Standard Operating Procedure

MANAGEMENT OF BREACHES IN RESEARCH

SETTING Trust-wide for research sponsored by UHBW

AUDIENCE All research staff involved in UHBW sponsored research

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

QUERIES Contact R&I department : Ext 29873 or research@uhbw.nhs.uk

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Document History

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-	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
29/JUL/19	V2.0	29/JUL/19	09/AUG/2019	Katharine Wale	Diana Benton
October 2020	V2.1	09/NOV/20	09/NOV/2020	Katharine Wale Sarah Bishop	Jess Bisset
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Version Number	Reason for change
Original V1.0	N/A
V1.1	Annual review and minor updates.
V2.0	Additional text in section 6 (Procedure) about completion of database.
V2.1	Biennial review with several minor updates and clarifications.
V2.2	Clarification on reporting timelines and guidance on completing CAPAs.

1. Introduction

All research must be conducted in compliance with the applicable regulations, Good Clinical Practice (GCP) participant consent and the approved research related documentation including the protocol and participant information sheets. Any non-compliance must be captured, assessed and managed appropriately by the research team delivering the research and the sponsor.

There are many types of breaches and with differing degrees of severity which may be identified during the course of a study. The terminology to describe those breaches is often used interchangeably (e.g. protocol non-compliance can also be referred to as a protocol deviation or a 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 or a breach. Both terms are used interchangeably in this SOP.

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 GCP and applicable regulations.
Protocol waivers are prospective deviations or waivers to the protocol. These types of non-compliances are not acceptable. They constitute an intentional breach of GCP and in the case of CTIMPs 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 must be submitted to the REC, HRA and MHRA (if applicable).

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 GCP. It describes the roles of:

- research personnel in identifying the breach and notifying UHBW as sponsor
- UHBW as sponsor in appropriate management of the breach.

3. Scope

In Scope:
UHBW sponsored research
Out of 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 UHBW 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 UHBW as Sponsor where required.

All Research & Innovation (R&I) staff managing UHBW 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 ethics and 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
HRA	Health Research Authority
ISF	Investigator Site File
MHRA	Medicines and Healthcare Products Regulatory Agency
R&I	Research & Innovation Department
REC	Research Ethics Committee
RMF	Research Management Facilitator
SMT	Senior Management Team
TMF	Trial Master File
Definitions	
Breach	Any departure from the applicable regulations (e.g. Clinical Trials Regulations, Data Protection Legislation 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

6.1 Potential breaches log

- Some types of breaches which occur during the conduct of a research study may not necessarily require immediate reporting to the Sponsor if they have been identified at study set up and the process described below has been put in place. The types of breaches may be added to or amended during the conduct of the study, in agreement with the sponsor.
- For UHBW sponsored CTIMPs and sponsored complex interventional studies managed by the R&I Research Projects Manager, an assessment may be undertaken at study set up with relevant study staff (including where applicable the statistician) of types of potential breaches which may not need immediate reporting to the Sponsor and what triggers should be put in place (e.g. if exceeds a certain threshold) for reporting to the Sponsor. The *Potential Breaches reporting log (TMPL_055)* will be used to document this. This will be prepared by the study team and reviewed and signed off by the Sponsor and the CI. The sponsor and the research team will agree at study set up how Sponsor oversight will be maintained e.g. a six monthly review of unreported breaches. All breaches which do not fall under the above must be reported to the Sponsor as soon as the breach has been identified (unless otherwise agreed).

6.2 CAPA submission

- The Principal Investigator or delegated personnel must assess a breach as soon as it is identified and report to the central study team within 24 hours of becoming aware of the event (unless it is the central study team or the Sponsor who have identified the breach). The central study team should onward report the breach to the Sponsor within 24 hours (unless it does not require immediate reporting because it is captured in *The Potential Breaches reporting log* as described in 6.1 above). This can be reported orally or in writing to Research@UHBW.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 9873 immediately and speak to either the Research Projects Manager or the Research Management Facilitator (RMF) allocated to the study in R&I.
- An initial *Corrective and Preventative Action (CAPA) form (TMPL_057)* must be submitted by the study team within 3 calendar days of the initial notification to the Sponsor and sent to Research@UHBW.nhs.uk for review unless the Sponsor confirms a CAPA is not required. The CAPA should include as much information as is available at the time of reporting. It should also be as specific as possible i.e. who (job role) did what, when (date) and how and why activities were undertaken and set out in chronological order.
- 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 UHBW sponsored CTIMPs and for complex non-interventional studies managed by the Research Projects Manager. For all other UHBW 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 6.3 below). A senior management team member will make this decision, referring to the definitions as provided in 6.3, and determining whether onward reporting to ethics and, if applicable to the study, the MHRA 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 Investigator (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 6.3. 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 folder and, where relevant, discuss with the R&I monitors whether any triggered monitoring is required. For those studies where an external trials unit has been given delegated responsibility for breaches management (see section 6.4 below), maintains its own database and routinely provides the Sponsor with cumulative reports of breaches at regular intervals, it is not necessary to record breaches on the Sponsor's database.
- The Chief 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. *TMPL_058 Study breaches log* may be used for this purpose.

6.3 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 calendar 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.
- For the purposes of this regulation, the timeline for reporting a serious breach applies from the date that the trials unit with the delegated function to manage the trial on behalf of the Sponsor is notified of the breach.
- 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.
- While non-CTIMP studies are not subject to Clinical Trials Regulations the same principles and definitions for serious breaches apply.
- For serious breaches the MHRA (if applicable) and Ethics committee **must be notified within 7 calendar days of the breach being identified**. Where UHBW 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 serious breach has a potential impact on patient safety, an assessment will be made by the 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 (applicable to clinical trials only).
- 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.

6.4 External trials unit's SOP

- If the study is managed by an external trials unit and if it has been agreed to follow the breaches SOP of the trials unit, then it is the responsibility of the trials unit to classify the types of breaches which need immediate reporting to the Sponsor, to identify those breaches which need immediate reporting and to record the breaches.

6.5 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 identified.
- Any non-compliance with *study specific SOPs* (i.e. breaches) should be recorded and reported to sponsor or delegated other as agreed. Any non-compliance will be reviewed and appropriate corrective and preventative actions put in place as applicable. These must be documented in the ISF and TMF.
- 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*.

REFERENCES	Medicines for Human Use Clinical Trials Regulations 2004 (and any amendments)
RELATED DOCUMENTS AND PAGES	• 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 Latest versions can all be found on the Research & Innovation section of UHBW's website: http://www.uhbristol.nhs.uk/research-innovation/
AUTHORISING BODY	Trust Research Group
SAFETY	N/A
QUERIES AND CONTACT	Research & Innovation on 0117 342 9873 or research@uhbw.nhs.uk