speaking trainees who, during the practical phase, were dependant on the translation by the study team and thus, could not have a direct interaction with the patients and parents both for the informed consent interview and discussion on, for example, inclusion criteria, symptoms, adverse events, and concomitant medications. This problem can be solved only by developing two courses, each of them adapted to either French-speaking or English-speaking settings, requiring additional funding currently not available. In addition, organizing a theoretical and practical GCP course is *per se* a complex task, firstly because of the obvious logistical difficulties of bringing together people from four different continents; but it is also difficult, because the trainees must be associated to the research staff of a clinical trial, and they must be able to work with them without altering the routine clinical and research activities. Trainees should also work in small linguistically and culturally balanced groups, which automatically limit the number of participants that, according to our experience, should not exceed 15–18. Therefore, we are aware that GCP courses combining a theoretical and practical phase cannot become routine practice, at least for the current time. However, our observations may also find more feasible short-term applications. For instance, an in-depth training (not limited to a couple of hours of refreshment) in GCP and related disciplines may be recommended for each study team at the beginning of a trial (e.g., by the monitor at the initiation visit), with the trainer remaining on site during the first few days of recruitment to actively supervise the team and help correcting practices. Usually, such training and supervision tasks would be carried out by the study monitor appointed by the sponsor. However, in North–South collaborative research, alternative mechanisms could be envisaged, such as reciprocal monitoring schemes,[27] where mutual training and monitoring are reciprocally offered among partner research organizations.

Noteworthy, the great variability of cultures and backgrounds did not cause problems in communication and daily management of activities. The residential nature of the course helped people exchange and compare their experiences throughout the training.

CONCLUSIONS

Our first experience of a combined theoretical and practical GCP training has shown the complexity of translating GCP requirements into practice, particularly when working in resource-limited settings with socioeconomically disadvantaged communities. Even if the GCP principles and standards have a universal scope, the current guidelines still reflect the situation in the early 1990s (World Health Organization GCPs were issued in 1995 and International Conference on Harmonization (ICH) GCPs were issued in 1996), with no consideration for the new scenarios of public health-oriented research for developing countries.[28] The latter has become increasingly important and involves a number of new challenges for the researchers: remote locations with limited structural resources (informatics, laboratory, infrastructures, etc.), socioeconomically disadvantaged populations with limited (financial and geographical) access to quality health care, and in the case of non-commercial trials, limited external funding. Combining theory with a practical module helps trainees translating rules into practices, taking into account and when possible, anticipating the ethical dilemmas and concrete challenges encountered in field conditions. This approach could contribute to increasing the number of young Southern researchers able to become qualified PIs, sponsor-investigators, or trials coordinators. Our experience could open the debate on how to rethink the conception of the current GCP trainings to take into account the context and the environment where the studies are implemented.

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