

Monitoring randomized clinical trials in Africa; pragmatic approaches and experiences from HIV trials

The Medical Research Council Clinical Trials Unit has coordinated HIV clinical trials in Africa for almost 15 years. Approaches to monitoring trial data have been developed using a combination of on-site and central (database) monitoring. Tools and templates have been designed to supplement trial protocols and help standardize trial processes. Local monitors supplement infrequent visits from the sponsor, enabling monitoring at the required intensity and allowing for capacity building. Database strategies have evolved to complement on-site visits, allowing more effective monitoring of data quality, and providing functionality in a cost-effective manner. Ongoing training and support of monitors and site staff is given via teleconferences, emails and meetings. Mentoring of site staff by monitors is encouraged, including cross-site visits where resources allow.

Keywords: Africa • clinical trial • GCP • HIV • monitoring • quality control • standard operating procedure

Introduction to monitoring of Medical Research Council Clinical Trials Unit-coordinated HIV trials in Africa

Monitoring is an integral part of the quality management of clinical trials. It 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 requirement(s)’ [1]. GCP requires trials to be monitored according to the type of trial and its complexity and, to achieve this; central data monitoring is usually complemented with on-site monitoring. Management of these activities, particularly in under-resourced settings, can present both ethical and logistical challenges.

The Medical Research Council Clinical Trials Unit at UCL (MRC CTU) has, since 2001, been responsible for the quality management of several trials of HIV treatment and prevention in sub-Saharan Africa (SSA). MRC CTU has acted as sponsor

for many of these trials, so under GCP has overall responsibility for monitoring, and has developed processes both for ensuring that the rights and well being of participants are protected and that reliable data are collected. MRC CTU also has a strong ethic of capacity development and training, so has an additional objective of passing on the skills for performing and monitoring clinical trials to those conducting these studies in country.

Details of the trials referred to throughout this paper are given in [Box 1 & Table 1](#).

CHAP [2] was the first MRC CTU-coordinated HIV trial in SSA from which our monitoring model evolved. This was a single center intervention trial of co-trimoxazole versus placebo in Lusaka, Zambia which started in 2001. On-site monitoring was done during MRC CTU visits and also with a trained data monitor in Lusaka. Central monitoring and database checks were run at MRC CTU.

Our first multicenter HIV trial in SSA was DART [3] which started in 2003 and was based in Uganda (three sites) and Zimbabwe (one site). Site initiation visits were of great

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Box 1. Acronyms and full names of Medical Research Council Clinical Trials Unit African HIV trials.

- Antiretroviral research for watoto (ARROW):
 - A randomized trial of monitoring practice and induction maintenance drug regimens in the management of antiretroviral therapy in children with HIV infection in Africa
- Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP):
 - A double-blind randomized placebo-controlled trial
- Children with HIV in Africa – pharmacokinetics and acceptability/adherence of simple antiretroviral regimens (CHAPAS):
 - A randomized trial to compare the toxicity and pharmacokinetics of three fixed dose combination-based antiretroviral regimens for treatment of HIV-infected children in Africa
- Development of antiretroviral therapy in Africa (DART):
 - A randomized trial of monitoring practices and structured treatment interruptions in the management of antiretroviral therapy in adults with HIV infection in Africa
- Europe–Africa research network for evaluation of second-line therapy (EARNEST):
 - Evaluating the options for second-line therapy in HIV-positive patients failing a first-line treatment regimen in Africa
- Microbicides development program (MDP)
- Reduction of early mortality in HIV-infected adults and children starting antiretroviral therapy (REALITY)

importance to ensure that prior to the trial start sites were familiar with study documentation, protocol procedures, the investigational products and their responsibilities toward the care of participants. On-site monitoring was initially all performed by MRC CTU which, as a nonprofit research group, has limited resources. It was recognized that more frequent visits would be beneficial so, rather than employing a contract research organization (CRO), local research nurses were recruited, trained and supported by MRC CTU to take on the role of monitors. Central database checks were coordinated by MRC CTU and are discussed later.

The DART model has been further revised for subsequent SSA multicenter, multicountry HIV treatment trials (ARROW [5], CHAPAS 1 [6] and CHAPAS 3 [7], EARNEST [8] and (REALITY [9]), and MRC CTU has developed monitoring plans and checklists that can be adapted to other studies, and templates to standardize data collection and procedures across sites. MRC CTU has also coordinated a number of HIV prevention trials in both Europe and Africa, the largest being MDP301 [4]. This Phase III, placebo-controlled double blind randomized trial started in 2005 and was based in South Africa (three sites), Uganda (one site), Zambia (one site) and Tanzania (one site). It investigated an unlicensed product in HIV-negative volunteers, and if successful the owners of the product would have applied for a new drug application with the US FDA. The risk assessment, and therefore the monitoring, that was undertaken was based upon the requirements for licensing.

Using a risk assessment to identify areas to monitor

There are potential hazards within clinical trials that could result in harm to a participant, an organization

or to the reliability of results. Those involved in the running of a trial must consider their responsibilities and undertake a risk assessment to identify potential hazards and assess the likelihood of them occurring. This process should be initiated at an early stage in protocol development and a plan for risk management developed, of which monitoring plays an important role. Risk assessments for HIV trials in SSA take into account risks inherent in running trials in general, as well as those specifically associated with trials in HIV and in resource-limited settings. The MRC CTU risk assessment is now a standardized procedure, with templates to assist with the process, and the outcomes are used to help develop the monitoring plan which includes follow-up on corrective actions. Areas to be considered include the following:

Experience of sites regarding clinical & research capacity

Many SSA sites that have conducted our trials were relatively naive to clinical research. The risk assessment helps to identify potential risks to trial performance and quality, and to mitigate these. Risks could range from lack of basic resources such as power to the availability of clinical staff. Training in both clinical research/GCP and the specific procedures of the trial is undertaken prior to starting the trial, together with ongoing training and support throughout.

Site assessment visits before the trial allow MRC CTU to assess clinical capacity and to determine training requirements and any site-specific aspects to monitor, and this training is then provided at initiation visits. Procedures often need to be altered and customized to each setting, while ensuring that the underlying requirements of the trial and GCP can be adhered to. Ongoing, regular on-site monitoring is also

Table 1. Main characteristics of Medical Research Council Clinical Trials Unit African HIV trials.

Characteristic	CHAP	DART	MDP301	ARROW	CHAPAS 1 and 3	EARNEST	REALITY
Type of trial	CTIMP: Treatment/intervention	Strategic/treatment	Prevention	CTIMP: strategic/treatment	CTIMP: pharmacokinetics/toxicity/adherence/treatment	CTIMP: treatment/intervention	CTIMP: treatment/intervention
Phase	III	III/IV	III	III/IV	I/II (CHAPAS 1) II/III (CHAPAS 3)	III	III
Blinded yes/no	Yes	No	Yes	No	No	No	No
Patients/volunteers recruited (n)	534	3321	9385	1206	210 (CHAPAS 1), 470 (CHAPAS 3)	1277	1800 (still recruiting)
Adults or children	Children	Adults	Adults	Children	Children	Adolescents and adults	Children and adults
Length of follow-up	Median 19 months	Median 4.9years	1 year in five sites, up to 2 years in one site	Median 4.0 years	Median 92 weeks (CHAPAS 1); 120 weeks (CHAPAS 3)	96–144 weeks	48 weeks
Sites (n)	1	4	6	4	1 (CHAPAS 1), 4 (CHAPAS 3)	14	8
Experience of sites	No previous experience	Little or no trials experience	Variable (some experienced, others naive to research)	Three sites experienced from DART, fourth site with little trials experience	Experienced (from CHAP, ARROW and EARNEST)	Variable (some experienced, others naive to research)	Experienced (seven/ eight from EARNEST, other site already doing other trials)
Countries participating	Zambia	Uganda, Zimbabwe	South Africa, Tanzania, Uganda, Zambia	Uganda, Zimbabwe	Zambia (CHAPAS 1), Uganda and Zambia (CHAPAS 3)	Kenya, Malawi, Uganda, Zambia, Zimbabwe	Kenya, Malawi, Uganda, Zimbabwe
Funding	£	££	££££	££	££	£	££
IMP licensed/unlicensed	Licensed	Licensed	Unlicensed	Both	Both	Licensed	Licensed except for one drug in children
Potential licensing application yes/no	No	No	Yes	Yes for frequency of dosing	Yes	No	Yes for above formulation
Year open	2001	2003	2005	2007	2006/2010 (CHAPAS 1/3)	2010	2013
Year closed	2003	2009	2009	2012	2008/2014 (CHAPAS 1/3)	2014	Ongoing (due 2016)
Ref.	[2]	[3]	[4]	[5]	[6,7]	[8]	[9]

CTIMP: Clinical trial of an investigational medicinal product; IMP: Investigational medicinal product.

helpful in this regard as monitors can provide training as issues are noted. Site staff often find it is beneficial to discuss problems and concerns face-to-face with monitors rather than via email, which is more impersonal and can be misunderstood, particularly across different languages and cultures. An operational assessment of sites has become part of MRC CTU monitoring plans. Cross-site training where an experienced clinician/pharmacist/data manager visits a less-experienced site to offer advice, and similarly where personnel from a less-experienced site visit one more experienced, often provide ideas to improve efficiency.

Clinic – standardization of procedures

Although it is ideal to have standardization of procedures across all sites within a trial, this is not always possible in SSA settings due to the variation in resources. Clinics in different countries, and even sometimes in the same area of the country, may follow very different procedures and therefore standardization may not work in that particular setting. At the initiation training the coordinating team walks through each step of the trial procedures with the clinic staff and identifies whether these need to be changed (without compromising the protocol) to accommodate the resources of the clinic, as well as some of the cultural differences that occur. These differences and the risk they pose should be included in the risk assessment, together with the mitigating actions taken to minimize them, which should then be checked by the monitor. The use of an investigator site file allows sites to have study standardized documentation, SOPs and procedures that use version control. These files should be monitored, as well as other standard documents such as trial registers, and also a predefined percentage (based on risk, resources and size of the trial) of the case record forms (CRFs) to check whether sites are recording data correctly.

Laboratory – reliability of results & standardization

Quality management in laboratories in resource-limited settings can be challenging as they do not always operate under the regulations imposed in resource-rich settings, and there is often less availability of senior staff and a high turnover of trained staff due to the opportunity to find better-paid positions elsewhere. Capacity may be limited if the laboratory involved in a clinical trial also runs routine patient assays for local clinics, and appropriate laboratory equipment and reagents are not always available. Maintenance and repair can be problematic, particularly in rural areas, and not all laboratories perform validations with recognized external quality assessment (EQA) schemes. It is important

to identify and mitigate any risks to the reliability of results and assess the quality assurance (QA) systems offered/in place that can help to oversee equipment maintenance and validation. Laboratories are encouraged to use the International Standard ISO 15189 [10] when developing their quality management systems and working toward accreditation, and ISO guidelines are very useful toward identifying what should be monitored in the laboratory. Study-specific training should be provided as appropriate by established and experienced laboratory staff, or by visiting experts, and training certificates and competency monitored. In addition, laboratories should be consulted to ensure all measurement units and expected tests are included on CRFs. Good clinical laboratory practice (GCLP) provides guidelines to help ensure the requirements of GCP are met during sample collection, processing and analysis. Training is offered where necessary to enable GCLP to be followed by clinical trial laboratories and all personal training recorded.

Pharmacy – temperature, security, record keeping

Temperature maintenance in African pharmacies can be problematic due to extremes in temperature coupled with erratic electricity supplies, and many do not have air conditioning. Providing thermometers and giving training on simple methods of temperature logging is part of MRC CTU site initiation. The space provided to dispense and to store study drug, and also to store investigator brochures and prescriptions, needs to be assessed and measures put in place to ensure restricted access and secure storage, which should be monitored during visits. Strict record keeping of drug accountability must be adhered to for clinical trials, and monitored. Templates for this have been developed by MRC CTU. In MDP301 and ARROW, a pharmacy database was developed whereby pharmacists could inventory stock, log dispensing and record returns. Database reports, all designed with input from the pharmacists, were used to check accountability and could be checked by monitors. Separate reports were made for trial close out and final accountability. A generic version of this database is now being designed at MRC CTU.

Resources – power, internet

Resources such as power and internet access in SSA are often unreliable so need to be assessed, and if necessary, measures put in place to deal with power outages (e.g., back-up generators). Internet bandwidth is often very expensive, compared with Europe or North America, and connectivity can vary depending on location and weather. This can impact on the frequency that sites can communicate, and internet-based databases

or electronic CRFs may not always be a viable option; paper-based backup systems are important to have in place. Furthermore, central monitoring can be difficult if there are long delays in data entry at site and in data being received centrally. Whenever possible, trial or institutional resources are directed toward improving the infrastructure.

Travel to sites

Travel to and within some African countries can be potentially hazardous and costly. MRC CTU visits require long haul flights of 8–14 h and sometimes long drives of several hours to sites following landing. The ability to safely travel to more remote sites, and the frequency that this can be done, impacts on the frequency of visits by both MRC CTU staff and local monitors. The resources required should be assessed prior to the start of the trial, which should also include costs for accommodation and sustenance/supplies for both monitors, and drivers.

Language & literacy, consent issues

Issues around language and literacy can be particularly difficult, especially when designing patient information sheets and consent forms and when obtaining consent. Sometimes the exact words required to translate clinical research concepts from English to African languages cannot be found and alternative words used by translators may change the meaning of the text. During the approval process back translations should be thoroughly reviewed to ensure that translations are as accurate and complete as possible. Tests or checklists of comprehension are used to ensure that key points have been understood. There is also often a low level of literacy in SSA countries, so witnesses may be required for the consent process which is sometimes difficult, particularly as there is still a large amount of stigma around HIV. Further challenges arise when children are being recruited, such as in ARROW, EARNEST and REALITY where it is possible that neither the child nor the parent can write and thumbprints and witnesses are used for both assent and consent. Monitoring of these consents can be confusing and requires careful checking to ensure that the process has been carried out correctly. Ongoing discussion and training with sites on the informed consent process is a critical part of mentoring and monitoring.

Written informed consent is the evidence that a participant has been given full information about the trial, in lay person's terms, and is willing and has agreed to all the eligibility conditions/clauses listed in the consent form. The process can be high risk if not completed correctly so it is important that opportunity is given for questions to be asked and that forms are always signed

and dated. Hundred percent of consent forms are normally monitored unless a different approach is agreed following the risk assessment. Consent monitoring is very detailed; items to review include version control, delegation log, eligibility, legibility, signature dates, initialing of check boxes, true independence of witnesses and evidence that the participant and/or witness completed and dated the form themselves. In some pediatric studies assent is additionally used, and all assent forms need to be monitored in the same way. If comprehension checklists are used, these should also be monitored to check that trial staff have verified that participants have understood the information given to them.

Follow-up, retention

Follow-up and retention of participants in an African setting can be challenging, particularly in areas where people tend to move a lot depending on work availability. Participants may not want to be seen to be linked to a particular clinic due to stigma around HIV. This is even more challenging in prevention trials where participants do not need to attend the clinic due to ill health or to receive treatment for an ongoing condition. MRC CTU relies on the flow of CRF data to determine if follow-up is on schedule, and so if follow-up seems low a monitor can check whether this is due to source CRFs being completed but not data entered or whether there is a genuine lack of visits. In trials where missed clinic visits are likely, participants are asked to give consent to be contacted at home, or even visited by field workers. Telephone calls from site have often found out that a participant may have missed a visit due to illness, which is important to know both for safety and data completeness. Monitoring reports are useful tools to highlight clinics where follow-up and retention may be declining.

Adherence to investigational medicinal product

Adherence to drug is critical for long-term effective antiretroviral therapy in treatment trials and prophylactic therapy in prevention trials, and so as well as recording drug returns in each trial, CRFs have questions to investigate adherence. As resources can be limited, monitors review a random sample of these source documents, to check that they are being completed correctly and also to note any overall patterns of nonadherence that may need to be addressed and monitored in finer detail.

Types of monitoring (site visits, database/central)

Both central monitoring and site visits were undertaken in the MRC CTU studies considered here, some

of which have been described elsewhere [11,12]. The emphasis of both types of monitoring may be adapted as the trial progresses, and both have proved mutually beneficial. The risk assessment helps to define the areas to be monitored, and how frequently, as discussed in further detail below.

Site Monitoring

Site monitoring plans

The DART monitoring plan was initially developed before the trial started in 2003 and organized the items to be monitored into a series of forms in order to:

- Facilitate monitoring and standardize it across sites and occasions;
- Allow monitors to briefly record findings (e.g., satisfactory, not satisfactory) and comments at the time of assessment;
- Be sufficiently clear and comprehensive that detailed transcriptions of notes on individual findings or problem CRFs were secondary and supplementary;
- Be easily referenced (by numbering each item to be monitored) by an overall summary report of the visit in general.

Site monitoring visits generally assessed:

- Compliance with GCP/protocol adherence;
- That the investigator site file contained the appropriate up-to-date documents;
- Source document validation/verification (CRFs, clinic, laboratory, pharmacy).

The plan was updated several times to reflect lessons learned and changing priorities as the trial moved from initiation and recruitment to follow-up and closure. It was also modified to allow for regular local monitor visits as well as periodic MRC CTU staff visits.

The MDP301 monitoring plan was developed at the start of the trial and based on a risk assessment taking into account that this was a licensing study. It was updated a number of times throughout the trial to better reflect the issues that arose during the trial. Guidance for monitoring was embedded in the monitoring report template in order to ensure uniformity of monitoring across a team of monitors.

The monitoring plans for subsequent HIV treatment studies (ARROW, CHAPAS 1, CHAPAS 3, EARNEST and REALITY) were based on the DART and MDP301 formats and modified relative to each study.

Frequency of site monitoring

The frequency of MRC CTU visits for DART was initially high but reduced as sites acted upon feedback from the monitoring visits and became more experienced, and also as the use of in-country or 'local' monitors increased.

MDP301 was a licensing trial requiring very intensive monitoring, undertaken initially by CRO and MRC CTU monitors. Each site had a number of early visits (weeks 4, 8, 12 depending on the site) where 100% of the data were monitored. Monitoring visits were scheduled every 3 months thereafter where all informed consents, serious adverse events (SAEs), pregnancy, HIV rapid test results and a sample of patient files (files of 10% of all participants) were monitored in full. When, according to the contract, this became too much for the CRO, more intensive visits from MRC CTU were instituted. This, however, was not cost effective and so two local monitors, based in South Africa, were employed.

Local monitors

Local monitors have become essential to enable the frequency and intensity of the monitoring needed to conduct MRC CTU HIV trials in SSA studies safely and efficiently. They relate well to site staff, understand local culture and language, and are more cost effective than international monitors. Additionally, MRC CTU can develop capacity at sites and assist with career development through local monitor training and mentoring.

Sites are visited on a regular basis by the local monitors, usually at least every 3 months depending upon the trial, to review the items described previously. The MRC CTU monitoring plan can be revised to allow for more flexibility based on monitoring findings and issues that arise during the trial. The monitors keep in close contact with MRC CTU and are informed of any targeted monitoring or issues that need further investigation and cannot be resolved remotely. Co-monitoring by MRC CTU staff is performed with the local monitors (and for MDP301 also with staff from the CRO) in order to ensure consistency. These visits help to maintain MRC CTU relations with monitors and site staff.

Local monitors log their findings in the following ways:

- Monitoring log: A list of time/dates spent at each site;
- Monitoring spreadsheet: Containing separate worksheets for the main monitoring areas above. This is sent to MRC CTU after each visit. The local monitor provides updates to the trial manager

at MRC CTU on any critical or major findings at the end of each monitoring day/visit;

- **Monitoring report:** Local monitors prepare a monitoring report summarizing the critical, major and minor findings recorded on the spreadsheets above. The site coordinator reviews the report and states what action is required to rectify each problem. This reply is sent both to the local monitor and MRC CTU.

It has been recognized that the value of cooperative relations needs to be given more emphasis in monitoring activities [13]. Teleconferences are held between the local monitors and the project manager/trial managers at MRC CTU to discuss any issues that have arisen during the recent monitoring visits, to answer any questions that the local monitor may have, and to ensure they feel supported. In addition, trial teams hold regular management calls to discuss the day-to-day running of the trial, including issues arising from central and on-site monitoring and training requirements. Some of the local monitors are now very experienced and able to coordinate corrective actions with minimal MRC CTU oversight. They have developed relationships and trust with key staff and are able to help train and mentor new monitors and site staff.

Site monitoring reports & feedback

Reports are reviewed by MRC CTU and then sent to the site coordinator and principal investigator (and delegates) within dedicated timelines. Findings are classified as 'critical', 'major' or 'minor/other':

- **Critical:** Findings that impact, or potentially could impact, directly on participant safety or confidentiality, or create serious doubt in the accuracy or credibility of trial data;
- **Major:** Deviations from the protocol that may result in questionable data being obtained, or errors that consist of a number of minor deviations from regulations, suggesting that procedures are not being followed. If not corrected, or if they recur after initial notification, these findings may be raised to critical status;
- **Minor/Other:** Errors or deviations from procedures that do not have an important impact on the data that are collected, or do not affect participant safety or confidentiality.

The timelines required to correct the issues found during monitoring differ according to the grading given. If any finding is not addressed by the time of the next monitoring visit it may be elevated to the next

higher category following communication with MRC CTU. A feedback session is held for site staff at the end of a site visit with an external monitor or if the local monitor has spent several days at a remote site. For sites where the local monitor visits every month for 1 or 2 days, the feedback session will generally be held every 3 months. When errors are identified from monitoring visits, corrective measures are carried out to reduce similar errors in future and reinforced procedures are discussed with appropriate staff from the site. Resolution of problems identified in previous reports is checked at monitoring visits.

Laboratory monitoring

The analysis of samples collected from participating subjects in a clinical trial allows safety and efficacy to be assessed and provides important data for a range of endpoints (the outcome measures of the trial). Therefore quality management of laboratories must be at a standard that ensures data are reliable and accurately reported, and that patient safety is not compromised. Markers of disease progression such as CD4 counts, and assays for drug toxicity are of particular importance in HIV trials for the management of patients. Laboratories require an appropriate level of monitoring although without a laboratory training background it can be challenging for monitors to review some of the processes and identify some of the issues addressed in the risk assessment.

In DART and ARROW the primary intervention was related to the value of routine laboratory testing on the efficacy and safety of antiretroviral therapy, so there was a balance to be struck between having valid results but at a quality level realistic for the region.

Prior to starting a trial, the roles and responsibilities within a laboratory should be documented and personnel identified for laboratory management, scientific analysis, quality control and assurance, training, reporting and archiving. All staff involved should receive GCP and GCLP training and be provided with the trial protocol and any study-specific SOPs or manuals of operations (MOPs). Laboratory accreditation status should be identified, as should capacity and EQA programs.

Following experience with DART and ARROW, laboratory questionnaires were developed by MRC CTU to assess capacity and contribute to the overall risk assessment. The questionnaires provide MRC CTU and monitors with a basis of information about the laboratory, its staff, equipment, validations, assays and documentation. It also aids the development of study-specific laboratory SOPs and a laboratory MOP.

In both DART and ARROW the MRC CTU trial managers were experienced in the laboratory which

helped toward the development of specific monitoring checklists. In addition to capacity development at sites through training in study-specific assays by these trial managers, a research coordinator role was developed at MRC CTU to oversee the monitoring of the site laboratories across a number of African-based HIV trials.

Further capacity development was achieved by sending the ARROW Zimbabwean local monitor, who had a laboratory background, for the South African National Accreditation System (SANAS) laboratory auditing training [14]. This accreditation gives formal recognition that laboratories are competent to carry out specific tasks following the GLP Act. The monitor then had the skills to perform cross-country laboratory monitoring which was a great benefit to the study.

Quality assurance

To ensure that laboratory policies and SOPs are adhered to, and that data are recorded and reported accurately, laboratories should appoint QA personnel who are not directly involved in generating trial data. QA personnel ensure regular internal audits and reviews of the laboratory's procedures and methodologies to conduct the analysis of clinical trial samples, and they ensure that both preventative and required maintenance is carried out. Reports and feedback of these audits adds to the monitoring process and QA personnel can assist with corrective actions. QA personnel can also review completed datasets before they are sent to the sponsor to confirm that the analysis has been conducted following the protocol and GCLP.

Quality control

Laboratory QC enables patient safety when using results to manage a study participant, and is also a requirement for data that will go to publication. Internal QC and participation in EQA schemes must be implemented and the laboratory monitor is asked to review reports and, if laboratory experienced, Levey–Jennings charts, where control values are plotted against analysis dates to show any trends/shifts in calibration or increased random error.

On-site laboratory monitoring

For DART, and the HIV treatment studies that followed, any laboratory monitoring would generally be done as part of the MRC CTU site-monitoring visit, or by the local monitor. Laboratories are asked to keep a study-specific file that is reviewed to check for correct documentation, and up-to-date versions of protocols, MOPs, SOPs and delegation logs. Laboratory normal ranges and any accreditation, validation and audit reports should also be filed here. General laboratory procedures are assessed, in particular the

QA/QC checks and flow of samples and results from their generation to CRF, and checks against source documents/data. Sample storage is fundamental to many research projects so the monitor reviews freezer temperature logs and storage facilities, and checks that samples are clearly labeled and can be located using the recorded storage details, and that a specimen receipt and shipping log/system is in place. Equipment calibrations and assay validations are also reviewed, as are back-up systems such as the presence of a generator and documentation of its function and availability of fuel.

In MDP301, a central reference laboratory evaluated the HIV testing assays, procedures, algorithms and QC mechanisms in place at each site laboratory. They also provided training for laboratory staff in GCLP where required, and acted as mentors for many of the site staff who were aware that if any laboratory issues arose they could be discussed with members of the oversight laboratory who would offer useful and workable solutions.

Database/central monitoring

Central monitoring using the data collected in the trial database can be conducted using functionality built into the database application, or can be done on data extracted from the database, typically in statistical packages. Both types of central checks are usually done in MRC CTU trials; the relative proportion of each type is dependent on the functionality offered by the database application as well as the experience, skills and resourcing of the trial team. For the majority of the HIV trials in Africa led by MRC CTU, the database application has been developed in-house. Over time, the set of features incorporated into those applications to enhance data quality has increased, based on feedback from data management teams (both centrally and at site). Aspects of these systems are each considered in turn below.

Infrastructure

Prior to the DART trial, the studies which MRC CTU coordinated were usually conducted at a single site, with data collected using a client-based tool such as Microsoft (MS) Access or Epi-Info. While this was a simple and inexpensive approach, the systems were limited in terms of functionality and resilience. With DART, we moved to using MS SQL Server, installed at site and also at MRC CTU, with front-end functionality provided by attaching to a compiled MS Access Project application. SQL Server was chosen as an industry standard which could provide role-based security, integrated backups and scalability, while still being (at that time) relatively inexpensive and not requiring extensive technical skills to administer. Data entered

at site were extracted on a regular basis (usually once per fortnight) and these extracts sent to MRC CTU by File Transfer Protocol, where they were merged into a central database available for monitoring and analysis.

Several large-scale trials were run using this architecture, and the advantages seen revolved around sites having a close relationship with their data, as well as knowledge transfer in the administration of the system. However, over time there were challenges:

- Site systems would be validated on installation, but the site institutions might then have infrastructure upgrades, such as versions of Windows, Office, or SQL Server, which may not be compatible with the application;
- Later versions of SQL Server also became more expensive, so setting up a new site could have significant budget implications if they were not able to use existing hardware and software;
- Receiving data only fortnightly, taking into account that there also may have been delays in both data oasis:entry and data transfer, meant that data available for monitoring and analysis were always somewhat out of date;
- Finally, the ongoing maintenance of receiving and merging the data, as well as supporting sites through upgrades and troubleshooting, required fairly constant input from MRC CTU technical staff.

To address these issues, and recognizing the improvements in internet connectivity throughout the SSA region, we have more recently changed our strategy for studies to have a single central database at MRC CTU, with a web-based application. A central database provides security and resilience according to unit SOPs, and access to the data and database can be limited to relevant staff via roles and delegation logs, protecting data confidentiality. Sites still do data oasis:entry and have access to data management tools via the application but data are available in real time at MRC CTU and sites no longer need to purchase and maintain either hardware or software. The reliability of internet connection and speed can still be a challenge at some remote sites, but this is generally improving and strategies to address issues (e.g., to increase bandwidth) are ongoing.

Application features

Functionality to improve data quality has been increasingly incorporated into our applications, including single or double-data oasis:entry modes (configurable by form), on-screen edit checks (date check, range

checks, valid trial number, etc.) and conditional navigation so that data are not entered where not logically applicable. In our latest systems, these checks and skips are generated from metadata, reducing system development time and providing traceable documentation for testing. It is also useful to be able to prevent duplicate CRFs from being entered, by checking identifiers against existing data.

From DART onward, the systems developed at MRC CTU for these trials have incorporated the trial randomization procedures into the data system. This allows for checks on eligibility and stratification variables from the entered CRFs before calling the randomization process, reducing the risk of randomization errors.

Query processing & reporting

Edit checks that happen on screen during data oasis:entry also produce queries to be tracked later (also known as data clarification forms), and queries can also be produced using more complex and cross-form checks that are less easily implemented as on-screen checks. Starting with MDP301, our systems incorporated automatic generation of queries for missing data and inconsistencies, using database views to populate a separate query table. These queries could then be managed (tracking the status of when sent to clinic, response received, database updated) and closed manually when unobtainable. Views have the advantage of presenting data in real time but can slow performance, and maintenance of the views was cumbersome. Our most recent system, as used in the REALITY trial, uses table-based triggers to populate the query table. These can be generated by script from metadata, and have the additional benefit of automatically closing queries once data have been corrected.

Closely linked to the generation and tracking of queries is the facility to be able to produce reports on these queries, to send out to sites when data monitoring is coordinated centrally, and to keep an overview on data quality for trial management purposes. Earlier systems such as DART reported on only key selected variables and CRFs; the system was expanded to be more comprehensive by the time of MDP301. However, long reports of all missing/inconsistent data can mean that it is harder to focus on priority queries. Our latest system allows user-defined filtering of query data from the query module to be output for reporting purposes. This more flexible approach allows for targeted reporting while still having the ability to report on overall data quality when desired.

Various other reports have been produced as per trial requirements, such as expected visit reports and participant summary reports. While not directly used as part

of the data quality control procedures, this functionality allowed sites to use their data for trial management purposes.

Central monitoring

For DART, in-house inconsistency checking programs were developed as part of the central monitoring, using a statistical package, Stata [15], rather than through the database. These were run monthly by a statistician to query missing or inconsistent data, or values out of range. Some queries were complex, referring across several CRF types. A report was generated for the site coordinator/data manager with all queries grouped by trial participant. The checks were dynamic, and once an item had been corrected it did not appear as an error again. Progress was monitored by plotting the size of the error file by center and through time with all queries being resolved before final data were analyzed. This phase of data cleaning was intensive and time consuming but essential for accurate reporting. Any changes to data items remaining in analysis programs at this point were clearly identified as 'administrative', in other words, clear changes were only required for unambiguous analysis of the data. Running such checks repeatedly throughout the trial ensured that sites were able to keep on top of data cleaning in a timely way, and while errors were still recent. These checks also improved data quality over time as staff at sites were made aware of misunderstandings about what to record on CRFs, and the errors which were occurring frequently, allowing retraining to be put in place quickly, both by site coordinators and by monitors. The inconsistency checking programs have further been refined as they have been taken forward into subsequent African HIV studies coordinated by MRC CTU.

The emphasis on the data architecture that began with DART, and has evolved into its current format, is to put data entry and data management functions into the hands of the site data team, allowing quicker resolution of queries and promoting ownership of the data cleaning activities while still retaining a central oversight of this activity. A number of our systems have supplemented this model with central monitoring modules, where certain key data – such as SAEs or endpoints – are subject to central (and often independent) review. Modules specific to pharmacy and social science have been developed in similar ways. This facilitates all trial data being co-located in the same database, but with different applications and roles accessing the separate functions by use of database roles.

Monitoring of endpoints

Primary endpoints are fundamental to a trial and to ensure rigorous collection of these data the clinical

and adverse events that contribute to these are generally subjected to 100% monitoring. Ideally this would happen before the event went to the independent Endpoint Review Committee (ERC) for review, although this target may be difficult to meet and so sometimes events and deaths may be monitored following review, and brought back to the ERC if findings deem this necessary.

ARROW began with 100% monitoring of all WHO Stage 4 and Stage 3 HIV events [16], all deaths, SAEs and malaria events. However, when 90% of all DART endpoints had been examined and major and minor findings sent to MRC CTU analysis showed that only 2% of the 90% monitored endpoints required changes that affected the original adjudications. Therefore, it was agreed that sampling could be used for the ARROW WHO 3 monitoring, as the number of events was very high.

Endpoint monitoring was a huge task for both DART and ARROW and there were concerns as to whether endpoints were being missed, so monitoring plans included complete CRF files of a 10% sample of participants in whom endpoints had been reported. It was also agreed to review a sample of complete CRF files of participants for whom there were no endpoints reported. Central database checks were also used to identify missed endpoints. For example, in ARROW, heights and weights could be used to look for missed WHO Stage 4 unexplained severe wasting/malnutrition.

Endpoint monitoring objectives

The objective of endpoint monitoring is to check that the clinical summary/narrative written by the study physician at the clinical site is a complete and accurate account of the events relevant to the endpoint being monitored. All statements in the summary must be adequately documented in the CRFs, and match source documents if applicable. All relevant details in the participant's CRFs should be reported in the summary. In DART, the source document verification did not extend to checking each blood result or test result at source, as this was judged to be too time consuming on a case-by-case basis. In ARROW, the monitor was asked to check all laboratory results relative to the WHO Stage 3 events as they were from a sample and not 100% monitored, as described earlier.

Some of the DART and ARROW local monitors were nurses, which was of great value where understanding of the medical background, diagnoses, clinical notes and relevance of various tests and their results was important. Site and visiting monitors with no clinical training would have access to WHO staging criteria, toxicity tables, laboratory ranges and clinical staff, doctors or nurses, to clarify or explain when necessary.

In MDP301 a clinician from MRC CTU visited each site at least once during the trial to specifically monitor safety events and any unresolved clinical queries.

Endpoint Review Committee

The purpose of the ERC is to adjudicate whether reported clinical episodes are trial endpoints according to the protocol-defined criteria. The committee may also be asked to review other events (e.g., SAEs or hypersensitivity reactions). The ERC consists of an independent chairperson and, as a minimum, one other independent member and a coordinator. The ERC remains blinded to randomizations relating to primary endpoints. ‘Barn Door’ (open and shut cases which can be clearly adjudicated) sessions and full ERC meetings (for less straightforward summaries, when the physician from the site will join by teleconference) are held to adjudicate events. According to the number and complexity of endpoints there may be up to four full ERC meetings per year, three by teleconference and one face-to-face. These meetings and sessions are a form of final monitoring of the clinical events and study endpoints.

Trial close-out monitoring

In addition to ensuring that all trial consents, endpoints and a percentage of complete files of CRFs of individual participants are monitored before close out, there may be specific areas that also require monitoring to ensure the correct transition of patients from study clinics into national programs. This is done through both local monitoring and during close-out visits by MRC CTU. A study-specific close-out MOP and close-out checklists are written, modified from those originally developed for the DART and MDP301 trials, to facilitate the monitoring. The length of time for trial close out is variable and often dependent on the original recruitment rate if all participants must meet a defined length of follow-up. The size of a trial and health of the participants will also impact on close-out time.

In general, before study close out the following tasks need to be monitored for successful completion:

- All forms should have been completed, verified, entered onto the database, filed and stored by the authorized local study personnel;
- Responses to all data queries required for database lock should be received, and entered on the database where appropriate;
- All essential study documents should be up-to-date, filed in an orderly manner and appropriately stored;

- All laboratory specimens should have been labeled and stored and records identifying storage locations of samples must be up-to-date;
- Appropriate arrangements should have been made for assigning local responsibility for stored samples immediately and in the long term;
- All outstanding documents should have been sent to the study team at the local trial center, for example, laboratory reports and other tests;
- All leftover or expired study drugs should have been appropriately disposed of.

Once written confirmation of the above is received by MRC CTU, and any country-specific requirements/guidelines have been met, the site is considered as closed. Database lock can proceed according to unit SOPs. Plans are also put in place for dissemination of the results to the trial participants when they became available.

Archived documents are rarely monitored. However, the process of archiving, the archiving locations/stores, long-term sample management and any destruction of documents are areas that need to be monitored following trial close out.

Future perspective

It is recognized that there is considerable variability in the systems for on-site monitoring of trials, with a paucity of evidence to support practice [17]. MRC CTU is currently running a prospective methodological study investigating the use of a targeted monitoring strategy which may be an efficient way to identify sites that would most benefit from a visit, reducing the site visit burden during a trial. During this study, sites are identified as requiring a visit based on certain triggers (e.g., concerns over protocol or data compliance, or notably high or low adverse event rates compared with other sites) and are matched (in terms of number of patients) with a site that did not meet these triggers and therefore would not routinely be monitored in the trials that are taking part in the study. Both sites are monitored, and findings are graded as critical, major or other. The number of serious findings will be compared across paired sites. If we demonstrate a substantially lower rate of serious findings in the untriggered sites, this would suggest that these triggers are effective at distinguishing between sites with or without serious concerns about trial conduct or data integrity, and also which triggers are likely to be most important.

As database software becomes more sophisticated, it becomes easier to generate and track data queries based

on defined inconsistencies, with the possible danger of too much information being generated to process efficiently. Future work in this area aims to look at prioritizing and targeting this effort – which data are the most important to have correct – and therefore to focus the most intensive monitoring toward these. Ongoing work includes system upgrades that will allow definition and maintenance of these priority levels, coupled with investigations into the effect of variance in different variable types on overall results.

In an ideal setting data would be collected directly using electronic CRFs and without the need for completion of paper forms followed by data entry. This would reduce the monitoring workload as the whole step of data transfer from paper to electronic is removed. However, for resource-limited settings and

remote sites with limited power this ideal is not yet obtainable.

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Executive summary

- Monitoring resource is often underestimated. When designing trials and considering financial planning, adequate resources should be assigned to monitoring (with contingency).
- Central monitoring and on-site visits are mutually beneficial, and should be used in tandem. However, any duplication of these should be avoided in order to maximize resources.
- When the coordinating center is not local to the site, local monitors are invaluable to allow for more regular site visits and to develop a good rapport with the sites which enables better reporting of issues.
- The capacity building provided by local monitors is amplified by their being able to train and mentor staff at study sites.
- Database strategies that provide data monitoring tools accessible by both site staff and central teams are important in enhancing data quality, as well as providing a platform for building data management capacity at sites.

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