International health research monitoring: The value of a scientific and co-operative approach

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International health research on-site monitoring: *The value of a scientific and co-operative approach*

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ABSTRACT

Objectives

To evaluate and determine the value of monitoring models developed by the Mahidol Oxford Tropical Research Unit and the East African Consortium for Clinical Research, consider how this value can be measured and explore monitors and investigators experiences of and views about the nature, purpose and practice of monitoring.

Research Design

The monitoring model case studies represent interventions aimed at changing practice hence a participatory action research methodology was applied and 34 interviews, 5 focus groups and observations of monitoring activities conducted.

Setting and Participants

Fieldwork occurred in the places where the monitoring models are coordinated and applied in Thailand, Cambodia, Uganda and Kenya. Participants included those coordinating the monitoring schemes, monitors, senior investigators and research staff.

Analysis

Transcribed textual data from field notes, interviews and focus groups was imported into a qualitative data software programme (NVIVO 10) and analysed inductively and thematically by a qualitative researcher. The initial coding framework was reviewed internally and two main categories emerged from the subsequent interrogation of the data.

Results

These categories identified related to the conceptual framing and nature of monitoring, and the practice of monitoring, including relational factors. Particular emphasis was give to the value of a scientific and cooperative style of monitoring as a means of enhancing data quality, trust and transparency. In terms of practice the primary purpose of monitoring was defines as improving the conduct or health research and increasing the capacity of researchers and trial sites.

Conclusions

The models studied utilize internal and network wide expertise to improve the ethics and quality of clinical research. They demonstrate how monitoring can be a scientific and constructive exercise rather than threatening process. The value of cooperative relations needs to given more emphasis in monitoring activities, which seek to ensure that research protects human rights and produces reliable data.

ARTICLE SUMMARY

Article Focus

- Escalating bureaucracy and regulatory burden is increasing the costs of conducting trials, and deterring researchers from conducting high quality science
- There is significant interest in innovative monitoring models which distil the essence of regulatory guidelines in a workable and scientific manner
- We evaluated two models developed in international health settings to document their implementation, describe the challenges encountered and the good practices developed, and increase our understanding of the purpose of monitoring.

Key Messages

- More emphasis needs to be placed on the cooperative nature of monitoring and the need for monitoring practice to have a clear scientific focus
- The primary purpose of on-site monitoring is to improve the conduct of health research and increase the capacity of researchers and trial sites, and the success of monitoring should be measured by corrective action rather than by identification of faults
- There is a need for mixed methods research to evaluate a combined approach of cooperative and scientifically guided on-site monitoring and central statistical monitoring

Strengths and Limitations

- Addresses a gap in the literature on on-site monitoring in low-income and middle income settings
- Lack of focus on and access to quantitative data which could be collated from monitoring reports and plans, and budgetary documents outlining trials costs
- Unable to compare the monitoring reports of studies monitored by our case studies and other sponsor delegated monitoring groups.

BACKGROUND

In the field of health research the practice of monitoring has become associated with compliance with the 'International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use'-Good Clinical Practice Guidelines' (ICH-GCP), and related Federal (United States) and European trial regulations [1-4]. In ICH-GCP sponsors are delegated responsibility for quality management of which monitoring is an integral component. Monitoring is defined as: *'The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirements'* [1]. Section 5.18 of ICH-GCP emphasises that the main purpose of monitoring is to verify that the rights and well being of human participants are protected. Whilst this overarching *ethical purpose* is reflected in the detailed ICH-GCP guidance, the intrinsic emphasis on record keeping can serve to obscure this primary purpose.

Escalating bureaucracy and regulatory burden is increasing the costs of conducting trials, and deterring researchers from conducting high quality science [5-7]. Whilst the role of ICH-GCP in improving quality is widely acknowledged there are questions about its' application in health research, specifically in trials not involving investigational medicinal products [8]. It is argued that the well-intended values and principles of ICH-GCP have become hampered by bureaucracy and misapplication [9 ,10]. An associated 'tick box' standard is considered to divert attention away from key questions about the ethical process, study endpoints and data validity. Delegating monitoring activities to 'contract research organisations' (CROs) can extenuate this bureaucracy and lead to the misconception that ICH-GCP is highly complex and only achievable with huge resources [9]. This can be particularly detrimental to research undertaken in low and middle income countries where competitive market forces have resulted in clinical research becoming more driven by profit than local health needs [11].

ICH-GCP requires that trials should be monitored according to the complexity and nature of the trial. The European Medicines Agency and the Food and Drugs Administration have released new guidance documents, which encourage sponsors to apply a risk and complexity assessment to trials. The aim is to reduce logistical and financial burdens of conducting 100% data validation [12 ,13]. This approach was endorsed at the Toronto 'Sensible Guidelines Meeting' in May 2012 [14]. Increasing attention is therefore being paid to rationalising monitoring activities to reflect the risks posed to participants, and to ensure trials generate accurate data to support decision-making about the safety, efficacy or effectiveness of new products and health interventions [15].

Central statistical monitoring (CSM), applied remotely through advanced statistical and bioinformatics methods, is proposed as a way of achieving the latter, particularly in multi-site trials [16 ,17]. Baigent et al cite the following taxonomy of errors affecting trials 1) Design Error/Procedural Error 2) Recording Error 3) Fraud, and 4) Analytical Error [17] . They argue that on-site monitoring should target errors, requiring due attention at specific trial sites. Hence CSM is not a stand-alone solution but needs to be complemented by proactive on-site monitoring. Experience shows that proactive on-site monitoring (e.g. peer-review) can enhance the quality of data and trial processes (e.g. participant consent) [18 ,19].

Diverse opinion exists amongst investigators, sponsors and regulators about the definition and organisation of monitoring. Points of debate are the balance between CSM and on-site monitoring, the difference between audit and monitoring, and who should undertake these activities. Be it external CROs, in-house pharmaceutical monitors, or quality management teams embedded at trial sites. In this discussion there is a dearth of literature from international settings. Macefield et al's recent systematic review of on-site monitoring methods for health care randomised controlled trials was only able to include 7 multi-national articles[20]. They concluded that there was a paucity of evidence and a need for further evaluation trials.

In our research we evaluated 2 innovative monitoring models, which are being implemented by Mahidol Oxford Tropical Medicine Research Unit in Thailand (MORU) and by the East African Consortium for Clinical Research (EACCR). Our aims were to determine the value of these models, consider how this could be measured and explore monitors and investigators experiences of and views about the nature, purpose and practice of monitoring.

METHODS

Research Design

We used a case study approach to evaluate the MORU and EACCR monitoring models in their real life contexts [21]. The case studies represent interventions which aim to change and improve practice therefore we applied a participatory methodological approach akin to action research [22]. Our research team included representatives from the case studies who could act on interim findings during the course of the research. A qualitative researcher (QR), who did not occupy an active or a collaborative role in the monitoring case studies, coordinated the study. The QR spent two weeks with members of each monitoring case study, during these fieldwork visits she observed monitoring activities, participated in a training workshop, reviewed documentary sources, and interviewed investigators and monitors associated with the case studies.

Study Participants

The sample was drawn purposively in order to select 'information rich' representatives from two groups: 1) Those actively involved in the development, coordination and implementation of the monitoring case studies, and 2) Investigators and research staff whose work is being monitored by the monitoring case studies. The first group includes monitors and key informants (KIs) some of who are senior researchers within the MORU and EACCR networks. Potential participants were informed about the purpose of the study and related research activities verbally and provided with study information sheet in advance of the researcher's fieldwork visits. At MORU the QR also presented an overview of the study at the central MORU offices. The QR obtained informed consent from monitors and investigators who were willing to be interviewed and agreed to her observing their research and monitoring activities.

A total of 56 participants were recruited (Group 1=35, Group 2=21) participants from the case studies, 26 from MORU and 30 from EACCR. Group 1 comprises 9 key informants (MORU=5, EACCR= 4) and 26 (MORU=6, EACCR=20) monitors. In the EACCR case study all of the monitors were also active researchers. Key informants were senior investigators and those with experience of quality management, who had played a significant role in the development of the respective monitoring schemes. Group 2 comprises different cadres of staff: senior investigators (MORU=2), site investigators/trial coordinators (MORU=4, EACCR=3) and trial staff (MORU=9, EACCR=3) including some who were specifically responsible for quality control. Table 1 provides details of participants' demographic characteristics. Of note is that the sample includes highly experienced and qualified international research professionals.

Fieldwork

In April 2012 the QR visited the MORU offices and research facilities in Bangkok and associated research centres/clinics on the Thai-Burmese border (Shoklo Medical Research Unit) and at Pailin District Hospital, Cambodia. All of these research facilities were involved in an antimalarial resistance trial and the researcher was able to observe monitoring activities at each facility. Interviews were held with 8 trial investigators, 5 KIs and 6 monitors. Two group interviews with members of trial staff based at Thai-Burmese border clinics were conducted, one with two participants and the other with 5. Thai and Karen translators helped facilitate the group interviews and 2 individual interviews with Thai researchers.

In May 2012 the QR travelled to sites connected with the EACCR monitoring case study and observed a workshop for EACCR monitors. In Uganda she visited the Ugandan Virus Research Institute, the International AIDS Vaccine Initiative and Medical Research Council

offices in Entebbe and observed a two-day monitoring visit of an observational HIV treatment trial at Masaka Referral Hospital. In Kenya she accompanied two monitors on a three day monitoring visit of an HIV prevention trial for sero-discordant couples. During the EACCR fieldwork 6 investigators, 4 KIs and 6 monitors were interviewed. Three group interviews were conducted with 15 (4, 5, 6) monitors during a two day monitors training and feedback workshop held in Nairobi in May 2012. This workshop provided rich insights into the challenges and successes experienced by EACCR monitors.

Across both case studies 34 individual interviews were conducted with 12 investigators, 9 key informants and 13 monitors, and 2 focus groups with investigators and 3 with monitors. The interviews covered a wide range of topics including the history, purpose and value of the monitoring models, experiences gained and practical and ethical challenges encountered during their implementation and, the definition of monitoring and how to measure or evaluate good practice.

Analysis

Data constituted of field notes, interview and focus groups recordings and transcripts, monitoring reports and other documents relating to the case studies. Recordings were transcribed verbatim with the exception of oral contributions in Thai or Karen. These were translated during the course of the interview and only the English translation was transcribed verbatim. To facilitate the organisation of the data and the development of a coding framework the data was imported into a qualitative data software programme (NVivo10). The recordings and transcripts were crosschecked for accuracy and then TC performed the primary analysis. This involved open coding the interview, focus group and field notes data in a thematic and inductive manner and developing a coding framework. Subsequent analytical meetings with TL helped refine this framework and led to the definition of two major categories namely; 'the conceptual framing and nature of monitoring', and 'the practice of monitoring', which included reference to relational factors.

CASE STUDY PROFILES

Case 1: MORU-clinical trials support group

MORU is a collaborative partnership between the Faculty of Tropical Medicine, Mahidol University, the University of Oxford and the Wellcome Trust, which was established in 1979 (www.tropmedres.ac). MORU's main office and laboratories are located within the Faculty of Tropical Medicine at Mahidol University in Bangkok, Thailand. Clinical trials take place at study sites across Asia and Africa. A 'Clinical Trials Support Group' (CTSG) was established at MORU in 2008 to provide help, guidance, and support to investigators conducting research involving human subjects. The defining feature and what sets the of the MORU monitoring

model apart from standard monitoring models is the way that CTSG is embedded within an established research unit. This positioning means that its members are familiar with the health research priorities of the unit, can maintain a constant feedback loop between themselves and investigators, and understand the diseases and the social context in which trials take place. Additional strengths are that all CTSG members are experienced health researchers and some have worked in the pharmaceutical industry or with contract research organisations. CTSG members support protocol development, assist with ethics submissions, provide project and data management support, deliver training and assist in the quality management of trials. The latter includes writing trial specific risk-based monitoring plans with investigators and conducting on-site monitoring at defined time points. The MORU monitoring model is not without challenges, however, particularly in relation to workload, travel logistics and ensuring monitoring activities are adequately budgeted for.

Figure 1 illustrates CTSG's involvement in monitoring a multicentre randomised trial to detect in vivo resistance of Plasmodium falciparum to artesunate in patients with uncomplicated malaria (Web registration number: NCT01350856). This trial is part of the 'Tracking Resistance to Artemisinin Collaboration' (TRAC).

Figure 1: Spatial Organisation and Infrastructure of CTSG TRAC monitoring

Case 2: EACCR-Network Reciprocal Monitoring Model

The EACCR (www.eaccr.org) is a partnership of 35 institutions in five countries (Tanzania, Uganda, Kenya, Sudan, and Ethiopia). This 'Network of Excellence' is funded by the European and Developing Countries Clinical Trials Partnership and was established in May 2009. At its' inception the potential for strengthening monitoring capacity across partner institutions was established as a priority. The vision was to increase capacity for monitoring and develop a pragmatic and cost-efficient network-wide monitoring service. A reciprocal monitoring system was designed and set up in 2007 within KEMRI-Wellcome Programme in Kilifi Kenya. This novel approach trained study staff to monitor studies and then this pool of trained monitors then spent a small portion of their time monitoring each others studies within the programme [18]. This system worked well because it enabled knowledge, best practice and skill sharing between different studies in the same organization whilst enabling the implementation of high quality clinical research monitoring. This approach was then taken up by EACCR and further developed for deployment across this network. This network-wide monitoring approach, which was launched at the start of 2011, is referred to as the EACCR reciprocal monitoring scheme (RMS). It involves two coordinators based in Uganda and Kenya and 22 trained monitors nominated by eleven partner institutions.

Figure 2: EACCR Partner Institutes involved in the RMS

The defining features and strengths of the RMS are that it is reciprocal and involves, on a part-time basis, health research professionals who have an in depth appreciation of the context where trials are conducted. It is reciprocal in two key ways; firstly it involves members of partner institutes monitoring each-others research, secondly it allows experienced monitors to share their expertise with novice monitors who have limited experience of trial monitoring. Initial challenges have also helped the scheme to improve its logistical functions, and increase its credibility by clarifying the schemes mandate and improving communication between the coordinators and investigators.

FINDINGS

The accounts given and the observations collected during the fieldwork convey rich information about the nature and practice of on-site monitoring. Accordingly our findings are presented under two main headings; first we explore participants' understandings and expectations of clinical trial monitoring, and then we examine what they think constitutes professional practice with reference to organisational ethos and accountability, monitors' expertise and approach, and the focus of monitoring activities.

What is on-site health research monitoring, and what should it be?

We distilled four core elements of monitoring from participants' accounts (Text Box 1). The latter two are of particular interest because they bring to the fore aspects of monitoring which are often overlooked. Our data suggest that whilst investigators appreciated the need for regulatory and ethics oversight, they want monitoring to be collaborative in nature and scientific in focus. Some investigators related how constructive interactions with monitors assuaged their initial fears and changed their perceptions about the value of monitoring. Others championed the need for cooperative monitoring as a result of encounters with monitors who questioned their intentions from the outset, or prioritised document verification and paperwork over observing critical research processes.

"My first experience was…to me actually I felt it was an activity of policing. I said, "Wow well they are going to find faults," ... I thought maybe it's worth hiding something so that they not know yeah. But with time I came to know really it is something very valuable, that I needed to be involved in. It's actually more to support me into the better conduct of the studies."

Investigator, EACCR 6

'I could see that something was, that a monster was being created…this is the whole area of sort of ethics regulation and so and it seemed to be only one direction of travel which was more and more heavy questions and demands and requirements and the net result was more and more paperwork, more and more time devoted towards it.'

Investigator, MORU 26

Investigators were keen to be involved in planning monitoring activities and valued the input of monitors who *"understand what we call the main focus of the study and give credit to the investigator who have long experience" (Investigator, MORU 11)*. They particularly appreciated monitors who worked with them to rectify faults and increase research capacity.

MORU investigators described how the establishment of the CTSG has allowed them to exercise more control over how trials are monitored. They can draw on the expertise of CTSG members to ensure that monitoring activities target the greatest risks to participants and the most scientifically relevant data points. This has helped them develop a counter argument against some of the bureaucracy they believe is hampering the conduct of biomedical research. The EACCR reciprocal monitoring scheme was credited with strengthening quality management across the network, and appreciated by monitors as means of professional development and exchange. Across both case studies much value was attributed to a non-threatening *'shared learning'* style of monitoring, which prioritized the resolution of problems.

'*…because it's a sort of cooperative monitoring and not hostile, you're much more likely to get problems sorted out rather than hidden.'*

Investigator, MORU 17

It was evident that participants wanted monitoring to be scientifically grounded to ensure that quality checks are tailored to primary study outcomes. This type of monitoring requires monitors to work closely with investigators from the planning stages of studies. Much emphasis was also placed on the need to complement checking activities with tailored support and training. Investigators were positive about the need for correction, especially when monitors worked with them to improve their work. Participants concurred that the purpose of monitoring should be to improve the conduct of health research and increase the capacity of researchers and trial sites. In other words monitoring should *'help sites achieve what they are supposed to achieve'* and offer *'assurance to investigators that they are doing things the right way'*. In practice this type of monitoring replaced negative associations with more positive views of monitoring.

'Yeah when a monitor they actually come in to help you do your work better, they're not coming to police you or to find mistakes…they're coming to help you do your work better.'

Monitor, EACCR 3

The Practice of Monitoring: What constitutes professional practice?

The 'who' of monitoring

Participants' experiences of monitoring suggest that the organisational ethos of monitoring bodies has a bearing on the practice of monitoring. It was evident from participants' accounts that monitors from external bodies sometimes distanced themselves from research staff. In contrast EACCR monitors conveyed the notion that *'we are doing this together'*, similarly the positioning of the CTSG as an internal monitoring group within MORU enhanced interactions between researchers and monitors and increased transparency. On the other hand some MORU investigators felt that research staff were more *'alert and ready'* during monitoring visits from external groups.

These observations about interactions between monitors from different organisations and investigators raise important points about accountability and professional relationships. EACCR monitors for example argued that monitors can identify with the site whilst remaining accountable to the study sponsor, and MORU investigators maintained that the positioning of the CTSG does not pose a conflict of interest. To the contrary they work together more easily because their professional relationship is built on trust and mutual understanding. According to a study nurse this prior knowledge reduced the stress associated with monitoring but it did not alter the need for correction. Internal monitors applied the same standards as external monitors but their proximity meant that they were more accessible and could provide on-going support.

Yeah for me I think it's not so hard because it's not like the investigator is against the sponsor. So it's not like they're trying to identify with you as opposed to the sponsor. They're just when they are on the site they're talking we. We can do this…and the way I see it, it's not hard for them to identify with the site.

Monitor EACCR, 27

CTSG they will know the protocol very well and they will know us quite well I have to admit it, but that doesn't provide conflict of interest…in a way it make us work together easier.

Investigator MORU, 11

Monitors background, training and expertise and their understanding of the research context were viewed as important in terms of professional practice. One investigator said

that he judged the value of monitors work by the *'quality of the information they are able to detect'* (Investigator, EACCR 7). Health professionals with experience of working in research were regarded as particularly well equipped to be monitors. A role, which was also thought to require motivation and commitment, attention to detail, good interpersonal and communication skills and the ability to apply and interpret ethics guidelines in practice. With reference to the latter an investigator emphasised that monitors needed to understand the scientific purpose of the research in order to *'think about the patient's interests and how they could advocate for those, or how they could check for those' (Investigator MORU, 20).*

Much value was attributed to context informed monitoring and investigators resented monitors who did little to consider cultural norms, logistical limitations and local regulations.

'They come and they have such little time and they will have to do so much so they're in a rush and sometimes they're really distressed to try and meet their milestones. And then the other thing that I have seen is inability to understand the culture and even local regulations sometimes, harmonising and local regulations and sponsors, SOPs and their own regulations back in their country, it's such a big issue. So they come out and they would like things done the way they understand it. A few times we took it upon ourselves to really train them on our culture, what is acceptable, what cannot be done'.

Investigator EACCR, 10

This investigator is arguing that an appreciation of local norms, customs and regulations is prerequisite for effective and professional monitoring practice. Local monitors were considered well placed to undertake context informed monitoring, and external monitors who demonstrated a willingness to learn rather than simply impose ideas were also highly valued. When it comes to the 'who' of monitoring what counts is mutual respect, communication, professionalism, and maintaining high standards irrespective of the positioning of the monitor in regards to the sponsor and researcher.

The 'what' and 'how' of monitoring

When it came to the practicalities of monitoring what counted was getting the focus and the approach right. Focus requires careful planning and CTSG participants stressed the importance of developing monitoring plans with investigators. This planning helped them to identify the main risks to a study's integrity with reference to ethics and key study outcomes. It helped them differentiate between minor and major errors thereby avoiding diverting unwarranted time to rectifying the former. Focus also involves achieving the right balance between paper work and observing research in practice.

'I mean sometimes documents don't, may not give, tell you, give you, the clear picture of how things are run. Sometimes talking to people, asking people questions, seeing what people are doing can assure you, can tell you a number of things that you can't see by looking at the documents.'

Key Informant EACCR, 28

Concerns were raised by investigators about the amount of time monitors (coming from long distances) end up spending sitting in rooms verifying files and source documents. It was argued that on-site monitoring should not be confined to document review but include observational and interactive activities, which allow monitors to gain greater insights into how a trial is being implemented and where corrective action is needed.

Two distinct ways of organising monitoring activities were described. One where the monitor performs their review presents findings in debriefing meetings, and sends a summary report with action points; and the other where the monitor actively engages research staff in resolving issues during the on-site visit. The components of monitoring visits were similar but the engagement differed. Investigators expressed preference for the latter but also noted that this method was time-consuming and impractical when the research clinics are busy.

A monitor's personal and professional approach was viewed as crucial to promoting positive interactions and improving the quality of trials.

'The key thing about successful monitoring is how you present, how the monitor presents themselves and involves themselves with the investigators'

Investigator MORU, 26

Monitors need to gain the trust of investigators and interviewees argued that the best way to do this is to work with investigators to improve study conduct. It was evident that investigators were anxious about discussing problems or disclosing important information to overly critical monitors. One investigator (Investigator EACCR, 7) described how his team's *'fear just melted away'* when they realised that their monitor's approach (an external CRO monitor) was not adversarial *'you did this wrong, we are going to beat you'*, but constructive *'he's like trying to make you improve'*.

The core features of a professional approach to monitoring were cited as a commitment to high standards, open communication and positive interactions, mutual respect and a friendly manner. Investigators appreciated monitors who maintained high standards in a strict and firm manner and worked with them to enhance the quality of their work.

DISCUSSION

Our participatory evaluation provides important insights about the practice of international on-site monitoring, and the value of utilizing internal and network expertise to enhance trial quality. Particular emphasis was given to a cooperative style of monitoring as a means of enhancing trust and transparency. Whilst this style of monitoring was associated with the EACCR and MORU models, it is important to note that some participants commented positively on interactions with CRO monitors. With reference to practice our findings suggest that the primary purpose of on-site monitoring is to improve the conduct of health research and increase the capacity of researchers and trial sites. Monitoring activities to be scientifically grounded, contextually and culturally informed with tailored support and training. Skills in the scientific evaluation of trials and a willingness to work closely with investigators were viewed as critical for the development of effective risked-based and context informed monitoring plans. It was argued that on-site monitoring should combine document verification with observational activities, and be complemented by training and mentoring to enable investigators to execute necessary corrective actions. Indeed our data suggest that the success of monitoring should be measured by corrective action rather than by identification of faults. Monitoring reports should only include findings, which could significantly impact on the scientific and ethical integrity of the trials.

The main benefits of the MORU and EACCR monitoring models are: 1) Reduced logistical costs, 2) Increased site capacity for quality management, 3) Investigators contribution to risk-based monitoring plans, 4) Professional development and exchange. The latter is of relevance given the increased value attributed in the health sector to 'Communities of Practice' (CoPs) as a means of encouraging situated learning and the practical application of knowledge[23]. CoPs are defined as: *'groups of people who share a concern, a set of problems, or a passion about a topic, and who deepen their knowledge and expertise in this area by interacting on an on-going basis'[24]*. The challenges relate to questions of sustainability and credibility. There is a need to consider the logistics and funding of these models to ensure that their benefits are sustainable. Currently both models rely heavily on grants rather than charging trials directly for their services. This needs to be remedied in order to reduce dependency on external funding.

The strengths of this empirical study are that it contributes to the literature documenting good practice at international trial sites in resource-constrained settings. As noted in the background section Macefield et al [20] were only able to include 7 multinational trials in their systematic review. Given the study design one inherent limitation is the paucity of quantitative findings. Follow up studies will need to systematically collate information on trial costs, and provide monitoring report templates. An additional weakness of our work is that we were not able to compare the monitoring reports of studies monitored by MORU and EACCR RMS, and other sponsor delegated monitoring groups. A key area for future

research will be to conduct a mixed methods study, which evaluates how the EACCR and MORU on-site monitoring models work in combination with CSM.

CONCLUSIONS

Innovative monitoring models, which prioritise the sensible application of regulations and ethical guidelines are imperative to facilitate vital global health research. The experience gained in developing the innovative international models studied in this paper offers valuable insights. Both models utilize internal and network wide expertise to improve the ethics and quality of clinical research. They demonstrate how monitoring can be a constructive exercise rather than threatening process. The value of cooperative relations needs more emphasis in this field given that sponsors, investigators and monitors are jointly responsible for ensuring that research protects human rights and produces reliable data, which can improve human health.

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CONTRIBUTORS

All authors participated in the study design from conception. TC conducted the case study fieldwork with the support of AN, EA, GM, EK, PYC and VH. TC performed the primary analysis and TL was involved in subsequent analytical review and decision-making. TC wrote the first draft of this paper and all authors critically revised the manuscript.

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COMPETING INTERESTS

None

ETHICS APPROVAL

The study was approved by the Oxford Tropical Research Ethics Committee (Ref: 09-12), the Kenyan Medical Research Institute Ethics Review Committee (No: 2253), the Ugandan Virus Research Institute Science and Ethics Committee (Ref: GC/127/12/03/04), and the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University (Ref TMEC 12-023).

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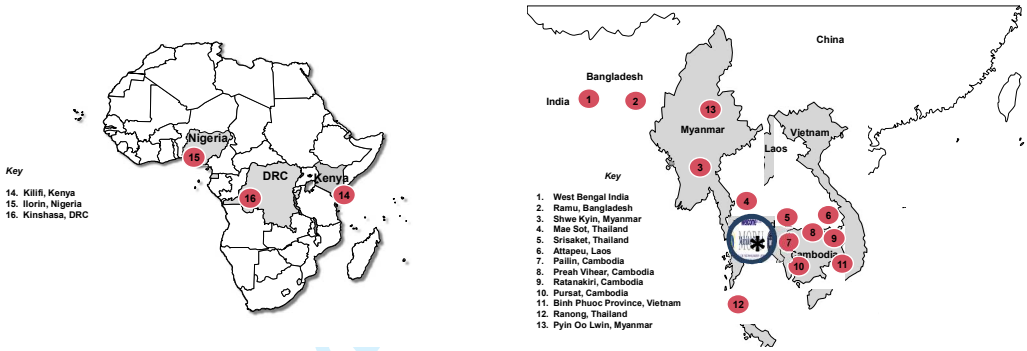
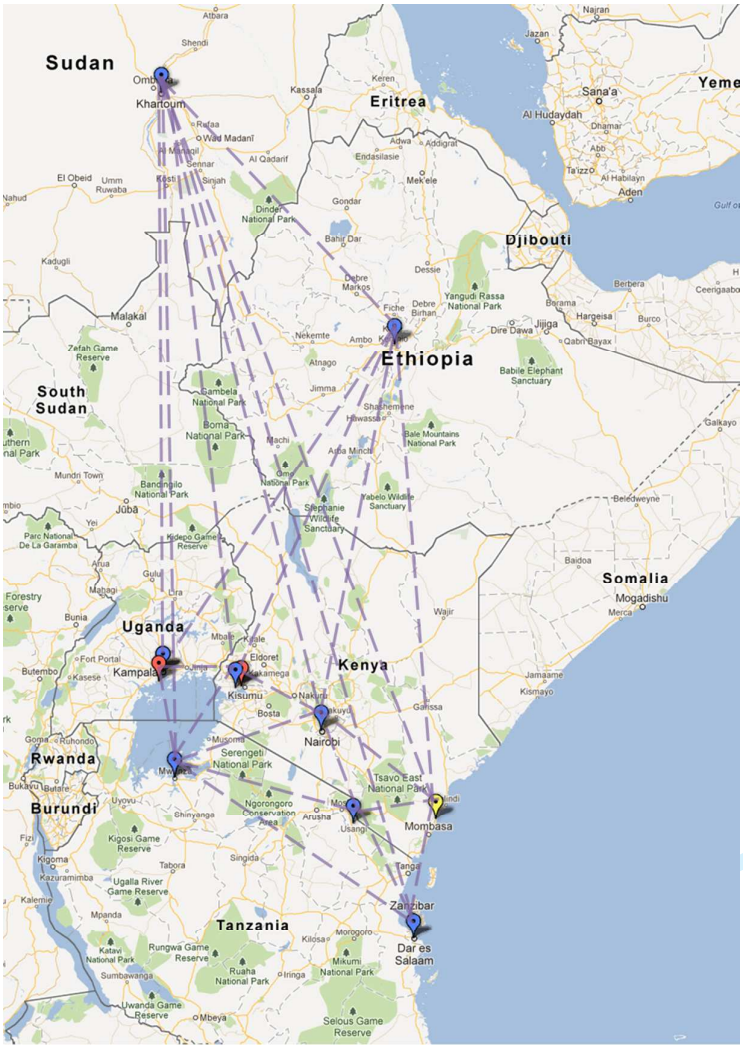
Figure 1: Spatial Organisation and Infrastructure of CTSG TRAC monitoring

Tracking Resistance to Artemisinin Collaboration (TRAC) project & collaborative sites



CTSG Monitors based at the Mahidol Research Unit in Bangkok* visit TRAC sites

Figure 2: EACCR Partner Institutes involved in the RMS



Legend:

Red Dots: RMS Coordinating Centres; UVRI, Entebbe Uganda & KEMRI/CDC, Kisumu, Kenya

Yellow Dots: Initial Training Centre; KEMRI-Wellcome Programme, Kilifi, Kenya

Blue Dots: Additional EACCR Institutes involved in EACCR RMS*

*

Tanzania:
Kilimanjaro Christian Medical Centre
National Institutes of Medical Research (Muhumbili, Mwanza)
Kenya:
KEMRI/Walter Reed Project (Kisumu)
Kenyan Aids Vaccine Initiative (Nairobi)
Uganda:
Makerere University (Kampala)
Uganda Virus Research Institute (Entebbe)
Nsambya Hospital (Kampala)
Ethiopia:
Armauer Hansen Research Institute (Addis Ababa)
Sudan:
University of Khartoum

Table 1: Participants Demographic Characteristics

Characteristics	MORU Case study (n=26)		EACCR Case study (n=30)	
	Group 1 (Monitors and KIs) (n=11)	Group 2 (Trial team members) (n=15)	Group 1 (n=24)	Group 2 (n=6)
Professional background				
Medical Doctor	5	7	10	2
Nurse	2	5	10	
Other Health Professional	1	3	1	
Biomedical Scientist	3		2	1
Social Scientist			1	3
Research Experience in years				
0-5	1	7	5	3
6-10	2	4	14	3
10-20	6	2	5	
20+	2	2		
Gender				
Female	5	8	14	2
Male	6	7	10	4
Age Range				
18-24	1	2		
25-44	5	10	22	6
45-64	5	3	2	
Nationality				
Bengali		2		
British	3			
Burmese/Karen		9		
Cambodian		1		
Dutch	1			
French				
Indian	1			
Kenyan	1		11	4
Malaysian				
Sudanese	1		2	
Tanzanian			5	
Thai	4	3		
Ugandan			6	2

Text Box 1: Elements of Monitoring

❖ **Ensuring protocol, ethics and regulatory compliance and increasing transparency**	"Monitoring is an act of ensuring that data is collected, reported and documented. Yeah, you know according to the regulatory standards and ethical standards that exist internationally and locally". *Monitor EACCR, 2* "Monitoring is a process through which I ensure that the processes within the study have been done in compliance with the protocol, the SOPs and the ICH GCP guidelines… with the documents that we know like our Bibles". *Investigator, EACCR 8* "So monitor is part of these complicated bodies that try to transparent the studies… " *Investigator MORU, 11*
❖ **Protecting study participants rights and safety**	"The purpose of monitoring is to make sure all the documents are being recorded accurately and the participants' safety, it is protected". *Monitor EACCR, 5* *"...*it's that process of evaluating or assessing the conduct of a trial…. but with emphasis on participants' well-being and rights…it's more an assurance to investigators that you are doing things the right way… so it's quite supportive to the investigator team and then it includes the spirit of science to get the best quality data." *Monitor EACCR, 4*
❖ **Evaluating the science and increasing data accuracy**	"… overseeing whether the things are being done well in terms of the regulations and the ethics and I swear on top of that helping the site to actually achieve what it's supposed to achieve". *Investigator EACCR, 10* "…the approach definitely should be helping the team not only figuring out the errors…so it should be complimentary. I mean supporting the team. That would be one thing…then I think too much paperwork, documentation. Rather they should focus on scientific aspects." *Investigator MORU, 25*
❖ **Supporting and training staff**	"Monitors may not necessarily organise a full training programme but I think that it's useful informally because there's a lot of it which has very formal kind of feel to it, but it doesn't have to be. There can be interactions with the staff and you can use those interactions to explain why certain things are important." *Monitor MORU, 18* "So I suppose it's an ongoing review of conduct of a trial and data collection with the purpose of assuring trial quality, data quality and protecting interests of the patients I suppose…in practice I think it's still leans too much towards checking the paper." *Investigator MORU, 20*

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International health research monitoring: Exploring a scientific and a co-operative approach using participatory action research

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International health research monitoring: *Exploring a scientific and a co-operative approach using participatory action research*

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Monitoring, trial regulation, good clinical practice, biomedical research, data quality, qualitative research, research methodology

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ABSTRACT

Objectives

To evaluate and determine the value of monitoring models developed by the Mahidol Oxford Tropical Research Unit and the East African Consortium for Clinical Research, consider how this can be measured and explore monitors and investigators experiences of and views about the nature, purpose and practice of monitoring.

Research Design

The monitoring model case studies represent interventions aimed at changing practice hence a participatory action research methodology was applied and 34 interviews, 5 focus groups and observations of monitoring activities conducted.

Setting and Participants

Fieldwork occurred in the places where the monitoring models are coordinated and applied in Thailand, Cambodia, Uganda and Kenya. Participants included those coordinating the monitoring schemes, monitors, senior investigators and research staff.

Analysis

Transcribed textual data from field notes, interviews and focus groups was imported into a qualitative data software programme (NVIVO 10) and analysed inductively and thematically by a qualitative researcher. The initial coding framework was reviewed internally and two main categories emerged from the subsequent interrogation of the data.

Results

The categories that were identified related to the conceptual framing and nature of monitoring, and the practice of monitoring, including relational factors. Particular emphasis was give to the value of a scientific and cooperative style of monitoring as a means of enhancing data quality, trust and transparency. In terms of practice the primary purpose of monitoring was defined as improving the conduct of health research and increasing the capacity of researchers and trial sites.

Conclusions

The models studied utilize internal and network wide expertise to improve the ethics and quality of clinical research. They demonstrate how monitoring can be a scientific and constructive exercise rather than threatening process. The value of cooperative relations needs to given more emphasis in monitoring activities, which seek to ensure that research protects human rights and produces reliable data.

ARTICLE SUMMARY

Article Focus

- Escalating bureaucracy and regulatory burden is increasing the costs of conducting trials, and deterring researchers from conducting high quality science
- There is significant interest in innovative monitoring models which distil the essence of regulatory guidelines in a workable and scientific manner
- We examined two models developed in international health settings to document their implementation, describe the challenges encountered and the good practices developed, and increase our understanding of the purpose of monitoring.

Key Messages

- More emphasis needs to be placed on the cooperative nature of monitoring and the need for monitoring practice to have a clear scientific focus
- The primary purpose of on-site monitoring is to improve the conduct of health research and increase the capacity of researchers and trial sites, and the success of monitoring should be measured by corrective action rather than by identification of faults
- There is a need for mixed-methods research to evaluate a combined approach of cooperative and scientifically guided on-site monitoring and central statistical monitoring

Strengths and Limitations

- Addresses a gap in the literature on on-site monitoring in low-income and middle income settings
- Lack of focus on and access to quantitative data which could be collated from monitoring reports and plans, and budgetary documents outlining trials costs
- Unable to compare the monitoring reports of studies monitored by our case studies and other sponsor delegated monitoring groups.

BACKGROUND

In the field of health research the practice of monitoring has become associated with compliance with the 'International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use'-Good Clinical Practice Guidelines' (ICH-GCP), and related Federal (United States) and European trial regulations [1-4]. In ICH-GCP sponsors are delegated responsibility for quality management of which monitoring is an integral component. Monitoring is defined as: *'The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirements'* [1]. Section 5.18 of ICH-GCP emphasises that the main purpose of monitoring is to verify that the rights and well being of human participants are protected. Whilst this overarching *ethical purpose* is reflected in the detailed ICH-GCP guidance, the intrinsic emphasis on record keeping can serve to obscure this primary purpose.

Escalating bureaucracy and regulatory burden is increasing the costs of conducting trials, and deterring researchers from conducting high quality science [5-7]. Whilst the role of ICH-GCP in improving quality is widely acknowledged there are questions about its' application in health research, specifically in trials not involving investigational medicinal products [8]. It is argued that the well-intended values and principles of ICH-GCP have become hampered by bureaucracy and misapplication [9 ,10]. An associated 'tick box' standard is considered to divert attention away from key questions about the ethical process, study endpoints and data validity. Delegating monitoring activities to 'contract research organisations' (CROs) can extenuate this bureaucracy and lead to the misconception that ICH-GCP is highly complex and only achievable with huge resources [9]. This can be particularly detrimental to research undertaken in low and middle income countries where competitive market forces have resulted in clinical research becoming more driven by profit than local health needs [11].

ICH-GCP requires that trials should be monitored according to the complexity and nature of the trial. The European Medicines Agency and the Food and Drugs Administration have released new guidance documents, which encourage sponsors to apply a risk and complexity assessment to trials. The aim is to reduce logistical and financial burdens of conducting 100% data validation [12 ,13]. This approach was endorsed at the Toronto 'Sensible Guidelines Meeting' in May 2012 [14]. Increasing attention is therefore being paid to rationalising monitoring activities to reflect the risks posed to participants, and to ensure trials generate accurate data to support decision-making about the safety, efficacy or effectiveness of new products and health interventions [15].

Central statistical monitoring applied remotely through advanced statistical and bioinformatics methods, is proposed as a way of achieving the latter, particularly in multi-site trials [16 ,17]. Baigent et al cite the following taxonomy of errors affecting trials 1) Design Error/Procedural Error 2) Recording Error 3) Fraud, and 4) Analytical Error [17] . They argue that on-site monitoring should target errors, requiring due attention at specific trial sites. Hence central statistical monitoring is not a stand-alone solution but needs to be complemented by proactive on-site monitoring. Experience shows that proactive on-site monitoring (e.g. peer-review) can enhance the quality of data and trial processes (e.g. participant consent) [18 ,19].

Diverse opinion exists amongst investigators, sponsors and regulators about the definition and organisation of monitoring. Points of debate are the balance between central statistical monitoring and on-site monitoring, the difference between audit and monitoring, and who should undertake these activities. Be it external CROs, in-house pharmaceutical monitors, or quality management teams embedded at trial sites. In this discussion there is a dearth of literature from international settings. Macefield et al's recent systematic review of on-site monitoring methods for health care randomised controlled trials was only able to include 7 multi-national articles[20]. They concluded that there was a paucity of evidence and a need for further evaluation trials.

In our research we evaluated 2 innovative monitoring models, which are being implemented by Mahidol Oxford Tropical Medicine Research Unit in Thailand and by the East African Consortium for Clinical Research. Our aims were to observe the approach of these models, consider how this could be measured and explore monitors and investigators experiences of and views about the nature, purpose and practice of monitoring.

METHODS

Research Design

We used a case study approach to evaluate the Thai unit's and African consortia's monitoring models in their real life contexts [21]. The case studies represent interventions which aim to change and improve practice therefore we applied a participatory methodological approach akin to action research [22]. Our research team included representatives from the case studies who could act on interim findings during the course of the research. A qualitative researcher, who did not occupy an active or a collaborative role in the monitoring case studies, coordinated the study. The researcher spent two weeks with members of each monitoring case study, during these fieldwork visits she observed monitoring activities, participated in a training workshop, reviewed documentary sources, and interviewed investigators and monitors associated with the case studies.

Study Participants

The sample was drawn purposively in order to select 'information rich' representatives from two groups: 1) Those actively involved in the development, coordination and implementation of the monitoring case studies, and 2) Investigators and research staff whose work is being monitored by the monitoring case studies. The first group includes monitors and key informants some of who are senior researchers within the Thai programme and the East African Consortia networks. Potential participants were informed about the purpose of the study and related research activities verbally and provided with study information sheet in advance of the researcher's fieldwork visits. At the Thai programme the Researcher also presented an overview of the study at the central the Thai programme offices. The Researcher obtained informed consent from monitors and investigators who were willing to be interviewed and agreed to her observing their research and monitoring activities. Interviewees were reassured that their contribution would be kept confidential, and focus group participants were asked to respect each other's privacy.

A total of 56 participants were recruited (Group 1=35, Group 2=21) participants from the case studies, 26 from the Thai programme and 30 from the East African Consortia. Group 1 comprises 9 key informants (the Thai programme=5, the East African Consortia= 4) and 26 (the Thai programme=6, the East African Consortia=20) monitors. In the East African Consortia case study all of the monitors were also active researchers. Key informants were senior investigators and those with experience of quality management, who had played a significant role in the development of the respective monitoring schemes. Group 2 comprises different cadres of staff: senior investigators (the Thai programme=2), site investigators/trial coordinators (the Thai programme=4, the East African Consortia=3) and trial staff (the Thai programme=9, the East African Consortia=3) including some who were specifically responsible for quality control. Table 1 provides details of participants' demographic characteristics. Of note is that the sample includes highly experienced and qualified international research professionals.

Fieldwork

In April 2012 the researcher visited the Thai programme offices and research facilities in Bangkok and associated research centres/clinics on the Thai-Burmese border (Shoklo Medical Research Unit) and at Pailin District Hospital, Cambodia. All of these research facilities were involved in an antimalarial resistance trial and the researcher was able to observe monitoring activities at each facility. Interviews were held with 8 trial investigators, 5 key informants and 6 monitors. Two group interviews with members of trial staff based at Thai-Burmese border clinics were conducted, one with two participants and the other with 5. Thai and Karen translators helped facilitate the group interviews and 2 individual interviews with Thai researchers.

In May 2012 the researcher travelled to sites connected with the East African Consortia monitoring case study and observed a workshop for the East African Consortia monitors. In Uganda she visited the Ugandan Virus Research Institute, the International AIDS Vaccine Initiative and Medical Research Council offices in Entebbe and observed a two-day monitoring visit of an observational HIV treatment trial at Masaka Referral Hospital. In Kenya she accompanied two monitors on a three day monitoring visit of an HIV prevention trial for sero-discordant couples. During the East African Consortia fieldwork 6 investigators, 4 key informants and 6 monitors were interviewed. Three group interviews were conducted with 15 (4, 5, 6) monitors during a two day monitors training and feedback workshop held in Nairobi in May 2012. This workshop provided rich insights into the challenges and successes experienced by the East African Consortia monitors.

Across both case studies 34 individual interviews were conducted with 12 investigators, 9 key informants and 13 monitors, and 2 focus groups with investigators and 3 with monitors. The interviews covered a wide range of topics including the history, purpose and value of the monitoring models, experiences gained and practical and ethical challenges encountered during their implementation and, the definition of monitoring and how to measure or evaluate good practice.

Analysis

Data constituted of field notes, interview and focus groups recordings and transcripts, monitoring reports and other documents relating to the case studies. Recordings were transcribed verbatim with the exception of oral contributions in Thai or Karen. These were translated during the course of the interview and only the English translation was transcribed verbatim. To facilitate the organisation of the data and the development of a coding framework the anonymised data was imported into a qualitative data software programme (NVivo10). The recordings and transcripts were crosschecked for accuracy and then TC performed the primary analysis. This involved open coding the interview, focus group and field notes data in a thematic and inductive manner and developing a coding framework. Subsequent analytical meetings with research team helped refine this framework and led to the definition of two major categories namely; 'the conceptual framing and nature of monitoring', and 'the practice of monitoring', which included reference to relational factors.

CASE STUDY PROFILES

Case 1: The Thai programme-clinical trials support group

The Thai programme is a collaborative partnership between the Faculty of Tropical Medicine, Mahidol University, the University of Oxford and the Wellcome Trust, which was established in 1979 (www.tropmedres.ac). The Thai programme's main office and laboratories are located within the Faculty of Tropical Medicine at Mahidol University in Bangkok, Thailand. Clinical trials take place at study sites across Asia and Africa. A 'Clinical Trials Support Group' was established at the Thai programme in 2008 to provide help, guidance, and support to investigators conducting research involving human subjects. The defining feature and what sets the Thai programme monitoring model apart from standard monitoring models is the way that clinical trial support group is embedded within an established research unit. This positioning means that its members are familiar with the health research priorities of the unit, can maintain a constant feedback loop between themselves and investigators, and understand the diseases and the social context in which trials take place. Additional strengths are that all clinical trial support group members are experienced health researchers and some have worked in the pharmaceutical industry or with contract research organisations. Clinical trial support group members support protocol development, assist with ethics submissions, provide project and data management support, deliver training and assist in the quality management of trials. The latter includes writing trial specific risk-based monitoring plans with investigators and conducting on-site monitoring at defined time points. The Thai programme's monitoring model is not without challenges, however, particularly in relation to workload, travel logistics and ensuring monitoring activities are adequately budgeted for.

Figure 1 illustrates clinical trial support group's involvement in monitoring a multicentre randomised trial to detect in vivo resistance of Plasmodium falciparum to artesunate in patients with uncomplicated malaria (Web registration number: NCT01350856). This trial is part of the 'Tracking Resistance to Artemisinin Collaboration' (TRAC).

Figure 1: Spatial Organisation and Infrastructure of clinical trial support group TRAC monitoring

Case 2:The East African Consortia Reciprocal Monitoring Model

The East Africa Consortium for Clinical Research (www.eaccr.org) is a partnership of 35 institutions in five countries (Tanzania, Uganda, Kenya, Sudan, and Ethiopia). This 'Network of Excellence' is funded by the European and Developing Countries Clinical Trials Partnership and was established in May 2009. At its' inception the potential for strengthening monitoring capacity across partner institutions was established as a priority. The vision was to increase capacity for monitoring and develop a pragmatic and cost-efficient network-

wide monitoring service. A reciprocal monitoring system was designed and set up in 2007 within KEMRI-Wellcome Programme in Kilifi Kenya. This novel approach trained study staff to monitor studies and then this pool of trained monitors then spent a small portion of their time monitoring each others studies within the programme [18]. This system worked well because it enabled knowledge, best practice and skill sharing between different studies in the same organization whilst enabling the implementation of high quality clinical research monitoring. This approach was then taken up by the East African Consortia and further developed for deployment across this network. This network-wide monitoring approach, which was launched at the start of 2011, is referred to as the East Africa Consortia for Clinical Research Scheme reciprocal monitoring scheme. It involves two coordinators based in Uganda and Kenya and 22 trained monitors nominated by eleven partner institutions.

Figure 2: the East African Consortia Partner Institutes involved in the RMS

The defining features and strengths of the reciprocal monitoring are of course that it is 'reciprocal' and thereby involves, on a part-time basis, health research professionals who have an in depth appreciation of the context where trials are conducted. It is reciprocal in two key ways; firstly it involves members of partner institutes monitoring each-others research, secondly it allows experienced monitors to share their expertise with novice monitors who have limited experience of trial monitoring. Initial challenges have also helped the scheme to improve its logistical functions, and increase its credibility by clarifying the schemes mandate and improving communication between the coordinators and investigators.

FINDINGS

The accounts given and the observations collected during the fieldwork convey rich information about the nature and practice of on-site monitoring. Accordingly our findings are presented under two main headings; first we explore participants' understandings and expectations of clinical trial monitoring, and then we examine what they think constitutes professional practice with reference to organisational ethos and accountability, monitors' expertise and approach, and the focus of monitoring activities.

What is on-site health research monitoring, and what should it be?

We distilled four core elements of monitoring from participants' accounts (Text Box 1). The latter two are of particular interest because they bring to the fore aspects of monitoring which are often overlooked. Our data suggest that whilst investigators appreciated the need for regulatory and ethics oversight, they want monitoring to be collaborative in nature and

scientific in focus. Some investigators related how constructive interactions with monitors assuaged their initial fears and changed their perceptions about the value of monitoring. Others championed the need for cooperative monitoring as a result of encounters with monitors who questioned their intentions from the outset, or prioritised document verification and paperwork over observing critical research processes.

"My first experience was…to me actually I felt it was an activity of policing. I said, "Wow well they are going to find faults," ... I thought maybe it's worth hiding something so that they not know yeah. But with time I came to know really it is something very valuable, that I needed to be involved in. It's actually more to support me into the better conduct of the studies."

Investigator, the East African Consortia 6

'I could see that something was, that a monster was being created…this is the whole area of sort of ethics regulation and so and it seemed to be only one direction of travel which was more and more heavy questions and demands and requirements and the net result was more and more paperwork, more and more time devoted towards it.'

Investigator, the Thai programme 26

Investigators were keen to be involved in planning monitoring activities and valued the input of monitors who *"understand what we call the main focus of the study and give credit to the investigator who have long experience" (Investigator, the Thai programme 11)*. They particularly appreciated monitors who worked with them to rectify faults and increase research capacity.

The Thai programme investigators described how the establishment of the clinical trial support group has allowed them to exercise more control over how trials are monitored. They can draw on the expertise of clinical trial support group members to ensure that monitoring activities target the greatest risks to participants and the most scientifically relevant data points. This has helped them develop a counter argument against some of the bureaucracy they believe is hampering the conduct of biomedical research. The East African Consortia reciprocal monitoring scheme was credited with strengthening quality management across the network, and appreciated by monitors as means of professional development and exchange. Across both case studies much value was attributed to a non-threatening *'shared learning'* style of monitoring, which prioritized the resolution of problems.

'*…because it's a sort of cooperative monitoring and not hostile, you're much more likely to get problems sorted out rather than hidden.'*

Investigator, the Thai programme 17

It was evident that participants wanted monitoring to be scientifically grounded to ensure that quality checks are tailored to primary study outcomes. This type of monitoring requires monitors to work closely with investigators from the planning stages of studies. Much emphasis was also placed on the need to complement checking activities with tailored support and training. Investigators were positive about the need for correction, especially when monitors worked with them to improve their work. Participants concurred that the purpose of monitoring should be to improve the conduct of health research and increase the capacity of researchers and trial sites. In other words monitoring should *'help sites achieve what they are supposed to achieve'* and offer *'assurance to investigators that they are doing things the right way'*. In practice this type of monitoring replaced negative associations with more positive views of monitoring.

'Yeah when a monitor they actually come in to help you do your work better, they're not coming to police you or to find mistakes…they're coming to help you do your work better.'

Monitor, the East African Consortia 3

The Practice of Monitoring: What constitutes professional practice?

The 'who' of monitoring

Participants' experiences of monitoring suggest that the organisational ethos of monitoring bodies has a bearing on the practice of monitoring. It was evident from participants' accounts that monitors from external bodies sometimes distanced themselves from research staff. In contrast the East African Consortia monitors conveyed the notion that '*we are doing this together'*, similarly the positioning of the clinical trial support group as an internal monitoring group within the Thai programme enhanced interactions between researchers and monitors and increased transparency. On the other hand some the Thai programme investigators felt that research staff were more *'alert and ready'* during monitoring visits from external groups.

These observations about interactions between monitors from different organisations and investigators raise important points about accountability and professional relationships. The East African Consortia monitors for example argued that monitors can identify with the site whilst remaining accountable to the study sponsor, and the Thai programme investigators maintained that the positioning of the clinical trial support group does not pose a conflict of interest. To the contrary they work together more easily because their professional relationship is built on trust and mutual understanding. According to a study nurse this prior knowledge reduced the stress associated with monitoring but it did not alter the need for correction. Internal monitors applied the same standards as external monitors but their

proximity meant that they were more accessible and could provide on-going support.

Yeah for me I think it's not so hard because it's not like the investigator is against the sponsor. So it's not like they're trying to identify with you as opposed to the sponsor. They're just when they are on the site they're talking we. We can do this…and the way I see it, it's not hard for them to identify with the site.

Monitor the East African Consortia, 27

clinical trial support group they will know the protocol very well and they will know us quite well I have to admit it, but that doesn't provide conflict of interest…in a way it make us work together easier.

Investigator the Thai programme, 11

Monitors background, training and expertise and their understanding of the research context were viewed as important in terms of professional practice. One investigator said that he judged the value of monitors work by the *'quality of the information they are able to detect'* (Investigator, the East African Consortia 7). Health professionals with experience of working in research were regarded as particularly well equipped to be monitors. A role, which was also thought to require motivation and commitment, attention to detail, good interpersonal and communication skills and the ability to apply and interpret ethics guidelines in practice. With reference to the latter an investigator emphasised that monitors needed to understand the scientific purpose of the research in order to *'think about the patient's interests and how they could advocate for those, or how they could check for those' (Investigator the Thai programme, 20).*

Much value was attributed to context informed monitoring and investigators resented monitors who did little to consider cultural norms, logistical limitations and local regulations.

'They come and they have such little time and they will have to do so much so they're in a rush and sometimes they're really distressed to try and meet their milestones. And then the other thing that I have seen is inability to understand the culture and even local regulations sometimes, harmonising and local regulations and sponsors, SOPs and their own regulations back in their country, it's such a big issue. So they come out and they would like things done the way they understand it. A few times we took it upon ourselves to really train them on our culture, what is acceptable, what cannot be done'.

Investigator the East African Consortia, 10

This investigator is arguing that an appreciation of local norms, customs and regulations is prerequisite for effective and professional monitoring practice. Local monitors were considered well placed to undertake context informed monitoring, and external monitors who demonstrated a willingness to learn rather than simply impose ideas were also highly

valued. When it comes to the 'who' of monitoring what counts is mutual respect, communication, professionalism, and maintaining high standards irrespective of the positioning of the monitor in regards to the sponsor and researcher.

The 'what' and 'how' of monitoring

When it came to the practicalities of monitoring what counted was getting the focus and the approach right. Focus requires careful planning and clinical trial support group participants stressed the importance of developing monitoring plans with investigators. This planning helped them to identify the main risks to a study's integrity with reference to ethics and key study outcomes. It helped them differentiate between minor and major errors thereby avoiding diverting unwarranted time to rectifying the former. Focus also involves achieving the right balance between paper work and observing research in practice.

'I mean sometimes documents don't, may not give, tell you, give you, the clear picture of how things are run. Sometimes talking to people, asking people questions, seeing what people are doing can assure you, can tell you a number of things that you can't see by looking at the documents.'

Key Informant the East African Consortia, 28

Concerns were raised by investigators about the amount of time monitors (coming from long distances) end up spending sitting in rooms verifying files and source documents. It was argued that on-site monitoring should not be confined to document review but include observational and interactive activities, which allow monitors to gain greater insights into how a trial is being implemented and where corrective action is needed.

Two distinct ways of organising monitoring activities were described. One where the monitor performs their review presents findings in debriefing meetings, and sends a summary report with action points; and the other where the monitor actively engages research staff in resolving issues during the on-site visit. The components of monitoring visits were similar but the engagement differed. Investigators expressed preference for the latter but also noted that this method was time-consuming and impractical when the research clinics are busy.

A monitor's personal and professional approach was viewed as crucial to promoting positive interactions and improving the quality of trials.

'The key thing about successful monitoring is how you present, how the monitor presents themselves and involves themselves with the investigators'

Investigator the Thai programme, 26

Monitors need to gain the trust of investigators and interviewees argued that the best way to do this is to work with investigators to improve study conduct. It was evident that investigators were anxious about discussing problems or disclosing important information to overly critical monitors. One investigator (Investigator the East African Consortia, 7) described how his team's *'fear just melted away'* when they realised that their monitor's approach (an external CRO monitor) was not adversarial *'you did this wrong, we are going to beat you'*, but constructive *'he's like trying to make you improve'*.

The core features of a professional approach to monitoring were cited as a commitment to high standards, open communication and positive interactions, mutual respect and a friendly manner. Investigators appreciated monitors who maintained high standards in a strict and firm manner and worked with them to enhance the quality of their work.

DISCUSSION

Our participatory evaluation provides important insights about the practice of international on-site monitoring, and the value of utilizing internal and network expertise to enhance trial quality. Particular emphasis was given to a cooperative style of monitoring as a means of enhancing trust and transparency. Whilst this style of monitoring was associated with the East African Consortia and the Thai programme models, it is important to note that some participants commented positively on interactions with CRO monitors. With reference to practice our findings suggest that the primary purpose of on-site monitoring is to improve the conduct of health research and increase the capacity of researchers and trial sites. Monitoring activities to be scientifically grounded, contextually and culturally informed with tailored support and training. Skills in the scientific evaluation of trials and a willingness to work closely with investigators were viewed as critical for the development of effective risked-based and context informed monitoring plans. It was argued that on-site monitoring should combine document verification with observational activities, and be complemented by training and mentoring to enable investigators to execute necessary corrective actions. Indeed our data suggest that the success of monitoring should be measured by corrective action rather than by identification of faults. Monitoring reports should only include findings, which could significantly impact on the scientific and ethical integrity of the trials.

The main benefits of the Thai programme and the East African Consortia monitoring models are: 1) Reduced logistical costs, 2) Increased site capacity for quality management, 3) Investigators contribution to risk-based monitoring plans, 4) Professional development and exchange. The latter is of relevance given the increased value attributed in the health sector to 'Communities of Practice' as a means of encouraging situated learning and the practical application of knowledge[23]. Communities of practice are defined as: *'groups of people*

who share a concern, a set of problems, or a passion about a topic, and who deepen their knowledge and expertise in this area by interacting on an on-going basis'[24]. The challenges relate to questions of sustainability and credibility. There is a need to consider the logistics and funding of these models to ensure that their benefits are sustainable. Currently both models rely heavily on grants rather than charging trials directly for their services. This needs to be remedied in order to reduce dependency on external funding.

The strengths of this empirical study are that it contributes to the literature documenting good practice at international trial sites in resource-constrained settings. As noted in the background section Macefield et al [20] were only able to include 7 multinational trials in their systematic review. Given the study design one inherent limitation is the paucity of quantitative findings. Follow up studies will need to systematically collate information on trial costs, and provide monitoring report templates. An additional weakness of our work is that we were not able to compare the monitoring reports of studies monitored by the Thai programme and the East African Consortia reciprocal monitoring scheme, and other sponsor delegated monitoring groups. A key area for future research will be to conduct a mixed methods study, which evaluates how the East African Consortia and the Thai programme on-site monitoring models work in combination with central monitoring systems.

CONCLUSIONS

Innovative monitoring models, which prioritise the sensible application of regulations and ethical guidelines are imperative to facilitate vital global health research. The experience gained in developing the innovative international models studied in this paper offers valuable insights and examples of alternative approaches. Both models utilize internal and network wide expertise to improve the ethical conduct and data quality of clinical research. They demonstrate how monitoring can be a constructive exercise rather than threatening process. The value of cooperative relations needs more emphasis in this field given that sponsors, investigators and monitors are jointly responsible for ensuring that research protects human rights and produces reliable data, which can improve human health.

FIGURE LEGENDS

Figure 1: Spatial Organisation and Infrastructure of clinical trial support group TRAC monitoring

Figure 2: The East African Consortia Partner Institutes involved in the RMS

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CONTRIBUTORS

All authors participated in the study design from conception. TC conducted the case study fieldwork with the support of AN, EA, GM, EK, PYC and VH. TC performed the primary analysis and TL was involved in subsequent analytical review and decision-making. TC wrote the first draft of this paper and all authors critically revised the manuscript.

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COMPETING INTERESTS

None

ETHICS APPROVAL

The study was approved by the Oxford Tropical Research Ethics Committee (Ref: 09-12), the Kenyan Medical Research Institute Ethics Review Committee (No: 2253), the Ugandan Virus

Research Institute Science and Ethics Committee (Ref: GC/127/12/03/04), and the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University (Ref TMEC 12-023).

DATA SHARING

The protocol is provided along with the paper. All the Data collection tools, templates and data will then be made available on http://globalresearchmethods.tghn.org when this paper is published.

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Table 1: Participants Demographic Characteristics

Characteristics	The Thai Unit (n=26)		The East African Consortia (n=30)	
	Group 1 (Monitors and KIs) (n=11)	Group 2 (Trial team members) (n=15)	Group 1 (n=24)	Group 2 (n=6)
Professional background				
Medical Doctor	5	7	10	2
Nurse	2	5	10	
Other Health Professional	1	3	1	
Biomedical Scientist	3		2	1
Social Scientist			1	3
Research Experience in years				
0-5	1	7	5	3
6-10	2	4	14	3
10-20	6	2	5	
20+	2	2		
Gender				
Female	5	8	14	2
Male	6	7	10	4
Age Range				

18-24	1	2		
25-44	5	10	22	6
45-64	5	3	2	
Nationality				
Bengali		2		
British	3			
Burmese/Karen		9		
Cambodian		1		
Dutch	1			
French				
Indian	1			
Kenyan	1		11	4
Malaysian				
Sudanese	1		2	
Tanzanian			5	
Thai	4	3		
Ugandan			6	2

Text Box 1: Elements of Monitoring

❖ **Ensuring protocol, ethics and regulatory compliance and increasing transparency**	"Monitoring is an act of ensuring that data is collected, reported and documented. Yeah, you know according to the regulatory standards and ethical standards that exist internationally and locally". *Monitor EACCR, 2* "Monitoring is a process through which I ensure that the processes within the study have been done in compliance with the protocol, the SOPs and the ICH GCP guidelines… with the documents that we know like our Bibles". *Investigator, EACCR 8* "So monitor is part of these complicated bodies that try to transparent the studies… " *Investigator MORU, 11* "The purpose of monitoring is to make sure all the documents are being recorded accurately and the participants' safety, it is protected". *Monitor EACCR, 5* "...it's that process of evaluating or assessing the conduct of a trial…. but with emphasis on participants' well-being and rights…it's more an

	assurance to investigators that you are doing things the right way… so it's quite supportive to the investigator team and then it includes the spirit of science to get the best quality data." *Monitor EACCR, 4* "… overseeing whether the things are being done well in terms of the regulations and the ethics and I swear on top of that helping the site to actually achieve what it's supposed to achieve". *Investigator EACCR, 10* "…the approach definitely should be helping the team not only figuring out the errors…so it should be complimentary. I mean supporting the team. That would be one thing…then I think too much paperwork, documentation. Rather they should focus on scientific aspects." *Investigator MORU, 25* "Monitors may not necessarily organise a full training programme but I think that it's useful informally because there's a lot of it which has very formal kind of feel to it, but it doesn't have to be. There can be interactions with the staff and you can use those interactions to explain why certain things are important." *Monitor MORU, 18* "So I suppose it's an ongoing review of conduct of a trial and data collection with the purpose of assuring trial quality, data quality and protecting interests of the patients I suppose…in practice I think it's still leans too much towards checking the paper." *Investigator MORU, 20*

International health research ~~on site~~ monitoring: *Evaluating a scientific and a co-operative approach using participatory action research*

Comment [TL1]: Changed the title to make it clearer for readers who do not necessarily understand different types of monitoring. We explain on-site and central later in the paper and reflecting the reviews comments (BF)

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Keywords

Monitoring, trial regulation, good clinical practice, biomedical research, data quality, qualitative research, research methodology

Word Count: 4896

ABSTRACT

Objectives

To evaluate and determine the value of monitoring models developed by the Mahidol Oxford Tropical Research Unit and the East African Consortium for Clinical Research, consider how this value can be measured and explore monitors and investigators experiences of and views about the nature, purpose and practice of monitoring.

Research Design

The monitoring model case studies represent interventions aimed at changing practice hence a participatory action research methodology was applied and 34 interviews, 5 focus groups and observations of monitoring activities conducted.

Setting and Participants

Fieldwork occurred in the places where the monitoring models are coordinated and applied in Thailand, Cambodia, Uganda and Kenya. Participants included those coordinating the monitoring schemes, monitors, senior investigators and research staff.

Analysis

Transcribed textual data from field notes, interviews and focus groups was imported into a qualitative data software programme (NVIVO 10) and analysed inductively and thematically by a qualitative researcher. The initial coding framework was reviewed internally and two main categories emerged from the subsequent interrogation of the data.

Results

The categories identified related to the conceptual framing and nature of monitoring, and the practice of monitoring, including relational factors. Particular emphasis was give to the value of a scientific and cooperative style of monitoring as a means of enhancing data quality, trust and transparency. In terms of practice the primary purpose of monitoring was defined as improving the conduct or health research and increasing the capacity of researchers and trial sites.

Conclusions

The models studied utilize internal and network wide expertise to improve the ethics and quality of clinical research. They demonstrate how monitoring can be a scientific and constructive exercise rather than threatening process. The value of cooperative relations needs to given more emphasis in monitoring activities, which seek to ensure that research protects human rights and produces reliable data.

Comment [TC2]:

Reviewer 2

The authors use many acronyms that hinder the readability of the manuscript. I recommend leaving only those that in the authors' opinion are essential.

Authors response

We agree and have now used abbreviated terms for the research institutes and limited them throughout to essential use only

They are not all shown on this version because it added too many comments and it was getting messy

ARTICLE SUMMARY

Article Focus

- Escalating bureaucracy and regulatory burden is increasing the costs of conducting trials, and deterring researchers from conducting high quality science
- There is significant interest in innovative monitoring models which distil the essence of regulatory guidelines in a workable and scientific manner
- We examined two models developed in international health settings to document their implementation, describe the challenges encountered and the good practices developed, and increase our understanding of the purpose of monitoring.

Key Messages

- More emphasis needs to be placed on the cooperative nature of monitoring and the need for monitoring practice to have a clear scientific focus
- The primary purpose of on-site monitoring is to improve the conduct of health research and increase the capacity of researchers and trial sites, and the success of monitoring should be measured by corrective action rather than by identification of faults
- There is a need for mixed-methods research to evaluate a combined approach of cooperative and scientifically guided on-site monitoring and central statistical monitoring

Strengths and Limitations

- Addresses a gap in the literature on on-site monitoring in low-income and middle income settings
- Lack of focus on and access to quantitative data which could be collated from monitoring reports and plans, and budgetary documents outlining trials costs
- Unable to compare the monitoring reports of studies monitored by our case studies and other sponsor delegated monitoring groups.

BACKGROUND

In the field of health research the practice of monitoring has become associated with compliance with the 'International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use'-Good Clinical Practice Guidelines' (ICH-GCP), and related Federal (United States) and European trial regulations [1-4]. In ICH-GCP sponsors are delegated responsibility for quality management of which monitoring is an integral component. Monitoring is defined as: *'The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirements'* [1]. Section 5.18 of ICH-GCP emphasises that the main purpose of monitoring is to verify that the rights and well being of human participants are protected. Whilst this overarching *ethical purpose* is reflected in the detailed ICH-GCP guidance, the intrinsic emphasis on record keeping can serve to obscure this primary purpose.

Escalating bureaucracy and regulatory burden is increasing the costs of conducting trials, and deterring researchers from conducting high quality science [5-7]. Whilst the role of ICH-GCP in improving quality is widely acknowledged there are questions about its' application in health research, specifically in trials not involving investigational medicinal products [8]. It is argued that the well-intended values and principles of ICH-GCP have become hampered by bureaucracy and misapplication [9 ,10]. An associated 'tick box' standard is considered to divert attention away from key questions about the ethical process, study endpoints and data validity. Delegating monitoring activities to 'contract research organisations' (CROs) can extenuate this bureaucracy and lead to the misconception that ICH-GCP is highly complex and only achievable with huge resources [9]. This can be particularly detrimental to research undertaken in low and middle income countries where competitive market forces have resulted in clinical research becoming more driven by profit than local health needs [11].

ICH-GCP requires that trials should be monitored according to the complexity and nature of the trial. The European Medicines Agency and the Food and Drugs Administration have released new guidance documents, which encourage sponsors to apply a risk and complexity assessment to trials. The aim is to reduce logistical and financial burdens of conducting 100% data validation [12 ,13]. This approach was endorsed at the Toronto 'Sensible Guidelines Meeting' in May 2012 [14]. Increasing attention is therefore being paid to rationalising monitoring activities to reflect the risks posed to participants, and to ensure trials generate accurate data to support decision-making about the safety, efficacy or effectiveness of new products and health interventions [15].

Central statistical monitoring (CSM), applied remotely through advanced statistical and bioinformatics methods, is proposed as a way of achieving the latter, particularly in multi-site trials [16 ,17]. Baigent et al cite the following taxonomy of errors affecting trials 1) Design Error/Procedural Error 2) Recording Error 3) Fraud, and 4) Analytical Error [17] . They argue that on-site monitoring should target errors, requiring due attention at specific trial sites. Hence CSM is not a stand-alone solution but needs to be complemented by proactive on-site monitoring. Experience shows that proactive on-site monitoring (e.g. peer-review) can enhance the quality of data and trial processes (e.g. participant consent) [18 ,19].

Diverse opinion exists amongst investigators, sponsors and regulators about the definition and organisation of monitoring. Points of debate are the balance between CSM and on-site monitoring, the difference between audit and monitoring, and who should undertake these activities. Be it external CROs, in-house pharmaceutical monitors, or quality management teams embedded at trial sites. In this discussion there is a dearth of literature from international settings. Macefield et al's recent systematic review of on-site monitoring methods for health care randomised controlled trials was only able to include 7 multi-national articles[20]. They concluded that there was a paucity of evidence and a need for further evaluation trials.

In our research we evaluated 2 innovative monitoring models, which are being implemented by Mahidol Oxford Tropical Medicine Research Unit in Thailand (MORU) and by the East African Consortium for Clinical Research (EACCR). Our aims were to ~~determine the value~~observe the approach of these models, consider how this could be measured and explore monitors and investigators experiences of and views about the nature, purpose and practice of monitoring.

Comment [TC3]:
Reviewer 3: My only concern is that, in my view, the aims of this project are slightly over-stated (closing paragraph of Background section). As indicated above, it is my opinion that the authors provide an excellent documentary of the process of statistical monitoring through the perspective of the monitors and those being monitored – so this aim is achieved totally.

Authors response
This is a very fair point and we have changed the wording from evaluate to observe and re-written that whole sentence

METHODS

Research Design

We used a case study approach to evaluate the MORU and EACCR monitoring models in their real life contexts [21]. The case studies represent interventions which aim to change and improve practice therefore we applied a participatory methodological approach akin to action research [22]. Our research team included representatives from the case studies who could act on interim findings during the course of the research. A qualitative researcher (QR), who did not occupy an active or a collaborative role in the monitoring case studies, coordinated the study. The QR spent two weeks with members of each monitoring case study, during these fieldwork visits she observed monitoring activities, participated in a training workshop, reviewed documentary sources, and interviewed investigators and monitors associated with the case studies.

Study Participants

The sample was drawn purposively in order to select 'information rich' representatives from two groups: 1) Those actively involved in the development, coordination and implementation of the monitoring case studies, and 2) Investigators and research staff whose work is being monitored by the monitoring case studies. The first group includes monitors and key informants (KIs) some of who are senior researchers within the MORU and EACCR networks. Potential participants were informed about the purpose of the study and related research activities verbally and provided with study information sheet in advance of the researcher's fieldwork visits. At MORU the QR also presented an overview of the study at the central MORU offices. The QR obtained informed consent from monitors and investigators who were willing to be interviewed and agreed to her observing their research and monitoring activities. Interviewees were reassured that their contribution would be kept confidential, and focus group participants were asked to respect each other's privacy.

A total of 56 participants were recruited (Group 1=35, Group 2=21) participants from the case studies, 26 from MORU and 30 from EACCR. Group 1 comprises 9 key informants (MORU=5, EACCR= 4) and 26 (MORU=6, EACCR=20) monitors. In the EACCR case study all of the monitors were also active researchers. Key informants were senior investigators and those with experience of quality management, who had played a significant role in the development of the respective monitoring schemes. Group 2 comprises different cadres of staff: senior investigators (MORU=2), site investigators/trial coordinators (MORU=4, EACCR=3) and trial staff (MORU=9, EACCR=3) including some who were specifically responsible for quality control. Table 1 provides details of participants' demographic characteristics. Of note is that the sample includes highly experienced and qualified international research professionals.

Fieldwork

In April 2012 the QR visited the MORU offices and research facilities in Bangkok and associated research centres/clinics on the Thai-Burmese border (Shoklo Medical Research Unit) and at Pailin District Hospital, Cambodia. All of these research facilities were involved in an antimalarial resistance trial and the researcher was able to observe monitoring activities at each facility. Interviews were held with 8 trial investigators, 5 KIs and 6 monitors. Two group interviews with members of trial staff based at Thai-Burmese border clinics were conducted, one with two participants and the other with 5. Thai and Karen translators helped facilitate the group interviews and 2 individual interviews with Thai researchers.

Comment [TC4]:
Reviewer 2: Study participants

The sampling strategy is appropriate and explained. Participants selected are adequate to provide the type of knowledge sought by the study. Nevertheless, it would be interesting to know how many potential participants were in EACCR and in MORU, and if someone had refused to participate and why.

One participant was happy to be observed but initially cautious about being interviewed but later agreed very willing having learnt more about this study. We are not sure whether writing about this would add anything to this paper because all the participants were happy to take part and were simply selected because they were the monitors and study staff

Comment [TC5]: Related to ethical aspects, in addition to informed consent, it would be important to know how the investigation team kept the anonymity and confidentiality, if they did. Although according to the type of study, the approval of a research ethics committee may not be necessary, I suggest specify this aspect.

Authors responses. Ethical approval details listed at the end of the paper and this sentence has been added.

In May 2012 the QR travelled to sites connected with the EACCR monitoring case study and observed a workshop for EACCR monitors. In Uganda she visited the Ugandan Virus Research Institute, the International AIDS Vaccine Initiative and Medical Research Council offices in Entebbe and observed a two-day monitoring visit of an observational HIV treatment trial at Masaka Referral Hospital. In Kenya she accompanied two monitors on a three day monitoring visit of an HIV prevention trial for sero-discordant couples. During the EACCR fieldwork 6 investigators, 4 KIs and 6 monitors were interviewed. Three group interviews were conducted with 15 (4, 5, 6) monitors during a two day monitors training and feedback workshop held in Nairobi in May 2012. This workshop provided rich insights into the challenges and successes experienced by EACCR monitors.

Across both case studies 34 individual interviews were conducted with 12 investigators, 9 key informants and 13 monitors, and 2 focus groups with investigators and 3 with monitors. The interviews covered a wide range of topics including the history, purpose and value of the monitoring models, experiences gained and practical and ethical challenges encountered during their implementation and, the definition of monitoring and how to measure or evaluate good practice.

Analysis

Data constituted of field notes, interview and focus groups recordings and transcripts, monitoring reports and other documents relating to the case studies. Recordings were transcribed verbatim with the exception of oral contributions in Thai or Karen. These were translated during the course of the interview and only the English translation was transcribed verbatim. To facilitate the organisation of the data and the development of a coding framework the anonymised data was imported into a qualitative data software programme (NVivo10). The recordings and transcripts were crosschecked for accuracy and then TC performed the primary analysis. This involved open coding the interview, focus group and field notes data in a thematic and inductive manner and developing a coding framework. Subsequent analytical meetings with TL helped refine this framework and led to the definition of two major categories namely; 'the conceptual framing and nature of monitoring', and 'the practice of monitoring', which included reference to relational factors.

Comment [TC6]: For example there is no reference to whether the authors would reach saturation of the discourse.

Authors response. We appreciate this question because it raises a good point. We analysed the data sufficiently to be confident about our findings. So yes, saturation of the discourse (or interviews and observations obtained during case study visits), however in the 'perfect world' of a much wider study (that was not practicable in any sense) we would have added others TRAC sites (i.e. Nigeria or Kongo) or EACCR sites then we could possibly have learnt more. However this is always the case with this form of methodology and you have to take a practical decision about how far you can go. However, the monitors interviewed in MORU and EACCR talked about their experiences in these different places and so this added to our confidence about saturation.

Due to word limit we do not think we need to add this to paper because it would be at the expense of another point.

CASE STUDY PROFILES

Case 1: MORU-clinical trials support group

MORU is a collaborative partnership between the Faculty of Tropical Medicine, Mahidol University, the University of Oxford and the Wellcome Trust, which was established in 1979 (www.tropmedres.ac). MORU's main office and laboratories are located within the Faculty of Tropical Medicine at Mahidol University in Bangkok, Thailand. Clinical trials take place at

study sites across Asia and Africa. A 'Clinical Trials Support Group' (CTSG) was established at MORU in 2008 to provide help, guidance, and support to investigators conducting research involving human subjects. The defining feature and what sets the of the MORU monitoring model apart from standard monitoring models is the way that CTSG is embedded within an established research unit. This positioning means that its members are familiar with the health research priorities of the unit, can maintain a constant feedback loop between themselves and investigators, and understand the diseases and the social context in which trials take place. Additional strengths are that all CTSG members are experienced health researchers and some have worked in the pharmaceutical industry or with contract research organisations. CTSG members support protocol development, assist with ethics submissions, provide project and data management support, deliver training and assist in the quality management of trials. The latter includes writing trial specific risk-based monitoring plans with investigators and conducting on-site monitoring at defined time points. The MORU monitoring model is not without challenges, however, particularly in relation to workload, travel logistics and ensuring monitoring activities are adequately budgeted for.

Figure 1 illustrates CTSG's involvement in monitoring a multicentre randomised trial to detect in vivo resistance of Plasmodium falciparum to artesunate in patients with uncomplicated malaria (Web registration number: NCT01350856). This trial is part of the 'Tracking Resistance to Artemisinin Collaboration' (TRAC).

Figure 1: Spatial Organisation and Infrastructure of CTSG TRAC monitoring

Case 2: EACCR-Network Reciprocal Monitoring Model

The EACCR (www.eaccr.org) is a partnership of 35 institutions in five countries (Tanzania, Uganda, Kenya, Sudan, and Ethiopia). This 'Network of Excellence' is funded by the European and Developing Countries Clinical Trials Partnership and was established in May 2009. At its' inception the potential for strengthening monitoring capacity across partner institutions was established as a priority. The vision was to increase capacity for monitoring and develop a pragmatic and cost-efficient network-wide monitoring service. A reciprocal monitoring system was designed and set up in 2007 within KEMRI-Wellcome Programme in Kilifi Kenya. This novel approach trained study staff to monitor studies and then this pool of trained monitors then spent a small portion of their time monitoring each others studies within the programme [18]. This system worked well because it enabled knowledge, best practice and skill sharing between different studies in the same organization whilst enabling the implementation of high quality clinical research monitoring. This approach was then taken up by EACCR and further developed for deployment across this network. This

network-wide monitoring approach, which was launched at the start of 2011, is referred to as the EACCR reciprocal monitoring scheme (RMS). It involves two coordinators based in Uganda and Kenya and 22 trained monitors nominated by eleven partner institutions.

Figure 2: EACCR Partner Institutes involved in the RMS

The defining features and strengths of the RMS are that it is reciprocal and involves, on a part-time basis, health research professionals who have an in depth appreciation of the context where trials are conducted. It is reciprocal in two key ways; firstly it involves members of partner institutes monitoring each-others research, secondly it allows experienced monitors to share their expertise with novice monitors who have limited experience of trial monitoring. Initial challenges have also helped the scheme to improve its logistical functions, and increase its credibility by clarifying the schemes mandate and improving communication between the coordinators and investigators.

FINDINGS

The accounts given and the observations collected during the fieldwork convey rich information about the nature and practice of on-site monitoring. Accordingly our findings are presented under two main headings; first we explore participants' understandings and expectations of clinical trial monitoring, and then we examine what they think constitutes professional practice with reference to organisational ethos and accountability, monitors' expertise and approach, and the focus of monitoring activities.

What is on-site health research monitoring, and what should it be?

We distilled four core elements of monitoring from participants' accounts (Text Box 1). The latter two are of particular interest because they bring to the fore aspects of monitoring which are often overlooked. Our data suggest that whilst investigators appreciated the need for regulatory and ethics oversight, they want monitoring to be collaborative in nature and scientific in focus. Some investigators related how constructive interactions with monitors assuaged their initial fears and changed their perceptions about the value of monitoring. Others championed the need for cooperative monitoring as a result of encounters with monitors who questioned their intentions from the outset, or prioritised document verification and paperwork over observing critical research processes.

"My first experience was…to me actually I felt it was an activity of policing. I said, "Wow well they are going to find faults," ... I thought maybe it's worth hiding something so that they not know yeah. But with time I came to know really it is something very valuable, that I

needed to be involved in. It's actually more to support me into the better conduct of the studies."

Investigator, EACCR 6

'I could see that something was, that a monster was being created…this is the whole area of sort of ethics regulation and so and it seemed to be only one direction of travel which was more and more heavy questions and demands and requirements and the net result was more and more paperwork, more and more time devoted towards it.'

Investigator, MORU 26

Investigators were keen to be involved in planning monitoring activities and valued the input of monitors who *"understand what we call the main focus of the study and give credit to the investigator who have long experience" (Investigator, MORU 11)*. They particularly appreciated monitors who worked with them to rectify faults and increase research capacity.

MORU investigators described how the establishment of the CTSG has allowed them to exercise more control over how trials are monitored. They can draw on the expertise of CTSG members to ensure that monitoring activities target the greatest risks to participants and the most scientifically relevant data points. This has helped them develop a counter argument against some of the bureaucracy they believe is hampering the conduct of biomedical research. The EACCR reciprocal monitoring scheme was credited with strengthening quality management across the network, and appreciated by monitors as means of professional development and exchange. Across both case studies much value was attributed to a non-threatening *'shared learning'* style of monitoring, which prioritized the resolution of problems.

'*…because it's a sort of cooperative monitoring and not hostile, you're much more likely to get problems sorted out rather than hidden.'*

Investigator, MORU 17

It was evident that participants wanted monitoring to be scientifically grounded to ensure that quality checks are tailored to primary study outcomes. This type of monitoring requires monitors to work closely with investigators from the planning stages of studies. Much emphasis was also placed on the need to complement checking activities with tailored support and training. Investigators were positive about the need for correction, especially when monitors worked with them to improve their work. Participants concurred that the purpose of monitoring should be to improve the conduct of health research and increase the capacity of researchers and trial sites. In other words monitoring should *'help sites achieve what they are supposed to achieve'* and offer *'assurance to investigators that they*

are doing things the right way'. In practice this type of monitoring replaced negative associations with more positive views of monitoring.

'Yeah when a monitor they actually come in to help you do your work better, they're not coming to police you or to find mistakes…they're coming to help you do your work better.'

Monitor, EACCR 3

The Practice of Monitoring: What constitutes professional practice?

The 'who' of monitoring

Participants' experiences of monitoring suggest that the organisational ethos of monitoring bodies has a bearing on the practice of monitoring. It was evident from participants' accounts that monitors from external bodies sometimes distanced themselves from research staff. In contrast EACCR monitors conveyed the notion that '*we are doing this together'*, similarly the positioning of the CTSG as an internal monitoring group within MORU enhanced interactions between researchers and monitors and increased transparency. On the other hand some MORU investigators felt that research staff were more *'alert and ready'* during monitoring visits from external groups.

These observations about interactions between monitors from different organisations and investigators raise important points about accountability and professional relationships. EACCR monitors for example argued that monitors can identify with the site whilst remaining accountable to the study sponsor, and MORU investigators maintained that the positioning of the CTSG does not pose a conflict of interest. To the contrary they work together more easily because their professional relationship is built on trust and mutual understanding. According to a study nurse this prior knowledge reduced the stress associated with monitoring but it did not alter the need for correction. Internal monitors applied the same standards as external monitors but their proximity meant that they were more accessible and could provide on-going support.

Yeah for me I think it's not so hard because it's not like the investigator is against the sponsor. So it's not like they're trying to identify with you as opposed to the sponsor. They're just when they are on the site they're talking we. We can do this…and the way I see it, it's not hard for them to identify with the site.

Monitor EACCR, 27

CTSG they will know the protocol very well and they will know us quite well I have to admit it, but that doesn't provide conflict of interest…in a way it make us work together easier.

Investigator MORU, 11

Monitors background, training and expertise and their understanding of the research context were viewed as important in terms of professional practice. One investigator said that he judged the value of monitors work by the *'quality of the information they are able to detect'* (Investigator, EACCR 7). Health professionals with experience of working in research were regarded as particularly well equipped to be monitors. A role, which was also thought to require motivation and commitment, attention to detail, good interpersonal and communication skills and the ability to apply and interpret ethics guidelines in practice. With reference to the latter an investigator emphasised that monitors needed to understand the scientific purpose of the research in order to *'think about the patient's interests and how they could advocate for those, or how they could check for those' (Investigator MORU, 20).*

Much value was attributed to context informed monitoring and investigators resented monitors who did little to consider cultural norms, logistical limitations and local regulations.

'They come and they have such little time and they will have to do so much so they're in a rush and sometimes they're really distressed to try and meet their milestones. And then the other thing that I have seen is inability to understand the culture and even local regulations sometimes, harmonising and local regulations and sponsors, SOPs and their own regulations back in their country, it's such a big issue. So they come out and they would like things done the way they understand it. A few times we took it upon ourselves to really train them on our culture, what is acceptable, what cannot be done'.

Investigator EACCR, 10

This investigator is arguing that an appreciation of local norms, customs and regulations is prerequisite for effective and professional monitoring practice. Local monitors were considered well placed to undertake context informed monitoring, and external monitors who demonstrated a willingness to learn rather than simply impose ideas were also highly valued. When it comes to the 'who' of monitoring what counts is mutual respect, communication, professionalism, and maintaining high standards irrespective of the positioning of the monitor in regards to the sponsor and researcher.

The 'what' and 'how' of monitoring

When it came to the practicalities of monitoring what counted was getting the focus and the approach right. Focus requires careful planning and CTSG participants stressed the importance of developing monitoring plans with investigators. This planning helped them to identify the main risks to a study's integrity with reference to ethics and key study outcomes. It helped them differentiate between minor and major errors thereby avoiding

diverting unwarranted time to rectifying the former. Focus also involves achieving the right balance between paper work and observing research in practice.

'I mean sometimes documents don't, may not give, tell you, give you, the clear picture of how things are run. Sometimes talking to people, asking people questions, seeing what people are doing can assure you, can tell you a number of things that you can't see by looking at the documents.'

Key Informant EACCR, 28

Concerns were raised by investigators about the amount of time monitors (coming from long distances) end up spending sitting in rooms verifying files and source documents. It was argued that on-site monitoring should not be confined to document review but include observational and interactive activities, which allow monitors to gain greater insights into how a trial is being implemented and where corrective action is needed.

Two distinct ways of organising monitoring activities were described. One where the monitor performs their review presents findings in debriefing meetings, and sends a summary report with action points; and the other where the monitor actively engages research staff in resolving issues during the on-site visit. The components of monitoring visits were similar but the engagement differed. Investigators expressed preference for the latter but also noted that this method was time-consuming and impractical when the research clinics are busy.

A monitor's personal and professional approach was viewed as crucial to promoting positive interactions and improving the quality of trials.

'The key thing about successful monitoring is how you present, how the monitor presents themselves and involves themselves with the investigators'

Investigator MORU, 26

Monitors need to gain the trust of investigators and interviewees argued that the best way to do this is to work with investigators to improve study conduct. It was evident that investigators were anxious about discussing problems or disclosing important information to overly critical monitors. One investigator (Investigator EACCR, 7) described how his team's *'fear just melted away'* when they realised that their monitor's approach (an external CRO monitor) was not adversarial *'you did this wrong, we are going to beat you'*, but constructive *'he's like trying to make you improve'*.

The core features of a professional approach to monitoring were cited as a commitment to high standards, open communication and positive interactions, mutual respect and a

friendly manner. Investigators appreciated monitors who maintained high standards in a strict and firm manner and worked with them to enhance the quality of their work.

DISCUSSION

Our participatory evaluation provides important insights about the practice of international on-site monitoring, and the value of utilizing internal and network expertise to enhance trial quality. Particular emphasis was given to a cooperative style of monitoring as a means of enhancing trust and transparency. Whilst this style of monitoring was associated with the EACCR and MORU models, it is important to note that some participants commented positively on interactions with CRO monitors. With reference to practice our findings suggest that the primary purpose of on-site monitoring is to improve the conduct of health research and increase the capacity of researchers and trial sites. Monitoring activities to be scientifically grounded, contextually and culturally informed with tailored support and training. Skills in the scientific evaluation of trials and a willingness to work closely with investigators were viewed as critical for the development of effective risked-based and context informed monitoring plans. It was argued that on-site monitoring should combine document verification with observational activities, and be complemented by training and mentoring to enable investigators to execute necessary corrective actions. Indeed our data suggest that the success of monitoring should be measured by corrective action rather than by identification of faults. Monitoring reports should only include findings, which could significantly impact on the scientific and ethical integrity of the trials.

The main benefits of the MORU and EACCR monitoring models are: 1) Reduced logistical costs, 2) Increased site capacity for quality management, 3) Investigators contribution to risk-based monitoring plans, 4) Professional development and exchange. The latter is of relevance given the increased value attributed in the health sector to 'Communities of Practice' as a means of encouraging situated learning and the practical application of knowledge[23]. Communities of practice are defined as: *'groups of people who share a concern, a set of problems, or a passion about a topic, and who deepen their knowledge and expertise in this area by interacting on an on-going basis'[24]*. The challenges relate to questions of sustainability and credibility. There is a need to consider the logistics and funding of these models to ensure that their benefits are sustainable. Currently both models rely heavily on grants rather than charging trials directly for their services. This needs to be remedied in order to reduce dependency on external funding.

The strengths of this empirical study are that it contributes to the literature documenting good practice at international trial sites in resource-constrained settings. As noted in the background section Macefield et al [20] were only able to include 7 multinational trials in their systematic review. Given the study design one inherent limitation is the paucity of

Comment [TC7]:

I am not convinced, however, that the authors have been able to determine the value of the two monitoring models assessed, nor have they been able to produce any insight as to how their value can be measured.

Authors responses.
We do think that this work brings new insight into the issues and practices involved in trial monitoring. There is hardly any research in this area and none using this methodology to determine the issues and establish the situation. We do agree that further studies should conduct quantitative evaluation on the quality of data produced and, indeed, the overall quality of the study. However this was not an aim in this work and this was clearly stated. Some excellent further studies would be, for example, were any processes identified that were having a major negative impact on data quality? - if so, would these have been detected anyway or would either monitoring model have been the only way in which such erroneous process could have been detected and rectified? We state that these further studies are the important next step but that this work was previously missing and had to be performed first to examine the issues and state the problems, as we feel we have.

Were any individuals found to need some additional training or advice on data management/quality? Were any issues identified that could have impacted negatively on patient safety and well-being while participating in either trial?
This is a good question and we are exploring the data management question in another study at the moment. However in this research this did not occur explicitly in the no comments raised specific comments on data integrity or safety. However we agree a focussed study looking at this would be excellent.

However, I would wish to argue ... [1]

Comment [TC8]: Dr Anil Kumar, Reviewer 1 main comment:

'Who shall be the person or agency to ensure on-site monitoring as a part of research protocol to make mandatory?. To me this could well be encouraged by funding agency. However there need to be convincing agreement between researchers and funding agencies with the aim of improving rather than threatening.

Authors response

We firmly agree and that the reviewer for this comment and we have strengthen our wording in the discussion to reflect this helpful endorsement of this view.

quantitative findings. Follow up studies will need to systematically collate information on trial costs, and provide monitoring report templates. An additional weakness of our work is that we were not able to compare the monitoring reports of studies monitored by MORU and EACCR RMS, and other sponsor delegated monitoring groups. A key area for future research will be to conduct a mixed methods study, which evaluates how the EACCR and MORU on-site monitoring models work in combination with CSM.

CONCLUSIONS

Innovative monitoring models, which prioritise the sensible application of regulations and ethical guidelines are imperative to facilitate vital global health research. The experience gained in developing the innovative international models studied in this paper offers valuable insights. Both models utilize internal and network wide expertise to improve the ethics and quality of clinical research. They demonstrate how monitoring can be a constructive exercise rather than threatening process. The value of cooperative relations needs more emphasis in this field given that sponsors, investigators and monitors are jointly responsible for ensuring that research protects human rights and produces reliable data, which can improve human health.

ACKNOWLEDGEMENTS

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CONTRIBUTORS

All authors participated in the study design from conception. TC conducted the case study fieldwork with the support of AN, EA, GM, EK, PYC and VH. TC performed the primary analysis and TL was involved in subsequent analytical review and decision-making. TC wrote the first draft of this paper and all authors critically revised the manuscript.

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COMPETING INTERESTS

None

ETHICS APPROVAL

Comment [TC9]:
We have added this as per comment

The study was approved by the Oxford Tropical Research Ethics Committee (Ref: 09-12), the Kenyan Medical Research Institute Ethics Review Committee (No: 2253), the Ugandan Virus Research Institute Science and Ethics Committee (Ref: GC/127/12/03/04), and the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University (Ref TMEC 12-023).

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Comment [TC10]: References
All references follow the rules, but in reference 9, the year of publication is missing. **DONE–I hope the numbers stays in place.**

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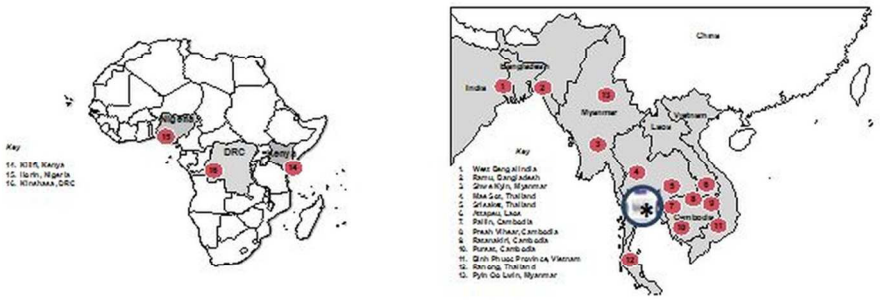
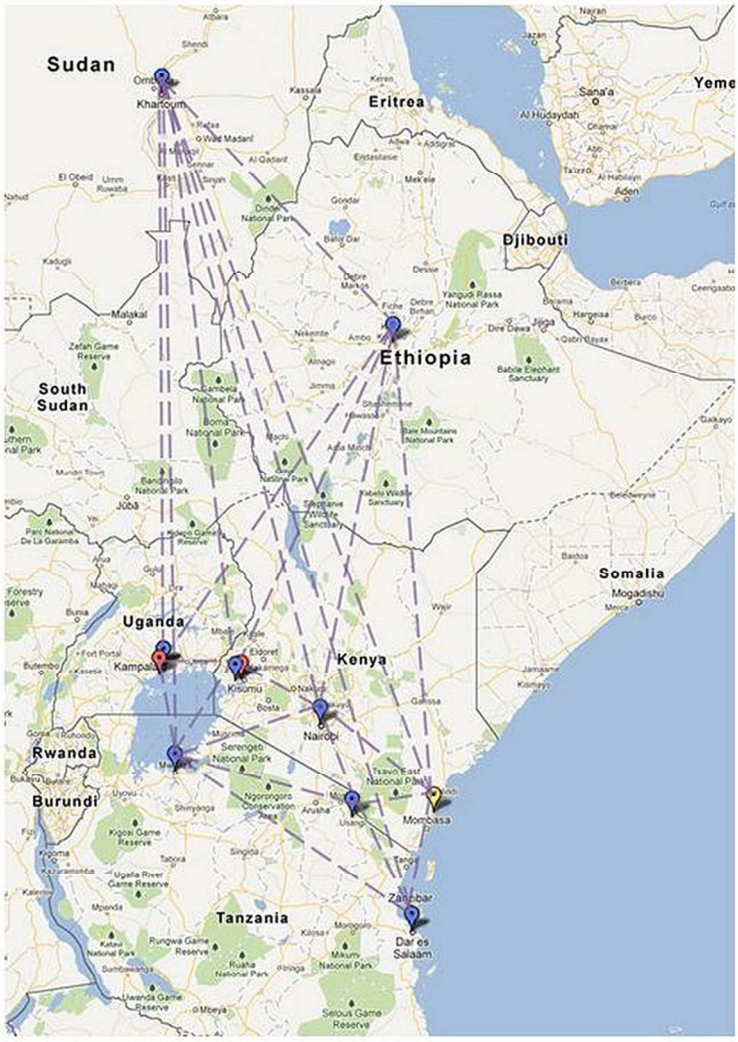


The Thai Unit Monitors based at the Mahidol Research Unit in Bangkok* visiting the Artemisinine trial

90x93mm (300 x 300 DPI)

Figure 2: The East African Consortia Partners involved in the reciprocal monitoring scheme



73x90mm (300 x 300 DPI)