SOP

MONITORING & OVERSIGHT OF RESEARCH ACTIVITY

SETTING Trust wide

FOR STAFF All staff involved in research

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-	V1.7	20/03/15	20/03/15	Annual review of SOP and minor updates made	Jess Bisset	Diana Benton
15/01/2016	V2.3	15/01/16	16/03/2016	Major update to previous monitoring SOP	Jess Bisset	Diana Benton
November 2016	V2.4	23/12/16	24/01/17	Annual review of all SOPs and minor updates made	Jess Bisset & Sarah Bishop	Diana Benton

1. Introduction

UHBristol has a responsibility for oversight of research conducted on its premises or which it sponsors. These responsibilities are driven by the Department of Health's Research Governance Framework for Health and Social Care (RGF) and the Medicines for Human Use (Clinical Trials) Regulations. Consequently, the Research & Innovation Department (R&I) undertakes to monitor research conducted within UH Bristol or where UH Bristol is acting as a research sponsor.

The purpose of monitoring is to ensure:

- That the dignity, rights, safety and wellbeing of the subjects participating in the study are protected
- The conduct of the study is in compliance with the current approved protocol/protocol amendment(s), with Good Clinical Practice (GCP) and with the applicable regulatory requirements
- The reported trial data are accurate, complete and verifiable from the source

2. Purpose and Scope

The purpose of this document is to describe the risk based procedures that will be used by UH Bristol R&I to monitor and give oversight of research sponsored by UH Bristol, conducted on Trust premises or which fall under a Service Level Agreement with other organisations.

In scope

This SOP applies to:

- UH Bristol and University of Bristol sponsored research selected for monitoring.
- Research conducted at UH Bristol which has been assessed as requiring monitoring but does not have sufficient external monitoring in place. This assessment is made by the R&I department.

Out of scope

This SOP does not apply to externally sponsored research which already has sufficient monitoring in place as assessed by a member of the R&I department. This SOP does not describe monitoring procedures carried out by personnel outside of R&I on behalf of UH Bristol as sponsor (e.g. where a study is managed and monitored by a Clinical Trials Unit).

3. Definitions/Abbreviations

AE	Adverse Event
ATIMP	Advanced Therapy Investigational Medicinal Product
CTIMP	Clinical Trial of an Investigational Medicinal Product
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
PIS	Patient Information Sheet
PI	Principal Investigator
RGF	Research Governance Framework
RGT	Research Governance Team
RMF	Research Management Facilitator
R&I	Research & Innovation Department
SAE	Serious Adverse Event
SUMP	Study set Up and Management Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
UoB	University of Bristol

The Sponsor is defined in 2 ways:

RGF: Sponsor: “Individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study”
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/139565/dh_4122427.pdf

Clinical Trials Regulations: ‘sponsor’ means, in relation to a clinical trial, the person who takes responsibility for the initiation, management and financing (or arranging the financing) of that trial.”
http://www.legislation.gov.uk/uksi/2004/1031/regulation/3/made

4. Risk Assessment and Risk Management

Prior to commencement in UHBristol, all research is reviewed and assessed by UHBristol R&I team in accordance with current national requirements. This is in order to support sponsor processes and ensure research can be delivered in the NHS. The areas reviewed include, but are not limited to, the following:

- Regulatory and contractual requirements
- Sponsorship arrangements
- Essential documents
- Consent
- Study type
- Data and tissue
- Research team
- Recruitment and retention
- Financial arrangements
- Resource use
- Organisational responsibilities

Please note for externally sponsored studies some of these areas will be reviewed by the Health Research Authority (HRA) as part of HRA assessment rather than within R&I, for example; data and tissue, essential documents etc.

During the assessment carried out by an allocated Research Management Facilitator (RMF), at the time of Capacity and Capability review, risks of conducting the research are identified. These are then documented, along with any mitigating circumstances in the monitoring section of the Capacity & Capability Review Workflow on EDGE. The RMF completing the study assessment should consider whether any monitoring of the study is required by reviewing the identified risks and referring to the R&I monitor and Research Operations Manager for guidance. Any monitoring requirements should be captured in the monitoring section of the Capacity & Capability Review Workflow on EDGE . If applicable, the RMF should flag the study to the R&I Monitor(s) who, in consultation with the Research Operations Manager, should add the study and type of monitoring to be conducted to the monitoring record spreadsheet which is located on the R&I J Drive. If the RMF is unclear whether a study should be identified for monitoring, they should raise the issue at the weekly R&I Operational meeting where a member of the senior management team should confirm requirements.

Examples of major risks which would flag the study for potential monitoring:

- UHB/UoB Sponsored CTIMP.
- UHB/UoB Sponsored.
- CTIMP with risk of harm and no clear monitoring arrangements.
- UHB lead site with no clear monitoring arrangements.
- Large scale research studies (200-250).
- Patients with poor prognosis.
- Patients with incapacity.
- Participants are children.
- Significant change from standard care/withholding care.
- Highly invasive clinical intervention– e.g. surgical techniques, radiotherapy & cytotoxic drugs.
- ATIMP (Advanced Therapy Investigational Medicinal Products) trial

During the course of a study there may be other reasons to flag the study for monitoring. For example, the research team in liaison with an RMF regarding study progress may highlight an issue relating to conduct, recruitment, governance or other reasons. For UoB sponsored studies, a member of University of Bristol (UoB) Research Governance Team (RGT) may highlight a study for monitoring, or new risks may be identified during planned monitoring visits which require additional monitoring. Whenever a study is flagged for monitoring, the R&I monitor should add the study to the monitoring record spreadsheet which documents identified risks and proposed monitoring. This spreadsheet is reviewed quarterly by the R&I monitor(s) with the Research Operations Manager. In addition, the UoB RGT should be alerted when a UoB study has been identified for monitoring, once the monitoring has taken place and receive copies of monitoring findings and responses.

5. Sponsor Set up and Management and Green Light Processes

For UH Bristol Sponsored Clinical Trials of Investigational Medicinal Products (CTIMPs), as soon as the sponsorship letter has been issued, the Research Projects Manager (Sponsored Trials) should organise a Study Set Up and Management Plan (SUMP) meeting. The purpose of the meeting is to review, document and agree the risks identified, agree any actions required to mitigate identified risks and document the study management plan for oversight of the research. Further details can be found in the R&I Sponsorship SOP.

6. Monitoring Plan

For UH Bristol and UoB Sponsored CTIMPs, a Monitoring Plan should be developed by the Research Projects Manager and R&I monitors during study set-up. The purpose of the monitoring plan is to describe the proposed monitoring to be undertaken throughout the course of the trial. The first version of the Monitoring Plan will detail the risks identified from the initial study assessment or SUMP. If an assessment does not exist (e.g. UoB studies carried out externally to UH Bristol), risks which have been identified/raised by the Sponsor, and the mitigating actions addressing those risks will be documented as part of the Monitoring Plan by the R&I Monitor(s).

Where a trial is complex and monitoring requirements are unclear an initial meeting may take place with the Chief Investigator (CI) and Point of Contact (PoC) to discuss monitoring and inform the Monitoring Plan. As a study progresses and monitoring is carried out, the Plan should be updated regularly by the R&I monitor(s) in order to document any monitoring undertaken, identification of new risks and subsequent proposed monitoring. The initial Monitoring Plan and any subsequent versions should be sent to the Chief Investigator and Sponsor (where the Sponsor is not UH Bristol) by the R&I monitor(s). The Monitoring Plan should be version controlled.

Monitoring responsibilities may be delegated to a Clinical Trials Unit, if appropriate. This should be documented on the Monitoring Plan.

For non CTIMPs the proposed monitoring should be recorded on the R&I monitoring record spreadsheet stored on the R&I J Drive. When the monitoring has been completed, or as the proposed monitoring requirements change, the record should be updated by the R&I monitor(s) on the spreadsheet. The monitoring record should be held confidentially by the R&I department. The Research Operations Manager should update the Head of Research Governance on the

planned monitoring of non CTIMPs sponsored by UoB within the upcoming quarter; the UoB RGT should be alerted by UHBristol R&I once monitoring has taken place and updated about monitoring findings and responses.

6. Types of Monitoring

The monitoring conducted by R&I will be targeted to specific elements of the study requiring review. For example, where a risk is identified during study setup whereby a research team is unfamiliar with required data management processes, a monitoring visit will take place to review data management and carry out source data verification.

In order to use monitoring resources effectively and efficiently, various target monitoring types have been developed as follows:

Self-monitoring

The R&I monitor should email a self-monitoring form to the PI and PoC to check recruitment, safety and overall study progress, including changes to the research team, training needs and status and study document updates. The form should be returned to the monitor **within two weeks of being sent to the PI/PoC;** the R&I monitor should chase a response if the completed form is not received on time. This form of monitoring is an opportunity for the research team to identify any issues with the study which need addressing. If any issues are identified, follow up via telephone calls or emails will be made by the R&I monitor until the issues are resolved. All actions will be documented. If the self-monitoring raises any concerns for the R&I monitor a site visit may be arranged.

Study set up visit

For new and inexperienced principal investigators a study set up monitoring visit may be offered prior to or at the point of the study starting. During the visit the R&I monitor should provide to the investigator/Point of Contact a copy UH Bristol's site file template (see essential research documents SOP) and explain the documentation that should be kept within a Site File, referring to the essential research documents SOP. Depending on the study type and identified risks, the R&I monitor should discuss key elements of the trial, e.g. informed consent, how to document PI oversight, data collection and verification etc. The principal investigator should use this visit as an opportunity to raise any queries with the R&I study monitor prior to the study start.

Site File Review

A site file review may be conducted to ensure it is complete. This may take place before the study starts or at any other time during the study. The purpose of the site file review is to ensure essential documentation is being stored correctly according to the requirements of Good Clinical Practice and in accordance with the UHBristol SOPs (as relevant). A site file review is not required at every site visit. The decision to conduct a site file review should be determined by the risks identified during approval of the study and/or where issues raised at a first site visit have not been adequately addressed. The standalone 'site file review template' which should be used for this visit is based on the essential documentation checklist (section 8) of ICH GCP E6.

Eligibility review

An eligibility review should be carried out on a sample of patients (at least 10% of total recruited) if there is a risk identified and documented in the study assessment - e.g., CTIMPs with inexperienced investigators or complex eligibility processes. The R&I monitor should use the

'eligibility review monitoring' standalone template to document the review. During the visit a member of the research team should be asked to describe how eligibility is reviewed, assessed and documented. For CTIMPs, the eligibility review should include ensuring that the decision regarding a patient's eligibility was made by an appropriately qualified doctor or dentist (if applicable), unless other arrangements have been agreed and documented in advance by the sponsor.

Informed consent review

An 'informed consent review' monitoring visit should be carried out for studies which have complex arrangements for informed consent e.g., parental consent/carer consent/incapacitated adults, or where risks have been identified in the study assessment relating to consent. The whole process of informed consent should be reviewed, including, but not limited to: checking the correct and current, REC approved versions of the patient information sheet (PIS) and informed consent form (ICF) are in use; that the ethically approved process is being followed for informing patients about the research, including ensuring they have adequate time to consider participation: that consent is being appropriately documented: and that members of staff taking informed consent have documented that they are adequately qualified and that this task has been delegated to them by the PI.

First Patient First Visit

For high risk trials e.g. using Advanced Therapy Investigational Medicinal Products (ATIMPs) it may be necessary to conduct a monitoring visit as soon as the first patient is recruited. During this visit the following monitoring elements should be conducted for the first patient: site file review, eligibility review, informed consent review and data management review. This should allow any issues identified to be rectified prior to further recruitment into the trial.

Protocol Compliance

The risks identified and documented during set up and assessment of a study will be used to guide the protocol compliance review. The 'protocol compliance monitoring' standalone template should be used.

The key aspects to be assessed during this type of monitoring visit include, but are not limited to the following:

- Verifying, for Investigational Medicinal Product(s) (IMPs):
- That the IMP(s) is/are supplied only to the participants who are eligible to receive it and at the dose(s) specified in the protocol
- That participants are provided with necessary instructions on proper use, handling, storage, and return of the IMP(s) (as applicable)
- That the receipt, use, and return of the IMP(s) is controlled and documented
- That the destruction of unused IMP(s) complies with applicable regulatory requirements and is in accordance with the protocol
- Verifying that the Investigator follows the approved protocol and all subsequent approved amendments to the protocol and associated documentation
- Checking the accuracy and completeness of the Case Report Form (CRF) entries, source documents and other study related records against each other, e.g. that:
- The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents
- Any dose and/or therapy modifications are adequately documented for each of the study participants
- Adverse Events (AEs) (including serious AEs), concomitant medications and illnesses are reported in accordance with the protocol and applicable SOPs

- Visits that the participants fail to attend, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs
- All withdrawals of enrolled participants from the study are reported and explained on the CRFs
- Reviewing CRF entry error, omission or illegibility.
- Checking the process by which changes should be made, and whether this process has been followed. This includes ensuring changes are made, explained (if necessary), and initialled by the Investigator or an authorised member of the research team
- Checking systems are in place to ensure compliance with data protection
- Checking the transportation and storage arrangements for any samples taken as part of the protocol

Pharmacovigilance

For UH Bristol and UoB sponsored studies this type of monitoring may be carried out within the R&I department to audit compliance with the UH Bristol Research Safety Reporting SOP by the R&I department. Where any risks or issues are identified with pharmacovigilance a visit may be undertaken with the study team to assess relevant paperwork including, but not limited to the process for assessing AEs (including SAEs), PI and CI oversight and Data Monitoring Committee reviews. This visit should also review whether all SAEs that are known to have happened have been reported, and whether all events documented in the source data that meet the definition of an SAE have been recorded and reported. The 'pharmacovigilance monitoring' standalone template will be used for this type of monitoring.

Data Management

If risks have been identified concerning data management (e.g. an inexperienced research team, multi-centre trials, high volume of data, complex database design/validation) a 'data management monitoring' visit should be carried out. The R&I monitor should refer to the Data Management Plan (if in place for a study) and decide in consultation with the R&I Operations Manager the percentage of data that should be reviewed. The R&I monitor should then carry out depending on the risk identified, either source data verification, computer system validation procedures, the whole life cycle of data management within the study or all of these.

Laboratory and Pharmacy

A 'lab monitoring visit' or 'pharmacy monitoring visit' using the applicable standalone templates may be carried out either to review systems and processes within the departments (e.g. to review the systems and processes that are in place and how they apply to a collection of studies) or specifically to monitor a particular study.

The key aspects to be assessed during this type of monitoring visit within **Pharmacy** include, but are not limited to, the following:
Verifying, for Investigational Medicinal Product(s) (IMPs), that:

- storage temperature and conditions are acceptable and comply with requirements
- sufficient supplies are in place throughout the study
- a risk assessment of storage conditions has been carried out where IMP is stored externally to Pharmacy
- appropriate labelling (in accordance with Annex 13) and handling of IMP according to manufacturer's requirements is in place
- IMP accountability

- unblinding procedures are in place and working (i.e. a test has been carried out)
- the destruction of unused IMP(s) complies with applicable regulatory requirements and is in accordance with the protocol

The key aspects to be assessed during this type of monitoring visit within **Labs** include, but are not limited to, the following:

Verifying that
- Consent for sample collection is in place
- Appropriate sample labelling is in place
- Sample storage and handling are appropriate and documented
- Destruction of samples is in compliance with ethical approval and procedures are in place for this
- Validation of methods and calibration of equipment has taken place

Recruitment and study progress

Each study entered onto the EDGE database at UH Bristol (the Trust's research management database) should have an RMF allocated to oversee the study progress. During the course of a study, both the R&I Information Officer and the allocated RMF should:
- Monitor the research management database records for accuracy, checking key essential documents where appropriate and updating EDGE notes as applicable.
- Maintain oversight of recruitment issues and study progress

Close out visit

If a close out visit is included within the Monitoring Plan, the R&I monitor should record the expected study end date on the monitoring record spreadsheet. Within 2 months prior to the expected date of closure, the R&I monitor should book a visit and review arrangements for study closure and archiving. The 'close out monitoring visit' standalone template should be used.

7. Monitoring process and required response from research teams

The template forms to be used by the R&I monitor are part of the R&I standalone templates as referenced in the Authorship, Review, Revision and Approval of Research Procedural Documents produced by Research & Innovation SOP. These are found in the Quality Systems Documents folder on the electronic shared drive in R&I and are version controlled. Any queries regarding the standalone templates need to be referred to the Research Operations Manager.

The process is as follows:

Before the visit

- Identify study for monitoring
- R&I monitor(s) adds study to the monitoring record spreadsheet. The R&I monitor(s) should regularly review this with the R&I Operations Manager to prioritise studies to monitor in the upcoming quarter.
- R&I monitor(s) email or phone the Point of Contact/PI to arrange a suitable date for the visit. In setting up the visit, the R&I monitor(s) should make a request that any paperwork or resources to be reviewed during the visit are available e.g. medical notes, CRFs, databases, site file etc.
- If the study is co-ordinated by a trial co-ordinator the R&I monitor(s) will inform them if the monitor will require a meeting with the Research Nurse and/or Principal Investigator on the day of the visit.

During the visit

- A suitable space should be made available for the R&I monitor to carry out the monitoring.
- A Point of Contact in the research team should be available throughout the visit to answer any queries.
- The PI should also be available at some agreed point during the visit (or where this is not possible, soon after the visit).
- Verbal feedback should be provided by the monitor to the Point of Contact at the end of the visit
- The PoC should be informed of the next steps and any further monitoring required.

After the visit

- R&I monitor writes the report and sends to the Point of Contact and PI within 3 weeks (15 working days) of the monitoring visit. UoB RGT will also be sent a copy of the report by R&I monitor if it relates to a UoB sponsored study.
- Point of Contact/PI has 20 working days in which to respond.
- If there are any queries from the visit report these must be raised with the R&I monitor within 10 working days of receipt of the report.
- If no response is received from the monitoring report within 20 working days the monitor should send a reminder email for the report to be returned within 5 working days.
- If a response is still not received, the monitor shall escalate the issue to the Research Operations Manager and the study may be halted at this site. For studies monitored on behalf of UoB, the Head of Research Governance will be informed in order to agree further actions. Following receipt of responses to the monitoring report, the monitor should either request further information and enter into correspondence until all issues are resolved, or send a final email confirming that responses received are acceptable and that the report is closed.
- The monitor should update the monitoring record spreadsheet to move the selected study/identified monitoring to the 'monitoring complete' tab (filling in the relevant details) as a record of the monitoring conducted. If any further monitoring is required a new record will be created in the spreadsheet detailing the risks identified and the proposed monitoring. For studies monitored on behalf of UoB, the UoB RGT will be updated accordingly.

If any monitoring is undertaken for UH Bristol or UoB sponsored studies by personnel other than UH Bristol R&I, a copy of the monitoring report must be provided to the R&I department. The R&I monitor should review the contents of the report and decide whether any follow up or future monitoring is required.

Staff who undertake monitoring of UH Bristol or UoB sponsored studies must be appropriately trained. UH Bristol R&I will determine whether the monitoring staff are appropriately trained, either through line management and training of their own staff, or, for external staff, by review of qualifications and assessment of whether further training is required. Prior to monitoring by non R&I staff, sponsor agreement must be gained. For any monitoring carried out, a copy of the monitoring report must be provided to R&I. The R&I monitor will review the contents of the report and decide whether any follow up or future monitoring is required. This excludes any external monitoring carried out on UH Bristol or UoB sponsored studies by host organisations for their own purposes.

8. Monitoring Quality Assurance

In order to ensure delivery of high quality effective monitoring at UHBristol, the following quality assurance checks will be undertaken;

- Every quarter a selection of monitoring reports should be reviewed by the Research Operations Manager or another member of the Senior Management Team. Content, accuracy, completeness and timeliness of the reports will be checked.
- Ad hoc reviews of the monitoring process may also be carried out by a member of the Senior Management Team or the Team Leader. The purpose of these reviews is to check whether the processes described within this SOP are being followed. If the SOP is not being followed, feedback should be provided to the line manager of the R&I monitor(s), who will address the issues. One potential outcome is that the SOP requires review, and the appropriate mechanisms will be followed to enact changes.

The R&I Quality Management System will also be monitored for compliance by the R&I monitors. Any areas of non-compliance will be reported to the Research Operations Manager who will act accordingly (e.g. re-train staff, revise procedural documents if appropriate).

9. Research Sponsored by UH Bristol

Research sponsored by UH Bristol can be split into three main categories:

- Clinical Trials of Investigational Medicinal Products (CTIMP) or Clinical Investigations of Devices (CID)
- Non CTIMP interventional trials, e.g. Randomised Controlled Trials (RCTs) and surgical trials
- Non CTIMP non-interventional trials

Study type influences the risks that are identified and subsequent level of monitoring required. As an example, the potential different monitoring requirements due to study type have been described below:

Clinical Trials of Investigational Medicinal Products (CTIMP) or Clinical Investigations of Devices (CID)

- Study Set up and Management Plan meeting and discussion to be carried out by Research Projects Manager (Sponsored Trials) , research team and any other appropriate personnel (e.g. support departments)
- Sponsorship initiation checklist (green light) for external sites to be carried out by research team in liaison with allocated R&I monitor
- Setup visit with research team conducted by R&I monitor(s) if required
- Site visit usually to take place after the first patient has been recruited
- Data management visit
- SAE/SUSAR reporting oversight to be monitored and managed by the Research Projects Manager and RMFs
- Pharmacovigilance monitoring conducted by R&I monitor(s) if required
- Close down visit with research team

Non CTIMP Interventional Trials

- Set up visit with research team conducted by R&I monitor, if required
- Site visit subject to current monitoring selection process, in accordance with identified risks during approval process

- SAE/SUSAR reporting oversight to be monitored and managed by RMFs and, Research Projects Manager (Sponsored Trials) where applicable
- Pharmacovigilance monitoring visit conducted by R&I monitor(s) if required

Non CTIMP Non-Interventional Trials

- Subject to current monitoring selection process, in accordance with identified risks during approval process
- End date of each study to be confirmed or amended following contact with study team

Although studies should be monitored and managed in different ways according to the type of study and the agreed Monitoring Plan, all studies should be:

- Managed throughout their lifetime
- Have a named individual in R&I (an allocated RMF) assigned to keep regular track of status and recruitment. For CTIMPs, Clinical Trials of Investigational Medical Devices and selected complex interventional trials the Research Projects Manager (Sponsored Trials) will carry out this role
- Assessed during sponsorship (where applicable) and during approval or confirmation of capacity and capability (as required according to national guidelines). These assessments should identify study risks (to patient safety, data integrity and success to study delivery)
- Monitored for recruitment of first patient within 70 days of valid application received and progress of delivery to agreed time to target to be monitored throughout study lifetime by allocated RMF and Information Officer (IO)

10. Research Sponsored by University of Bristol (UoB)

The University of Bristol holds a Service Level Agreement (SLA) with UH Bristol. Under the Agreement the Trust undertakes to monitor and carry out pharmacovigilance for certain UoB sponsored studies. These activities should be carried out in accordance with the SLA, the identified risks, subsequent proposed monitoring and where applicable the study's specific Monitoring Plan.

11. Research Sponsored by Other Organisations

Monitoring should be carried out according to risks identified, a study-specific Monitoring Plan (where relevant) and in accordance with any agreement in place with the sponsor.

Appendix 1 – List of standalone templates and location

- **01 Monitoring plan**
- **02 Self-monitoring form**
- **03 Site File review**
- **04 Eligibility review monitoring visit**
- **05 Informed consent review**
- **06 Protocol compliance visit**
- **07 Pharmacovigilance monitoring visit**
- **08 Data management review**
- **08a Quality control monitoring spreadsheet (linked to 08 Data management review)**
- **09 Pharmacy monitoring visit**
- **10 Laboratory monitoring visit**
- **11 Close out visit**

These standalone templates are all located on the R&I shared drive under the Quality Systems Document Folder. They are version controlled and cannot be amended without appropriate sign off in accordance with the Authorship, Review, Revision and Approval of Research Procedural Documents Produced by Research & Innovation SOP.