Article ID: WMC00891 2046-1690

A Sensible Approach to Monitoring Trials: Finding effective solutions in-house

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Article ID: WMC00891

Article Type: Case Report

Submitted on:05-Oct-2010, 07:35:18 AM GMT **Published on:** 05-Oct-2010, 07:44:59 PM GMT

Article URL: http://www.webmedcentral.com/article_view/891

Subject Categories:CLINICAL TRIALS

Keywords:A, sensible, approach, to, monitoring, in-house, monitoring

How to cite the article: Chilengi R , Ogetii G , Lang T . A Sensible Approach to Monitoring Trials: Finding effective solutions in-house . WebmedCentral CLINICAL TRIALS 2010;1(10):WMC00891

Source(s) of Funding:

The authors did not receive any specific funding for this article

Competing Interests:

The authors declare no competing interest

Additional Files:

Additional file 1

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Abstract

There has been a trend over recent years towards the use of expensive contract organisations (1, 2)to monitor trials and clinical researchers describe a shift from a protocol or disease related discussion and guidance style of monitoring to a tick box checking process carried out by less experienced monitors. Alongside this, clinical trials are becoming more expensive and more cumbersome. We and others also observe that good clinical practice guidelines are being over interpreted by some sponsors and regulatory agencies. As an academic clinical research facility we needed to find an optimum way to monitor all our trials that ensured our studies were being conducted according to the protocol, that high ethical standards were being maintained and that the data was being accurately captured.

Our solution is an in-house system where clinical trial staff are trained as trial monitors and then monitor studies of which they are completely independent. This system has now been in place for over 2 years and we report our experiences here to offer this as an inexpensive and practical method for monitoring clinical trials. We have found the system raised standards across all trials (as it created a platform for sharing best practice), increased the profile of trial staff and has been well received by investigators, sponsors and trial staff teams. We conclude that in our site a mentoring rather than monitoring approach has been well accepted and supports the aim of conducting high quality clinical research in accordance to the international conference on harmonisation of Good Clinical Practice (ICH GCP) and yet pragmatic. There is a need to now expand and formally evaluate this approach. Therefore we are in the process of rolling out a scaled-up version of this approach between many sites within an integrated evaluation scheme.

Introduction

Our observation of the way clinical monitoring has been implemented by various sponsors (including ourselves) and our efforts in trying to rationalise the activity has led us to write this paper. The recent past has seen a trend for monitoring in clinical trials increasingly being performed by contract research organisations [1-3]. This markedly increases the costs of trials and there have been concerns as to whether the resources could be better used in the quest to get answers to critical scientific questions [4]. Illustration 1 shows the trend in CRO income in recent years. Using central statistical monitoring in properly designed trials to augment focused on-site monitoring has been suggested as one of the ways to ensure trial quality whilst reducing the resources spent. The implementation of this dual approach is not well documented and if central statistical monitoring has to be used, further thought will be needed to counter the increasing risk of type I error owing to the multiple analyses the data will be subjected to [4] . As an academic clinical research facility we needed to find an optimum way to monitor all our trials that was economically viable as well as ensuring our studies were being conducted according to the protocol, that high ethical standards were being maintained and that the data was being accurately captured. We report our experiences here to offer this as a relatively inexpensive and practical method for monitoring clinical trials.

Case Report(s)

Monitoring - the essentials

Monitoring should be a helpful and fundamental part of a clinical trial. It is not an 'audit' but an ongoing process of working with the trial team to help achieve compliance to the protocol and standard operating procedures (SOPs). Another fundamental object of monitoring a study seems to be less often applied. This is the need to ensure that the question set is being answered and that the answer can be relied upon. It is possible that many clinical trials produce answers that are either a false positive, false negative or false no difference, This is worrying as new and changes to treatments are driven by such data, and usually that false results (especially if they are negative) never come to light[5]. Whilst such errors might originate from the design or power of the study, these flaws might not be possible to predict until the trial is running. Often it is not possible to account for all eventualities when designing trials and statistical plans

are then based upon assumptions, Therefore once the trial is running it is necessary that the monitors have a cognitive role as they need to be constantly thinking about whether any process or issues could impact the reliability of a study endpoint, This is the light in which we insist that the monitor should be familiar with the protocol and their role is far more that passively checking that text boxes are filled.

Monitoring need not be an arduous general task, but it should be commensurate with the risks and complexity of the trial. ICH GCP (5.18.3) requires the sponsor to ensure that the trial is adequately monitored. “The sponsor should determine the appropriate extent and nature of monitoring which should be based on the considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is need for on-site monitoring, before, during and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigator’s trainings and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP” [6]

GCP for all clinical research

GCP was championed by pharmaceutical industries and regulatory authorities within the ICH regions and originally agreed as a tripartite agreement between the United States (US), European union and Japan. Over the years GCP has become an accepted global standard for clinical trials. Regardless of the historical context, GCP today is to be applied for all trials that involve participation of human subjects and is required by most funders, sponsors and indeed publishers [6, 7] .This is widely recognised as being positive as in its basic principles GCP demands high ethical standards and reliable data, which surely no researcher would dispute. However, there is need to interpret GCP in a way that ensures it serves its important purpose without becoming simply an end in itself. It is the interpretation, and specifically one-size-fits-all interpretations of GCP that are giving GCP an unfair reputation [8]

The last 10-15 years brought an increasing number of product development trials to Africa. Most of these have been pharmaceutical industry led, World Health Organisation (WHO), Universities (both foreign and local) and a few trials are generated by research institutions themselves, as shown in Illustration 2. With the increased funding for research into diseases affecting poor communities, the number and complexity of trials will continue to increase and this will further exert demand on the already limited pool of skilled human resources in developing countries [5]

Current Monitoring Practices

Unfortunately, sponsored studies tend to approach GCP as something requiring huge resources. Contract Research Organizations (CROs) have thus mushroomed to take advantage of the booming business, especially for provision of clinical study monitoring services and other regulatory aspects [1, 2]. We have observed that pharmaceutical companies and contract research organisation place people into the role of monitor having had little experience of clinical trials and research and having been given quite narrow training. In our experience of working with many external monitors, the role is mainly limited to sitting with the case record forms and checking these for missing fields against the source data. It is not unusual for the monitors to demonstrate limited understanding of the protocol, or lack of knowledge in the disease area. Since CRO employees must be kept “fully billable,” they are shifted from project to project as the need arises and may never build up expertise on a particular project. It is not unusual in our experience to host such monitors who would then focus their effort on completing the tick boxes without a reasonable understanding of the relative importance of key fields. For instance, we do not think that absence the curriculum vitae (CV) of a driver should be ticked with the same weight as informed consent or eligibility criteria! Clearly some issues identified will be important but across our broad network of research sites we have repeatedly had reports of frustration by researchers when they have experienced what they perceive as overly ‘picky’ monitoring taking up valuable time on issues would have no impact on the validity of the end points of the trial. Such misapplication of the well intended values of GCP has led to others being critical of the GCP standards [8, 9]. We suggest the focus needs to be weighted on ensuring that the data that influences the trial endpoints are accurately captured. Here we come back to the point about making the role a more intelligent and ‘think’ one. We do meet monitors like this, who are experienced and interested in the study and its outcomes. It is much more beneficial to the site staff and the trial itself if a monitor has previous experience in research and talks through the trial steps and issues with the staff and thereby either resolve or prevent data inaccuracies arising. We need to be assured that the number is correct and the mechanism by which is obtained has been consistent. This is particularly crucial in multi-centre studies, and therefore monitors are so important.

We argue here that unless the monitor themselves have an appreciation of research, it is very difficult to make a good monitor based on check boxes. We therefore welcome the approach by WHO Special

Programme for Research and Training in Tropical Diseases (WHO TDR) who adopted a strategy of training young African investigators to also serve as clinical monitors.

Discussion

A PRAGMATIC WAY FORWARD

The Kilifi experience: an in-house solution

The Kenya Medical Research Institute(KEMRI)-Wellcome centre has more than 15 years experience in conducting clinical studies ranging from large pharmaceutical initiated (and sponsored) regulatory trials to small academic/investigator-sponsor trials. The Clinical Trials Facility which has been running since its inception two years ago currently oversees 11 clinical trials (3 vaccine trials, 4 large academic led trials and a mix of phase I and II trials either pharmaceutical sponsored or academic trials).

As part of ensuring GCP for our clinical studies, we were faced with the challenge of ensuring that all our clinical trials are adequately monitored. The CRO model was unattractive for the reasons outlined above as well as its obvious cost implications. Therefore, we opted to utilize our available pool of experienced study coordinators and nurses who get annual training as monitors.

In our experience, monitoring is a mutually beneficial exercise for the study monitored and the individual monitors. The basic principles of clinical trial conduct are generic and applicable across studies. The process of developing monitoring tools, training and management of the monitors group has turned out to be a highly rewarding experience to the monitors cum coordinators. This cadre of staff has become the key implementers and driving force of GCP. With a pool of at least 20 trained monitors, we have managed to allocate at least two monitors to each study. Thus all studies are similarly monitored and reported to the head of clinical trials and respective principal investigators.

Has is it worked?

To date the trial investigators, sponsors and funders report to be impressed and satisfied with the monitoring that the trials have received. Before this scheme was implemented only the externally sponsored drug development trials were monitored. Presently all clinical trials in the programme are subject to the in-house reciprocal monitoring scheme, even if they are also externally monitored by the sponsor. Previously many of our locally sponsored or academic research studies were not able to finance monitoring (as CRO's would have been the only option) and they did not have the skills or capacity to monitor themselves. This reciprocal scheme has made quality and ethical standards assurance achievable and feasible.

This monitoring system has become a popular activity within our programme. This is because it has also bought an additional benefit, that of staff motivation and skill enhancement. The opportunity to train to join the monitoring pool has allowed a research nurse from the ward, for example, to gain experience of clinical trials in the community out in our field sites. Another good example is that spending two days a month monitoring trials gives the trial laboratory staff, or the trial pharmacists, hands on experience of clinical trials from a perspective they do not normally experience. Our monitoring programme has been particularly attractive to our collaborators who happen to run studies at other sites for which formal requests to extend the service have been made.

With this system, we also have the possibility of scheduling monitoring visits according to the complexity of the trial. In the CRO monitored trials, such decisions would normally heavily weigh on availability of finances rather than study designs. An additional benefit is that it creates an opportunity for mentoring of trial staff through continued interaction between the more experienced and lesser experienced trial staff during and after the monitoring activities. In the CRO model the amount of interaction would be limited to the resources available for on-site monitoring.

The In-House Monitoring Scheme

Any member of a clinical trial research team can train as a monitor. Nurses, data managers, pharmacists and trial coordinators all make excellent trial monitors. Trial monitoring can be built into people's roles so they do not do this full time. This is a good way to give staff an extra dimension to their role and is an excellent continuous training experience. The training for these monitors can also be organized in-house (and so for relatively less cost), as long as sufficiently experienced and senior monitors/trainers are available.

At Kilifi, this was possible as two staff members are highly experienced monitors and appropriately qualified to design and implement monitor training. There is a plethora of expensive courses for trial monitors but nowhere in ICH GCP, or in any other regulations, are there specific requirements or certification for monitors – or their trainers. What can be found are statements around appropriate experience and qualifications. Here, as with monitoring

itself, it seems that the commercial needs of training companies and contract organisation have created a market and a perceived need for external training courses, certification and accreditation. We chose instead to apply our experience and a pragmatic approach to develop a high standard course internally. The fact that 7 of our monitors who have attempted the international certification course by the Association of Clinical Research Professionals (ACRP) have all passed examinations at one attempt suggests that the approach is a reasonable one. Once we had trained our staff agreement was gained with the PI's (as typically their grants or contracts with sponsors paid for their trial team members salaries) to allocate a proportion of the relevant staff time (typically 1 or 2 days a month) to monitor other trials within the programme. In return their trials would be monitored through this scheme at no cost.

We thus have evolved a robust monitoring group with regular activities. On average, 3-4 studies are monitored each month. Following each visit, the monitoring reports are reviewed with the head of clinical trials, which serves as an opportunity for continuous on-the-job training. The monitoring group gets refresher training at least once each year and they are fully involved in developing and refining our standardized monitoring tools as well as procedures.

For every new trial coming up the lead monitor in consultation with the trials facility manager allocates internal monitors who will be responsible for this trial. Typically trial staffs (study coordinators, nurses & data managers) involved in field based trials are allocated to monitor hospital/ward based trials and vice versa. The lead monitor drafts a quarterly schedule detailing which trials are to be monitored within that period. The frequency of monitoring for each study is determined based on the complexity of the study, the extent of external monitoring and specific protocol requirements. This is clearly documented in the study specific monitoring plan.

Conclusion

Monitoring is important, but it needs to revert to mentoring - supporting the site rather than checking tick boxes[4]. Monitoring does not have to be expensive and an in-house scheme where staffs are trained on monitoring is an inexpensive way of assuring the quality of the trial data. Training can be offered by an experienced monitor but if there is no-one on site appropriately skilled to train, a consultant or an appropriate individual from another site could provide training on-site. If sites are too small they could collaborate with nearby groups – this might be a good opportunity to exchange experiences and support each other. Indeed we have trained monitors from other sites at no cost and will continue to offer places for any course we run,

A monitoring plan needs to be appropriate to the relative complexity of the trial and should be focused on supporting the trial teams and ensuring operational success. The nature and extent of monitoring must also be influenced by the risks involved; so a short trial in relatively well adults with an approved drug will need less monitoring than a long paediatric trial with many visits and interventions assessing an investigational new drug.

We recommend an objective assessment of this approach that would consider assessing economic aspects, relative risk of the trial to the participants, assessment of data quality and perceptions of all parties. Suffice to add that institutional will at the highest administrative level is critical for the success of such a model.

In recognition of the need for full evaluation and in light of the perceived success in our programme we are now scaling up this scheme and working in partnership with the East African Consortium for Clinical Research (www.EACCR.org), the World-Wide Anti-Malarial Resistance Network (www.WWARN.org) and the Global Health Clinical Trials Programme (www.GlobalHealthTrials.org). Through this partnership we are establishing reciprocal monitoring schemes in South East Asia and East Africa, across many sites and different regions. These schemes will share a comprehensive evaluation process through which we aim to establish the benefits, limitations and cost effectiveness of this approach to monitoring.

Back in Kilifi the system is working well everyone is positive, and perhaps best of all it is free! We have made the tools, resources and training material that we use for our in-house scheme freely available on the Global Health Clinical Trials website in order that any other site can have access to our resource and adapt them for their own use (www.globalhealthclinicaltrials.org).

Abbreviations(s)

ACRP - Association Of Clinical Research Professional

CRO - Contract Research Organisation

CV - Curriculum Vitae

EACCR - East African Consortium For Clinical Research

ICH GCP - International Conference On

Harmonisation Of Good Clinical Practice
KEMRI - Kenya Medical Research Institute
SOP - Standard Operating Procedure
US - United States
WHO - World Health Organisation
WWARN - World-Wide Anti-Malarial Resistance Network

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Illustrations

Illustration 1

Source: Wademan M. (Nature 2006)

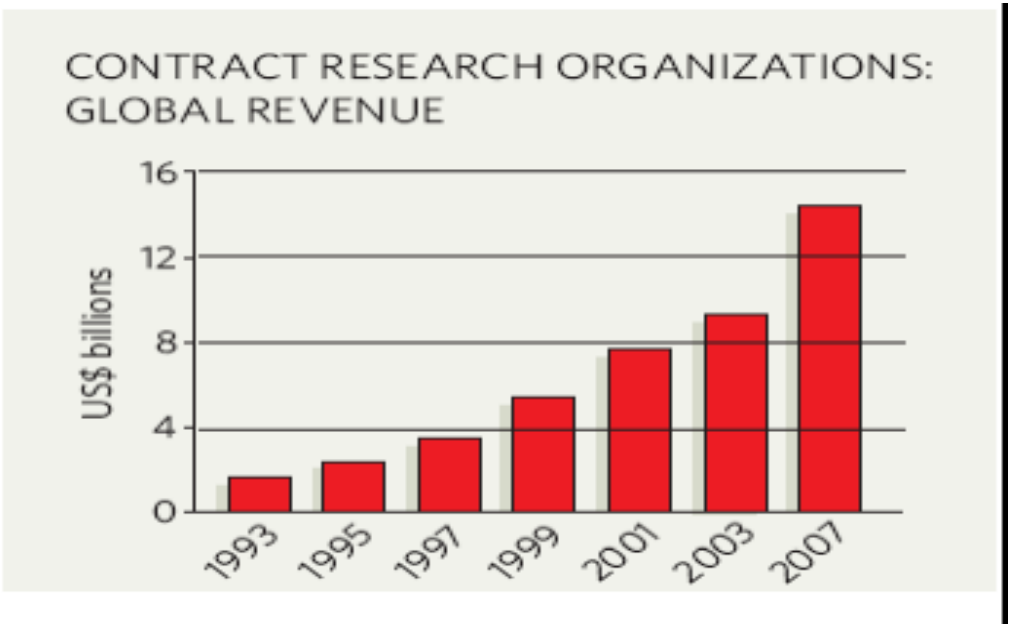

Illustration 2

Sources of funding for Trials in Africa. *Numbers in parenthesis represent active studies.

FUNDER	NUMBER OF STUDIES*
National Institutes of Health	211 (55)
Industry (pharmaceutical)	1078 (236)
Other US federal agency	74 (22)
University/organisation/other institution	557 (175)

Source: clinical trials.gov 14th September 2010

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