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Regulatory challenges associated with conducting multi-country clinical trials in resource-limited settings

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Abstract

International public health and infectious diseases research has expanded to become a global enterprise transcending national and continental borders in organized networks addressing high impact diseases. In conducting multi-country clinical trials, sponsors and investigators have to ensure that they meet regulatory requirements in all countries in which the clinical trials will be conducted (1). Some of these requirements include review and approval by national drug regulatory authorities (NDRAs) as well as recognized research ethics committees (REC). A limiting factor to the efficient conduct of multi-country clinical trials is the regulatory environment in each collaborating country, with significant differences determined by various factors including the laws and the procedures used in each country. The long regulatory processes in resource limited countries may hinder the efficient implementation of multi-site clinical trials, delaying research important to the health of populations in these countries and costing millions of dollars a year.

Keywords

regulatory guidelines; ethics committee; institutional review board; data transfer; repository

Introduction

This paper discusses the regulatory challenges associated with conducting multi-country clinical trials in resource-limited settings. It is based on the experience of the authors who include researchers in the AIDS Clinical Trials Group [ACTG, an National Institutes of Health (NIH) supported international network conducting international research in the area of HIV/AIDS] and other individuals with experience in the regulation of international research. The NIH Network experience in the international setting has led to research success, but has also experienced slow progress towards regulatory approvals. As a measure of the harmonization of research conduct, protocols developed under the auspices of the NIH Networks, often developed by some of the best researchers in the world both in and outside the United States of America (USA), are received with varying responses in

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participating countries around the world. Differences in the international approach to regulatory processes, research prioritization, and research outcomes including intellectual property issues may create tensions between the network researchers and the regulatory authorities (2).

A survey was conducted of regulatory timelines at 23 ACTG trial sites covering 21 protocols released between 2004 and 2012, including twelve countries in Africa, Asia, South America, and the Caribbean. The mean regulatory timeline was 17.84 months for all sites and all studies from release to registration, with a range of 3 and 37 months. The timelines largely depended on complexity of the proposed studies, from observational to investigational new drug or diagnostic, and access to study medication in the trial and in the country where the research was being conducted (Blanchard-Horan C., Sanne I. et al., personal communication).

Drug regulatory authorities

Clear guidelines are available in the USA determining the authority of the Food and Drug Administration (FDA). Sponsors interact with the FDA in early stage protocol development to determine the design, data and monitoring requirements for research in new drug indications. However, in the international setting, each country has their own drug regulatory authority, and policies regarding the rational use of medicines. In most of the countries in which the NIH Networks supports clinical research sites and laboratories, there are some laws that require the drug regulatory authority to review all research involving medicines, including phase IV post-marketing or strategy studies designed to inform guidelines.

In the experience of the authors, drug regulatory authorities have become increasingly vigilant about internationally sponsored research, with escalating capacity to review and approve studies. During the evolution of in-country drug regulators, three distinct phases can be identified: (1) initial establishment of the drug regulator shifting from broad acceptance of the World Health Organization (WHO) guidelines, or routine approval of drugs from the FDA or European Medicines Agency (EMEA) environment, to in-country review. (2) Increased political independence of in-country regulators often driven by concerns about potential research abuse and participant confusion, but without the necessary resources and expertise to conduct independent reviews. (3) Maturation of the review process with increasing in-country capacity and experience, often supported by exchange programs with the FDA, EMEA or WHO. In the first two phases, novel new drug development research may be treated with significant mistrust. In addition, lack of qualified experts and infrequent meetings with inadequate administrative support contribute to significant delays in the approval process.

In review of complex Investigational New Drug (IND) studies such as vaccine trials, regulatory bodies from low and middle-income countries that lack the expertise to review and monitor such trials in turn rely on regional regulatory bodies. Very often, governments and institutions in resource limited settings (RLS) do not set aside adequate resources for the operations of the regulatory bodies (3, 4) and capacity development and training become important. Interaction between in-country regulators and the more established FDA or EMEA to facilitate training and expertise is a preferred mechanism to achieve training and capacity development. Where researchers are expected to do the training, an inherent conflict of interest may be the consequence.

Research Ethics Committees /Institutional Review Boards

Research Ethics Committees (REC) in many RLS are still in their early stages of development with limited meetings, development of operating procedures, and paper based review and archiving systems (5). In some countries, proposals have to be approved at various levels including institutional and national levels, with a sequential process requiring approval before submission to the next level, and finally to the national drug regulatory authority, leading to inherent delays. A multi-center trial from an NIH Network may be reviewed and approved by over 30 ethics (6) committees, each with different approaches to key ethical criteria for research.

In our experience the most important stumbling blocks to research approval include:

1. Appropriate priority of the research for the country including long-term commitment to provide the treatment proven by the study. An example of this is the current round of research for third-line antiretroviral therapy; in some instances in-country approval is withheld as long-term commitment to the provision of treatment is not feasible.
2. Participant compensation for trial related injury, in its simplest form a requirement for insurance to meet the requirements of the Association for British Pharmaceutical Industries (ABPI) standards for medical treatment of research related injury (7). Recent developments in India have led to the most stringent form of compensation, not only for trial related injury but also non-efficacy, making the financial risk impossible to insure (6, 8).
3. Multiple research ethics committees reviewing the same protocol for the same site, with both international in-country and domestic US universities engaged leading to conflicting findings without a clear definition of an authority hierarchy. This leads to significant delays in the review process, and in certain instances withheld approval. An example is the initiation of “Timing of antiretroviral therapy for HIV-1 infection and tuberculosis” (9), in Botswana the inclusion criteria were modified in the informed consent, differing from all other sites, as the USA institutional ethics committee considered the strategy inappropriate for participants with a CD4+ count below 50 cells/mm^3.
4. Biobanking and sample repository research is rapidly becoming an important topic potentially restricting the international exchange of research, and restricting the clinic to laboratory linkage. There are a wide variety of responses to sample collection, with increasing review of the long-term research use of stored specimens. Biorepository facilities are coming under increasing scrutiny with a focus on participant protection, informed consent, use of samples, approval of future sub-studies, and governance and sustainability of storage facilities. Conflicting international commercial, intellectual property and trade laws lead to protracted material transfer agreement negotiations. Differences in the approach to the storage, use and export of clinical samples is seen across the globe, ranging from the requirement for prior ethics approval for each new evaluation proposed, to complete refusal to permit the storage and or export of samples from clinical trials. Material transfer agreements are required in many settings governing the storage of samples, ethics requirements, identification of specific samples, and participant level right to withdraw samples from the storage facility. Overarching material transfer agreements governing research collaborations would be preferable for multi-center, multi-study collaborative efforts and could lay the ground work for funding agencies to address the international concerns related to the conduct of future research on stored samples (10, 11).

5. Emergence of requirements for data transfer agreements focused on public domain and access to data from clinical trials is emerging. Tensions arise between the ethos of the funding agencies and the in-country regulators. Funders focus on ethical conduct of studies and release of results, as well as confidentiality agreements with sponsors such as drug companies that restrict the release of proprietary information. Certain RLS wish to retain access to the in-country data, collaborative publication rights for local investigators, and open-access to data within one year of completing a multi-national study. These conflicting policies also affect the reporting of serious adverse events, monitoring of safety data, and interpretation of results.

6. Changes in the regulatory frameworks have led to significant delays in approvals in countries such as Zambia, India, South Africa and more recently Zimbabwe. Most of the changes in the framework were politically motivated, and in some instances led to more stringent application of in-country laws. Unpredictable regulatory environments make the allocation of resources difficult and study site setup, recruitment and retention of staff may become cost prohibitive.

7. Regulatory bodies should also provide continued monitoring of clinical trials from initial approval up to study completion, to ensure the integrity of the data and safety of trial participants. While standards of monitoring in resourced countries have improved over the years, in some RLS, the continuous monitoring of trials is a dream that is yet to be achieved. Limited or no monitoring in some countries translates into differences in levels of data integrity and human research protections across the countries. International trialists and sponsors have to ensure high standards at all sites, despite inconsistent levels of monitoring by regulatory authorities.

8. Besides the regulatory bodies, various other monitoring bodies may be involved including independent monitoring committees, and monitors hired by sponsors. In addition, there are also human rights organizations and the media who serve as watchdogs for any abuses of human beings including research participants. In some cases, there can be limited understanding of the roles of the various bodies with some of them overstepping their authority.

9. When research using a new drug has identified some benefit, the new drug has to be registered and shipped so that it can be available to the host country population. Trial sponsors may face challenges in registering the new drug in some RLS in part due to limited experience in dealing with new drug applications. They may also face challenges in shipping the drugs because of logistical issues associated with shipping, including unclear procedures, and weak NDRA systems.

Future direction of regulatory processes

Negotiations with the drug regulators and departments of health for controversial research proposals such as those involving microbicides, novel vaccines, and combination drug treatments for tuberculosis are required, preferably before final version of the protocol so that applicable comments may be addressed in the design. Although difficult to achieve, continuous efforts to harmonize processes will lead to improved interoperability between regulators and ethics committees. Significant effort to exchange expertise between the FDA or EMEA and international drug regulators is required, to ensure that standards are similar and upheld. Training and early discussions on novel approaches to drug regulation, such as adaptive design of studies in oncology and tuberculosis, are required to ensure agreement between regulators. Potential solutions include a dedicated effort to train international regulators and harmonize review processes, permitting exchange between the in-country

regulators and the FDA. One consideration may be to permit international regulators to review studies earlier in the protocol development, similar to the FDA consultation process.

Conclusion

Despite the above challenges, international clinical trials remain critically important for global diseases that require international cooperation. International researchers and sponsors have to be aware of the regulatory requirements and expectations in the various countries in which they operate. For example, over 12 years of research conducted by the ACTG and other NIH Networks in RLS, recognition of the regulatory process and the potential for significant delay, has led to intervention by the sponsors, networks and the in-country investigators. Rapid and early submission, a dedicated regulatory administrator at the site level, and investigator attention to the processes, have all led to improvement in regulatory timelines.

Regulatory authorities in RLS are an important cog and regardless of the prevailing political or philosophical ideology, regulatory authorities can play an important role in promoting health of their citizens by facilitating the efficient conduct of clinical trials.

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References

1. Emanuel EJ, Menikoff J. Reforming the regulations governing research with human subjects. N Engl J Med. 2011; 365:1145–1150. [PubMed: 21787202]
2. Andanda PA. Human-tissue-related inventions: ownership and intellectual property rights in international collaborative research in developing countries. J Med Ethics. 2008; 34:171–179. [PubMed: 18316458]
3. Milford C, Wassenaar D, Slack C. Resource and needs of research ethics committees in Africa: preparations for HIV vaccine trials. IRB. 2006; 28:1–9. [PubMed: 16770882]
4. Kass NE, Hyder AA, Ajuwon A, et al. The structure and function of research ethics committees in Africa: a case study. PLoS Med. 2007; 4:e3. [PubMed: 17253898]
5. Nyika A, Kilama W, Tangwa GB, et al. Capacity building of ethics review committees across Africa based on the results of a comprehensive needs assessment survey. Dev World Bioethics. 2009; 9:149–156.
6. Bhattacharjee Y. Public health. Clinical trials paused as India adopts new rules. Science. 2013; 341:327. [PubMed: 23888009]
7. Industries AoBP. Clinical Trial Compensation Guidelines. 1994.
8. Chatterjee S. Regulatory changes in conduct of clinical trials: A need for review. Indian J Pharmacol. 2013; 45:323–324. [PubMed: 24014903]
9. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. N Engl J Med. 2011; 365:1482–1491. [PubMed: 22010914]
10. Sathar MA, Dhai A. Laws, regulations and guidelines of developed countries, developing countries in Africa, and BRICS regions pertaining to the use of human biological material (HBM) in research. South African Journal of Bioethics and Law. 2012; 5:51–54.
11. Zhang X, Matsui K, Krohmal B, et al. Attitudes towards transfers of human tissue samples across borders: An international survey of researchers and policy makers in five countries. BMC Med Ethics. 2010; 11:16. [PubMed: 20843366]

Executive Summary

Potential regulatory challenges in international clinical trials:

- Limited expertise and capacity of local regulatory bodies
- Multiple layers of review with inconsistent findings
- Post-study drug provision and long term commitment to the provision of treatment
- Variation in standards for participant compensation for trial-related injury
- Increased scrutiny and restriction of biobanking and repository research
- Ownership of data and publication rights