Article Type: Original Article

Monitoring clinical trials: A practical guide

Síle Molloy[1*] and Patricia Henley[2*]

1 Institute of Infection and Immunity, St George's University of London, UK
2 London School of Hygiene and Tropical Medicine, UK

*Joint first authors

Summary
This paper describes the processes and procedures involved in planning, conducting and reporting monitoring activities for large clinical trials of investigational medicinal products, focusing on those conducted in resource-limited settings.

Keywords: Clinical trial, monitoring, resource-limited setting, Good Clinical Practice, risk-based monitoring

Introduction

The aim of this paper is to describe the processes and procedures involved in planning, conducting and reporting monitoring activities for large clinical trials of investigational medicinal products, with a focus on those done in resource-limited settings. Although the framework and guidelines underpinning these procedures will be the same regardless of setting, the approaches taken and the needs to be addressed may differ. Thus we aim to ensure that the guidance presented is relevant and applicable to all settings.

The paper is divided into three main sections: *Rationale for monitoring clinical trials*; *Trial oversight and risk assessment procedures*, including considerations for trial design; and *Guidance for on-site monitoring*. The first section provides an overview for all readers, while the second may be most useful for investigators when designing the trial and applying for funding. The third section is aimed at trial managers/monitors travelling to sites for on-site monitoring visits.

This guide is based on International Council for Harmonisation - Good Clinical Practice (ICH GCP 1996). It is intended for use as a reference text but local/international requirements should always be adhered to as procedures and requirements may vary across institutes and countries.

Rationale for Monitoring Clinical Trials

A number of regulations, standards and guidelines create the framework for the conduct of clinical trials globally, all of which hold, at their core, the ethical principles as set out by the Declaration of Helsinki (WMA 2013). Whether conducted in rich or poor settings, all trials must follow this same framework, though the way in which trials are implemented may differ across regions.

Building on the principles of the Declaration of Helsinki, ICH-GCP (1996) is the guideline on which all other references are based and which is considered the gold standard for clinical trials

globally. Monitoring is an integral part of Good Clinical Practice and ensures that a trial is being conducted in compliance with international regulations, standards and guidelines (ICH GCP 1996).

From the perspective of trial investigators, effective monitoring is paramount to the conduct of robust clinical trial research ensuring that:

(a) procedures are consistent and safe for each participant throughout the trial;

b) stringent checks on data collection and procedures provide quality data and credibility to results; and

(c) there is sufficient oversight to help the trial reach its objectives and does not, for example, continue any longer than initially planned due to unforeseen issues which could have been identified during monitoring.

Monitoring is critical for the protection of the rights and well-being of trial participants and for the collection and analysis of high-quality data on which new products/indications and guidelines will be based. Regardless of the trial sites' location, whether in settings with many or few resources, the need for, and importance of, monitoring does not alter.

Trial Oversight and Risk Assessment Procedures

Roles and responsibilities

There are a number of roles and responsibilities that must be considered and delegated when conducting clinical trials. The sponsor is responsible for ensuring that the trial is adequately monitored. Monitoring may be carried out by the sponsor or delegated (ICH GCP 1996). It is recommended that monitoring procedures are detailed in a Monitoring Standard Operating Procedure, so that staff responsibilities are clearly defined (NIHR 2012). Depending on the outcome of the risk assessment, this internal monitoring may be supplemented with an external audit at some point towards the beginning of the trial.

Types of monitoring

There are a number of ways in which a clinical trial can be monitored both off -site (through specifically appointed committees and/or central/statistical monitoring) and on-site. Types of monitoring are unlikely to differ for resource-limited settings, although the level of monitoring may be raised in various areas if the risk is deemed higher.

Trial committees for oversight

A clinical trial may be overseen by a number of committees, depending on the extent and nature of the trial. For example:

The Trial Steering Committee is generally comprised of an independent chair, at least two additional independent members, up to two principal investigators and a trial manager or statistician as appropriate (MRC 1998). The role of the Trial Steering Committee is to provide overall supervision and advice, and the ultimate decision for the continuation of the trial lies with it.

The Data Monitoring Committee /Data Safety Monitoring Board is group of experts usually, but not always, independent of the management of the trial. In a blinded trial, this is the only committee to review unblinded clinical data. Its main duty is to monitor safety of the trial, in particular to review serious adverse events, suspected unexpected serious adverse events and mortality, across the arms of the trial and overall. The Data Monitoring Committee makes recommendations to the Trial Steering Committee, the chief investigator and the sponsor on continuation or early stopping of the trial based on safety or ethical issues.

According to guidelines, trials involving subjects with life-threatening illnesses, vulnerable populations and/or involving significant potential risks require a Data Monitoring Committee /Data Safety Monitoring Board (DAMOCLES study group 2005 and WHO 2005) and the Medical Research Council of the UK recommends that an element of expert advice, independent of the chief or principal investigator should be incorporated into the conduct of a trial (MRC 1998). The terms of reference for each committee can be detailed in a specific charter. The Medical Research Council and WHO have created templates of such charters, which can be used as a reference (DAMOCLES study group 2005 and WHO 2005).

Central monitoring

In addition to trial oversight committees, the trial may be centrally monitored. For example, key data may be identified and reviewed by the central coordinating study team at periods specified in advance. Eligibility criteria may be reviewed monthly (or more frequently at the beginning of the trial); adverse events may be reviewed routinely by members of the Trial Management Group; consent forms may be reviewed centrally to assure the trial team of the timing of consent and that the forms have been completed correctly. Consent forms can only be reviewed centrally if a specific clause has been agreed to in the consent form, stating that the participant is aware that his/her data will be reviewed outside their medical centre and, if applicable, country of origin. The trial team may also review drug accountability logs centrally to ensure that the site has sufficient stock, and dosing and enrolment data.

Information relating to the primary endpoint may be reviewed centrally at specific time points and in cumulative weekly or monthly reports with data pertaining to recruitment rates, withdrawal and losses to follow-up. Safety reports may be submitted to the Data Monitoring Committee /Data Safety Monitoring Board at specified time points, e.g. 6-monthly, and statistical analyses could be used at regular intervals to identify unusual patterns of data, or detect deviations from the protocol.

In resource-limited settings, one factor to consider when monitoring centrally is the reliability of the internet connection for uploading trial data. Depending on the method of data collection, and whether or not data are uploaded to a central database in real time, provision may need to be made for poor internet connections and/or occasional power outages.

Central statistical monitoring

Statistical algorithms can be developed to identify any unusual patterns of data within the trial database, and to review data at participant or site level. This can help determine systemic data errors or the manufacture of falsified data. Examples of central statistical monitoring are:

(a) looking for missing or invalid data: range checks to identify unexpected or abnormal values, e.g. extreme laboratory results or inverted blood pressure measurements.

(b) discovering unusual data patterns: identifying data similarity (inliers), or data extremes (outliers) within or between sites. These checks will highlight whether a site shows preference for certain values or digits, how they have rounded up or down values, or unusual frequency distributions (mean, variance, skewness).

(c) Pharmacovigilance: signal surveillance of the adverse event data should also be reviewed to determine quickly whether there is an increase in frequency or type of particular events.

For trials where regular on-site visits are not possible, e.g. where sites are scattered across the globe, the use of statistical monitoring can help pinpoint areas on which to focus on-site monitoring activities (Buyse et al 1999, Venet et al 2012; Kirkwood & Hackshaw 2011).

Minimizing errors from the beginning can also help to reduce the amount of on-site monitoring visits required. Errors can be minimized by careful and detailed training for data collectors and through real-time centralized monitoring as described above. Regular training updates may also be useful.

On-site monitoring

On-site monitoring may consist of periodic site visits by a designated monitor (often the Trial Manager for noncommercial trials, or contracted independent monitors depending on the type of trial. Contracting local monitors may also be beneficial, as they will have relevant expertise in the local language, culture and practices). Early-phase trials, e.g. first in human studies, which carry an inherently higher risk, will usually take a 100% approach, ensuring that every data point is accurate and verifiable against source data. For later-phase trials, or trials which incur less risk, a selection of key data may be verified at site, for a certain percentage of participants. The visits can generally be divided into an initiation visit (prior to site opening and recruitment of the first patient), interim visits and a final close-out visit. Each visit is followed by production of a report.

Risk-adapted monitoring

Over the past decade there has been a significant rise in the number and complexity of clinical trials worldwide and, with this increase, a shift from traditional on-site monitoring to a more risk-adapted approach. According to ICH-GCP '*the extent and nature of clinical trial monitoring should be determined by aspects of the trial including objective, purpose, design, complexity, blinding, size and endpoints*'. Risk-adapted approaches allow for a more targeted, flexible and less costly approach. The European Medicines Agency and the Food and Drug Administration recently published papers on the merits of risk-based monitoring (EMA 2010, FDA 2013b), describing a more systematic approach that prioritizes monitoring procedures based on level of risk, setting priorities based on these risks and identifying risk mitigation measures, thus reducing the cost and time associated with monitoring while ensuring patient safety and high-quality data collection.

Risk assessment

The type of monitoring considered for a trial (i.e. level of oversight, on-site, central and/or statistical monitoring) should be proportionate to the level of risk of the study. The chief investigator/trial manager, or designate, should review the risks to the participant and sponsor, and to the study itself (e.g. in terms of data integrity), before submitting grant applications in order to fully reflect the needs of the trial. If the trial is high-risk, more frequent site visits may need to be considered, while low-risk trials may require only remote or central monitoring. Table 1 identifies the specific areas that should be considered in a risk assessment and in determining the extent and nature of monitoring required for a clinical trial (Box 1 for general examples).

Guidance for on-site monitoring

Monitoring plans

On completion of the risk assessment a monitoring plan should be devised. The monitoring plan is a living document that will be adapted as required over the course of the trial. The monitoring plan encompasses all the elements that relate to monitoring, comprising:

- On-site and central monitoring activities;
- Data monitoring and other oversight committees;
- Supply and vendor oversight.

Monitoring activities may change over the course of the study. For example, at the beginning frequent monitoring should take place until the site and study management team are satisfied with progress. At this point visits may happen less often, or move to solely central and statistical-based monitoring methods. Monitoring may also become more frequent if issues are identified at any stage. Rules for raising or lowering the rate of monitoring, or a change in the type of monitoring, should be included in the monitoring plan. If independent monitors are contracted to undertake this role in the trial, the agreement must contain some degree of flexibility so that the principal investigator may amend the monitoring plan during the trial; this may be done through payment of monitoring days with the proviso that these may increase or decrease during the trial.

Monitoring process

The following section identifies the key areas of trial conduct that should be monitored during a site visit and identifies issues that may arise specifically in resource-poor settings.

Source Documents / Data Quality Verification

One of the key activities performed during an on-site monitoring visit is source data verification. This entails checking data from the database or case report form against data collected in source documents such as medical records, laboratory results, radiology films etc. The aim of source data verification is to ensure data accuracy and protecting the integrity of the final trial results. The monitor should query any discrepancies with the local site team and arrange for corrections of the database, as necessary.

Specific problems can arise during conducting source data verification in resource-poor settings. Source documents (e.g. medical records) may not be available after patient discharge, or sufficient detail may not be captured in the records. In many countries patients purchase the medical record booklet and take it home with them at discharge. Full electronic patient management systems may not exist in such settings.

The trial team should determine the site's capacity to retain source documents for monitoring before site initiation. If source documents are unavailable, or problems with retaining the data at a site are foreseeable, the trial team can create a *pro forma* source document including all case report form questions, in addition to other data required by the medical team to ensure adequate care of the participant (this information should also be accessible to any clinical staff not involved in the trial who is caring for the patient). All data to be included in the case report form should then be transcribed from this source document. Where patients take home their medical records, it may be possible to photocopy or scan the records prior to discharge and to store them as a source document. The scanned copy of the record can be certified as a true copy of the rec-

ord i.e. the scan and original copy should be reviewed for conformity and include a note to state that this is a true copy (EMA 2010, FDA 2003, FDA 2013a).

If source documents are adequately and appropriately maintained by the site staff, it is important that the medical record and other associated source documents are not shredded prematurely. They must be available for the lifetime of the trial, and archived for a minimum of 5 years after its end (ICH GCP 1996). It is helpful to use stickers on the outside of the medical records (with permission from hospital administration) to flag to administrators the need for archiving. Further areas for consideration when conducting SDV are detailed in Table 2.

Informed Consent

Monitoring informed consent is a fundamental part of the conduct of a clinical trial and ensures that the rights of participants are respected. Monitoring of consent forms can be completed centrally or on-site. If consent forms are monitored centrally, permission to transfer identifiable information to the trial team (possibly based outside the country) must first be obtained from the participant during the consenting process, with the inclusion of an appropriate clause in the consent form. Monitoring of consent forms, however, is typically conducted as an on-site activity (Table 3).

Pharmacy Monitoring

Particular attention should be paid to the pharmacy during on-site monitoring visits. It is crucial to ensure that the investigational medicinal product is stored securely, under the correct conditions for each specific product, with appropriate accountability logs in place (Table 4).

Laboratory Monitoring

There are a number of areas in the laboratory that should be checked during the monitoring visit. Points to consider are listed in Table 5.

Adverse Events

Monitoring adverse events is crucial for all trials as the safety of participants is of paramount importance. Adverse events can be monitored centrally by means of signal surveillance, allowing the team to react quickly to any increase in the frequency of any side effects. Monitoring can also take place at site during review of the source documents to ensure that all adverse events are reported to the trial team and ethics and regulatory authorities as required, and within the timeframes specified in the trial Standard Operating Procedure (Table 6).

Other Documents

Table 7 details a number of additional trial documents that should also be reviewed during the monitoring visit.

Monitoring reports, corrective action, preventive action

After the monitoring visit, the monitor should provide the site with a monitoring report that should be filed in the trial master file/investigator site file. The report will provide a review of activities, progress, difficulties and issues of concern.

Sponsor have their own templates for the monitoring report, but these are typically in a tick-box format to simplify the reporting as monitors may have several sites to review in a short time.

There will be space for comments, but these should always be a presentation of facts, without opinion.

The site should then develop a Corrective and Preventive Action plan to correct any issues identified. The site should undertake a root cause analysis to determine why something might have gone wrong, and to prevent the issue from recurring. The monitor will check the Corrective and Preventive Action plan for completeness and will follow up as required.

Conclusion

The value of effective monitoring for clinical trials should not be underestimated, and it should be incorporated at the very early stages of trial design. Conducting clinical trials in resource-poor settings can be challenging, but careful planning and effective, well conducted monitoring can assist in ensuring reliable and accurate scientific results while adhering to local and international guidelines and maintaining patient safety throughout.

References

Buyse M, George, SL, Evans S, Geller NL, Ranstam J, Scherrer B, Lesaffre E, Murray G, Edler L, Hutton J, Colton T, Lachenbruch P, Verma BL (1999) The role of biostatistics in the prevention, detection and treatment of fraud in clinical trials. Statistics in Medicine Volume 18, Issue 24. 30 December 1999; Pages 3435–3451

DAMOCLES study group (2005) A proposed charter for clinical trial data monitoring committees: helping them to do their job well. The Lancet 2005; 365:711-722

European Medicines Agency (EMA) (2010) Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/08/WC500095754.pdf

Food and Drug Administration (FDA) (2003) Guidance for Industry Part 11, Electronic Records; Electronic Signatures — Scope and Application, available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125125.pdf

Food and Drug Administration (FDA) (2013a) Guidance for industry – electronic source data for clinical investigations, available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf

Food and Drug Administration (FDA) (2013b) Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring, available at: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf

International Council for HarmonisationGood Clinical Practice (ICH GCP) (1996), available at: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html Relevant sections on monitoring are 5.18, 5.20.2, 5.1.2, 5.6.3, 5.15.2,5.15.1, 6.10, 4.1.4, 6.3.3

Kirkwood A & Hackshaw A (2011) Central statistical monitoring in clinical trials. Trials. 2011; 12(Suppl 1): A55.

Medical Research Council (MRC) (1998) Guidelines for GCP, available at: https://www.mrc.ac.uk/documents/pdf/good-clinical-practice-in-clinical-trials/

National Institute for Health Research (NIHR) Clinical Trials Toolkit (2012) Trial management and monitoring, available at: http://www.ct-toolkit.ac.uk/routemap/trial-management-and-monitoring

Venet D, Doffagne E, Burzykowski T, Beckers F, Tellier Y, Genevois-Marlin E, Becker U, Bee V, Wilson V, Legrand C, Buyse M(2012) A statistical approach to central monitoring of data quality in clinical trials. Clinical Trials. 2012 Dec;9(6):705-13

World Medical Association (WMA) (2013) Declaration of Helsinki, available at: http://www.wma.net/en/30publications/10policies/b3/

World Health Organisation (WHO) (2005) Guide on the establishment and functioning of DSMBs, available at: http://whqlibdoc.who.int/hq/2005/TDR_GEN_Guidelines_05.1_eng.pdf

Corresponding author: Síle Molloy, Institute of Infection and Immunity, St George's University of London, Cranmer Terrace, London SW17 0RE, UK. Email smolloy@sgul.ac.uk

Table 1: Areas to consider when conducting a risk assessment to determine the extent and nature of monitoring required for a clinical trial

Disease Area	Short-acting illnesses e.g. pneumonia / flu	▪ Short-acting illnesses will often have a shorter course of treatment, thus requiring a more intensive period of monitoring to capture the short treatment times.
	Long-lasting illnesses e.g. HIV	▪ For trials with longer treatment periods, monitoring may be less frequent and less intense as there is more time to capture the information required and correct any errors.
Design	Complex versus simple	▪ A complex design such as a double-blind randomised, placebo-controlled may require more intense monitoring due to the potential for more errors to occur.
	Randomisation and stratification	▪ Complex randomisation systems have an increased risk of potential errors occurring and thus may require increased monitoring and verification to ensure procedures are conducted correctly.
Sites	Number and location	▪ Increasing the number of sites will increase the complexity of the trial. ▪ Both very fast and very slow recruitment may require more monitoring visits. For recruitment that is faster than expected errors may be more likely to occur if the trial team have a heavier workload. Conversely, if recruitment is slower than expected, monitoring may be required to encourage the team and identify issues that may be contributing to slow recruitment rates.
	Experience	▪ The education, training and experience of the investigator team also play a role in determining monitoring requirements. If the teams lack experience, more intense monitoring may be required.
	Resources	▪ The resources and facilities available at the site may also determine the level of monitoring required as there may be few resources and little space accessible to staff at the site and this could hinder the efficient conduct of the trial.
Study population	Vulnerable groups	Monitoring may need to be intensified where: ▪ Vulnerable groups are enrolled, e.g. children or pregnant women, and the risk of adverse effects may be higher. ▪ Healthy volunteers are enrolled with a risk of a healthy individual becoming unwell. ▪ Capacity to consent is impaired, i.e. participants are unconscious or suffering a traumatic brain injury.

		▪ Participants are illiterate. Additional safeguards may be needed to ensure participant rights are respected.
Investigational Medicinal Product (IMP):	Licensed	▪ If side effects are not well known, AE reporting and review may need to be intensified. ▪ Alternatively, if side effects are well-known, but the drug will be used in a new population, more frequent reporting may be warranted.
	Unlicensed	▪ Is a new drug is used, or an old drug is used outside its marketing authorisation, more intense monitoring may be required. For first in man studies, monitoring is conducted in close to real time. When a participant is dosed and data are collected, the monitor may check these data against the source document. ▪ Data that will be used in licensing applications will normally require a larger number of on-site visits.
	Type of IMP	▪ Need to consider whether the IMP requires refrigeration and cold chain transport. The method for maintaining cold chain and IMP integrity need to be monitored closely. ▪ If placebo is administered details of manufacture will need to be documented and procedures for identifying the product, if the study is blinded, put in place.
Data Management systems	Electronic	▪ Increasingly trials are using electronic data management systems to collect, collate and analyse data. Databases are likely to differ in terms of their testing and validation procedures and this will influence the level of monitoring required. ▪ Electronic database systems usually require a good internet connection. This may raise issues where the internet connectivity is poor, delaying the submission of data and possibly reporting of AEs, rendering the process high-risk with more monitoring requirements.
	Paper Case Report Forms	▪ Important to check how data will be entered into the database (e.g. with double data entry or other checks in place). Procedures for transferring data must be documented and may have an impact on the level of associated risk and thus the level of monitoring required.

	Confidentiality	▪ There is increasing awareness of breaches in confidentiality, which might take place with the transfer of identifiable data across boundaries. The risk associated with confidentiality should be assessed and the level of monitoring detailed accordingly.
Oversight mechanisms	TSC, DMC/DSMB, Trial Management Group	▪ These committees provide an additional means of monitoring the trial data and may help to reduce some risks associated with trial conduct.

Table 2. Areas to consider when undertaking SDV

What is the source document?	▪ Determine this prior to site initiation ▪ Create source files if required ▪ Take certified copies of any records that go home with the patient
Variability of access to source	▪ Conduct risk assessment as part of site initiation to determine associated risks
Variability of quality of source document	▪ Ensure site understands the importance of source documents ▪ Help site to annotate medical records appropriately and create study proforma notes, if required
Discrepancies and query resolution	▪ Monitoring plan (or Data Management Standard Operating Procedures) to detail how queries will be resolved, including changes to the database ▪ Site principal investigator to sign off all changes to case report forms after the monitoring visit (if specified in the Data Management Operating Procedures). ▪ Data to be entered into database in a timely fashion to permit interim analyses on maximum number of data points.

Table 3. Areas to consider when monitoring informed consent

The participant information sheet and consent form	▪ Ensure the current ethically approved version is in use. ▪ Ensure translation and back-translation has been performed, with appropriate documentation. ▪ Specific consent should be obtained for genetic analyses and retention of samples. ▪ The documents should be written in line with cultural beliefs of the community (local ethics committees will help ensure the consenting documents are appropriate).
Provision of consent	▪ The monitor should check if only the individual themselves can provide consent for inclusion in the study or if the protocol allows others to also provide consent on the individual's behalf – e.g. head of household, community leader, guardian etc. ▪ Emergency trial – use of legal representatives to provide consent. ▪ Community assent, e.g. as part of the sensitization process in approaching a community to take part in the trial. ▪ Ensure age of consent is documented and checked and that guardians/parents have counter-signed as required.
Impartial witness	If impartial witnesses are involved (e.g. for illiterate patients): ▪ Ensure the impartial witness is not on the trial delegation log. ▪ Ensure the participant thumbprints the consent form, and witness signs attesting that the participant is happy to take part in the study.
Completion of the consent form	▪ Check all elements of the consent form o Participant study number added to form o Appropriate person has signed o Appropriate person has taken consent (trained and included on delegation log) o Dated on same day as enrolled o Most up-to-date version in use ▪ Ensure that consent forms are filed for all participants. ▪ Ensure that participants are eligible. ▪ Ensure that the participant had capacity to consent, e.g. if abnormal mental status reported, was the participant capable of understanding the information provided? This is particularly important in emergency trials.
Data protection	▪ Ensure that there is a clause in the consent form for allowing monitors to review identifiable data, e.g. source documents. ▪ If identifiable data will be transferred outside the country, this must be included on the PIS and consent form.
Waivers of consent	▪ Usually only in emergency trials. ▪ Must be agreed by the relevant ethics committees. ▪ Consent from participant to be obtained as soon as possible once they recover capacity.

Table 4. Areas to consider when monitoring the pharmacy

Pharmacy	Points to consider
Documentation/ Delegation log	▪ Ensure a pharmacy file is in place with all relevant SOPs and logs relating to the IMP. Pharmacy personnel working on the trial must be included on the delegation log and have evidence of appropriate training on GCP and trial-specific procedures relating to the pharmacy.
Protocol compliance/SOPs/ Local regulations	▪ Ensure that pharmacy procedures comply with the trial protocol, pharmacy specific standard operating procedures and local regulations. ▪ Many regulatory authorities (though not all) will have guidelines for local requirements for conducting clinical trials and these should be strictly adhered to. ▪ Compliance with Pharmacy Investigator Brochure should be checked and Summary of Product Characteristics and the Certificate of Analyses examined.
Investigational medicinal product Storage	▪ Temperature monitoring logs should be complete and within range where required for specific investigational medicinal products. ▪ Access to the investigational medicinal product should be secure and back-up facilities available in case of issues with electricity supply. ▪ Procedures for dealing with such issues should be documented and understood by the pharmacist.
Labeling	▪ Investigational medicinal products should be appropriately labelled in the pharmacy and on dispensing to the study team/patient.
Expiry dates	▪ All expiry dates should be in range and noted on the accountability logs.
Randomisation	▪ Procedures for randomization should be clear and prescriptions/dispensing conducted according to the correct randomization assignment.
Accountability	▪ Accountability logs should be in place for receiving shipments and dispensing investigational medicinal products and should balance with a physical stock check.
Breaking blind	▪ Understanding should be checked and procedures clearly described in standard operating procedures.
Shipment	▪ Chain of custody and information on temperature stability during shipment (if required) should be documented.

Table 5 Areas to consider when monitoring the laboratory

Laboratory	Points to consider
Documentation	▪ Protocol and laboratory specific standard operating procedures for sample collection, analysis, storage, shipment and disposal should be reviewed. ▪ Lab personnel working on the trial must be included on the delegation log and have evidence of appropriate training on Good Clinical Practice and trial-specific procedures relating to laboratory procedures.
Agreements and contracts	▪ Material Transfer Agreements should be in place if samples are to be shipped outside the country for analysis.
Logistics	▪ Traceability of tissue samples: the monitor should follow the journey of a sample from the documentation, from clinic to lab to dissemination of results, storage and shipment, if applicable. ▪ Details relating to sample tracking, processes for dealing with issues and identification of any samples that should not to be stored (e.g. if consent not given) should all be documented and checked. ▪ Procedure for reporting / logging results(e.g. LIMS system used in some countries) should also be checked to ensure that critical values and adverse events are fed back to the clinical team as soon as possible
Facilities/ Equipment/supply	▪ Check the Quality Control process for machines (e.g. incubators, hoods etc), ensure back-up generators are in place for sample storage (or process for electricity losses in place) and that adequate supply of reagents, kits, storage tubes etc are in place. ▪ Review references ranges and lab accreditation certificates.
Sample storage	▪ Check temperature of freezers (e.g. -80 ^{o}C freezers) and duration of storage. Identify any freeze-thaw problems and how this is handled, if appropriate. ▪ Labels on samples should be reviewed to ensure that there are no patient identifiers, that they comply with standard operating procedure requirements, and that there is no label deterioration.

Table 6. Areas to consider when monitoring adverse events

Reporting to the chief investigatorand the coordinating centre/trial team	▪ Ensure protocol contains detailed adverse event reporting requirements, particularly serious adverse events and suspected unexpected serious adverse events. A separate standard oprating procedure for adverse events monitoring and reporting may be in place and this should also be checked.
Difference in concomitant medication terminology	▪ Monitor should have local knowledge of terminology used if different to the protocol.
Adverse events in source documentation	▪ Ensure that the adverse event is adequately described in the on-site medical notes, as well as in the CRF. ▪ Check the medical record also for any adverse event that had not been submitted to the trial team.
Reporting to ethics and regulatory authorities	▪ Many regulatory authorities, ethics committees and sponsors have differing timelines for reporting. All timelines for reporting should be detailed in a Standard Operating Procedure (SOP). ▪ Review reporting timelines during monitoring visit.

Table 7. Areas to consider for monitoring remaining trial documents

Training log	▪ Ensures that all site staff have the appropriate training, education and experience to undertake their roles in the study ▪ To be used in conjunction with delegation logs
Delegation logs	▪ Ensure that staff who undertake specific roles have been delegated these correctly and details are included on the log, e.g. for staff taking consent they must have been trained accordingly and delegated the task as detailed on the log.
Screening logs	▪ Helps to determine issues surrounding enrolment; e.g. can demonstrate where small changes to the eligibility criteria, which will not affect the overall trial, may increase recruitment.
Randomisation log	▪ Can be compared against drug accountability logs to ensure that the appropriate investigational medicinal product (randomisation arm) is given to the correct participant.
Ethics and regulatory	▪ Ensure that all appropriate approvals are in place. ▪ Ensure that any conditions applicable to the trial have been met. ▪ Ensure that all amendments have been submitted to all parties.
Contracts and agreements	▪ Check conditions and instructions noted in contracts. ▪ Check compliance with terms and conditions, particularly restrictions with Material Transfer Agreements and Data Transfer Agreements.

Box 1

A phase III placebo-controlled trial of a licensed drug, but used outside of its standard indication, at a dose higher than what would normally be given.

Although the drug is licensed, and there should be good data on expected adverse events, in this instance the drug is being used outside its licensed indication and at a higher dose. Therefore, there might be a higher frequency of adverse events, or the adverse events may be more severe. It would be advisable to undertake adaptive monitoring in this situation, with more frequent on-site monitoring at the beginning of the trial. When the rate and severity of events are known, monitoring intensity can slowly decrease.

A phase II dose-escalation trial of a new unlicensed drug to be used for the treatment of pneumonia

Earlier-phase trials tend to be higher-risk and will thus require close monitoring throughout the trial. Dose-escalation trials, in particular, need to be monitored in real-time (i.e. as participants are registered and receive their dose, the monitor should be reviewing their data) as it is crucial that the data are verified as accurate before moving to the next dosing level.

A phase III RCT comparing efficacy of two statins, both used within their licensed indication. The trials team use central statistical monitoring.

Here the risk profile of the investigational product is known, and the side effects are minimal. In addition, the trial management team is monitoring data in real time. In this instance, regular on-site monitoring would not be required unless the statistical monitoring highlights an issue at a site, triggering a monitoring visit. This may include: missing outcome data, increased frequency of adverse events, or increased adverse event severity.