Standard Operating Procedure

MANAGEMENT OF BREACHES IN RESEARCH

SETTING Trustwide for research sponsored by UHBristol

AUDIENCE All research staff involved in UH Bristol sponsored research

ISSUE This SOP relates to the identification and management of breaches in research sponsored by UH Bristol.

QUERIES Contact R&I department : Ext 20233 or research@uhbristol.nhs.uk

SOP number	SOP_018	**SOP Version**	1.1
Effective Date	22/FEB/2018	**Review Date**	22/FEB/2020

Document History

Review date	Version number	Version date	Effective date	Author/ Reviewer	Authorised by
-	V1.0	12/JAN/17	14/FEB/2017	Jess Bisset	Diana Benton
05/JAN/18	V1.1	05/JAN/18	22/FEB/2018	Jess Bisset	Katharine Wale

Version Number	Reason for change
Original V1.0	N/A
V1.1	Annual review and minor updates.

1. Introduction

All research must be conducted in compliance with the applicable regulations and approved research related documentation e.g. protocol, information sheets, etc. Any non-compliance must be captured, assessed and managed appropriately by the research team and sponsor delivering the research.

Many different breaches may be identified during the course of a study and terminology to describe those breaches may be interchangeable (i.e. protocol non-compliance can also be referred to as a protocol deviation or violation). There is no definitive guidance regarding the meaning of the term protocol violation and therefore it is not used in this document. Any unintended departure from the protocol is therefore referred to as a protocol deviation. All deviations are breaches.

A risk proportionate approach must be adopted for each study to determine how best to report breaches to the sponsor to allow pragmatic and effective assessment in compliance with applicable regulations.
Protocol waivers are prospective deviations or waivers to the protocol. These types of non-compliances are not acceptable. They constitute a deliberate breach of regulation 29 of SI 2004/1031:

'Subject to regulation 30, no person shall conduct a clinical trial otherwise than in accordance with – (a) the protocol relating to that trial, as may be amended from time to time in accordance with regulations 22 to 25'
An example of this is to allow subjects entry into a trial when the subjects do not meet one or more eligibility criteria of the approved protocol. If the eligibility criteria require amending, a substantial amendment will be submitted to the MHRA, REC and HRA.

2. Purpose

To describe the procedure for identifying and managing all types of breaches (serious and non-serious) of an approved research protocol and/or deviation of Good Clinical Practice (GCP). It describes both the role of the research personnel in identifying and notifying UH Bristol as sponsor of the breach and the role of UH Bristol as sponsor in appropriate management of the breach.

3. Scope

In Scope: UH Bristol sponsored research
Out scope: Research sponsored by other organisations whose own procedures should be followed. Breaches which are not related to research.

4. Responsibilities

All research staff delivering UH Bristol sponsored research have a responsibility to ensure that any identified breaches are processed in accordance with this SOP. This will include maintaining clear and comprehensive documentation of the breach, implementing corrective and preventative actions where appropriate and reporting to UH Bristol as sponsor where required.
All Research & Innovation (R&I) staff managing UH Bristol sponsored research have a responsibility to ensure that any reported breaches are reviewed for completeness, seriousness, have appropriate corrective and preventative actions in place including any onward reporting to the regulatory authorities are fully signed and documented and are managed in accordance with this SOP.

5. Abbreviations and Definitions

Abbreviations	
CAPA	Corrective and Preventative Action
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
GCP	Good Clinical Practice
ISF	Investigator Site File
MHRA	Medicines and Healthcare Products Regulatory Agency
R&I	Research & Innovation Department
REC	Research Ethics Committee
RMF	Research Management Facilitator
SAE	Serious Adverse Event
SMT	Senior Management Team
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

Definitions	
Breach	Any departure from the applicable regulations (e.g. Clinical Trials Regulations, Data Protection Act etc.), Good Clinical Practice, the approved protocol and any other applicable research documents e.g. SOPs. All deviations and non-compliances are breaches.
Protocol non-compliance	Any departure from the approved research protocol which is identified ***retrospectively***. This can also be referred to as a *protocol deviation*.
Deviation of the Protocol or GCP	Any unintended departure from the research protocol/GCP. Examples include but are not limited to: -Missed visit window (if patient did not attend) -Malfunctioning equipment -An incorrectly consented participant

6. Procedure

- Some breaches which occur during a research study may not necessarily require immediate reporting to the Sponsor. These types of breaches will be identified at study set up and reviewed during the course of the research.
- If the study is managed by an external trials unit and it has been agreed to follow their organisation's breaches SOP, the identification of what types of breaches need immediate reporting to the Sponsor will be managed by the trials unit and it is their responsibility to identify which breaches need immediate reporting to the Sponsor.
- For UH Bristol sponsored CTIMPs and complex interventional studies as managed by the R&I Research Projects Manager, an assessment will be undertaken at study set up with relevant study staff (including where applicable the statistician) of potential breaches and what triggers should be put in place (e.g. if exceeds a certain threshold) for reporting to sponsor as applicable. The *Potential Breaches reporting log (TMPL_055)* will be used to document this. For these types of breaches the sponsor and the research team will agree at study set up how Sponsor oversight will be maintained e.g. a quarterly review might be agreed as adequate. All breaches which do not fall into the above must be reported to the Sponsor as soon as the breach has been identified (unless otherwise agreed).

- The Investigator or delegated personnel must assess a breach as soon as it is identified and where required (as described above), report to the Sponsor within 24 hours of becoming aware of the event (unless it is the Sponsor that has identified the breach). This can be reported orally or in writing to Research@UHBristol.nhs.uk. Where an oral report has been received the personnel within R&I managing the study will record the conversation using *TMPL_056 File note* and will save it within the electronic study folder in the 'breaches' section.
- Where the breach is considered to have an impact on patient safety the Investigator must also call 0117 342 0233 immediately and speak to either the Research Projects Manager or the Research Management Facilitator (RMF) allocated to the study in R&I.
- A *Corrective and Preventative Action (CAPA) form (TMPL_057)* must be completed by the study team within 3 days of the initial notification to the Sponsor and sent to Research@UHBristol.nhs.uk for review unless the Sponsor confirms a CAPA is not required.
- Where a CAPA is not required, the decision should be fully documented in the Trial Master File (TMF) and Investigator Site File (ISF).
- The Research Projects Manager will review the breach for UH Bristol sponsored CTIMPs. For all other UH Bristol sponsored research the allocated RMF will review the breach and consult with any of the senior managers within R&I as required.

- The review of the breach by R&I will involve assessing whether the breach is considered serious (as defined in section 6.1 below). A senior management team member will make this decision, referring to the MHRA definitions as provided in 6.1, and whether onward reporting to regulatory authorities is required.
- The Sponsor will assess the CAPA for completeness and will also assess the adequacy of the corrective and preventative actions. The relevant personnel in R&I will liaise with the study team if any changes are required. Once agreed, the Sponsor and PI (and also support departments where applicable) must sign the CAPA form. This will be carried out within the required timelines if the breach is assessed as serious as described in section 6. For non-serious breaches, every effort must be made to complete and sign off the CAPA in a timely manner.
- The RMF/Research Projects Manager allocated to the study must document all correspondence relating to the breach, complete the breach database located on the R&I shared J Drive in the monitoring SAE-breaches database folder and discuss with the R&I monitors whether any triggered monitoring is required.
- The Investigator or delegated personnel must keep a log of all breaches identified throughout the trial which can be shared with the study statistician to ensure data integrity has not been affected using *TMPL_058 Study breaches log*; where agreed by sponsor an alternative template may be used.

6.1 Serious breaches

- The sponsor of a clinical trial is obliged to notify the licensing authority in writing of any ***serious breach*** **of**
    - the conditions and principles of GCP in connection with that trial; or
    - the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25, within 7 days of becoming aware of that breach.

- For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:
    - the safety or physical or mental integrity of the subjects of the trial;
    - the scientific value of the trial.

- It is the sponsor’s responsibility to review a breach and decide whether it fulfils the criteria set out above. Further details can be found on the MHRA website.
- For serious breaches the MHRA and Ethics committee **must be notified within 7 days of the breach being identified**. Where UH Bristol is Sponsor either the Research Projects Manager or the RMF in R&I will liaise with the research team in order to make the required notification. *TMPL_059 Serious Breach report form* will be used.
- Where the breach has a potential impact on patient safety, an assessment will be made by Sponsor and Chief Investigator of immediate actions required, for example: halting the trial; withdrawing a participant; closing study sites. Where there is an urgent safety concern the Chief Investigator and Principal Investigators will follow the required action as described in the SOP_009 Research Safety Reporting on urgent safety measures (or, other applicable documentation if it has been agreed to follow an external trial unit’s urgent safety reporting procedures). Where there is no urgent safety concern the proposed action may be discussed with the MHRA prior to implementation.
- All documentation relating to breaches must be stored in both the Investigator Site File where the breach was identified and in the Trial Master File.

6.2 SOP breaches

- Occasionally, the need may arise to deviate from an SOP. Alternatively, there may be situations where unplanned or accidental deviations from SOPs are discovered.

- Any *study specific SOP* breaches should be dealt with in accordance with section 6 and 6.1 above.
- Any breaches relating to R&I SOPs should be reviewed by a member of the R&I Senior Management Team (SMT) and corrective and preventative actions put in place (which may involve updating the SOPs).

7. Dissemination and training in the SOP

This SOP will be disseminated to applicable research staff (including R&I) and will be available on the R&I website.

All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP. The personal training log of the individual (and the Investigator Site File/Trial Master File if required) should be completed to document that the content of this SOP has been read and understood as described in *SOP_007 Research Training*.

8. Related documents

- SOP_007 Research Training
- SOP_009 Research Safety Reporting
- TMPL_055 Potential breaches reporting log
- TMPL_056 File Notes
- TMPL_057 Corrective and Preventative Actions (CAPA) Form
- TMPL_058 Study breaches log
- TMPL _059 Serious breach report form