Standard Operating Procedure:

Deviations and Serious Breach Reporting

# Purpose

This standard operating procedure (SOP) describes the procedures to manage deviations relating to the study specific protocol and plans, good clinical Practice (GCP) or any other good practice guidelines (GxP), any applicable regulatory requirements and/or the University of Birmingham (UoB) Quality Management System (QMS). The SOP also describes the procedure for serious breach reporting.

# Scope

This SOP applies to clinical research where the UoB is the sponsor or takes on sponsor responsibilities for deviations and serious breach reporting. Where clinical research is sponsored by another institution, this procedure should be followed as far as possible, and in line with the contractual agreement between the UoB and the other institution. This SOP (excluding serious breach reporting) also applies to clinical research approved by a UoB research ethics committee (REC) that is required to follow the UoB Principles of GCP for Clinical Research (UoB-GCP-POL-001). This SOP may be used as a guidance document in all other cases.

# Implementation plan

This SOP will be implemented in line with this document’s effective date.

# Stakeholders

Note that where the UoB takes on the sponsor responsibility for deviations and serious breach reporting, the UoB will delegate the majority of these duties to the chief investigator (CI) and/or to a clinical trials unit (CTU), who may delegate these duties further to their trials team(s). All delegation of duties will be documented (e.g. using the CI declaration and/or the Clinical Trials Task Delegation Log (UoB-SPO-QCD-001).

* Manager (or delegate) - this term is used to define the role that has the responsibility for oversight of deviations and serious breach reporting. This may include the CI for clinical trials, or the supervisor for postgraduate research students, for clinical research approved by a UoB REC, or the UoB lead.
* Clinical research staff member; refers to any person who has a role in clinical research either sponsored by UoB or located at UoB premises, either directly or indirectly. This may include those holding honorary contracts with the University or not directly employed by the UoB but who contribute to research either sponsored and/or located at UoB.
* Head of Research Governance and Integrity (or delegate)
* Research Governance and Ethics Team (RG&ET)
* Clinical Research Compliance Team (CRCT)
* Chair of Clinical Trials Oversight Committee (CTOC; or delegate)
* UKCRC registered UoB CTU
* Serious breach referral panel

# Background and rationale

For the purposes of this SOP the terms ‘clinical research’ or ‘research project’ will cover clinical trials of investigational medicinal products (CTIMPs), other interventional trials (e.g. surgical trials, device trials and non-CTIMP trials, and any other projects deemed to be ‘interventional’ by the sponsor), clinical studies and clinical research approved by a UoB REC.

## Deviations

A deviation is a departure from a framework such as an agreed process, principle, procedure or protocol which may, or may not, be intentional. A deviation is also known as a non-compliance, breach or violation. Deviations include major or critical findings and serious breaches of GCP or the trial protocol. Deviations can be either planned or detected e.g. during on-site monitoring. For consistency, the term ‘deviation’ is used within UoB to mean all of the above.

Deviations from agreed processes or practice can affect the safety of participants and/or quality of the output of that process. UoB Principles of GCP for Clinical Research (UoB-GCP-POL-001) states that research is designed, reviewed, managed and undertaken in a way that ensures integrity, quality and transparency, and it is expected that those conducting clinical research have systems and procedures in place to manage deviations.

## Serious Breaches

A serious breach is defined as a breach which is likely to affect to a significant degree:

* the safety or physical or mental integrity of the participants of the trial; or
* the scientific value of the trial.

For CTIMPs, [The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006](http://www.legislation.gov.uk/uksi/2006/1928/contents/made) require that the sponsor of a clinical trial shall notify the licensing authority and REC in writing within 7 days of becoming aware 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.

Examples of what constitutes as serious breach can be found in Appendix II of the MHRA’s [Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol (PDF - 211 KB)](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/705179/Guidance_for_the_Notification_of_Serious_Breaches_of_GCP_or_the_Trial_Protocol_Version_5.1__04-05-2018_.pdf).

For non-CTIMPs and clinical studies, the [Health Research Authority (HRA) SOPs for NHS RECs](https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/research-ethics-committee-standard-operating-procedures/) define the requirements for reporting of serious breaches to the REC, as defined by the study protocol.

Note: the section on serious breach reporting in this document does not apply to UoB REC approved clinical research. The reader should refer to clause 13 (misconduct) of the [UoB Code of Practice for Research (PDF – 357KB)](https://www.birmingham.ac.uk/documents/university/legal/research.pdf).

# Procedure

Significant research related events or serious breaches may be identified by clinical research staff through various means, including monitoring, audits, team meetings, feedback from site staff or participants. Members of the research team may also receive allegations of deviations from the protocol, the principles of GCP (or applicable GxP requirements), or legal requirements that may affect the safety of participants or the integrity of the research project. This information may be received directly or indirectly from whistle blowers or complaints from within or outside of the UoB.

All deviations follow the procedures described below in the section ‘Deviations’. For (suspected) serious breaches, these are additionally addressed in the section below marked ‘Serious breach reporting outside the UoB CTUs’ and ‘Serious breach reporting in the UoB CTUs’ respectively.

Within the UoB, any deviations or serious breaches that may have resulted from misconduct will be investigated and subject to the procedures outlined in clause 13 (misconduct) of the [UoB Code of Practice for Research (PDF – 357KB)](https://www.birmingham.ac.uk/documents/university/legal/research.pdf).

Information regarding deviations from the protocol, GxP or legal requirements and possible serious breach reports should be treated as confidential to relevant UoB staff and site(s). All relevant documentation should be kept as part of the study/trial master file (S/TMF) and relevant investigator site file (ISF)/laboratory master file (LMF) including any emails. Details of the ensuing investigation will be made available to UoB and site staff on a need-to-know basis. All individuals interviewed during the investigation will be asked to respect this confidentiality.

## Deviations

### Deviation administration

1. The manager (or delegate) will set up a process for deviation management, which will include the following.
* A written procedure detailing deviation reporting, review, investigation and escalation (where appropriate) and who has been delegated what duties from the manager (or delegate) within this procedure. See Deviation Management (UoB-DSB-QCD-001) for a template.
* Tools to capture deviations (where applicable); see Deviation Form (UoB-DSB-QCD-002) for a template.
1. Where appropriate, the manager (or delegate) will set up a process to ensure any corrective action and preventative action (CAPA) plans arising from deviations are executed within the set timeframe.
2. For laboratories performing analyses that contribute to the endpoints of CTIMPs, the manager (or delegate) will follow the procedures as described in Reportable Issues SOP (UoB-CRL-SOP-005).
3. The manager (or delegate) will ensure clinical research staff members are appropriately trained on the process for deviation management; see also Training SOP (UoB-TRN-SOP-001).

### Deviation management

1. The clinical research staff member identifying a deviation, will follow the local procedure for deviation reporting, ensuring the deviation is documented (e.g., in e-mails, a note to file (NtF) or a deviation form, see Deviation Form (UoB-DSB-QCD-002).
2. The manager (or delegate) will review the deviation, assessing whether the deviation could be categorised as a serious breach and is likely to affect participant safety, participant confidentiality and/or data integrity, and whether it is relating to a significant GxP non-compliance and/or a failure to comply with applicable regulations. For serious breaches also refer to the serious breach reporting section below.
* The recording of the deviation will include the impact of the deviation as well as any corrective action(s) required, and the preventative action(s) required to prevent re-occurrence (CAPA plan, where appropriate).
* The assessment of the impact may require communication with the relevant trial team or other stakeholders involved.
1. The manager (or delegate) will identify if the deviation is recurring and whether the deviations suggest a systematic quality assurance failure.
2. The manager (no delegation allowed) will assess the impact of the deviation and where appropriate approve the appropriate CAPA plan and provide oversight that the agreed CAPA plan has been completed.
3. For serious breaches, the manager (or delegate) will adhere to all applicable regulations and reporting requirements.
4. Where the deviation relates to the loss of personal data or a breach of the [Data Protection Act](https://www.legislation.gov.uk/ukpga/2018/12/contents/enacted), the manager (or delegate) will report this to [Legal Services](https://intranet.birmingham.ac.uk/executive-support/legal-services/what-we-do/data-protection/index.aspx#id_token=eyJ0eXAiOiJKV1QiLCJhbGciOiJSUzI1NiIsIng1dCI6Ild3dXdRSWFCSWZvRURkbHd4VXpSRUVJbmtvMCIsImtpZCI6Ild3dXdRSWFCSWZvRURkbHd4VXpSRUVJbmtvMCJ9.eyJpc3MiOiJodHRwczovL2Ntcy11b2IuY2xvdWQuY29udGVuc2lzLmNvbS9hdXRoZW50aWNhdGUiLCJhdWQiOiJXZWJzaXRlQWRmc0NsaWVudCIsImV4cCI6MTY1Nzg3MDQzNCwibmJmIjoxNjU3ODcwMTM0LCJub25jZSI6IjFhZTkxMTQzY2Y1YjQyZjU5NDQyNTA1NGU5MzhhNjRlIiwiaWF0IjoxNjU3ODcwMTM0LCJzaWQiOiIxOWY0NzdlOGJiNTc1MDhhZDc3NjJjZDBkYTMzNDE1MCIsInN1YiI6ImM0ZDZmYzZiLTE5ZWEtNDllZC05NDk0LWNlYjIxMzU2YmQ3OCIsImF1dGhfdGltZSI6MTY1Nzg3MDEzNCwiaWRwIjoiaWRzcnYiLCJhbXIiOlsicGFzc3dvcmQiXX0.EikjpgUNV75Txv8bz9mjOFhflZHGmPsyymQKRuZY5ThzLO4gRHewQeM4cTQJjvqtIPgVp8l2lGqB1Jz8bYMlhCZaQRayMbPTnDGzS56i_kyBoASZ2SLUUwTFSPZ72cGoC-pQhTLUhXnkDjlc_kcYz16W-3g-TdlJxNC4qHFYDn8boxzW0HGAjaPXOtnz-x_W2VAO7hdInNM7ITXPYhusOomUwD2T063WVQzsIqzDunu_Acw4KtGINkapBLyCVDQxMvpIQW6LCUX_JifiOqjHfwb4vYYnTK76kzoTP1mqeYj2__bOZRt6ft2yIWczvUl5SLnTL4NhXfSZcSItEqgLAA&scope=openid&state=a20d35a49e1248d7b10d76dbcd2409fd&session_state=Ka_XVkbq0wOD6kbk7Y0mHCxZnfYc6K0qwwIf2lp_jug.fb1184d16c50ab514353a6041deaceee) (UoB login required) immediately, and will ensure any local (e.g. College/School-level) reporting procedures are followed.
5. The manager (or delegate) will file evidence of the deviation in the relevant S/TMF and ISF/LMF file as applicable.

## Serious breach reporting outside the UoB CTUs

Note: this section is not applicable to UoB REC approved projects, please refer to clause 13 (misconduct) of the [UoB Code of Practice for Research (PDF – 357KB)](https://www.birmingham.ac.uk/documents/university/legal/research.pdf).

### Initial receipt of information

1. Immediately upon identification of an event that is a deviation of the protocol, the principles of GCP (or applicable GxP requirements), or legal requirements that may affect participant safety, participant confidentiality and/or the integrity of the project, the manager (or delegate) will liaise with a member of the RG&ET (for contact details please see References below), providing as much detail as possible, for example:
* location where the deviation occurred
* name of the PI at the site where the deviation occurred (if applicable)
* full title of the clinical trial
* name of the CI for the trial
* whether the trial is sponsored or co-sponsored by UoB
* internal UoB ERN/RG Number, REC and/or EudraCT references (where applicable)
* an explanation of how the deviation was identified
* details of the deviation
* details of any initial corrective action
* assessment of the impact the deviation will have on the participants and/or the scientific integrity of the trial.
1. Where the events identified raise the likelihood of any sort of legal action, disciplinary procedure or other dispute, the manager (or delegate) will inform [Legal Services](https://intranet.birmingham.ac.uk/legal-services/who-we-are.aspx) and follow any instructions with respect to investigation.
2. The RG&ET will liaise with Legal Services as required, providing an initial report of the breach and requesting their advice on the matter.
3. The RG&ET will request further information from the reporter and will ask the reporter to include Legal Services in their correspondence (where relevant).

### Review of suspected serious breaches, reporting of serious breaches and follow-up

1. The Head of Research Governance and Integrity (or delegate) will discuss if the deviation is a suspected serious breach that requires further referral. Where this is not the case, the manager (or delegate) will work with RG&ET to develop a CAPA plan, and the manager (or delegate) will ensure the relevant members of the clinical research team are informed accordingly.
2. Where it has been decided that the deviation is a suspected serious breach that requires further referral: the Head of Research Governance and Integrity (or delegate) will provide information about the suspected serious breach to the chair of the CTOC. Note that Legal Services may stay involved in the communication loop as per their request.
3. The chair of the CTOC (or delegate) will convene a serious breach referral panel and then refer the deviation to them to determine whether it constitutes a serious breach, as outlined in the background section, within 5 days of initial receipt of the information (but not beyond the 7-day reporting window, see point 22 below) and consulting colleagues as necessary. The format of the meeting will be determined based on the timeline. Where major risks to the UoB sponsored project, participants and/or the organisation have been identified, the chair of the CTOC (or delegate) may up-escalate to the heads of college or the UoB Research Governance, Ethics and Integrity Committee (RGEIC).
4. The serious breach referral panel will enquire after more information as necessary and determine if the deviation is a serious breach and should be reported as such.
5. For CTIMPs - In the event that the serious breach referral panel is unable to agree on whether to classify the event as a serious breach, or in the eventuality that there are not enough members of the panel available to make a decision, the Head of Research Governance and Integrity (or delegate) will liaise directly with the [MHRA](https://www.gov.uk/guidance/contact-mhra) for advice.
6. If the event is determined to be a serious breach the manager (or delegate) will complete a serious breach report incorporating any feedback from the chair of CTOC (or delegate) as appropriate.
7. The manger (or delegate) will submit the report to the REC, and for CTIMPs, the competent authority, and any applicable regulatory agencies, within 7 days of becoming aware of the breach. It is expected that the 7-day timescale commences at the moment there is a strong suspicion of a serious breach.
* The manager (or delegate) will also send the report to the CRCT for awareness.
* Where a site is involved, the manager (or delegate) will liaise with the PI and research and development (R&D) department for the site.
* For CTIMPs in the UK, the [Notification of Serious Breach of GCP or the Trial Protocol Form (Word - 205 KB)](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/779472/Notification_of_serious_breaches_of_GCP_or_the_trial_protocol_form__V6__18-02-19_.odt) should be used and a copy provided to the REC.
1. The chair of CTOC (or delegate) will monitor the CAPA plan through CTOC meetings.
2. The manager (or delegate) and the Head of Research Governance and Integrity (or delegate) will ensure any relevant essential documents are filed appropriately in the S/TMF and sponsor file respectively.

## Serious breach reporting in the UoB CTUs

1. In the UKCRC-registered UoB CTUs, the UoB CTUs will be responsible for investigating, reporting and following up suspected serious breaches within the CTU.
* The UoB CTUs will send a copy of the serious breach report to the Research Governance Team (RGT) and CRCT at the time the serious breach report is submitted to the REC and competent authority if applicable. The RGT and CRCT will review the serious breach report to ensure the proposed CAPA plan is appropriate and liaise directly with the UoB CTU where further actions are required.
* The UoB CTUs will inform the CTOC of any reported serious breaches in 6-monthly reports.

# List of expected outputs

* Evidence of a documented process for the identification, recording and review of deviations and escalation, where appropriate.
* Evidence of the process for recording and reviewing being followed.
* Evidence that reporting timelines have been followed, and that appropriate staff have been contacted.
* Evidence of the serious breach process described above being followed, where applicable.

# Related documents

* UoB-CRL-SOP-005 Reportable Issues
* UoB-DSB-QCD-001 Deviation Management
* UoB-DSB-QCD-002 Deviation Form
* UoB-GCP-POL-001 UoB Principles of GCP for Clinical Research
* UoB-SPO-QCD-001 Clinical Trials Task Delegation Log
* UoB-TRN-SOP-001 Training

UoB QMS documents can be found on the [CRCT website](https://www.birmingham.ac.uk/research/activity/mds/mds-rkto/governance/index.aspx). Internal work instructions can be obtained from the CRCT (crct@contacts.bham.ac.uk) and/or from the RGT (researchgovernance@contacts.bham.ac.uk).

# References and frameworks

* Contact details for serious breach reporting:
* CRCT: crct@contacts.bham.ac.uk
* RG&ET: phone; +44 (0)121 415 8011 (Ext. 58011), email; researchgovernance@contacts.bham.ac.uk
* Legal services: <https://intranet.birmingham.ac.uk/legal-services/who-we-are.aspx>
* MHRA: <https://www.gov.uk/guidance/contact-mhra>.
* Data Protection Act 2018: <https://www.legislation.gov.uk/ukpga/2018/12/contents/enacted>
* The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006: <http://www.legislation.gov.uk/uksi/2006/1928/contents/made>
* MHRA Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol: <https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/705179/Guidance_for_the_Notification_of_Serious_Breaches_of_GCP_or_the_Trial_Protocol_Version_5.1__04-05-2018_.pdf>
* HRA SOPs for RECs: <https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/research-ethics-committee-standard-operating-procedures/>
* Notification of Serious Breach of GCP or Trial Protocol Form: <https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/779472/Notification_of_serious_breaches_of_GCP_or_the_trial_protocol_form__V6__18-02-19_.odt>
* UoB Code of Practice for Research: <https://www.birmingham.ac.uk/documents/university/legal/research.pdf>
* UoB Legal Services – Data Protection (UoB login required): <https://intranet.birmingham.ac.uk/executive-support/legal-services/what-we-do/data-protection/index.aspx>

# Abbreviations and definitions

| Term | Description |
| --- | --- |
| CAPA | Corrective action and preventative action |
| CI | Chief investigator |
| CRCT | Clinical Research Compliance Team  |
| CTIMP | Clinical trial of an investigational medicinal product |
| CTOC | Clinical Trials Oversight Committee  |
| CTU | Clinical trials unit  |
| GCP | Good Clinical Practice |
| GMP MU | Good Manufacturing Practice Manufacturing Unit |
| GxP | Good practice guidelines |
| HRA | Health Research Authority |
| ISF | Investigator site file |
| LMF | Laboratory master file |
| MHRA | Medicines and Healthcare Products Regulatory Authority |
| NtF | Note to file |
| PI | Principal investigator |
| QMS | Quality management system  |
| REC | Research ethics committee |
| RGEIC | Research Governance, Ethics and Integrity Committee |
| RG&ET | Research Governance and Ethics Team |
| SOP | Standard operating procedure |
| S/TMF | Study/trial master file |
| UoB | University of Birmingham |

See also the [Glossary of Terms](https://www.birmingham.ac.uk/research/activity/mds/mds-rkto/governance/Glossary-of-Terms.aspx).