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Ensuring Participant Safety and Trial Integrity with Clinical Trials Oversight

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Abstract

Clinical trial oversight is a critical element that ensures the protection of research participants and integrity of the data collected. The trial sponsor, a local IRB and independent monitoring committees all contribute with complementary but overlapping responsibilities. Consistency among these groups is essential for the smooth conduct of a clinical trial, but may be challenging in resource-limited settings (RLS). Capacity building and training for RLS may improve clinical trials oversight and ultimately medical management. In this paper, we review the components necessary for optimal clinical trial oversight and the issues that arise in the RLS, with some suggested strategies for improvement.

Keywords

Quality management; pharmacovigilance; monitoring; clinical trials oversight

Protecting research participants and ensuring the collection of high quality, meaningful data are the guiding principles for the oversight of clinical trials. The International Conference of Harmonization Good Clinical Practice (ICH GCP) guidelines provide uniform standards for the conduct of clinical trials and inform the regulatory framework for monitoring, while it is the sponsor's responsibility to ensure that the conduct of the trial meets specific standards.¹ Data must be verifiable from source documents, and the conduct of clinical trial must match the approved protocol and be in compliance with applicable regulatory requirements. For multicenter trials, sponsors must ensure that data are comparable across trial sites and that all study personnel meet minimum training requirements which are clearly documented.² Quality management approaches support the dual priorities of participant protection and data quality and are embraced by regulatory authorities.^{3,4}

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In the US, the trial sponsor is the primary responsible party for the management of the clinical trial, however, Institutional Review Boards (IRBs) and Independent Safety Monitoring Committees also provide oversight of trial conduct. IRBs assure that appropriate steps are taken to protect the rights and welfare of participants in research, both in advance and by periodic review. They perform ethical review of the proposed research at particular sites and are required by US regulations for institutions receiving US government funds.^{5,6} In some resource limited setting (RLS), review capacity may be limited by poor financial and human resources, insufficient training in ethics and inadequate standard operating procedures, highlighted in a recent review of the educational background, standard operating procedures and compliance with national guidelines of ethics committees.⁷ A mapping exercise of research ethics capacity in Africa highlighted the need for ongoing research capacity growth and identified specific areas for development.⁸ The authors described a web-based interactive approach, which allows for resource and process sharing and may ultimately improve both capacity and the quality of the reviews.

Study monitoring committees (SMCs) and data safety monitoring boards (DSMBs) are composed of experts in the field and may also include statisticians, and bioethicists and often community representatives. They review accumulating data during the conduct of the trial and assess general progress and safety. Efficacy is frequently reviewed by treatment arm and decisions may be made whether the trial has answered its primary question, or is capable of answering the question. The committee typically receives unblinded data, and this information remains confidential.⁹ These committees make recommendations to the trial sponsors: the trials may be stopped early for efficacy, futility or safety concerns. The sponsors, the independent monitoring committees and the IRBs have distinct but overlapping functions for the oversight of clinical trial conduct. The distinction between the roles may not always be clear, and a review of correspondence from several international clinical trials suggests that this may lead to tension between investigators, regulatory bodies and sponsors.

Critical elements to monitor in all trials include adherence to informed consent procedures, inclusion and exclusion requirements, adequate and timely safety monitoring, adherence to protocol mandated investigations and follow-up, and the review of regulatory documents. Specific methods of monitoring are not dictated by regulatory authorities, and may include risk based approaches, site visits triggered by specific events, and/or routine site visits. A risk assessment to identify the optimal means of monitoring, taking into account the likely sources of error, their consequences for the participants, and the available resources is a proactive approach taken by the sponsors which may minimize risk to the participants. The use of electronic systems and modern statistical methods provide opportunities for creative monitoring approaches. Indeed, a flexible approach may be needed in order to ensure that the trial meets research goals.¹⁰ Targeted risk-based monitoring strategies rather than routine visits to all clinical sites with complete data verification streamline the approach to monitoring, and may be cost effective.^{11,12} Although the approach is attractive, and may be more likely to ensure overall study quality, onsite monitoring remains critical in many cases. Since inexperienced sites in RLS may meet criteria for high risk, there may be continued need for significant onsite monitoring efforts even with a risk-based approach. In a retrospective review of research site monitoring reports in Uganda, onsite monitors added value by identifying significant areas to be improved.¹³ A risk-based plan, therefore, might include both central monitoring and targeted local monitoring.^{14,15} The Division of AIDS has developed and is using risk-based criteria for monitoring intensity, but this rigor may not be widespread [Figure].¹⁶ The evaluation of risk-adapted monitoring strategies for clinical trials is under investigation in two trials using a prospective cluster randomized approach.^{11,12,17}

Pharmacovigilance is the specific evaluation in real time of drug safety, and may identify safety signals in investigational agents. With the ongoing assessment of the safety of investigational agents for the participants it is a critical element of trial conduct in both resource-rich and resource-limited settings. In addition to addressing the broad ethical requirement to protect research participant health, safety monitoring can also conserve resources by prompting the early discontinuation of unsafe investigational therapies and allow for timely changes to trial conduct that enhance participant safety. For example, eligibility criteria might be changed to exclude participants with evidence of hepatic or renal disease in response to an emerging safety signal. Safety monitoring may also increase the willingness of individuals to participate in trials due to greater confidence in the conduct of the study. However, currently there appears to be limited awareness by participants of the safety monitoring incorporated into trial designs.^{18,19}

In the RLS, clinical trials intended to provide pivotal data have additional considerations with respect to safety monitoring. A crucial goal of these trials is to demonstrate the safety of therapies in a clinically meaningful way. However, if safety monitoring depends on strategies or tools that are not otherwise available where a trial is being conducted, then even if the trial is successful, the therapy under investigation may not ultimately be available to participants and trial participants may undergo the risks of the clinical trial without receiving the potential long term benefits of having the investigational agent available for long term use. There is an obligation to protect research participants to the extent possible, and providing less than optimal safety monitoring in RLS could be viewed as a failure of the sponsor to meet their obligations.⁵ While there are no simple solutions, one approach is to consistently provide all safety monitoring considered medically necessary, regardless of the resources in that setting. If it is known in advance that clinical use of the therapy will require monitoring not available outside of the trial, and that particular monitoring capacity is unlikely to be developed, it has been argued that the research should be avoided.⁵ However, HIV-related research in RLS has been an iterative process, and enhanced laboratory and safety monitoring has led to increased availability of the recommended tests. For example, the requirement for liver function test availability when nevirapine is used has led to the support of the availability of this test at the district hospital level in PEPFAR-supported countries.^{20,21} Provision of additional resources and training in RLS that would enable more advanced safety monitoring should be strongly encouraged. This would allow a broader range of trials to be performed ethically in RLS, and could significantly impact the long-term health of individuals living in those communities and improve the standard of care.

While monitoring represents an important mechanism for ensuring high quality data, it should be considered only one element of an overall program of quality management. The site's role in driving quality improvements is a key tenet of an effective quality management program. It has been well described that third party identification and correction of errors does not lead to sustained process improvement.²² Development of a robust site quality management program which emphasizes self-identification of errors through continuous evaluation, root cause analysis, and implementation of corrective actions that may take the form of re-training, process modification and implementation of new processes is essential to achieve sustained improvement. Other elements of a quality management plan include a well-designed protocol and case report forms, site staff training and appropriate policies and procedures to oversee monitoring activities delegated to contractors.

In RLS there may be unique practical challenges associated with monitoring and a proactive approach may avoid many issues (Table 1). Thinking about these issues during the protocol design and site activation phases may prevent significant risks to data quality that are difficult to manage once a study is enrolling, even with intense onsite monitoring. The practice of medicine is different than the conduct of a clinical trial, and clinicians may

underestimate the time needed for clinical trial participation. Physicians may be used to making clinical diagnoses and treating empirically, frequent testing, and follow up for laboratory abnormalities may be outside the usual practice patterns. Patients and clinicians may consider new symptoms and health events as part of the natural outcome of illness and not seek care or record symptoms in a medical record. Standards for record keeping may be very different: clinical records, if existent, may only document the chief complaint and prescribed medication. Shortages of ancillary personnel may delay filing of medical records, completion of data entry and critical reports, including laboratory results, may be lost. Power supply fluctuations may create difficulties in uploading data over the internet and may have an impact on the compliance with guidelines for refrigeration of drugs and supplies. Space may be at a premium, and records may be stacked in storage areas that are not well protected from the environment and insects or rodents. This issue may also impact monitoring visits and there may be little space for the study team and study monitors to review records when the clinic is open. Onsite monitoring is further impacted by the physical environment: road conditions may prevent monitoring teams from accessing sites during rainy season, and monitoring teams may not have places to stay in remote areas overnight. In addition, sites in RLS participating in multiple networks and interacting with different trial sponsors may have to accommodate many different monitoring teams at varying intervals, adding to the workload of the already overburdened study staff. Data collection and reporting systems may also vary. All of these considerations compound the challenges of monitoring in RLS and emphasize the need for harmonization among trial sponsors and adequate resources to ensure compliance with ICH guidelines.

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References

1. ICH. [Accessed September 11, 2013] ICH HARMONISED TRIPARTITE GUIDELINE: GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R1). 1996. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf
2. Khin NA, Yang P, Hung HM, et al. Regulatory and scientific issues regarding use of foreign data in support of new drug applications in the United States: an FDA perspective. *Clin Pharmacol Ther.* Aug; 2013 94(2):230–242. [PubMed: 23588316]
3. FDA. Concept Paper: Quality in FDA-Regulated Clinical Research; Background to HSP/BIMO Workshop 5/10-5/11/07; 2007.
4. FDA. [Accessed September 20, 2013] Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring. 2013. <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf>
5. [Accessed September 20, 2013] The Belmont Report. 1979. <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>
6. FDA. [Accessed September 27, 2013] Institutional Review Boards Frequently Asked Questions - Information Sheet. 2013. <http://www.fda.gov/regulatoryinformation/guidances/ucm126420.htm>
7. Kadam R, Karandikar S. Ethics committees in India: Facing the challenges! Perspectives in clinical research. *Apr; 2012 3(2):50–56.* [PubMed: 22701820]
8. CIJ, Marais D, Wassenaar D, Mokgatla-Moipolai B. Mapping African ethical review committee activity onto capacity needs: the MARC initiative and HRWeb's interactive database of RECs in Africa. *Developing world bioethics.* Aug; 2012 12(2):74–86. [PubMed: 22512919]

9. FDA. [Accessed September 27, 2013] Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees. 2006. <http://www.fda.gov/downloads/Regulatoryinformation/Guidances/ucm127073.pdf>
10. Glickman SW, McHutchison JG, Peterson ED, et al. Ethical and scientific implications of the globalization of clinical research. *N Engl J Med*. Feb 19; 2009 360(8):816–823. [PubMed: 19228627]
11. [Accessed September 22, 2013] Optimon Trial. 2007. <https://ssl2.isped.u-bordeaux2.fr/OPTIMON/Default.aspx>
12. [Accessed September 22, 2013] Optimisation of Monitoring for Clinical Research Studies (OPTIMON). 2008. <http://clinicaltrials.gov/show/NCT00780091>
13. Ochieng J, Ecuru J, Nakwagala F, Kutyaabami P. Research site monitoring for compliance with ethics regulatory standards: review of experience from Uganda. *BMC medical ethics*. 2013; 14:23. [PubMed: 23738971]
14. Baigent C, Harrell FE, Buyse M, Emberson JR, Altman DG. Ensuring trial validity by data quality assurance and diversification of monitoring methods. *Clin Trials*. 2008; 5(1):49–55. [PubMed: 18283080]
15. Bakobaki JM, Rauchenberger M, Joffe N, McCormack S, Stenning S, Meredith S. The potential for central monitoring techniques to replace onsite monitoring: findings from an international multi-centre clinical trial. *Clin Trials*. Apr; 2012 9(2):257–264. [PubMed: 22064687]
16. Morrison BW, Cochran CJ, White JG, et al. Monitoring the quality of conduct of clinical trials: a survey of current practices. *Clin Trials*. Jun; 2011 8(3):342–349. [PubMed: 21730082]
17. [Accessed September 11, 2013] Prospective cluster-randomized investigation into strategies adapted on a study-specific basis for onsite monitoring in conjunction with additional quality assurance measures. http://www.adamon.de/ADAMON_EN/Home.aspx
18. Flynn KE, Kramer JM, Dombeck CB, Weinfurt KP. Participants' perspectives on safety monitoring in clinical trials. *Clin Trials*. 2013; 10(4):552–559. [PubMed: 23644503]
19. Brosteanu O, Houben P, Ihrig K, et al. Risk analysis and risk adapted onsite monitoring in noncommercial clinical trials. *Clin Trials*. Dec; 2009 6(6):585–596. [PubMed: 19897532]
20. Spira T, Lindegren ML, Ferris R, Habiyambere V, Ellerbrock T. The WHO/PEPFAR collaboration to prepare an operations manual for HIV prevention, care, and treatment at primary health centers in high-prevalence, resource-constrained settings: defining laboratory services. *American journal of clinical pathology*. Jun; 2009 131(6):887–894. [PubMed: 19461098]
21. Olmsted SS, Moore M, Meili RC, et al. Strengthening laboratory systems in resource-limited settings. *American journal of clinical pathology*. Sep; 2010 134(3):374–380. [PubMed: 20716792]
22. Ansmann EB, Hecht A, Henn DK, Leptien S, Stelzer HG. The future of monitoring in clinical research - a holistic approach: linking risk-based monitoring with quality management principles. *German medical science: GMS e-journal*. 2013; 11:Doc04. [PubMed: 23382708]

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Table 1**Strategies to Minimize Challenges Associated with Study Monitoring in RLS**

Protocol design	<ul style="list-style-type: none"> • Simplify entry criteria and outcome measures. • Avoid criteria that are dependent on documented past history. • Only collect data that is critically important. • Create wide windows for follow up visits. • Minimize lab monitoring to that critically important for patient safety and study objectives. • Review design with investigators and clinic staff in the field before finalizing the protocol.
Lab review	<ul style="list-style-type: none"> • Encourage staff to block time for lab reviews during clinic day. • Have clear stopping rules and well defined processes for handling critical laboratory values.
Adverse event reporting	<ul style="list-style-type: none"> • As part of the consent process instruct patients to report new symptoms to study team and instruct team to ask for new symptoms. • Have clear processes to record and report new symptoms as AEs. • Consider whether syndromic adverse event reporting is sufficient. • Review SOPs for evaluation of new symptoms as part of study start up.
Documentation and Record keeping	<ul style="list-style-type: none"> • Review existing clinical practices regarding documentation before starting study. • Decide in advance of the study if separate source documentation is required, or whether sites can enter clinical data directly into electronic case report form on a smart phone or tablet. • Have systems in place so that data entry can proceed even if internet linkages are down. • Review plans for record storage and maintenance as part of study start up.
Monitoring plan	<ul style="list-style-type: none"> • Evaluate best location and time of day for onsite monitoring (Is there room? Will study staff be available or busy with clinical responsibilities?). • Develop back up plans for data transmission for central monitoring if internet connection is poor or there is a power outage. • Think through transportation challenges and housing needs for monitors as part of study set up.