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UKCRC Registered CTU Network – Monitoring of clinical trials: a handbook



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Monitoring of clinical trials: A UKCRC Registered CTU Network Handbook

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1. Abbreviations

AE – Adverse Event

AESI – Adverse Event of Special Interest

CI – Chief Investigator

CRA – Clinical Research Associate

CRF – Case Report Form

CRO- Clinical Research Organisation

CTU – Clinical Trials Unit

eCRF – Electronic Case Report Form

CTIMP – Clinical Trial of an Investigational Medicinal Product

CTM/CTPM – Clinical Trial Manager/Clinical Trial Project Manager

DH – Department of Health

DM – Data Management

DLT – Dose Limiting Toxicity

EPR – Electronic Patient Record

FPFV – First participant first visit

GCP – Good Clinical Practice

IB – Investigator Brochure

ICF – Informed Consent Form

ICH – International Conference on Harmonisation

IDMC – Independent Data Monitoring Committee

IMP – Investigational Medicinal Product

ISF – Investigator Site File

LPLV – Last participant last visit

MHRA – Medicines and Healthcare products Regulatory Agency

MRC – Medical Research Council

MV – Monitoring Visit

MVR – Monitoring Visit Report

nIMP/AMP – Non-investigational medicinal product/Auxiliary Medicinal Product

PI – Principal Investigator

PII – Participant Identifiable Information

PSF – Pharmacy Site File

QC – Quality Control

RSI – Reference Safety Information
SAE – Serious Adverse Event
SAR – Serious Adverse Reaction
SDR – Source Data Review
SDV – Source Data Verification
SIV – Site Initiation Visit
SoC – Standard of Care
SOP – Standard Operating Procedure
SPC – Summary of Product Characteristics
SUSAR – Suspected Unexpected Serious Adverse Reaction
TMF – Trial Master File
TMG - Trial Management Group

2. Introduction

This monitoring handbook is aimed at academic trialists undertaking monitoring activities such as on-site, remote and central monitoring. It is intended as a resource to be used to support initial training and as a point of reference thereafter. The handbook provides general information about monitoring, which should be supported by training on CTU/Sponsor specific SOPs, guidance documents and templates. This handbook provides information on the theory of monitoring, tips on conduct and real life examples that may help to explain and support possible monitoring approaches and their application.

The handbook is intended to describe the monitoring approaches applied to clinical trials of investigational medicinal products and references are included to support this. All CTIMPs must adhere to The Medicines for Human Use (Clinical Trial) Regulations – including Good Clinical Practice (GCP) as stated in SI 2004/1031 [1]. The principles of ICH GCP are expected to be followed, but for any trials where data will be used to support a marketing authorisation, then ICH GCP [2] must be followed.

This handbook can be used to support the monitoring activities of non-CTIMP research studies in which case, other appropriate standards can be applied. Specific sections of the document describe considerations for monitoring specific types of trials including non-CTIMPs and early phase CTIMP trials.

3. Definitions

Monitoring can be defined as those activities which provide oversight during the conduct of a trial to give reassurance that the study protocol and procedures are being followed, that the legal and governance requirements are being complied with and that the critical (key efficacy and safety) data collected are reliable.

The type and extent of monitoring required in a trial is informed by the trial-specific risks. A Risk Assessment is the process by which the potential hazards associated with a trial are identified and the likelihood of those hazards occurring and resulting in harm are assessed. The risks assessed will include the risks to participant safety in relation to the IMP or study interventions and other risks associated with the design and conduct of the study including the rights and well-being of patients and the reliability of results.

Three types of monitoring activity are described in this handbook and can be defined as follows:

On-site monitoring – This is the monitoring performed at research sites at which the clinical trial is being conducted, via a physical visit by appropriately trained individuals from the Sponsor and/or its delegated representatives. It requires access to medical records and other source documents of trial participants for the purposes of protecting the rights, safety and well-being of patients, Source Data Verification (SDV)/Source Data Review (SDR), to confirm the accuracy of data transcription, compliance with the protocol, GCP and applicable regulatory requirements and verification of the existence of participants.

Remote monitoring – This is the remote evaluation performed by appropriately trained individuals from the Sponsor and/or its representatives, at a location remote from the investigator research site and which replicate some on-site activities. It may include documentation being sent to the central office (with appropriate encryption and consent for any document including patient identifiers) to enable a number of checks to be performed. Remote monitoring can also be conducted by review of site self-completed monitoring

checklists, telephone/video monitoring calls with screen sharing or those performing monitoring activities having direct access to trial participants' electronic medical records and electronic site master files.

Central monitoring – This is the monitoring performed in a location away from the investigator research site and often at a CTU/Sponsor office. It involves an evaluation of accumulating data (or lack thereof), performed in a timely manner, supported by appropriately qualified and trained persons (e.g. data managers, statisticians, trial managers, data scientists). The aim of central monitoring is to mitigate specific risks defined in the trial Risk Assessment completed before recruitment commences and updated with the assessment of any new risks added as the trial progresses. Sponsor-held data sources are examined to identify trends, outliers, anomalies, protocol deviations and inconsistencies. Concerns from members of the CTU trial team/Sponsor discovered during contact with the site are also taken into consideration. Centralised monitoring may be the only monitoring activity undertaken, or it may lead to additional monitoring including on-site or remote visits. Centralised monitoring can complement and reduce the extent and/or frequency of on-site and/or remote monitoring and help distinguish between reliable data and potentially unreliable data. It is dependent on having the appropriate sources of information available in sufficient quantities such that informed decisions or outputs can be derived. Centralised monitoring does not require trial site staff input but may lead to requesting follow-up information from a trial site, hosting of an on-site/remote visit or additional queries.

4. Role of monitoring in clinical trials

The MHRA's Good Clinical Practice Guide (Grey Guide) [3] has a useful definition of the role of monitoring in that "Monitoring is one of the key mechanisms whereby the Sponsor can be assured that it is in compliance with the legislation and the trial protocol/procedures. Effective monitoring may also provide useful feedback to the Sponsor for continuous process improvement."

Breaking this down, monitoring of trial data is conducted in order to:

- Ensure the safety, rights and well-being of clinical trial participants are protected.
- Ensure trial data is accurate, complete and verifiable from source documents.
- Ensure the conduct of the trial is in compliance with the currently approved protocol, GCP and any applicable regulatory requirements.
- Investigators are appropriately selected, trained and supported to complete the proposed clinical trial.

The level of monitoring is dependent upon the risk and nature of the trial and can vary throughout the duration of the trial. More detail on the level of the monitoring required is detailed in Section 5.

5. Risk based approach to monitoring

5.1. Risk Assessment and Monitoring Plan

As defined in the MRC/DH/MHRA Joint project on risk-adapted approaches to clinical trials [4], risk in clinical trials is defined as the likelihood of a potential hazard occurring and resulting in harm to the participant or organisation or the reliability of the results.

In clinical trials, a risk assessment should be undertaken by or on behalf of the Sponsor and documented as early as possible in protocol development to identify the potential risks to participants, the organisation and the reliability of results. The risks should be assessed for

the likelihood of occurrence and if applicable, the data used to monitor those risks throughout the trial should be identified. The Risk Assessment will usually result in an overall assessment of risk for the trial of low, medium or high. In line with the MRC/DH/MHRA Joint project on risk-adapted approaches, a CTIMP trial may be categorised as Type A (No higher than the risk of standard medical care), Type B (Somewhat higher than the risk of standard medical care) or Type C (Markedly higher than the risk of standard medical care) [4].

A plan to mitigate and manage the individual risks identified should be developed and documented. The protocol and other relevant trial documentation (e.g. Monitoring Plan, Data Management Plan, Laboratory Manual) should then incorporate the relevant risk management strategies identified in the risk assessment.

The Monitoring Plan should describe the monitoring strategy based on the trial Risk Assessment, the responsibilities of parties involved, the methods to be used and the rationale for their use. The outcome of the risk assessment (e.g. low, medium or high or type A, B or C) will help inform the type, frequency and level of monitoring required and the critical data subject to monitoring activities. For example, if triggered monitoring is chosen, once critical data has been identified, the 'metrics' used to quantify risk and the 'triggers' that form the threshold beyond which a concern is raised can be defined, often in the Monitoring Plan. Further detail on this triggered monitoring approach and the types of data that could be considered critical are included in the central monitoring sections of this document.

The likelihood of a risk occurring can evolve and is often informed once a trial is underway. Therefore, it is essential that the Risk Assessment and Monitoring Plan are reviewed periodically and revised accordingly to ensure risk management measures and the monitoring strategy remain effective. Consideration should also be given to the impact of any substantial amendments, new information that becomes available during the course of the trial, new regulatory or legislative requirements or any unanticipated risks that emerge. This may increase or decrease the risk profile of the trial and inform the intensity, frequency and type of monitoring accordingly.

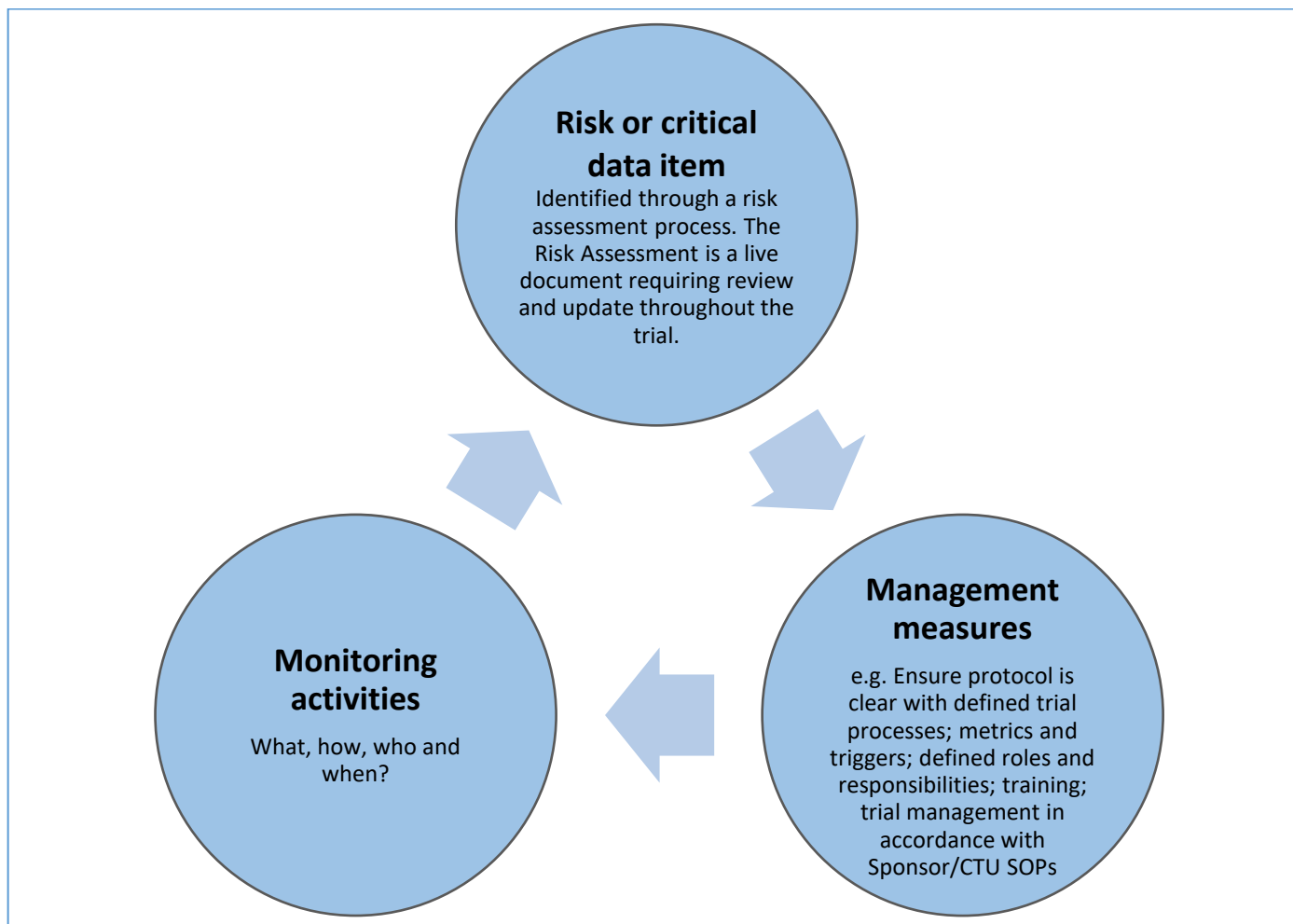


Figure 1. The Risk Assessment is a live document that requires review throughout the life of a trial

It is the Sponsor's responsibility to ensure that a risk assessment has been undertaken but initial completion and review through the course of the trial may be delegated to a CTU, CRO or CI depending on the nature, complexity and organisation of the trial.

Most organisations will have their own Sponsor/CTU SOPs or local policies specific to their organisation and trial portfolio which should be referred to when undertaking a Risk Assessment and developing a Monitoring Plan. Considerations for a trial Risk Assessment should include all aspects of the trial from trial design to reporting and archiving. It is important to involve a multidisciplinary team (e.g. clinical, statistical, operational, translational, pharmacy) in the assessment process to ensure all areas of the trial are risk assessed by individuals with relevant expertise in that area. It is important that all stakeholders are made aware of the risk assessment process and final document and any updates made to it over the course of the trial are disseminated appropriately.

5.2. Deciding the level, frequency and type of monitoring

5.2.1 Level and frequency of monitoring

Monitoring is not a standardised activity that must be implemented in an identical way in all trials. The level, frequency and type of monitoring required for each trial will vary according to the nature of the trial and should be proportionate to the risks highlighted in the Risk Assessment. The level of monitoring required will be based upon considerations such as the objective, purpose, nature of the intervention, participant safety in relation to the IMP,

design, complexity, blinding, size and endpoints of the trial. It is not necessary to monitor everything in detail but instead more intensive forms of monitoring should be focused on the areas of greatest risk to ensure participant safety and the critical data informing the integrity of trial results. More intense monitoring does not necessarily need to be in the form of an on-site visit but could be through increased central or remote monitoring activities. Justification for the type and frequency of monitoring should be documented within the Monitoring Plan.

Table 1 below is based on information from the MHRA Good Clinical Practice guide (Grey Guide) [3] and provides some examples of where high and low intensity monitoring may be appropriate.

Table 1: Examples of instances requiring high and low intensity monitoring

Trial activity	Example(s) where high intensity monitoring may be required	Example(s) where low intensity monitoring may be required
Sample processing/handling	<ul style="list-style-type: none"> • Sensitivity of sample analysis is dependent on how the sample is taken. • Analysis linked to primary objective of trial. 	Collection, storage and transfer of samples has little or no impact on reliability of results from analysis.
IMP storage	<ul style="list-style-type: none"> • Storage of IMP is critical to endpoints of trial. • IMP requires refrigeration within specific temperature range. • IMP requires refrigerated/frozen transport. • IMP has short expiry date. 	Licenced product from general stock, stored at ambient temperatures.
IMP administration	<ul style="list-style-type: none"> • Unlicensed IMP/advanced therapy that poses higher risk to participant safety. • Compliance of delivery is critical to endpoints of the trial. 	Licenced product being used within licensed indication.
Equipment	Equipment used to make endpoint assessments or to calculate doses/ dose adjustments are suitable for use and being used correctly e.g. spirometers or equipment supplied specifically for the trial.	No equipment used or equipment used as per site's standard procedures or will not affect credibility of results.
Data and Source Data Verification	Large proportion of critical data relates to safety, endpoint assessments and/or eligibility criteria. <i>(critical in early phase trials, pivotal trials or where publications could result in a major change in standard clinical practice, 100% SDV of critical data may be required)</i>	<ul style="list-style-type: none"> • Not all data considered to be critical although important to still be accurate. • Minor discrepancies will not affect the safety profile of the IMP or statistical power of the analysis <i>(consider whether SDV is required or the % SDV of some data points, rather than 100% of all)</i>. • Adequate training and control measures in place at site to ensure reliable data collection. • Equipment collecting data transferred to Sponsor directly so no SDV required.

Trial activity	Example(s) where high intensity monitoring may be required	Example(s) where low intensity monitoring may be required
Investigator site experience	Inexperienced site staff/new to research/frequent staff turnover.	Experienced site staff.

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In line with a risk-based approach to monitoring, statistically controlled sampling may be used as a method for selecting data to be verified. The sampling method and metrics used to determine this should be detailed in the Monitoring Plan and should be proportionate to the level and impact of risk identified. Monitoring a sample of sites or participants can be beneficial at the start of a trial when the impact of certain risks are unknown and can influence the monitoring strategy to either increase or decrease the intensity or frequency of the monitoring activities (regardless of the type) depending on the findings. This could be an increase or decrease in the percentage of sites monitored or frequency of central monitoring, the number of scheduled visits (if any) at a site, the number of participants monitored at a particular site or the volume of data checks completed for each participant. This flexible and adaptive approach to monitoring allows resources to be focused on sites/areas that identify as high risk, improving the effectiveness and efficiency of monitoring.

Frequency and timeliness of monitoring activities largely depend on trial design and can be determined by critical timepoints or milestones during the recruitment, intervention, follow-up or close out of a trial. These timepoints or milestones should be prospectively agreed when developing the Monitoring Plan so the person(s) responsible for the monitoring of these items can ensure the tasks are achievable and can be performed in a timely manner, particularly where they relate to participant safety e.g. eligibility checks, IMP dose escalations or interim safety analyses. Completion of such monitoring activities may rely on the timeliness of sites completing and returning (e)CRF data so it is important these timelines are also highlighted to the site during site initiation visits or any trial specific training.

For trials with higher risk elements that require routine on-site/remote monitoring, these visits usually commence once the first participant has been recruited or randomised. In some early phase trials, the Sponsor may request that on-site/remote monitoring visits be completed for each participant recruited. Where the level of immediate safety risk is lower, but on-site/remote monitoring visits are still required, this may be scheduled after a particular number of participants have been recruited or within a particular timeframe after recruitment of the first participant so a larger volume of data can be checked during a visit. Timepoints and milestones will be specific to each trial (and maybe to each site) and should be proportionate to the level and potential impact of risk identified by the Risk Assessment. Measures should be in place to review monitoring plans should milestones be reached more quickly or more slowly than anticipated.

5.2.2 Types of Monitoring

The type of monitoring required is also dependent on the factors outlined above, in particular trial design, as well as the resource and funding available to support monitoring activities. Some methods will be more appropriate than others for different aspects of the trial and in most cases, it is likely that a combination of on-site, central and remote monitoring will be used to make the best use of the resources available without compromising subject safety and data integrity.

Table 2 below is taken and adapted from The MHRA Good Clinical Practice Guide (Grey Guide) (Table 7.2, page 244) [3] and outlines aspects of central and on-site monitoring and

what can be achieved by each. We have adapted the table to include considerations for Remote Monitoring. To note, technologies and systems improving remote monitoring capabilities continue to evolve and improve the effectiveness of remote monitoring.

Table 2: Types of activity achievable via central, on-site and remote monitoring

Criteria	Central Monitoring	On-Site monitoring	Remote monitoring
Face-face interaction with the site personnel to build rapport	x	✓✓	✓
Travel burden (e.g. time away from office)	x	✓✓	x
Allows ongoing training and motivation of the site	x ^a	✓✓	✓
More remote contact with sites (e.g. by telephone or email) as not out on the road	✓✓	x	✓✓
Access to and assessment of information not captured on case report forms (source data verification)	x ^a	✓✓	✓
Ability to verify subjects' existence (e.g. review consents and identification)	x ^a	✓✓	✓
Identification of unreported AEs	x x ^a	✓✓	✓
Identification of non-case report form protocol deviations/violations	x ^a	✓✓	✓
Statistical monitoring to identify site outliers and obvious data patterns and trends across the trial	✓✓	x	x
Automatic data checks to identify issues with plausibility or consistency	✓✓	x	x
Early safety signal detection (e.g. increase of values close to defined limits)	✓✓	x	x
Early identification of sites not completing or submitting case report forms or other data	✓✓	x ^a	x ^a
Direct viewing of facilities and equipment (e.g. the location of investigational medicinal products, trial records)	x	✓✓	✓
Identification of new staff and hands-on mentoring/support for new staff/sites	x	✓✓	✓

x Not achievable x^a Limited ability ✓ Partially achievable ✓✓ Achievable

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5.2.3 Considering the most appropriate type of monitoring activity for your trial

The traditional method for monitoring of clinical trials that most organisations will be familiar with is the on-site approach. Whilst this approach has many advantages, it is resource intensive and many of the on-site processes can now be undertaken remotely or centrally due to the move towards the use of eCRFs, access to Electronic Health Records (EHRs) and the ability for regular reports to be pulled from trial databases. For trials where there are a large number of sites involved and a large amount of data to monitor, central monitoring may be used in the first instance to inform and direct on-site or remote monitoring to areas/sites of concern, particularly in relation to participant safety or data integrity. This is often referred to as triggered monitoring, see section 5.4 for further information.

For trials considered to be low risk (Type A) or for specific low risk areas within a trial, routine trial management plus some central monitoring, with no on-site monitoring may be sufficient. The Risk Assessment may have indicated that central monitoring in conjunction with trial specific procedures such as investigators' training and meetings and written guidance can ensure appropriate conduct of the trial.

Remote monitoring can be considered as an addition to or substitute for some on-site monitoring activities. The ability to conduct remote monitoring relies on the capacity at sites to complete remote checklists and provide redacted, scanned copies of source data/consent forms and as such, the sites ability to participate in remote monitoring activities must be carefully considered. Where remote access to electronic participant records is employed the ability to conduct monitoring in this way is dependent on the appropriate participant consent to access EHRs, the required software and adherence to required data protection requirements. The MHRA published guidance on remote direct access to EHRs by Sponsor representatives in clinical trials [7].

Whilst remote monitoring can be a resource and cost-effective tool, it is currently not possible to completely replicate all on-site activities, for example it is not as easy to review IMP returns at pharmacy prior to destruction or to view sample storage areas in a laboratory. Some sites are starting to offer alternative approaches, including webcam review of such areas. The acceptability of not conducting these activities on-site will depend on the type of risk and its potential impact on participant safety or reliability of the data.

The value of developing a relationship with site staff should also be taken into consideration when considering monitoring methods. Where on-site visits are reduced in favour of remote activities, mitigations and alternative methods should be considered to ensure the benefits of in person contact and the relationships this can foster, are not lost.

The rationale and justification for the chosen monitoring strategy should be considered early on, during the risk assessment process and documented in the Monitoring Plan and be reviewed periodically. Further details on the conduct of on-site, remote and central monitoring can be found in section 6.

5.3. The role of monitoring

5.3.1 Who does what?

Monitoring activities can be undertaken by a number of different research/trial personnel and are not limited to the role of a Clinical Trials Monitor/CRA. There are many different models that may involve multiple individuals in different roles in any one trial and this will often depend on the type, complexity and size of the trial, the organisation managing the trial and the funding and resource available for monitoring. It is the Sponsor's responsibility to ensure that trials are adequately monitored by appropriately trained individuals and that the details of who is responsible for monitoring activities is clearly documented in the protocol and/or Monitoring Plan, so all stakeholders are aware of their roles and responsibilities.

Expectations for the reporting and escalation of findings, including appropriate timelines to both Sponsor and regulatory bodies where appropriate, should be clearly documented and agreed by all parties at the trial set up phase, regardless of who is undertaking the monitoring.

Where the Risk Assessment and Monitoring Plan indicate that minimal monitoring is required, routine trial management plus some central monitoring may be appropriate. Central monitoring activities could be undertaken by the Trial/Data Manager and/or Trial Statistician focusing on areas of risk identified in the Risk Assessment and the monitoring could be escalated to an on-site/remote visit carried out by a Trial Monitor or Trial Manager where concerns with data integrity or participant safety are identified.

For a large, multi-site trial where intense monitoring is required across numerous areas according to the Risk Assessment, the Sponsor may require a dedicated Trial Monitor or team of monitors to carry out the required monitoring activities, particularly if it is to be predominantly completed on-site. These individuals may be part of the CTU/Sponsor trial team, part of the wider unit/organisation managing the trial but independent to the CTU/Sponsor trial team or contracted from a third-party/external company. The Sponsor should ensure appropriate vendor assessments have been completed to ensure the trialist(s) conducting the monitoring are appropriately qualified and trained and relevant contracts or agreements are in place.

5.3.2 Training and qualifications required for monitoring

The Conditions and Principles of GCP as stated in Schedule 1 of The Medicines for Human Use (Clinical Trials) Regulations SI 2004/1031 state that each individual involved in conducting a trial shall be qualified by education, training, and experience to perform his or her respective task(s) [1].

Members of the team undertaking monitoring should be familiar with Sponsor/CTU SOPs, clinical trial regulatory requirements and GCP, along with sufficient knowledge of the trial protocol, written informed consent documents and any other information to be provided to participants and relevant IMP information (where applicable). Any training and/or knowledge of the above should be documented to evidence suitability to perform the role.

Training requirements vary across organisations but common activities include: attendance at external courses run by various professional bodies and research support groups, in house-training using mock resources and fictitious trial data, co-monitoring or shadowing of experienced monitors and competency based assessments.

5.3.3 Responsibilities of a person undertaking monitoring activities

The Trial Monitor (or person undertaking monitoring activities) is an integrated member of the trial team and should attend trial team meetings to report on monitoring activities.

Monitors are responsible for verifying that the trial is conducted and documented appropriately at investigator sites. They should work in accordance with Sponsor/CTU SOPs or specific procedures for monitoring of that trial, as documented in the Monitoring Plan and Risk Assessment. This includes the writing of a report after each site visit that details the documents, processes and departments reviewed, including any findings, non-compliances and any actions taken or recommended actions to ensure compliance. These reports should be in sufficient detail to allow verification of compliance with the Monitoring Plan. Reports should be reviewed and approved within an appropriate timeframe defined in Sponsor/CTU SOPs. Monitors are responsible for the follow-up of monitoring actions until resolution.

Details of centralised monitoring activities and related findings may not be recorded in a formal report as with on-site or remote visits. Central monitoring should however be documented to evidence what has been reviewed, when and by whom the review was conducted. Any findings identified through central monitoring and the appropriate actions taken to rectify these or escalation of concerns to the appropriate person(s) e.g. Data Manager, Trial Manager, CI, TMG, Quality Assurance, Sponsor etc. should also be documented as per Sponsor/CTU SOPs/procedures.

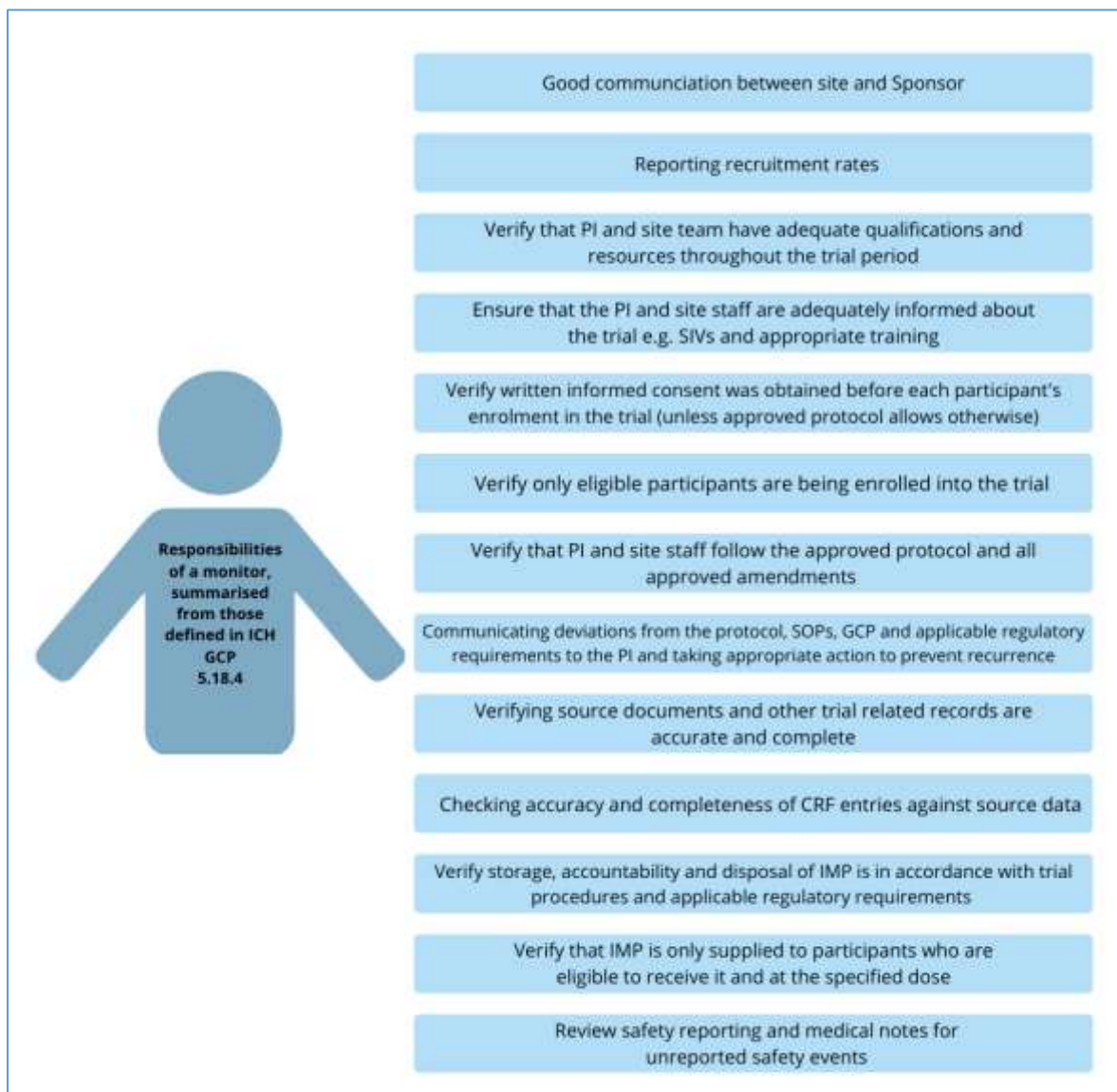


Figure 2. Example responsibilities of a person undertaking monitoring activities, examples listed are some of those included as responsibilities of a monitor as listed in ICH GCP guidelines [2].

5.4. Triggered vs routine monitoring visits

Triggered monitoring in clinical trials is a risk-based monitoring approach where triggers (derived from centralised reports and data, using predefined key risk and performance indicators) drive the nature, extent, timing and frequency of monitoring activity [5]. Triggered monitoring can be in the form of increased centralised or remote monitoring and where necessary an on-site visit.

Monitoring activity may be triggered if/where:

- Information comes to light that suggests persistent non-compliance with the trial protocol, GCP or regulatory requirements at a particular site.
- Issues have been raised from central monitoring activities that require further investigation at site level (e.g. appropriate storage of IMP supply).

Metrics and pre-determined thresholds of acceptability should be set out at the beginning of the trial and be clearly documented in the Monitoring Plan. Once an appropriate threshold has been met, this would trigger the need for increased centralised or remote monitoring or,

in some circumstances, an on-site visit to further investigate the associated metric. Metrics may include recruitment levels, incidence of protocol non-compliances, safety reporting timelines, data return rates and missing data levels.

Section 5 Questions

Use these questions to test your understanding of the above section. Answers can be found in the appendices. There is no right answer to the reflection, it is to be used as a tool to assist you with the application of the above information.

1. What is the purpose of a Risk Assessment?
2. Once the Risk Assessment has been finalised and signed-off for use, should it be amended? Give an example of what might initiate an update to the Risk Assessment.
3. Who can carry out monitoring activities?
 - a) Monitor
 - b) Trial Manager
 - c) Data Manager
 - d) Sponsor representative
 - e) Anyone suitably trained and with the relevant experience and knowledge to do so.
4. If equipment is used to make endpoint assessments and the equipment is specific to the trial and not covered in a site's standard procedures, would monitoring intensity be low or high?

Reflection: think of a trial you are responsible for monitoring and the specific data points identified to be monitored. What are they and why have they been identified as critical data to monitor?

6. Conduct of monitoring activities

6.1. On-site monitoring

6.1.1 Preparing for an on-site monitoring visit

A number of steps may be considered when preparing for on-site monitoring visits:

- The Monitoring Plan should be reviewed to ensure the visit is being conducted in line with the required timeframe, nature and scope of the visit (such as initiation, close out, scheduled or triggered).
- Care should be taken when planning monitoring activities that the blinded status of a monitor is not compromised by the assigned monitoring activities (e.g. by assigning the review of unblinded pharmacy or dosing records)
- An assessment should be made in terms of the time needed to prepare for and complete the visit and subsequent follow-up, taking the following into consideration:
 - Time to prepare for the visits (identify participants for SDV, identify outstanding data and safety queries, identify outstanding monitoring visit actions).
 - Travel time to and from site.
 - Time needed at site:
 - Number of participants required for review (including complexity of trial procedures and how much needs to be reviewed per participant).
 - The size of the Investigator Site File (ISF) (i.e. CTIMP, non-CTIMP, progress of trial, number of amendments etc.).

- The need to visit pharmacy (if CTIMP) – extent and complexity of accountability logs, storage arrangements and Pharmacy Site File (PSF).
 - The need to visit other departments e.g. laboratories or radiology.
 - Time required with the site research team to discuss findings and provide feedback. On-site visits require time commitment from the investigator research team and their availability and capacity to support visits must be taken into consideration and every effort made to minimize the burden on their time.
- Contact should be made with the site to make arrangements, including the reason for visit, time required, space required, members of the site research team that need to be involved and the type of notes/records that will be required for review. Provide suitable dates for the site research team to attend, requesting time with the Research Nurse, Pharmacist (if applicable), PI and other departments as required (e.g. Radiologist, Data Manager, Pathologist) during the visit. Space considerations should be taken into account and the number of monitors that can be accommodated during the visit based on the space available. Again, when discussing the plans for an on-site visit with a site it is important to consider the burden on site research team. Communication with the site is important to establish what can be achieved with the estimated time required for the site research team to participate.
 - Transport should be arranged and accommodation as required for the dates agreed.
 - If applicable, participants should be selected for monitoring by the relevant Sponsor/CTU trial team member(s) in accordance with the trial specific Monitoring Plan. Once confirmed, provide a list of participants to the site research team to ensure the participant files and (e)CRFs are accessible for the visit.
 - Where the site utilises electronic systems, check the site policy/procedures for monitoring. If applicable, request access to the site's electronic systems for the duration of the visit and confirm if any system-specific training is required in advance of the visit. If training is required to access electronic systems, then determine whether this can be undertaken in advance of the visit to maximise the time on site.
 - Checklists and verification tools greatly aide completion of SDV/SDR and as such, resources could be created (as defined in Sponsor/CTU SOPs) for the visit to include SDV/SDR, ISF review, PSF review and accountability (where required) based on the scope of the visit outlined in the Risk Assessment and Monitoring Plan. Critical data for review in such checklists may be defined in the Risk Assessment and if time on site is limited, priority data for review could be identified (for example safety data and data pertaining to primary endpoints).
 - Review the overall compliance of the site to identify any potential systematic findings, including errors with data entry, protocol/GCP non-compliances, unreported SAEs etc.
 - Review and consider previous monitoring reports and actions, including anything previously identified by any monitoring activities that may need additional consideration during the visit.
 - Ensure electronic access or printouts of databases, SAEs and verification aids/checklists to be used during the visit are available. Consider that an internet connection may not be reliably available and printed documents may be more appropriate.

6.1.2 Conducting an on-site monitoring visit

The endpoints (primary, secondary and exploratory) and data that could affect them, data that have a safety implication or impact treatment are considered critical data points. This critical data should be identified in the Risk Assessment and Monitoring Plan and selected for review during monitoring visits to ensure the accuracy and completeness of the data, as

described earlier. Once the data to check has been identified, checklists and working documents can be created to record how this checking is performed.

The scope of on-site monitoring visits should be detailed in the Monitoring Plan. Typically an on-site visit may include:

- SDV and/or SDR of pre-defined data.
- Review of the ISF.
- Pharmacy Visit – including review of PSF and IMP stock levels and accountability (only applicable for CTIMPs).
- Visits to other applicable departments (laboratories, radiology, participant identification centres).
- Meeting with the Principal Investigator and site research team.

This sub-section provides considerations and suggestions of activities to be performed during any on-site monitoring visits. This is not exhaustive and may vary depending on the trial and nature of the on-site monitoring visit. The order and priority of monitoring tasks to be performed may also differ based on the Monitoring Plan, nature and scope of the visit.

6.1.3a Source data

Source data is the location a data point is first captured and is therefore the original record of information. Exactly what constitutes source data should be defined in discussion with site research teams for each trial and documented. Documentation may be in the protocol, Data Management Plan or Monitoring Plan or may be a site-specific source data location log, dependent on Sponsor/CTU SOPs.

Source data can be defined as all information in original records (or verified copies of original records) of informed consent, clinical findings, observations and any other trial activities that are necessary for the reconstruction and evaluation of the trial.

Source data is a vital aspect of trial management and should be attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available.

Source data collection methods may vary depending on the type of data collected by a trial but should be captured in accordance with any protocol mandated requirements. Source data can be in both paper and electronic formats and in some instances may be the (e)CRF itself (although the protocol must specify this). Common examples of source data include, but are not restricted to:

- Patient consent forms
- Annotations in paper or electronic medical notes.
- Clinician assessment and causality of any AEs.
- Trial specific worksheets and workbooks.
- Participant completed diaries.^x
- Participant completed questionnaires.^x
- IMP accountability records.
- Laboratory data and results, including blood results, urinalysis and other biospecimens.
- Clinical trial prescriptions.
- Scan images.
- Results from investigative tests, such as ECGs.
- Clinic and referral letters.

^x Not all participant completed documents may be kept at site, some may be completed by participants and returned directly to the CTU.

Monitors should be aware that sites often generate a paper workbook to be completed at each visit due to the practical limitations of completing the (e)CRF at the time of the visit which is then transcribed into the (e)CRF at a later date. If this practice is undertaken then monitors should review the workbook data which is likely to be the source. Monitors should also undertake a review of the workbook (or ensure that the site have done) to ensure that all required information is captured appropriately.

The location of source data varies between trials and investigator research sites as it depends on the type of data that is collected as well as any departmental systems and processes that are in place.

If data is captured in more than one place it is important to determine which is the original source data e.g. if entries are made in both the medical record and a source data workbook.

All protocol mandated data should be evident in source documents and be available for review. If this data is not available, consider if this could constitute a protocol non-compliance and appropriate escalation. In the first instance, discuss with the site research team during the visit.

6.1.3b Source Data Verification

Source data verification can be divided into 2 main processes:

1. Checking that the data reported for analyses accurately reflects source data at the clinical trial site i.e. data within the (e)CRF is compared to original source and vice versa (e.g. transcription checking)
2. Checking the quality of source documentation for protocol and GCP compliance and ensuring critical processes and source documentation are adequate i.e. local and Protocol processes are being followed (e.g. process for AE identification, documentation and reporting). This is sometimes referred to as Source Data Review (SDR).

During on-site monitoring, verification/review of source data may include (but is not limited to) checking:

- Consent forms and consent process.
- Eligibility criteria.
- Safety reporting e.g. AEs, SAEs, SUSAR reporting and follow-up.
- Key safety assessments e.g. Bloods, Urine, ECG.
- Trial endpoint data/information.
- Treatment compliance and details (including any dose modifications).
- Screening logs.

Examples of the practical checks that this may include:

- Checking assessments and visits are conducted in accordance with protocol requirements and timeframes.
- Checking assessments are conducted by a suitably delegated and qualified person.
- Reviewing evidence of PI involvement and oversight.
- Assessing GCP compliance.
- Reviewing evidence of the investigator review of trial test results.
- Checking participant diary cards against data in the (e)CRF.
- Treatment dosing and compliance and reasons for stopping trial treatment.
- Reviewing source data (medical records) for unreported safety events and accuracy of safety data (start stop dates and associated concomitant medications).
- Maintenance of trial blinding.

Examples of common source data findings include:

- No documented review of lab reports, scans or X-rays prior to confirmation of eligibility.
- Start and stop dates of AEs and concomitant medications omitted and not followed up.
- Unreported AEs/SAEs.
- Duplicated and contradictory data (i.e. data recorded in more than one source).
- Retrospective alterations to original data with no explanation.
- Missing data.

6.1.3c Consent

A key component of source data verification is to confirm that trial participants provided informed consent prior to any trial-specific activity and that participants were confirmed to be eligible for inclusion in the trial prior to trial entry. Informed consent should be taken by a researcher with appropriate qualifications and documented delegation of this responsibility. Monitors should be familiar with the protocol-defined and REC approved requirements for consent as requirements can vary depending on the type of trial, for example in trials conducted in the emergency care, paediatric and vulnerable population settings.

The steps taken to obtain informed consent and confirm eligibility should be documented in the source documents and medical records to allow reconstruction of a participant's participation throughout a trial, from the point they were initially approached, through to the end of their participation. An important consideration of monitoring is to ensure the participant has consented to the access to their medical records before such access for monitoring activities is undertaken.

The process for approaching and pre-screening eligible participants should be recorded in source documentation in accordance with the protocol, for example when and how the current PIS was provided (for example by clinical appointment or via post), the date the participant or representative was first approached and by whom, what was discussed, how long the participant considered trial participation and the next planned visit (if applicable).

An example entry in the medical notes to document participant consent may include the following points:

- Date of consent, who provided consent (participant, personal legal representative, witness where verbal consent is permitted etc.) name of consenting clinician or relevant health care professional, the version and date of the PIS and consent form provided.
- Evidence of discussion prior to consent and that the participant or representative had ample time to consider the trial and ask any questions.
- Evidence that a copy of the current, signed consent form was provided to the participant or representative and a copy was filed in their notes.

The individual obtaining informed consent should be authorised and delegated to do so on the delegation log. Consent forms should be signed by the person obtaining consent and the participant or representative in real time and usually on the same date (although there may be scenarios where trial procedures allow for sequential consent e.g. where verbal consent is taken in advance of written consent). It is also good practice for a participant's ongoing willingness to continue in the trial to be documented in source medical notes at selected time points. Review of continued consent is particularly important to consider in the monitoring of trials where participants may lack, lose or regain capacity for consent.

The patient information sheet and consent form may be subject to amendment over the course of a trial and verifying re-consent is an important element of the monitoring of informed consent. An updated PIS and ICF should be submitted and approved by the local R&D department and updated information disseminated to patients in a timely manner.

eConsent is an approach sponsors and researchers are increasingly keen to adopt, which enables potential research participants to be provided with the information they need to make a decision via a tablet, smartphone or digital multimedia. It also enables a participant's informed consent to be documented using electronic signatures. eConsent can be used to supplement the traditional paper-based approach or, where appropriate, replace it. The MHRA and HRA have written a joint statement on seeking consent by electronic methods [6] which describes the considerations of employing electronics signatures, electronic presentation of information and recording and documenting eConsent.

Examples of common consent related monitoring findings include:

- Initial provision of PIS to participant and subsequent consent process not fully documented in source medical notes (e.g. when participant was approached, evidence of consent discussion, version/dates of PIS and date ICF signed etc.).
- Copies of PIS and signed ICF not filed in source medical notes and/or in the ISF.
- Informed consent obtained by individuals not authorised and/or not delegated to do so.
- If applicable, no evidence of continued consent being obtained from the participant throughout the trial.
- Use of an incorrect or superseded version of the PIS or ICF.
- If applicable, participants not re-consented to the most recent version of the PIS or the correct version is used but re-consent is not conducted in a timely manner.
- Incorrect completion of ICF by participant or representative (e.g. consent boxes are ticked, not initialled).
- Untimely evidence of consent or re-consent; issues with different dates of signature between person taking consent and the trial participant
- Failure to ensure additional consent forms for exploratory analyses signed prior to obtaining samples

6.1.3d Eligibility

During the identification of potential trial participants, medical notes may be reviewed against the eligibility criteria prior to approach of the potential participant. This is sometimes referred to as pre-screening and can often be conducted by any member of the site research team. It is important to note that while review of eligibility can usually be conducted by any members of the site research team, in most instances only medically qualified doctors with the appropriate delegation of duty can confirm participant eligibility. If confirmation of a patient's eligibility requires trial-specific assessments or interventions, it is critical to ensure informed consent is in place prior to any trial specific assessments being conducted.

Confirmation of eligibility should be recorded in both source documentation and/or medical notes by an authorised and delegated appropriately qualified researcher prior to randomisation or registration. In CTIMP trials this would usually be a medically qualified doctor.

An example entry in the source medical notes to document confirmation of participant eligibility would include the following points:

- Date of screening/baseline visit and a record of all protocol-defined eligibility assessments undertaken and results required to deem the participant eligible.
- A clear statement of eligibility confirmation by an appropriately qualified researcher (medically qualified doctor for CTIMP trials) with the appropriate delegation of duty, provided prior to trial intervention/treatment (for example, results were within the acceptable protocol-defined ranges and that the participant meets all of the inclusion criteria and none of the exclusion criteria).

Entering a participant into a trial who is not eligible is a protocol deviation that has the potential to be a serious breach. If identified during on-site monitoring this should be escalated according to Sponsor/CTU SOPs/policies.

Where eligibility criteria change during the course of a trial, it is important that anyone performing monitoring understands and is familiar with the reason behind the change (safety concerns, administrative errors) as this will inform the level of concern and escalation required if eligibility is assessed using a superseded version of the criteria.

Examples of common eligibility related monitoring findings include:

- Eligibility confirmed by a clinician with the appropriate delegation of duty on the (e)CRF, but not documented in source notes.
- No evidence of review of screening results by a clinician prior to confirmation of eligibility (e.g. results not filed, or not signed and dated by the clinician, signatures dated after confirmation of eligibility).
- Participant enrolled onto a trial despite not meeting eligibility criteria. This can also include confirmation of eligibility being completed according to a previous, superseded version of the eligibility criteria.

6.1.3e Safety Reporting

AE and SAE reporting are an integral part of safety monitoring for clinical trials. Monitoring of AEs and SAEs are crucial for all trials as the safety of participants is of paramount importance. On-site monitoring of source documents involves review to ensure that all AEs are reported in the (e)CRF, and to ethics and regulatory authorities as required and within the timeframes specified in The Medicines for Human Use (Clinical Trials) Regulations and/or Sponsor/CTU SOPs and trial protocol for non-CTIMP research studies.

The process for identifying and recording AEs/SAEs should follow the specific requirements of the protocol. All relevant information required by the protocol should be recorded in source documents (either trial specific or site specific). This could include start/stop dates, assessments performed and any changes to trial treatment as a result. Trial participants should be assessed for AEs/SAEs at each trial time defined in the trial protocol. Reported AEs and SAEs should be followed up to resolution or resolution with sequelae by the site research team.

Each reported AE or SAE must be assessed for seriousness according to the definitions listed in The Medicines for Human Use (Clinical Trials) Regulations and/or protocol. Severity of each AE or SAE must also be assessed according to the protocol. An appropriately qualified individual (medical doctor for CTIMP trials) who is authorised this responsibility on the trial delegation log must assess the causality of an AE or SAE and this assessment cannot subsequently be downgraded by the sponsor/CI. All events assessed as having a reasonable causal relationship with the IMP qualify as Serious Adverse Reactions (SARs) or Adverse Reactions (ARs) (see glossary).

All SAEs (other than those defined in the Protocol as not requiring reporting) must be reported to the Sponsor or delegated persons immediately, but usually within 24 hours, of the site research team becoming aware of the event being defined as serious.

Review of SAEs should be timely, taking into account the reporting time for a potential SUSAR and if the site have been delegated the responsibility, include the assessment of expectedness using the current, approved Reference Safety Information (RSI) at the time the event occurred.

The protocol may define other safety events that require expedited reporting to the CTU or Sponsor including pregnancies, AEs of special interest (AESI) and overdose. The safety reporting timeframe is protocol specific. Review of source data should include identification

of any such relevant event and the verification that the correct reporting procedures have been followed.

On-site monitoring of safety may include the following:

- Ensuring that AEs/SAEs are adequately described in medical notes, as well as in the source documents.
- Checking all source documents for any AEs/SAEs (pregnancies, overdose, AESIs or any other protocol defined event requiring expedited reporting) that have not been reported to the CTU trial team. Safety events may be recorded in multiple locations such as medical notes, EPR system and clinic letters.
- Checking whether there is evidence within source documents of blood results review by a clinician within expected timeframes and any results out of range are assessed for clinical significance.
- Checking whether out of range blood results, that have determined to be clinically significant, have been recorded as an AE or SAE if required.
- Ensuring all associated/incidental AEs or clinically significant findings are recorded for reported SAEs.
- Ensuring the 'final diagnosis' for reported SAEs is consistent with source documentation.
- Checking that medical input into the assessment of causality can be demonstrated.

Examples of common safety related monitoring findings include:

- Clinic letters referring to symptoms on physical examination (e.g. unusually high blood pressure) without an associated AE.
- Multiple out-of-range analyses on a lab report without confirmation of whether this was clinically significant and/or acknowledgement of an AE where applicable.
- Incidental adverse events identified at the time of admission, the serious event is often well reported but incidental findings contributing to admission may be missed.
- Prolongation of hospital stays that may constitute an SAE requiring separate reporting.

6.1.3f Review of ISF

Prior to the visit, a list of all documents (including version numbers) expected to be located in the ISF should be compiled (if not already in use or present). It is helpful to list the approval dates (each of ethics, Health Research Authority (HRA) and MHRA where appropriate and date of confirmation of capacity and capability). This will allow cross check of all documents in the ISF for completeness. The structure and content requirements of the ISF is determined by Sponsor/CTU SOPs.

Where a hard copy ISF is used, reference to any documents stored electronically should be present in the ISF and access to such locations should be made available for monitoring review. Often, hard copy ISFs can be extensive, where possible additional folders should be provided or suggested to the team if the volume of documents in individual folders limits ease of review.

Key checks of an ISF include:

- That the ISF and associated trial documentation are stored within a secure location with appropriate access.
- That all essential documents as defined by the contents page are present in the ISF and are up to date.
- That current essential documents are clearly marked as 'current'.
- That superseded documents are clearly marked as 'superseded'.

- That staff who undertake specific roles have been delegated these appropriately and this is documented and approved by the PI on the delegation log. That all required tasks have been delegated to at least one person.
- That the delegation log is accurate, complete, up-to-date and page numbers added for multiple pages.
- That the site research team have been added to the delegation log (and approved by the PI) prior to commencing any trial activity and that any changes to site research staff are appropriately documented on the delegation log.
- That the CV and evidence of GCP training of the PI (and site research staff, if required for the trial) is present in the ISF and has been updated in line with local policy.
- That consent forms and SAE reports are filed and checked (see safety and consent sections).
- Relevant correspondence and meeting minutes have been filed where these are necessary to support key decision making.
- File notes documenting points to note are included and generated within a timely manner.

6.1.3g Pharmacy checks

Review of PSF and accountability

A review of pharmacy is usually required for any CTIMP trials. Pharmacy checks should not normally be required in non-CTIMP trials.

As per the ISF review, a list of all documents (including version numbers) expected to be located in the Pharmacy Site File (PSF) should be compiled (if not already in use or present). It is helpful to list the approval dates (each of ethics, HRA and MHRA where appropriate and date of confirmation of capacity and capability). This will allow cross check of all documents in the PSF for completeness. The structure and content requirements of the ISF is determined by Sponsor/CTU SOPs. Where a hard copy PSF is used reference to any documents stored electronically or in the ISF should be present in the PSF and access to such locations should be made available for monitoring to complete the review during the visit.

The key checks listed above for the ISF are also applicable for the PSF with the addition of accountability log review as described below. The pharmacy checks required can vary widely depending upon the licensing status, IMP preparation requirements and storage conditions. These factors should be considered in the trial Risk Assessment and Monitoring Plan to inform the level of checks required.

IMP Stock and Accountability

It is important to ensure that the IMP(s) is/are stored securely, under the correct conditions for each specific product, with the appropriate accountability logs in place.

The monitoring of IMP stock levels and accountability is carried out to ensure that there are always sufficient supplies for dispensing to trial participants, as well as ensuring IMP is fit for use, in accordance with the protocol and Investigator Brochure or Summary of Product Characteristics (IB/SPC).

Key checks for pharmacy, IMP and accountability:

1. Compliance with the protocol, SOPs and local policy
 - Ensure that pharmacy procedures comply with the trial protocol, Sponsor/CTU SOPs on IMP management, investigator site SOPs and the IB/SPC.

2. IMP storage

- Ensure the IMP is stored under the conditions detailed in the trial protocol, pharmacy manual SPC/IB.
- Temperature monitoring logs are complete and within range and accessible for the monitor to review. Ensure any temperature excursions have been reported to Sponsor/CTU trial team and any required actions resulting from any reported temperature excursions have been managed (e.g. quarantine of stock).
- Access to the IMP is secure and back-up storage facilities are available if required. Ensure IMP is stored in a dedicated fridge/area and separately from expired IMP, participant returns or other trial IMPs.
- Where alternative locations are to be used outside of pharmacy that these have been assessed by the pharmacy team and appropriate processes implemented for safe and secure storage, provision of medication and documentation. Pharmacy should maintain oversight of any alternative locations and have the ability to require that storage and dispensing activities be returned to the pharmacy if required arrangements are not maintained.

3. Labelling

- Ensure IMP stock is appropriately labelled in compliance with the trial approved label.
- Ensure that labels are complete and legible.
- Ensure that any addition of local labels does not obscure the approved label.

4. Stock levels and Expiry dates

- Ensure there is sufficient available IMP supplies within the expiry date.
- Ensure all expiry dates of current/available stock are in range and noted on the accountability logs.
- Ensure any expired stock is stored separately/quarantined.
- Where expiry of an IMP is extended that the Sponsor approved processes are followed and suitable documentation maintained of this activity.

5. Randomisation

- Ensure procedures for randomisation are clear and carried out by suitably delegated site pharmacy staff.
- Ensure prescriptions and dispensing is conducted according to the correct randomisation assignment.
- Blinding has been maintained.

6. Accountability

- Ensure accountability logs are in place for receiving shipments and dispensing IMP, taking into account:
 - Subject ID/Randomisation number.
 - IMP number/code.
 - Date dispensed.
 - Dose.
 - Quantity dispensed.
 - Batch number.
 - Date returned (if applicable).
 - Quantity returned (if applicable).
 - Destruction date (if applicable).
 - Recorder's initials.
 - Running stock total.
- Ensure accountability log data matches the physical stock in pharmacy.

7. Unblinding

- If applicable, ensure unblinding procedures are easily accessible for delegated site research team members.
- If unblinding information (including log in details if randomisation is conducted by an IWRS/IVRS system) is stored in a sealed envelope or similar, ensure seals are intact where applicable.

8. Drug shipments

- Ensure the chain of custody and information on temperature stability during shipment (if required) is documented.
- Ensure receipt records are in place and correspond with the accountability logs.
- That documentation exists to support any queries associated with IMP shipment or issues with the chain of custody.

9. Returns/Destruction

- Ensure returned IMP is appropriately quarantined (if required).
- Ensure IMP is appropriately destroyed following receipt of any necessary approvals. Destruction records are present and correspond with accountability logs.
- Ensure returns are handled and documented as per protocol and/or pharmacy manual.
- Ensure unused or expired IMP is managed in accordance with the trial Protocol and/or pharmacy manual.
- Ensure that documentation exists to support the return or destruction of trial medication.

6.1.3h Laboratory and radiology procedures

Review of laboratories, lab manuals and sample tracking logs

Where biological or histological samples are obtained per protocol and are processed to inform eligibility, directing treatment or key primary/secondary endpoints, monitoring of processing and storage may be required. Checks to consider are as follows:

- That the current lab manual is present, accessible and stored in a secure location with appropriate access.
- That the laboratory files are complete (See list of checks for the ISF above, though not all essential documents may be required in the laboratory files. The laboratory file contents will be defined by Sponsor/CTU SOPs).
- That each participant consented to storage of their sample(s) and to use of the samples for future research (if applicable) and that the laboratory research team have access to this information.
- That the samples are being stored and labelled appropriately (e.g. temperature controlled, restricted access).
- That the sample tracking logs/records correspond with the samples stored.
- If samples are analysed on site, that results are available for review. That any abnormal results have been communicated as required and reviewed by a delegated clinician, if required. This would be particularly important where results are required to confirm participant eligibility or inclusion into the trial.
- If samples are analysed on site then documentation should exist regarding the method to be used including relevant validation, laboratory accreditation status etc.
- Is there evidence that the samples have been processed correctly? (e.g. centrifuge details, time processed).

- That equipment has been maintained and calibrated in line with the protocol and/or laboratory manual.

Review of imaging departments, images and imaging reports

Medical imaging results may be required for trial endpoint data or confirming a participant is eligible. The scans could be required to diagnose a condition, monitor disease progression and/or evaluate the impact of the IMP or intervention.

Unlike quantitative results, such as that from blood samples where reference ranges are provided, the results of medical imaging cannot be verified by a non-medical monitor. If medical imaging scans are required to be reviewed as per the Monitoring Plan, the checks could involve ensuring:

- The medical imaging scan was conducted and at the correct time point(s). Any deviation from this is documented and reported to the CTU trial team if applicable.
- If the scan was not conducted as part of standard of care, consent for the imaging was obtained prior to the procedure.
- The results were reviewed by a delegated member of the site investigator team and the details of the review/diagnosis are clearly documented (particularly if the scan is to confirm eligibility) and a copy filed in the participant's notes.
- Where imaging data is submitted to the Sponsor/CTU for central review that scans were suitably labelled and all patient identifiable data were removed prior to submission.

6.1.4 Conclusion of on-site visits

The activities to be completed at the conclusion of a visit will depend on the trial design complexity, nature of findings and the trial Risk Assessment and Monitoring Plan.

Ideally, a meeting should take place and should include relevant members of the site research team and PI (if available) to discuss the outcome of the visit and any findings. Where this is not possible due to availability or time constraints, efforts should be made to contact the site research team following the visit.

The discussion can be used as an opportunity to:

- Provide an overview of the visit including findings (positive and negative).
- Ask the site research team for any comments or feedback regarding the trial, for any questions on trial conduct and provide support to the trial team to resolve any issues encountered.
- Highlight any immediate discrepancies/concerns that may be easier to resolve in person.
- Help locate any missing information or data.
- Any discussion (face to face or remote) should be documented in the monitoring report or follow-up letter.

Meeting with the trial team and Principal Investigator gives a valuable insight into the team's engagement with the trial and is a valuable opportunity to build a relationship with the investigator research team. If there have not been significant issues identified during the visit in person discussion with the Principal Investigator may not be required at every visit. However if issues are identified that warrant action and discussion or if there are any concerns regarding the PI's oversight of the site's activities then an in person discussion with the PI is recommended. Following a visit, the monitor should write a report in an appropriate timeframe defined in Sponsor/CTU SOPs. The report should include an overview of all monitoring activity, findings, discussions with the site research team and resulting actions.

A written report of findings and associated actions should be provided to the site research team following the visit. This may be in the form of a report or follow-up letter. A timeframe for the completion of actions for the site research team should be agreed and communicated.

If any urgent findings are identified (including unreported SAEs, major non-compliances, potential serious breaches), these must be reported to the site research team and PI as soon as possible (and ideally during the visit). The findings may also require reporting to the CTU/Sponsor immediately, in line with Sponsor/CTU SOPs. If any concerns relate to potential fraudulent activity by a participating site, such concerns should be raised immediately with the Sponsor/CTU and not communicated to the investigator research team.

6.1.5 Site close out and archiving

Where on-site close out visits are required, arrangement of these visits should take place once the end of trial has been declared (or LPLV has been completed for the site and there are no outstanding data/queries for the site).

The checks required at this visit will vary between trials and a risk-based approach should be utilised where possible. Close out visits can be performed on-site or remotely, but there are a number of monitoring considerations to bear in mind before a site can be closed:

- That all required monitoring has been completed in accordance to the Monitoring Plan (e.g. critical data points, the number/percentage of checks completed, number of required visits have been conducted).
- That any previous monitoring actions have been completed and closed and whether any further on-site checks are required to close them?
- The monitoring activities that can be completed remotely prior to close out e.g. by receiving documents via email such as delegation logs.

As well as ensuring the ISF/PSF is up to date prior to close out, the following may also be considered:

- That any biological or histological samples that require shipment to central laboratories have been shipped.
- That any unused IMP is shipped back to the supplier or destroyed at site. That IMP reconciliation checks required by the monitor prior to destruction/shipping have been completed.
- That any equipment supplied (e.g. fridges, centrifuges) that need to be returned to a central location have been returned.
- That any supplies provided to obtain required samples (e.g. blood kits, aspirators) are either destroyed or returned to a central location.

Archiving

Prior to trial archiving at site, all previous monitoring actions and data queries must be completed and evidence filed in the ISF/PSF.

If the site store trial documentation electronically or if there is an eCRF, electronic records must be archived in accordance with local SOPs/policies. If the Sponsor provides a copy of the site's eCRF data at the time of archiving, a copy of the data must be provided prior to the sites access to electronic systems being revoked.

Authorisation to archive at a site may be sought from the Sponsor/CTU. Once all sites are closed and archived, the Sponsor/CTU can proceed to archiving the TMF as per local SOP/policies.

6.1.6 Hints/Tips for on-site visits

- Useful things to have when performing on-site monitoring: pens, paper, sticky notes, page tags, highlighters, checklists, laptop, internet connection.
- Maintain confidentiality by ensuring site research staff only provide access to participant notes for trial participants who have provided consent for access to their medical notes wherever possible. Where this is not possible due to electronic access to medical records, mitigations should include reliance on research governance principles and requirements as laid out in the site agreement and contracts of employment, for further information refer to joint guidance developed by the MHRA, HRA and ICO on on-site access to EHRs by Sponsor Representatives in clinical trials [6]
- Prior to the visit ensure you have a contact at your CTU for an escalation route if needed i.e. serious breach identified at site during the visit.
- Prior to the visit, ensure you are aware of the location, distance and access requirements of the departments you need to visit.
- Complete any training to access medical notes before visiting site if possible.
- Collect contact details for the site research team to minimise any time wasting when locating the departments.
- As most of the CTU trial team would not typically meet the site face to face post initiation, consider if they would like anything discussing with the site research team during the on-site visit.
- When reviewing delegation logs, be aware of job titles such as physician associate and nurse associate when checking delegated tasks.

Section 6.1 Questions

Use these questions to test your understanding of the above section. Answers can be found in the appendices. There is no right answer to the reflection, it is to be used as a tool to assist you with the application of the above information.

1. Whilst at an on-site visit, you discover something that might be a serious breach. What should you do?
 - a. Write it up on the Monitoring Visit Report (MVR) as soon as possible after the site visit
 - b. Discuss with your trial contact back at the CTU/sponsor office by phone/video conference whilst on-site.
2. Does a participant's ongoing willingness to consent always have to be documented in source medical notes
 - a. Yes
 - b. No
3. If a participant has ticked consent boxes when the consent form instructions asked them to initial the boxes, is this a monitoring finding?
 - a. Yes
 - b. No
4. How should the results of an on-site visit be transmitted to the site?
 - a. Verbally at the end of the visit
 - b. By written MVR after the visit
 - c. Both

5. You find that the ISF is not held in a secure location, but all contents of the file are as required and the local team assure you no one will access the files. Is this a monitoring finding?
 - a. Yes
 - b. No
6. You run out of time to complete your monitoring activities. Do you submit a report of what you were able to monitor or do you plan for a return visit to complete the monitoring activities?
 - a. Submit a report of what you were able to monitor
 - b. Book a return visit as soon as possible to complete monitoring activities

Reflection: For a trial that you monitor and a site you are assigned, consider the time it would take to complete an on-site visit, what you would aim to do in a single visit and what order you would do it in.

6.2. Remote monitoring

Remote monitoring is evaluation performed by appropriately trained individuals from the Sponsor and/or delegated representatives, at a location remote from the investigator research site. It replicates some on-site activities and can include remote source data verification; site self-completed monitoring checklists or telephone/video monitoring calls.

Whilst some UK CRC Registered CTUs had started incorporating aspects of remote monitoring it had not been widely used in the UK until March 2020, when in response to the COVID-19 pandemic its use was accelerated. During this time, trial teams and sites were required to find new and innovative methods to allow essential monitoring activities to continue.

The HRA and MHRA support the use of remote monitoring where appropriate but participant confidentiality must be maintained [7] and burden on site research staff must be considered.

Whilst an increase in remote monitoring occurred in response to the COVID-19 pandemic lessons learned and methods utilised may offer an opportunity for remote monitoring to continue to be adopted more widely, using a risk-based approach.

6.2.1 Considerations for remote monitoring

The main challenge for remote monitoring is to allow the monitoring team access to the source documents ensuring participant confidentiality is protected and without creating unreasonable burden to sites. The following aspects should be taken into consideration:

Maintaining confidentiality

As per HRA instructions, remote monitoring must not result in participant confidential information being sent to the Sponsor or stored by the Sponsor unless this has already been addressed in the PIS. Unredacted copies of medical notes and documents, from which individuals may be identified, must not be emailed or posted to or retained by the Sponsor.

When accessing or viewing source documents, consider where this takes place and who else may be able to view sensitive information. Identify a suitable location, such as a private office when viewing personal/sensitive information on a screen.

Ensure your computer has appropriate security systems in place such as firewalls.

Consent

Participants must consent to any sharing of their personal information outside the clinical trial site. When planning to include remote monitoring in a trial Monitoring Plan, consider items that you may want to include on the participant consent form to allow for this. Items may include but are not limited to:

- Permission for the consent form to be sent to the organisation responsible for monitoring (e.g. Sponsor or CTU).
- Permission for the site research team or those responsible for monitoring to access their medical records remotely.

Burden on site staff

It is important to consider the burden on site research staff when designing your Monitoring Plan, especially when conducting remote monitoring. It must also allow some flexibility as not all sites will have the ability or approvals to allow for certain aspects of remote monitoring, such as direct access to electronic records or screen sharing of medical records.

Communication with the site is important to establish what can be achieved remotely and is often established at trial feasibility stage and the estimated time required for the site research team to participate in remote monitoring should be reflected in the Schedule of Events and Cost Attribution Tool (SOECAT).

Sites policies and methods available

Sites may create a formal policy for remote monitoring or wish to consult their Caldicot Guardian before agreeing to remote monitoring procedures. Different technologies and methods for remote monitoring may be implemented by clinical trial sites. The current established approaches are described below.

Table 3: Current approaches to Remote Monitoring with an indication of the level of burden to the site and usefulness for monitoring.

Method	Description	Burden to site	Usefulness for monitoring
Remote and direct access to the Electronic Medical Records	<p>The monitor will be able to remotely access the electronic records for the trial participants. This method allows extensive review of data for sites where the source data is kept electronically. For this, sites will provide the monitor with a login to the EMR, which can be accessed via the Internet. Alternatively, the sites may provide the monitor with a VPN access to their systems.</p> <p>Monitors must ensure that no data will be copied, downloaded, screenshot, emailed or printed from the EMR and that only data for trial patients who have provided appropriate consent is accessed. It is also recommended that monitors clear the cache information from the browser used to access the EMR, to ensure no information is retained.</p>	+	+++

Method	Description	Burden to site	Usefulness for monitoring
Source documents shared via video conference	<p>A site representative will share their screen with the monitor via a secure conferencing platform. Some sites are also able to share control over their screen. Depending on the sites' policy, this method will allow direct view of the electronic records, electronic copies of source documents and/or scanned paper documents.</p> <p>Prior to remote monitoring, the monitor should provide the site with a list of specific source documents to be reviewed, allowing enough time for the site to prepare them.</p> <p>No recording of the video conference, copying of documents, screenshots or printing are permitted.</p>	+++	++
Source documents shared via secure document repository	<p>For this approach, the site representative will upload copies of source documents into a secure document repository which can be accessed by the monitor. The document repository system must ensure that the documents cannot be copied, downloaded or printed. Alternatively, the system may have instructions prohibiting saving, downloading, emailing or printing source documents.</p> <p>Prior to remote monitoring, the monitor should provide the site with a list of specific source documents to be reviewed, allowing enough time for the site to prepare them.</p> <p>Sites should also confirm the copies are good representations of the originals.</p>	+++	++
Pseudonymised source documents shared via email or secure platforms	<p>Where the approaches above are not feasible, sites may agree to provide pseudonymised copies of source documents via e-mail or secure platforms. All participant identifiable information, such as name, date of birth, NHS number, address etc. must be redacted.</p> <p>Prior to remote monitoring, the monitor should provide the site with a list of specific source documents to be reviewed, allowing enough time for the site to prepare them. This method causes high burden to sites.</p> <p>Sites should confirm the copies are good representations of the originals.</p>	+++	++

Method	Description	Burden to site	Usefulness for monitoring
	Once reviewed the data must be deleted from the email box and any download or temporary folders.		
Information shared verbally or via specific checklist	If only telephone or a video conference are possible, participant status, participant recruitment and site trial processes can be discussed and documented in a monitoring report. A trial-specific checklist can be developed and used if applicable. This can be completed either over the phone, or sent to sites to complete by self-review of documentation. Such calls should not be recorded.	++	+

+ limited
 ++ moderate
 +++ considerable

6.2.2 Conduct

Preparing for monitoring

- For sites with full and direct access to electronic medical records, verify if the documents required for monitoring will be available for remote review.
- If the remote monitoring method available does not allow full and direct access to electronic medical records, review the trial Monitoring Plan and data already available (e.g. (e)CRF) and determine which source documents need to be reviewed. Discuss with the site research team if it is feasible to prepare the documents selected for monitoring.

Table 4: Examples of source documents available for remote review

Item to be reviewed	Examples of source documents
Consent	<ul style="list-style-type: none"> ✓ Consent form* ✓ Medical note documenting the consent process
Eligibility	<ul style="list-style-type: none"> ✓ Medical note/clinic letter summarising the participant medical history ✓ Eligibility assessment specific results (e.g. blood results, imaging results etc.) ✓ Medical note (or proforma if used by site) where the investigator documented eligibility review and confirmation
Safety reporting	<ul style="list-style-type: none"> ✓ Trial visit proformas ✓ Clinic letters ✓ AE worksheet (if used by site)
SAE	<ul style="list-style-type: none"> ✓ Discharge summary
Protocol compliance	<ul style="list-style-type: none"> ✓ IMP prescriptions ✓ Trial-specific assessments (e.g. blood results, imaging results, etc.)
Endpoints	<ul style="list-style-type: none"> ✓ Endpoints assessment specific results (e.g. blood results, imaging etc.) ✓ Disease assessment worksheet

Item to be reviewed	Examples of source documents
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* It might not be possible to review the consent form itself if pseudonymisation is required for remote monitoring, or if not included in ICF.

- Check the Monitoring Plan for the essential documents to be requested to site. These documents usually do not contain participant direct identifiable information. Examples include:
 - ✓ Delegation Log.
 - ✓ Screening Log.
 - ✓ IMP Accountability Log.
 - ✓ Biological Sample Tracking Logs.
 - ✓ Calibration certificates and/monitoring logs for equipment used for the trial.
- Discuss appropriate visit date(s) and times for the review of data and for the monitoring call to discuss the findings if applicable. The remote monitoring visit may be organised in different sessions. Consider which sessions should be attended by the applicable site research staff, e.g. PI, Research Nurse, Data Manager, Pharmacist, Lab Manager etc.
- If applicable, request the site to confirm that the participant(s) selected for review have consented to allow remote review of their medical records.
- Reconfirm the remote monitoring shortly before the planned date (e.g. by sending a confirmation email/letter) to remind sites to ensure that all relevant source data, documents and (e)CRFs are complete and available for monitoring.

Conducting remote monitoring review

- Conduct remote monitoring in compliance with the site's policy (if applicable) and data protection requirements.
- Conduct remote monitoring via a device with adequate security.
- Ensure participant confidentiality is maintained at all times and monitoring activities are conducted in an appropriate environment where no unauthorised viewing or overhearing of conversations is possible by third parties.
- Do not copy, download, screenshot, email or print any source document reviewed during the remote monitoring. An exception is made for pseudonymised documents, which can be downloaded for review if necessary. However, all pseudonymised documents should be deleted after monitoring. Similarly, do not record telephone calls or video-conferences.
- Review the source data according to the Monitoring Plan requirements as per the guidance described in the conduct of on-site monitoring section above. Details on the specific review of documents is described in the on-site monitoring section and is not repeated to avoid duplication.
- Checklists for remote monitoring may be created to facilitate the review process. These will generally cover the critical data and process for the site/trial for review and may also include points for discussion with site staff. All details captured in checklists should be recorded on a monitoring visit report.
- For methods with limited access to the source data, make notes of which specific documents were reviewed.
- Clear the cache information retained on the Internet browser used to access the electronic medical records/documents repository and, if applicable, delete any temporary or download folders.
- After reviewing, delete any pseudonymised documents from the email inbox and all drive folders, including 'download' and 'temporary' folders.

6.2.3 Completion of remote monitoring visits

Remote Monitoring follow-up

Discuss the monitoring findings with the site research team via phone, email or videoconference. The aim is to clarify and resolve as many monitoring queries as possible during this time (not all Monitoring Plans require a follow-up call for remote monitoring if no major issues are identified, refer to Sponsor/CTU SOPs for specific guidance with regard to the communication of findings with the site research team).

During follow-up activities, consider asking general monitoring questions, such as:

Table 5: Example questions for follow-up monitoring calls

Examples of Questions	Comments
Have there been any changes to the site staff?	<ul style="list-style-type: none"> • Check if the response is consistent with the Delegation Log. • If there are new site staff, ask the site to confirm if trial-specific training has been documented and CVs/GCP training certificates filed at site. • If applicable, check if site requires a training session.
Have there been any changes to the site's facilities and equipment?	<ul style="list-style-type: none"> • Depending on the response, check if any document needs to be updated (e.g. source data location form)
How is recruitment going?	<ul style="list-style-type: none"> • Check if the response is consistent with the Screening Log.
What is participant X status?	<ul style="list-style-type: none"> • Check if the response is consistent with the information in the (e)CRF and with the SAE reporting if applicable
Is the site file up to date?	<ul style="list-style-type: none"> • If applicable, ask the site if the latest released/updated documents have been filed. • If applicable, ask the site to complete a site file checklist.
How has the trial procedure X been performed at site?	<p>For example:</p> <ul style="list-style-type: none"> • How have the investigators documented the clinical results/AEs causality review? • How have the investigators assessed the trial endpoint?
How are the stock levels of trial supplies (e.g. IMP, biological samples tubes, etc.) at site? What is their expiry date?	<ul style="list-style-type: none"> • Check if supplies are sufficient and within expiry dates.
Do you have any questions about the trial or any request to the Sponsor?	<ul style="list-style-type: none"> • Let the site representative talk! Some issues will not be noted by monitors unless voiced by the site representative.

Reporting findings to site and follow-up

Following a remote visit, complete a monitoring visit report within the timeframe specified in the Monitoring Plan. The report should contain a summary of data reviewed, findings, actions taken or to be taken and/or actions recommended to secure compliance.

Provide the site with a summary of the remote monitoring findings, including the actions to be taken (e.g. via a follow-up email).

Section 6.2 Questions

Use these questions to test your understanding of the above section. Answers can be found in the appendices. There is no right answer to the reflection, it is to be used as a tool to assist you with the application of the above information.

1. Can you perform SDV (source data verification) remotely?
 - a. Yes
 - b. No
2. If the correct agreements are in place, can source documents be shared via video conference?
 - a. Yes
 - b. No
3. You are finding it difficult to do SDV between the screen shown by the site and your local data, can you print the screen to check later?
 - a. Yes
 - b. No
4. You have a finding from your remote monitoring. Which of these can be your first approach to the site? (select all that apply)
 - a. Send a MVR
 - b. Video Conference with the site research team
 - c. Phone the site research team
 - d. Email the site research team
5. Delegation logs are often reviewed remotely. What are you checking for?
 - a. all required data are complete on the log,
 - b. That tasks are delegated appropriately,
 - c. That all tasks are delegated
 - d. The PI has authorized delegated staff prior to starting work on the trial
 - e. All of the above

Reflection: For a trial you monitor and an investigator site you are assigned, consider how you would organise your time to complete a remote monitoring review and identify the key contacts at site who will be assisting with the review and how you should both prepare for the remote visit.

6.3. Central monitoring

Central monitoring is monitoring performed in a location away from the investigator research site and often at CTU/Sponsor offices. It usually involves an evaluation of accumulating data (or lack thereof), performed in a timely manner, supported by appropriately qualified and trained persons (e.g. data managers, statisticians, trial managers, data scientists). The aim is to mitigate specific trial risks defined in the Risk Assessment which is completed before recruitment and continually reviewed during the lifetime of the trial.

Data provided by investigator sites are examined to identify trends, outliers, anomalies, protocol deviations and inconsistencies. Concerns raised by members of the Sponsor/the CTU trial team discovered during their contact with the site are also taken into consideration.

Centralised monitoring may be the only monitoring, or it may lead to remote monitoring or an on-site monitoring visit. Centralised monitoring helps to distinguish between reliable data and potentially unreliable data and complements and reduces the extent and/or frequency of remote and on-site monitoring. Centralised monitoring does not require site research staff input unless an issue is identified.

6.3.1 Data is often grouped by site

Central monitoring on trial data is usually performed on a site basis. It analyses data collected by sites and identifies if any action is required. Some issues are noted by considering levels and thresholds and some by comparison between sites. In some cases, this type of monitoring is done at trial level and could involve a comparison between trials. There are additional activities that may be defined as central monitoring that are not related to clinical data, these are further described in Section 6.3.5.

6.3.2 Metrics, thresholds, triggers

Metrics are numeric measurements, mostly obtained and calculated from data held in the trial database, that are used to evaluate a sites' risk or performance.

Triggers compare metrics with acceptability thresholds to highlight and assess potential or actual risks and/or under performance.

It is often neither possible nor necessary to check all the data in a clinical trial. The data which will be subject to central monitoring will be defined by the Risk Assessment. As much of the monitoring as possible is performed by devising a metric which can be calculated using site data to see if any action is required. For example, if there is concern that the primary outcome data will be required at short notice, it may be advisable to check the extent of data completion using the metric “% participants with primary outcome data” at a site. This metric can then be compared to a threshold for escalation. For example, prior to final analysis, 100% of primary outcome data may be required and therefore any site with primary outcome data below 100% would require consideration at an escalation of action meeting.

As risks can change throughout a trial, metrics and thresholds may also need to change. In the example above, a primary outcome data threshold of 100% would not be plausible early on in the trial when recruitment is ongoing, as many participants will not have reached their primary endpoint.

As well as metrics calculated from accruing data, manual metrics may be specified that are not possible to calculate from the data. For example, if during the contact with a site a trial manager or monitor has concerns about a site, this information should be brought to the meeting where the escalation of actions is discussed. See section 6.3.5 for other manual central monitoring tasks.

Action may not be required for each triggered metric. Some knowledge of the site by the CTU trial team may indicate a watch and wait policy would be more appropriate or it may be that several triggered metrics are required to warrant individual site action.

6.3.3 Central statistical monitoring

Central monitoring covers several sub-categories of monitoring. One of these is central statistical monitoring which is the statistical review of the data often by site:

- to identify procedural errors (for example where weight is only measured to the nearest kilogram rather than to one decimal place).
- to identify where data indicates a piece of equipment may be incorrectly calibrated (for example a blood pressure machine measuring high).
- to check for fraud (for example fictitious follow-up visits).

This is done by looking for outliers and anomalies using statistical methods. For example, fabricated values will often be strangely close to the mean or have low variances or an unusual correlation structure [8]. Statisticians traditionally carry out this type of monitoring and report results to the meeting where the escalation of action is discussed.

6.3.4 Protocol deviations

Another sub-category of central monitoring is the identification and categorisation of protocol deviations. To be able to interpret the results from a trial, there must be confidence that the trial was conducted according to the protocol and applicable regulations. Protocol deviations may be defined in the protocol if this is the case, those protocol defined deviations need to be identified through monitoring and documented to enable reporting as per protocol.

A statistician may program the identification of protocol deviations from the data in the clinical database. Sites may also notify the CTU trial team of site deviations. Trial managers, data managers or monitors may discover a protocol deviation throughout the course of their work.

If there is a definition of the protocol deviations requiring reporting in the protocol, deviations should be assessed and coded as meeting the definition or not. This may be a trial management or monitoring task.

6.3.5 Other central monitoring activities

There are a number of activities performed away from investigator research sites that constitute central monitoring. For example, the central collection and review of delegation logs against (e)CRF signatures, central review of eligibility checklists, central review of IMP accountability. It is possible that this and other tasks could be automated, but currently these are often manual tasks. Any concerns highlighted from the completion of these tasks should be brought to the meeting where the escalation of action is discussed.

6.3.6 Frequency

The frequency of central monitoring depends on the trial parameters. Central monitoring should be frequent enough to improve the quality of trial data and conduct but with sufficient interval for actions identified previously to have been addressed. As central monitoring is a collection of tasks, each task needs to be completed at a frequency dependent on their individual risk. For example, for a cancer trial with all participants recruited and annual follow-up occurring, daily central monitoring is unnecessary. On the other hand for a COVID trial with a 28 day primary endpoint and 500 participants being randomised per day, central monitoring every 3 months is too risky.

6.3.7 Escalation

Escalation plans should be described in the Monitoring Plan. Escalation may be checking data again at the next round of central monitoring, by providing training or a newsletter to all sites, by phoning or emailing a site to discuss a specific issue, by providing training on an aspect of the trial for a specific site or a remote or on-site monitoring visit. The decision to escalate should be discussed promptly after the central monitoring is complete (preferably within 2 weeks) by a group with the relevant skills to consider central monitoring reports. The CTU trial team, the trial management group or a subset of either of these is often chosen. The group need representatives who have experience of the data collection, site contact, statistical implications and clinical knowledge.

Escalation of findings beyond that discussed above are discussed in section 7 below and can be applied to all types of monitoring activity.

6.3.8 Documentation

As with all trial processes, central monitoring needs to be documented. Apart from the trial Monitoring Plan, the runs of central monitoring, the discussion and actions on escalation based on central monitoring results and the actions at the site (maybe completion of a CAPA) need to be logged. This enables processes to be tracked, preventive actions to be put in place to prevent recurrence and to improve compliance.

6.3.9 Independent Data monitoring committee

The independent data monitoring committee (IDMC) will review a summary of the monitoring achieved and may also review some data by site (e.g. CRF return rate) within the IDMC report. They may ask for information on particular sites or may ask for particular sites to have escalated monitoring (as in section 6.3.7 or section 7). The IDMC is part of the monitoring framework. Based on the risk assessment, central monitoring may be carried out and escalated more frequently than that reviewed at IDMC meetings.

6.3.10 Hints and tips

Central monitoring should be performed based upon potential risks identified in the Risk Assessment which should be a live document, updated as the trial progresses and risks evolve or updated at least annually. The Risk Assessment is the foundation of effective central monitoring.

For a phase III randomised controlled trial with more than 500 participants of a cancer therapy with a time to event outcome and 5 years follow-up, central monitoring may be done every 6 months. If there are fewer participants, annual central monitoring may be sufficient. If there are more participants, every 3 months may be more appropriate. If the follow-up is shorter monitoring needs to be more frequent. The plans for use of the data also need to be factored in. For example, in a platform trial, where trial decisions are made based on the interim analyses, monitoring may need to happen more often.

In a phase III trial of a COVID-19 therapy with a 28-day primary outcome and recruitment of more than 300 participants a month, central monitoring might occur every 2 weeks. In a phase I trial with 100% SDV and dose escalation decisions taking place every few months, central monitoring may happen monthly.

The frequency of central monitoring can vary through the life of a trial due to amendments. It may be appropriate for monitoring to be more frequent during recruitment and treatment when there is a high volume of data and less frequent when all participants are in follow-up and the volume of data reduces. The frequency of central monitoring can also be altered if it proves ineffective. For example, if findings are the same as the last time it was conducted or findings were identified too late to correct for future participants.

In a trial of longer duration, for example with a planned duration of 3 or more years, it would be worthwhile automating the process as much as possible. A central monitoring report, complete with graphs and thresholds can be automated. The escalation decisions could be stored in a document template and the response from a site could also have a template. A storage or coding system is required to link all information produced via a central monitoring run.

Central monitoring is much more effective on clean data. It is worthwhile aligning the plans for data cleaning defined in the Data Management Plan with the Monitoring Plan and coordinating routine data management and data cleaning activities to occur prior to central monitoring.

Section 6.3 Questions

Use these questions to test your understanding of the above section. Answers can be found in the appendices.

1. Are metrics and thresholds fixed for the duration of the trial?
 - a. Both can change
 - b. Only metrics can change
 - c. Only thresholds can change
 - d. Neither can change
2. Through central monitoring it is found that (e)CRFs at a site are signed by someone not on the delegation log. What follow-up activities should take place?
3. Central monitoring identifies a site with a lower-than-expected rate of SAE reporting. Should this lead to on-site monitoring?
4. Will central monitoring always be at fixed intervals? If not, why not?
5. Are protocol deviations noted by
 - a. Statisticians
 - b. Monitors
 - c. Trial managers
 - d. Data managers
 - e. Sites
 - f. Any of the above

7. Escalation of findings

All monitoring activities described may generate findings of concern that require escalation. The appropriate route of escalation will vary dependent on the seriousness of the finding, the route of identification, the subsequent investigation required, Sponsor/CTU SOPs and regulatory reporting requirements.

Escalation by a monitor or trial manager may initially be via the CTU trial team, with the involvement of Quality Assurance (QA) or Sponsor representatives to determine the required reporting steps. Issues may also require discussion with or reporting to the Trial Management Group or Chief Investigator in order to ascertain the impact of the issue on the patient concerned or the trial as a whole.

Escalation of issues from the perspective of the investigator research site should first be discussed with the PI and where appropriate, the local R&D department.

Issues may require a full investigation to determine their extent and cause, and in such instances, depending on Sponsor/CTU SOPs, the Chief Investigator or Sponsor representatives may need to consider whether the issue constitutes a serious breach requiring onward reporting to the MHRA. Findings from monitoring activities may be referred to in any such investigations and the monitoring team may be involved in liaison with the site as part of any required investigations.

8. Additional considerations

8.1. Early phase trials

Phase I and II trials involve the use of IMPs whose spectrum of toxicity and likelihood of benefit is not well defined, as such the close monitoring of safety data is of upmost importance to ensure it is safe for new participants to enrol on the trial and for existing participants to continue their treatment programme.

In phase I trials, toxicity may be the outcome measure that informs the dose escalation plan and early stopping rules. In phase II trials, although efficacy is the outcome of interest, safety is an embedded outcome that may also inform stopping rules. The monitoring of adverse events in early phase trials therefore requires significant and careful consideration in the trial Risk Assessment and Monitoring Plan.

The most common method for monitoring toxicity in early phase trials is to design formal sequential stopping rules based on the limit of acceptable side-effect rates (or dose limiting toxicity). The sequential nature of these rules allows investigators to stop the trial as soon as the event rate is excessive.

The trial risk assessment for early phase trials will therefore often necessitate high intensity and timely SDV of safety data, primary and secondary endpoint assessments and eligibility criteria. A particular focus of monitoring activities will be to review participant notes for toxicities of interest and confirm all events have been reported accurately and completely and in a timely manner.

A Safety Review Committee (SRC) or IDMC will review safety data and advise on cohort management e.g. dose escalations, at agreed intervals. Quality control of safety data prior to such reviews are required and it is therefore important that the monitoring team and trial management team responsible for these meetings communicate well. It is common practice for data being reviewed at SRC meetings to require source data verification to be complete; therefore, these trials require real time monitoring in a way that later phase trials may not. This can be challenging when managing monitoring resource to ensure priority is given to the early phase trials based on risk. The Monitoring Plan may also include the requirement to review for eligibility in a timely manner, to ensure any incorrectly recruited participants are identified early to minimise any potential risk to participants.

In addition to on-site, remote or central monitoring of data, quality control of data entry (if data entry is performed at the CTU), statistical analysis and reports produced for IDMC is also an important consideration.

8.2. Non-CTIMP studies

Trials which do not involve an IMP, as defined by the MHRA, do not fall under the UK Statutory Instrument 2004:1031, The Medicines for Human Use (Clinical Trial) Regulations and its subsequent amendments [1]. The Research Governance Framework outlines principles of good governance that apply to all research conducted in the NHS [9]. The framework notes that organisations and individuals are expected to be able to demonstrate adherence to the framework and that mechanisms to monitor the quality of clinical work, such as inspection, audit, risk management and staff appraisal, can assist in the monitoring of research governance.

Non-CTIMP studies should still be subject to a Risk Assessment which will inform the critical data for monitoring as for CTIMP trials. Non-CTIMPs are divided into randomised controlled trials of non-CTIMP interventions and other non-randomised or observational studies and are generally considered lower risk than CTIMP trials, but exceptions to this exist and the assessment of risk should be performed on a case-by-case basis.

Interventional non-CTIMP trials (e.g. use of medical devices, surgical interventions or radiotherapy) are higher risk than observational studies (e.g. cohort and case studies). Listed below are some considerations of some specific types of non-CTIMP studies.

i) Interventional studies of medical devices

Medical devices are regulated by the UK Statutory Instrument 2002:618, The Medical Devices Regulations as amended and the MHRA expect that the principles of Good Clinical Practice are followed in medical device trials. Recent MHRA guidance on legislation for clinical investigations of medical devices notes that there must be adequate monitoring in place to ensure that the rights, safety and well-being of subjects are protected [10].

Medical devices are defined as any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories, including the software intended by its manufacturer to be used specifically for diagnosis or therapeutic purposes or both and necessary for its proper application, which is intended by the manufacturer to be used for human beings.

Medical devices are placed into 3 main categories according to their risk and mode of action (general, active implantable and in vitro diagnostic). As a result, the monitoring requirements differ between these categories and high-risk areas should be identified and considered in the trial Risk Assessment.

Some specific examples of areas which may need monitoring include:

- Evidence that the device was sterilised before use (if not provided to the site in a sterilised condition).
- Evidence of calibration and maintenance of the device to ensure there is no device malfunction.
- Evidence that all AEs and SAEs are reviewed for relatedness to the device.

ii) Surgical intervention trials

Surgical trials involve a procedure, the outcome of which can be directly influenced by the surgeon, participant and operating conditions. Monitoring of such external factors will be an important component of the trial Risk Assessment.

Some examples of additional considerations for surgical trials are:

- The participant group and therapeutic area and the impact on safety reporting.
- How the surgical intervention is standardised across sites and the impact on monitoring of this standardisation.

iii) Low risk interventions and observational studies

Monitoring requirements are often minimal in observational studies; however, informed consent and endpoint data may require some level of monitoring.

Some examples of additional considerations for the monitoring of observational studies include:

- Whether all monitoring can be conducted remotely or centrally, especially given the geographical spread and size of such studies.
- The proportion of data requiring monitoring to ensure data integrity, considering observational trials often have a large sample size.

Appendices

Appendix A – Glossary

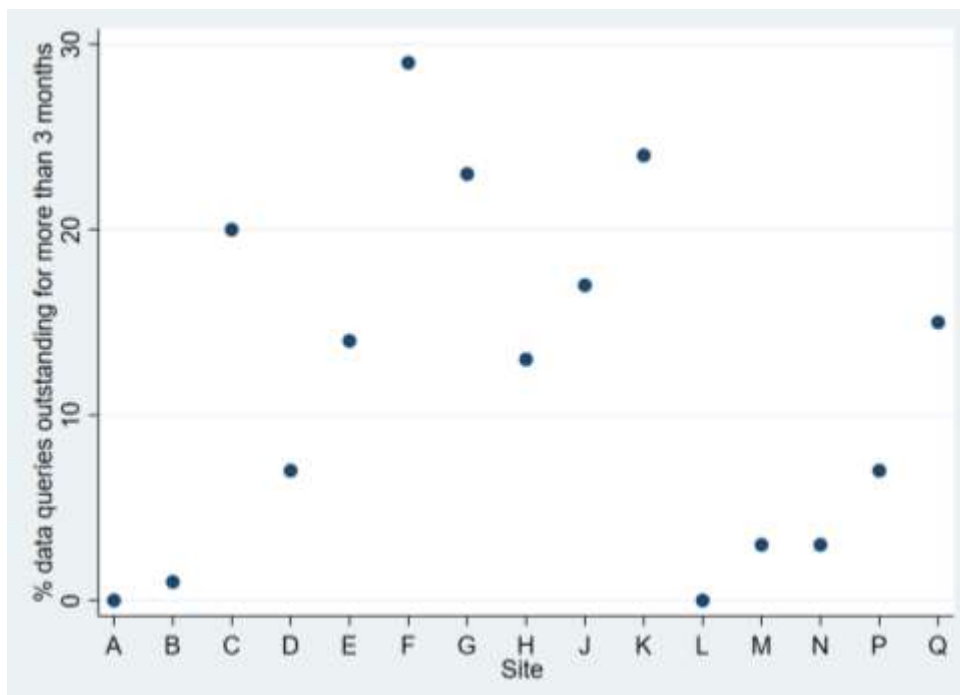
Deviation	A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the approved protocol.
Non-compliance	A failure to act in line with agreed trial processes and procedures.
Reference safety information	Reference Safety Information defines which reactions are expected for the Investigational Medicinal Product (IMP) being administered to subjects participating in a clinical trial.
Serious Breach	Regulation 29A of SI 2004/1031 (as amended) defines a serious breach as a 'breach which is likely to effect to a significant degree; a) The safety or physical or mental integrity of the subjects of the trial; or b) The scientific value of the trial'.
Site activation	Confirmation that the site can commence recruitment.
Site feasibility	A process by which a hospital site confirm capacity to run the trial effectively. Access for monitors is often considered as part of feasibility (i.e. are the medical notes paper or electronic, can monitors access these notes, how much notice is required for a monitoring visit).
Site initiation	Activities performed to train the participating site staff on all relevant aspects of the trial.
Site selection	A process by which a hospital site is identified as a potential trial site. This is often identified by the CI or Sponsor/CTU trial team and the site is approached to confirm their interest and provide feasibility.
Source Data Review	A review of source documentation to check quality of source, review protocol compliance, ensure critical processes and source documentation are adequate.
Source Data Verification	The process of ensuring that data accurately represents the source data from which it was derived.
Sponsor	A clinical trial sponsor means the person or organisation who takes responsibility for the initiation, management and financing (or arranging the financing) of that trial.

Appendix B – Mock resources

i. Resource for central monitoring

Below is an output of a review from 2 defined risks (1. unanswered data queries and 2. actual recruitment as a percentage of target recruitment). The data is presented for participating sites (A-Q) in a trial. Do you think follow-up with any of the sites is necessary?

1. Risk 1 - Data queries not being answered presented by participating site (A-Q)



2. Risk 2 – actual recruitment as a percentage of target recruitment

Site	% actual vs target recruitment
A	12
B	33
C	80
D	65
E	50
F	48
G	35
H	74
J	34
K	63
L	52
M	71
N	78
P	68
Q	21

ii. Fictitious consent forms for review

Below are 2 fictitious, completed informed consent forms. Review the ICFs and identify any issues with their completion.

<p>Study Title: A randomised double-blind, placebo controlled trial of chocolate in the management of low mood.</p> <p style="text-align: center;">PARTICIPANT CONSENT FORM</p> <p>Patient's name: <u>Edward Thompson</u></p> <p style="text-align: right; font-size: small;">Please initial each box</p> <p>1. I confirm that I have read, or had read to me, and understand the Patient Information Sheet v1.0 dated 22nd November 2017 for the above study. I have had the opportunity to ask questions and these have been fully answered. ET</p> <p>2. I confirm that I have had sufficient time to consider whether or not to participate in the study ET</p> <p>3. I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason and without my legal rights or medical care being affected. ET</p> <p>4. I understand that data collected as part of this study and relevant sections in my medical records may be looked at by authorised individuals from NHS Trust and University where it is relevant to my taking part in this research. I give permission for these individuals to have access to this information. ET</p> <p style="font-size: x-small; margin-top: 20px;"><u>Copies:</u> 1 original for patient. 1 original in Investigator Site File.1 copy on Patient's Medical Records Patient Consent Form Version 1.0 22.11.2017</p>	<p>5. I understand that the information gathered as a result of this study will be published. Confidentiality and anonymity will be maintained and it will not be possible to identify me from any publications. ET</p> <p>6. I agree to my GP being informed of my participation in the study. ET</p> <p>7. I agree to take part in the above study. </p> <p style="margin-top: 20px;"><u>Edward Thompson</u> <u>E. Thompson</u> <u>07/09/2018</u></p> <p style="font-size: x-small;">Name of Participant (Please print) Signature Date</p> <p style="margin-top: 20px;"><u>Sharon Smith</u> <u>Sharon Smith</u> _____</p> <p style="font-size: x-small;">Name of Person Taking Consent (please print) Signature Date</p> <p style="margin-top: 20px;">_____ Name of Witness (if appropriate) Signature Date</p> <p style="font-size: x-small; margin-top: 20px;"><u>Copies:</u> 1 original for patient. 1 original in Investigator Site File.1 copy on Patient's Medical Records Patient Consent Form Version 1.0 22.11.2017</p>
--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Study Title: A randomised double-blind, placebo controlled trial of chocolate in the management of low mood.

PARTICIPANT CONSENT FORM

Patient's name: Jane Green

Please initial
each box

1. I confirm that I have read, or had read to me, and understand the Patient Information Sheet v1.0 dated 22nd November 2017 for the above study. I have had the opportunity to ask questions and these have been fully answered.
2. I confirm that I have had sufficient time to consider whether or not to participate in the study
3. I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason and without my legal rights or medical care being affected.
4. I understand that data collected as part of this study and relevant sections in my medical records may be looked at by authorised individuals from NHS Trust and University where it is relevant to my taking part in this research. I give permission for these individuals to have access to this information.

5. I understand that the information gathered as a result of this study will be published. Confidentiality and anonymity will be maintained and it will not be possible to identify me from any publications.
6. I agree to my GP being informed of my participation in the study.
7. I agree to take part in the above study.

Jane Green J Green 10/12/19
Name of Participant (Please print) Signature Date

Dr Paul Young Dr P Young 10/12/18
Name of Person Taking Consent (please print) Signature Date

Name of Witness (if appropriate) Signature Date

Copies: 1 original for patient. 1 original in Investigator Site File.1 copy on Patient's Medical Records

Patient Consent Form

Version 1.0 22.11.2017

Copies: 1 original for patient. 1 original in Investigator Site File.1 copy on Patient's Medical Records

Patient Consent Form

Version 1.0 22.11.2017

BeLL Trial

SCREENING

Site No: 01 Screening No: 10011 Subject initials: JP

Visit Date: 02 / SEP / 19 (DD/MMM/YY)

**Informed
Consent**

Date consent obtained: 02 / SEP / 19 (DD/MMM/YY)

Time consent obtained: 11 : 20 (24 hr clock)

Consent process conducted by: Sharon Smith Research Nurse

Demographics:

Gender: Male Date of Birth: 12 / 12 / 1978
Female (DD/MMM/YY)

Race: White/Caucasian Hispanic
 Black (African) Asian
 Black (African American) Middle Eastern
 Other (please specify):

Females
(Check all
that
apply)

- N/A (Subject is Male)
- Potentially able to bear children
- Barrier form of contraceptive
- Pregnant (if yes participant is not eligible)
- Breast feeding (if yes participant is not eligible)
- Surgically sterile
- IUCD
- >1 year post menopause

If participant is potentially able to bear children has a pregnancy test been completed?

Yes No

Date of test: ___/___/___ (DD/MMM/YY)

Result: Positive Negative

Screening

Site No: 01 Screening number: 10001 Subject Initials: JP

Medical History page 1 (2)

Does patient have history of diseases/disorders/surgeries in any of these systems?	Diagnosis	Onset Date	Resolution Date	Grade 1-4
Eyes, Ears, Nose & Throat				
<input type="checkbox"/> Yes				
<input checked="" type="checkbox"/> No				
Cardiovascular	<i>Pericardial effusion</i>	<i>Jul 19</i>	<i>ongoing</i>	<i>1</i>
<input checked="" type="checkbox"/> Yes				
<input type="checkbox"/> No				
Gastrointestinal				
<input type="checkbox"/> Yes				
<input checked="" type="checkbox"/> No				
Endocrine/Metabolic				
<input type="checkbox"/> Yes				
<input type="checkbox"/> No				
Genitourinary				
<input type="checkbox"/> Yes				
<input type="checkbox"/> No				

Medical History page 2 (2)

Does patient have history of diseases/disorders/surgeries in any of these systems?	Diagnosis	Onset Date mmm yy (at least year)	Resolution Date mmm yy (at least year)	Grade 1-4
Reproductive				
<input type="checkbox"/> Yes				
<input checked="" type="checkbox"/> No				
Neurological				
<input type="checkbox"/> Yes				
<input checked="" type="checkbox"/> No				
Psychiatric/psychological				
<input type="checkbox"/> Yes				
<input checked="" type="checkbox"/> No				
Musculoskeletal	<i>Rheumatoid Arthritis</i>	<i>Jan 18</i>	<i>Ongoing</i>	<i>3</i>
<input checked="" type="checkbox"/> Yes				
<input type="checkbox"/> No				
Allergies				
<input type="checkbox"/> Yes				
<input checked="" type="checkbox"/> No (Include Reactions)				
Other				
<input type="checkbox"/> Yes				
<input type="checkbox"/> No				

Completed By: _____ Date: _____

TRUST Trial Eligibility Form – Clinical Screening

Site No: 01 Screening number: 10011 Subject Initials: JP

Page 1 of 2

Visit Date: 02 / SEP / 19 (DD/MMM/YY)

Date of Birth: 12/DEC/78

Age: (years) 40

Sex (M/F): F

1. Inclusion Criteria	YES	NO	NA
i. ASA class I-III	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
ii. Patients able to give written informed consent or Witnessed oral consent	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
iii. Patients requiring general anaesthesia	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
iv. Patients aged 18 – 65	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
v. Pre-menopausal women must be using a barrier form of contraceptive, be surgically sterilised, or have an IUCD in place	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
vi. Negative pregnancy test for women with child bearing potential	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If No is selected for any of the criteria above the patient is not eligible for the trial.

2. Exclusion Criteria	YES	NO
Page 2 of 2		
i. History of dementia or difficulty in providing informed consent	<input type="checkbox"/>	<input checked="" type="checkbox"/>
ii. Patients with chronic obstructive pulmonary disease (COPD)	<input type="checkbox"/>	<input checked="" type="checkbox"/>
iii. Patients with a history of ischaemic heart disease (IHD)	<input type="checkbox"/>	<input checked="" type="checkbox"/>
iv. Patients with a haemoglobin concentration of less than 10g dl ⁻¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>
v. Patients with a history of known difficulty in intubation or with an anticipated challenging airway	<input type="checkbox"/>	<input checked="" type="checkbox"/>
vi. Pregnancy	<input type="checkbox"/>	<input checked="" type="checkbox"/>
vii. Patients with a history of allergy to any of the medications used in the study (Suxamethonium, Propofol, Rocuronium, Sugammadex)	<input type="checkbox"/>	<input checked="" type="checkbox"/>

TRUST Trial Eligibility Form – Clinical Screening

Site No: 01 screening No: 10011 Subject initials: JP

If YES is selected for any of the criteria above the patient is not eligible for the trial.

3. Confirmation of Eligibility	YES	NO
Is the patient eligible for the trial i.e. they have met all the inclusion criteria and none of the exclusion criteria?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Eligibility confirmed by:		
Name (print): <u>Dr Paul Johnson</u> Signature: <u>P Johnson</u>		
Date: <u>02</u> / <u>SEP</u> / <u>19</u> - (DD/MMM/YY)		

Appendix C – Answers to Questions/Mock Resource Exercises

Section 5 answers

1. To identify the potential risks to participants, the organisation and the reliability of results.
2. Yes. Examples of when a risk assessment may need updating are: protocol amendment, RSI update, a change to the inclusion and/or exclusion criteria.
3. (E)
4. High

Section 6.1 answers

1. (B) Discuss with your trial contact back at the CTU/sponsor office by phone/VC whilst on-site.
2. (A) Yes
3. (A) Yes
4. (C) Both
5. (A) Yes
6. (A) Submit a report of what you were able to monitor. *Note: if critical/high risk data could not be checked, a return to site may be required.*

Section 6.2 answers

1. (A) Yes
2. (A) Yes
3. (B) No
4. All. Note: it depends on the finding, any critical findings (e.g. potential serious breach), the site research team should be contacted as soon as possible. Less critical findings (e.g. missing initials on a delegation log) can be sent later in the MVR.
5. (E) All

Section 6.3 answers

1. (A) both can change
2. Process as a protocol deviation
3. Not in all circumstances. In the first instance, the site should be contacted to ascertain if there could be an underlying reason (e.g. is it due to the participant population recruited at that particular site).
4. No, it depends on a number of factors surrounding the trial parameters.
5. (F) Any of the above

Central Monitoring Resource exercise

The main advice is to follow your escalation plans in the Monitoring Plan. For example, in our monitoring plans we often plan to discuss at the escalation meeting the sites with more than 20% of data queries outstanding for more than 3 months i.e. sites F,G and K.

Similarly, for example, we often plan to discuss at the escalation meeting the sites with less than 50% target recruitment i.e. A, B, F, G and J.

Sometimes our plans note an escalation action for sites appearing in more than one category i.e. F and G in this case.

Fictitious consent forms

Fictitious Consent Form 1 – the patient has not initialed item 7 of the consent form & Sharon Smith (the person taking consent) has not recorded the date she signed the consent form

Fictitious Consent Form 2 – the patient's name at the top of the consent form (Jane Green) does not match the name given in the signature section (Joan Green), the consent items require the patient to initial to confirm their understanding of each item, but the patient has ticked each box & the dates of signature of the patient and person taking consent do not match.

Fictitious source documents and medical notes

The Research Nurse assisted in completion of consent form. Review the consent form and determine what sections were completed by the Research Nurse. Was a witness present? Is additional documentation required to fully explain how consent form was completed?

The pregnancy test was not completed. According to the details in the Eligibility form, inclusion criteria vi was not met 'Negative pregnancy test for women with child bearing potential'. This participant should not have been confirmed as eligible on this occasion.

Appendix D – References

1. The Medicines for Human Use (Clinical Trials) Regulations 2004 UK Statutory Instruments 2004 No. 1031 (as amended)
<https://www.legislation.gov.uk/ukxi/2004/1031/schedule/1/made>
2. ICH harmonised guideline integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2) ICH Consensus Guideline. <https://ichgcp.net/>
3. MHRA Good Clinical Practise Guide (Grey Guide) 2012
4. MRC/DH/MHRA Joint Project Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products:
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf
5. Diaz-Montana, C., Cragg, W., Choudhury, R., Joffe, N., Sydes, M. and Stenning, S. (2019) Implementing monitoring triggers and matching of triggered and control sites in the TEMPER study: a description and evaluation of a triggered monitoring management system. *Trials* [20] Article number 227
(<https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3301-z>)
6. MHRA and HRA Joint statement on seeking consent by electronic methods Sep 2018 <https://s3.eu-west-2.amazonaws.com/www.hra.nhs.uk/media/documents/hra-mhra-econsent-statement-sept-18.pdf>
7. On-site access to Electronic Health Records by Sponsor representatives in clinical trials - GOV.UK 2020 (<https://www.gov.uk/guidance/on-site-access-to-electronic-health-records-by-sponsor-representatives-in-clinical-trials>)
8. Kirkwood, A., Cox, T. and Hackshaw A (2013) Application of methods for central statistical monitoring in clinical trials. *Clinical Trials* 2013; 10: 783–806. DOI: 10.1177/1740774513494504
9. The Research Governance Framework for Health and Social Care
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/139565/dh_4122427.pdf
10. MHRA Guidance on legislation Clinical investigations of medical devices – guidance for investigators
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/989421/Information_for_clinical_investigators_-_May_2021.pdf

Additional useful links

NIHR Clinical Trials Toolkit - <https://www.ct-toolkit.ac.uk/routemap/trial-management-and-monitoring/>

Monitoring in practice – How are UK academic clinical trials monitored? A survey
<https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3976-1>

Appendix E – Greener monitoring

Appendix E – Greener monitoring” was added to this handbook in December 2024 without further review by the MHRA.

This appendix is also available as a stand-alone document at <https://ukcrc-ctu.org.uk/download/20347/?tmstv=1733147314>.

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1. Abbreviations

CTU – Clinical Trials Unit

EHR – Electronic Healthcare Records

GCP – Good Clinical Practice

NIHR – National Institute for Health and Care Research

SDV – Source Data Verification

UKCRC - UK Clinical Research Collaboration

UKTMN – UK Trial Managers' Network

2. Background

Healthcare contributes an estimated 4-5% of global greenhouse emissions^[1], and clinical trials contribute to this overall footprint^[2, 3, 4]. Initiatives are underway in the UK to identify ways to de-carbonise healthcare, and as clinical trials are considered a fundamental part of routine health and social care, we must include clinical trials in our efforts to decarbonise. Many human activities result in the emission of greenhouse gases, like carbon dioxide and methane, because they require energy which is produced by burning fossil fuels. Decarbonisation means stopping or reducing the greenhouse gas emission of a particular process.

The travel associated with on-site monitoring of clinical trials contributes significantly to a clinical trial's carbon footprint and from recent studies can equate to roughly 10-15% of a trial's overall footprint^[3, 4]. As a community of clinical trialists, there are ways that we can consider the environment in how we design and deliver trials. However, there is a clear need to balance this with the risk-based approach to conducting trials and compliance with the protocol, GCP and regulatory requirements. It is also important to ensure that any proposed changes to monitoring practice do not adversely impact trial resources.

3. Resources

A resource developed to help UK health researchers consider sustainability of study design is the [NIHR Carbon Reduction Guidelines | NIHR](#). These guidelines include recommendations for 'sensible clinical trial monitoring'.

The Low Carbon Clinical Trials group published a [strategy to reduce the carbon footprint of clinical trials - The Lancet](#), and a number of initiatives are underway in line with that strategy.

The NIHR funded a project to develop methodology and guidance for estimating the carbon footprint of academic clinical trials and their component activities, to inform future lower carbon trial design. The associated [guidance](#) has now been published for use by the academic trials community and drop in clinics to support trialists in using this method are held monthly (contact cict-icrctsu@icr.ac.uk for more information).

The NIHR MRC Trials Methodology Partnership have convened a group to facilitate research and collaboration in the area of [Greener Trials](#). If you are interested in finding out more or joining the group, see Expression of Interest details on the TMRP website.

¹ Karliner J et al Health care's climate footprint. Health Care Without Harm, Reston, VA2019

² Lyle K, Dent L, Bailey S, Kerridge L, Roberts I, Milne R et al. Carbon cost of pragmatic randomised controlled trials: retrospective analysis of sample of trials BMJ 2009; 339:b4187 doi:10.1136/bmj.b4187

³ Griffiths J, Fox L, Williamson PR on behalf of the Low Carbon Clinical Trials Group. Quantifying the carbon footprint of clinical trials: guidance development and case studies BMJ Open 2024;14:e075755. doi: 10.1136/bmjopen-2023-075755

⁴ Mackillop N, Shah J, Collins M, et al. Carbon footprint of industry-sponsored late-stage clinical trials BMJ Open 2023;13:e072491. doi: 10.1136/bmjopen-2023-072491

4. Recommendations

The above resources can be used within the scope of trial monitoring activities to identify ways in which monitoring processes can be designed (for new trials) and implemented (in new and ongoing trials), with consideration given to greenhouse gas emissions resulting from personal, trial, and institutional level activities. By raising awareness and sharing strategies to reduce carbon consumption, the academic monitoring community can play a part in reducing carbon emissions from health research. Global change requires engagement and commitment at all levels and small, practical steps have the potential to have a meaningful impact when implemented on a large scale.

The recommendations below pertain to academic trial monitoring activities. For more information about other aspects of trial design and delivery, please refer to the resources given above.

4.1. Institutional level

1. Adhere to institutional level guidance on sustainability initiatives, relating to energy saving measures, commuting and sustainable travel.
2. Maximise use of institutional level hybrid-working policies, to enable monitoring staff to minimise unnecessary travel between monitoring visits. Promote the use of public transport and incentives for using zero-emission vehicles/transport for commuting.

4.2. CTU level

3. Use email, video conferencing and telephone as the main means of communication between sites and monitors to avoid the use of paper and postage.
4. Produce monitoring reports electronically and share via a cloud-based systems to facilitate review and response in a timely manner, removing the need for paper versions.
5. Make use of the NIHR Study Support Service to help engage with sites and monitor performance (e.g. collating site level information to provide study-wide oversight).
6. Consider whether field-based monitors could monitor specific geographical areas to reduce the travel time to sites.
7. Work across trial portfolios to identify monitoring activities which can be carried out for more than one trial at a given site.

4.3. Trial level

8. Consider NIHR carbon reduction guidelines when designing new trials in particular in avoiding the collection of unnecessary data.
9. Develop a robust trial risk assessment with clearly defined critical data, maximising the use of central and remote monitoring, where appropriate. See the [UKCRC Monitoring Handbook](#) for guidance and references on this topic.
10. Conduct robust feasibility assessments to ensure that only sites which can deliver the trial are opened.
11. Consider where electronic documents can be provided to sites instead of printed versions. Where possible electronic documents should be reviewed remotely.
12. Decide whether site initiation visits and training activities need to be in-person or if they can be done remotely. If a visit to the site is important, consider if initial training could be remote, with an on-site visit once recruitment has started to provide additional training and combine with monitoring.

13. Ensure the trial monitoring plan is developed with a proportionate approach to monitoring. On-site visits should be reserved for essential activities and where review of critical data which cannot be done centrally/remotely.
14. Investigate the use of direct access to electronic healthcare records (EHRs) for remote source data verification (SDV).
15. Investigate use of e-consent strategies where possible and appropriate ^[5], to reduce patient travel specifically for informed consent.
16. Where direct access to EHRs cannot be achieved, other SDV strategies could be considered, (e.g. the remote review of redacted source documents).
17. Where triggers are identified during central monitoring, use remote monitoring as an escalation strategy. Where issues cannot be resolved via remote monitoring, consider if an on-site visit is the appropriate escalation.

4.4. Resourcing & travel for on-site visits

18. Consider more sustainable modes of transport, for example replacing driving and short-haul flights with public transport.
19. Consider combining site visits that are geographically close to each other, to reduce longer distance travel frequency.
20. Ensure the number of data items subject to SDV is proportionate to the risks, so that maximum value can be gained from a single day visit and reducing the need for a second visit.
21. Combine the provision/collection of site materials with a site visit to avoid the need for separate shipments.

4.5. CTU staff training

22. Utilise online resources to train new monitoring staff (e.g.: [UKCRC Guidance for CTUs](#)).
23. New monitors should shadow existing staff during remote visits prior to an on-site visit to reduce the number of training visits needed.
24. Encourage external groups (UKCRC Registered CTU Network, UKTMN, etc.) to hold conferences, meetings and training activities remotely to maximise participation but significantly reduce the need for travel and overnight stays.

4.6. Individual level

25. Organise workspace to maximise natural light and moderate temperature in order to use fewer resources for heating and lighting.
26. Travel on foot, bike or use public transport rather than using the car.
27. Take a refillable water bottle and re-usable hot drink cup for the day.
28. Take a packed lunch, with locally sourced and seasonal non-meat/dairy content, carried in re-usable packaging.
29. Plan on-site visits well in advance to maximise activities for minimal travel.
30. Share strategies with colleagues and other stakeholders to promote individual actions and potential benefits.
31. Challenge organisational processes where sustainability may not be prioritised.

⁵ Mitchell E et al. e-Consent in UK academic-led clinical trials: current practice, challenges and the need for more evidence. *Trials* 24(1) 2023 doi: [10.1186/s13063-023-07656-8](https://doi.org/10.1186/s13063-023-07656-8)

Appendix A – Case Studies

Case Study 1 Quantifying the carbon footprint of monitoring: comparing on-site, remote and central monitoring

Quantifying the carbon footprint of monitoring: comparing on-site, remote and central monitoring

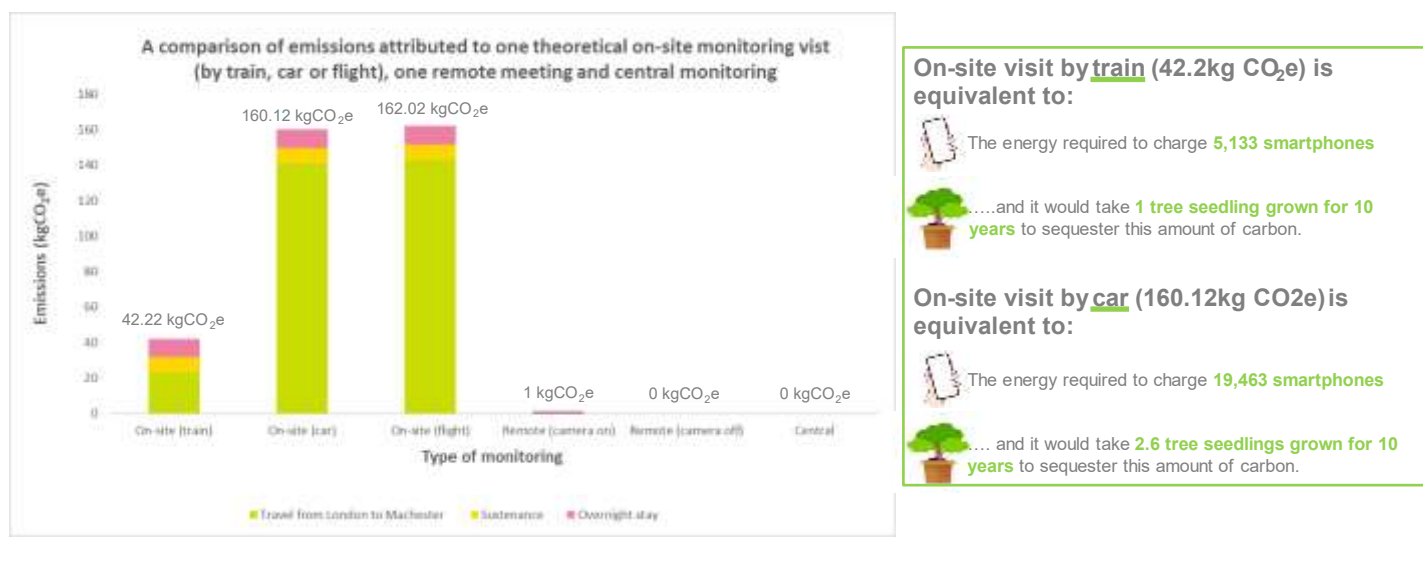
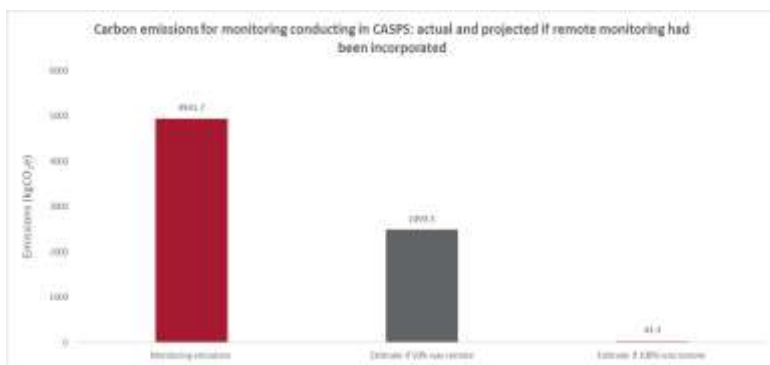


Figure 1. The above summarises the carbon footprint of a theoretical monitoring visit, with the monitor being based in London, and the participating site being in Manchester. The bar chart displays the difference in carbon footprint if the monitoring visit was conducted on-site with travel by train, car or plane compared with the visit being conducted remotely (with and without a video camera) or via central monitoring. The carbon footprint was calculated using the NIHR-funded [method and guidance](#) to carbon footprint clinical trials. The resulting estimated carbon footprint can be considered in a number of ways; in this example we have portrayed the footprint in terms of the energy required to charge a smart phone and the number of newly planted tree seedlings required to sequester the amount of carbon generated.

What is the impact of swapping on-site visits with remote monitoring?

CASPS was a phase II, international CTIMP with prospective on-site monitoring visits, which totalled:

- 35 on-site visits in the UK
- 8 on-site visits in Spain
- 8 on-site visits in Australia



100% on-site visits (4941.7kg CO₂e)



Energy required to charge **601,121 smartphones**
 Would take **81.7 tree seedlings grown for 10 years** to sequester this carbon

50% on-site: 50% remote visits (2493.5kg CO₂e)



Energy required to charge **303,316 smartphones**
 Would take **41.2 tree seedlings grown for 10 years** to sequester this carbon

0% on-site: 100% remote visits (43.3kg CO₂e)



Energy required to charge **5,267 smartphones**
 Would take **1 tree seedlings grown for 10 years** to sequester this carbon

Figure 2. The second example summarises the carbon footprint of all on-site monitoring visits conducted in the CRUK-funded, ICR-CTSU managed CASPS trial (CRUK/10/021). The carbon footprint was calculated using the NIHR-funded [method and guidance to carbon footprint clinical trials](#). We have estimated the reduction in carbon emissions that would have resulted if half or all of the monitoring in CASPS had been conducted remotely. As previously, the estimated carbon footprint can be considered in a number of ways, in this example we have portrayed it in terms of the energy required to charge a smart phone and the number of newly planted tree seedlings required to sequester the amount of carbon generated.

Appendix B – References

1. Karliner J et al Health care's climate footprint. Health Care Without Harm, Reston, VA2019
2. Lyle K, Dent L, Bailey S, Kerridge L, Roberts I, Milne R et al. Carbon cost of pragmatic randomised controlled trials: retrospective analysis of sample of trials BMJ 2009; 339:b4187 doi:10.1136/bmj.b4187
3. Griffiths J, Fox L, Williamson PR on behalf of the Low Carbon Clinical Trials Group. Quantifying the carbon footprint of clinical trials: guidance development and case studies BMJ Open 2024;14:e075755. doi: 10.1136/bmjopen-2023-075755
4. Mackillop N, Shah J, Collins M, et al. Carbon footprint of industry-sponsored late-stage clinical trials BMJ Open 2023;13:e072491. doi: 10.1136/bmjopen-2023-072491
5. Mitchell E et al. e-Consent in UK academic-led clinical trials: current practice, challenges and the need for more evidence. Trials 24(1) 2023 doi: [10.1186/s13063-023-07656-8](https://doi.org/10.1186/s13063-023-07656-8)