

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.

Standard Operating Procedure (SOP)

Author:	Jess Bisset	Role:	Research Operations Manager
Approved by:	Trust Research Group		
Date for review:	November 2017		

Review date	Version number	Version Date	Effective Date	Reason for change	Author/Responsible person	Authorised by
-	V1.0	12/01/17	14/02/2017	Original	Jess Bisset	Diana Benton

1. 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 in appropriate management of the breach.

2. Scope

In scope: UH Bristol sponsored research

Out of scope: Research sponsored by other organisations whose own procedures should be followed; breaches not related to research.

3. Definitions/Abbreviations

CAPA	Corrective and Preventative Action
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
GCP	Good Clinical Practice
MHRA	Medicines and Healthcare Products Regulatory Agency
REC	Research Ethics Committee
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction

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. These can also be referred to as <i>protocol deviations</i> .
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

4. Background

- 4.1 All research must be conducted in compliance with the applicable regulations and approved research related documentation e.g. protocol, Information Sheets, etc.
- 4.2 Any non-compliance must be captured, assessed and managed appropriately by the research team and sponsor delivering the research.
- 4.3 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). Due to the lack of clear guidance regarding the meaning of the term protocol violation, this will not be used within this document. Any unintended departure from the Protocol will therefore be referred to as a Protocol Deviation. All deviations are breaches.
- 4.4 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.
- 4.5 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.

5. Procedure

- 5.1 Some breaches that occur during a research study may not necessarily require immediate reporting to the Sponsor. These types of breaches will be identified at the study set up and will be reviewed during the course of the research. 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. The potential breaches reporting log (Appendix 1) 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 that do not fall into this category – i.e. those not documented on a log and those occurring in all other UH Bristol sponsored research must be reported to the Sponsor as soon as the breach has been identified (unless otherwise agreed).
- 5.2 The Investigator or delegated personnel must assess a breach as soon as it is identified and where required (in line with 5.1 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@UH Bristol.nhs.uk
- 5.3 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 allocated RMF in R&I
- 5.4 After initial notification to the Sponsor a Corrective and Preventative Action (CAPA) form (Appendix 2) must be completed by the study team within 3 days and sent to Research@UH Bristol.nhs.uk for review.
- 5.5 For UH Bristol sponsored CTIMPs the Research Projects Manager will review the breach. For all other UH Bristol sponsored research the allocated Research Management Facilitator will review the breach and liaise with any of the senior managers within R&I. A senior management team member will decide whether the breach is serious, referring to the MHRA definitions as provided in 6.1, and whether onward reporting to regulatory authorities is required.
- 5.6 The adequacy of the preventative actions on the CAPA will be assessed and the relevant personnel in R&I will liaise with the study team if any changes are required. Once agreed the Sponsor and PI 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.
- 5.7 The Research Management Facilitator/Research Projects Manager allocated to the study must document all correspondence relating to the breach, complete the breaches log located on the R&I shared J Drive in the monitoring/safety reporting folder and discuss with the R&I monitors whether any triggered monitoring is required.
- 5.8 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. A template is provided at appendix 3; where agreed by sponsor an alternative template may be used.

6. Serious Breaches

6.1 The sponsor of a clinical trial is obliged to notify the licensing authority in writing of any **serious breach of**

- (a) the conditions and principles of GCP in connection with that trial; or
- (b) 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

- (a) the safety or physical or mental integrity of the subjects of the trial;
- (b) the scientific value of the trial.

It is the sponsor responsibility to review a breach and decide whether it fulfils the criteria set out above. Further details can be found on the MHRA website.

6.2 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 the R&I department will liaise with the research team in order to make the required notification. The ‘serious breach report form’ standalone template will be used.

6.3 Where the breach has a potential impact on patient safety, an assessment will be made by Sponsor and Principal Investigator of immediate actions required, for example: halting the trial; withdrawing a participant; closing study sites. Where there is an urgent safety concern the Investigator will follow the required action as described in the Safety Reporting SOP on urgent safety measures. Where there is no urgent safety concern the proposed action may be discussed with the MHRA prior to implementation.

6.4 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.

7. Dissemination and training in the SOP

7.1 Dissemination of this SOP

7.1.1 New SOPs and new versions of existing SOPs: The Research Operations Manager will be responsible for ensuring authorised SOPs are uploaded to the DMS in line with Trust policy and on the R&I website as described in the SOP “Authorship, review, revision and approval of research procedural documents produced by Research & Innovation”. Internal Trust Staff are expected use the DMS to access latest versions of SOPs and to check the website regularly for updates, as communicated in the Training SOP.

Notice of new or amended procedural documents that have undergone a major amendment will be given via the following routes:

- Inclusion in the R&I e-bulletin (monthly);
- Direct email to Research Leads, Research Unit Managers and Band 7 staff for

onward cascade ;

- Direct email to Chief Investigators of CTIMPs sponsored by UHBristol;
- Direct email to the Head of Research Governance at the University of Bristol (as relevant).

7.2 Training in this SOP

- 7.2.1** All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP.
- 7.2.2** The training log within the Investigator Site File/Trial Master File should be completed to document that members of staff have read and understood the content of the SOP and its amendments.

8. Appendices

Appendix 1 – Potential breaches reporting log

Appendix 2 – Corrective and Preventative Actions (CAPA) Form

Appendix 3 – Study breaches log

RELATED DOCUMENTS	Safety Reporting SOP
AUTHORISING BODY	Trust Research Group
SAFETY	N/A
QUERIES	Contact Research & Innovation on 0117 342 0233

Appendix 1 – Potential breaches reporting log

Study Title:			
R&I Reference Number:		Date log completed:	
EudraCT number (where applicable):			

Potential breach (data/safety/GCP)	Occasions after which agreed need to report to Sponsor for assessment	Justification	Sponsor Oversight during the trial (e.g. quarterly review/review during routine monitoring visits etc)

Appendix 2

Corrective and Preventative Action Template

Title and Acronym (if available)		
R&I ref number: EudraCT number: Principal Investigator:		
Target recruitment:	Recruitment at time of breach:	Study start date: Study end date:

Summary:

How the issue/breach was identified and short summary (3-4 lines). Include date breach occurred and date breach identified.

Finding:

Corrective Actions:

Preventative Actions:

Name of personnel making the report:

Signature of personnel making the report:

Date:

Sponsor comments:

Reviewed and agreed by:

Sponsor representative

.....
 Name Position Signature Date

Name of Support Department (if relevant)

.....
 Name Position Signature Date

Principal Investigator

.....
 Name Position Signature Date

Please note that all incidents should be reported in line with relevant incident reporting policies at the NHS Trust involved. For further guidance on UH Bristol Incident Reporting processes, please follow the UH Bristol Policy for the Management of Incidents available on DMS (accessed through Connect).

Appendix 3 – Breaches log

Study title:

R&I reference number:

Short description of breach identified	Date breach occurred	Date breach notified to Sponsor (as applicable)	Corrective Action (if CAPA completed refer to relevant CAPA form)	Preventative Action (if CAPA completed refer to relevant CAPA form)	Date all actions completed	If identified as Serious date reported to REC/MHRA	Additional comments