STANDARD OPERATING PROCEDURE 31
Handling non-compliances, research misconduct and serious breaches of GCP and/or Study Protocol

Version:	V4.0	Effective Date:	25 July 2023
Issue Date:	11 July 2023	Review Date:	25 July 2025
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Contents

Revision Chronology:	Effective date:	Reason for change:
Version 4.0	25 July 2023	Biennial review: Change to new format. Minor amends to text including addition of references to SOP 36 'Data Breach Incident Management Procedure'.
Version 3.0	30 April 2021	Biennial review: Change to new format. Addition of new process for WCTU managed studies and new sections on oversight and communicating with recruiting sites.
Version 2.0	22 January 2019	Review of procedures. Clarification of definitions and processes relating to CAPAs. Inclusion of supplementary documentation. Change text from 'trial' to 'study' throughout.
Version 1.2	27 July 2016	Biennial review: Minor text amends for clarification mainly to the 'misconduct' section. Change to new format.
Version 1.1	2 May 2014	Biennial review: Web links updated including MHRA guidance on reporting serious breaches.
Version 1.0	19 March 2012	

STANDARD OPERATING PROCEDURE 31
Handling non-compliances, research misconduct and serious breaches of GCP and/or Study Protocol

1. Purpose and Scope

This Standard Operating Procedure (SOP) describes the actions to be taken if a non-compliance with a study protocol, Good Clinical Practice (GCP) or any other applicable regulation is suspected or reported in University of Warwick sponsored studies.

It describes the procedures for identifying, documenting, reporting and resolving non-compliances, and determining if the non-compliance is a serious breach. It also details how to manage a report of suspected or actual research misconduct.

The SOP is applicable to all individuals working on University of Warwick sponsored studies or externally sponsored studies where it has been agreed the Warwick SOPs are to be followed. This includes University staff, students and any external third parties engaged through site agreements, service or other contractual arrangements. Staff working on studies sponsored by other institutions must ensure they are aware of, and comply with, their sponsor's requirements.

2. Definitions

Non-compliance	Non-compliances are non-adherence to study-related requirements, GCP and all applicable regulatory requirements. A non-compliance may be categorised as a deviation, violation or serious breach.
Deviation	A deviation is a change or departure from the protocol, other key trial documents and/or GCP that does not result in harm to the participants or significantly affect the scientific value of the reported results of the study. Deviations are usually due to unavoidable circumstances or events that are planned due to clinical need.
Violation	A violation is a failure to comply with, or variance from, GCP and/or the protocol or other key trial documents as approved by Sponsor, REC, MHRA (where applicable) and NHS Trust Research & Development (R&D) departments. It is also a variance from any regulations or legislation relevant to the delivery of clinical research e.g., UK GDPR, Common Law Duty of Confidentiality etc. Violations are serious non-compliances resulting from error, fraud, or misconduct which have the potential to harm participants or significantly affect the scientific value of the reported results of the study.
Serious Breach	A serious breach is a non-compliance that is likely to affect to a significant degree either the safety or physical or mental integrity of the participants of the study, or the scientific value of the study.
Research Misconduct	Research misconduct is defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results

Corrective action	Action taken to rectify or reduce the impact of a non-compliance (where possible)
Preventative action	Action taken to prevent the reoccurrence of a non-compliance
Root cause	The fundamental reason for the occurrence of a problem

3. Background

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting of research studies involving human participants, their tissue or data. Compliance with this standard provides public assurance that the rights, safety and well-being of study participants are protected, consistent with the principles that have their origin in the Declaration of Helsinki; and that the study data are credible.

The study protocol is written by key personnel within the study team, and it describes the requirements and management of the study in detail. The study protocol must be adhered to unless there is an event which would require an Urgent Safety Measure to be taken (see SOP 17 part 3 'Urgent Safety Measures'). Any other departures from the protocol are deemed to be non-compliances and need to be dealt with appropriately.

In the case of Clinical Trials of Investigational Medicinal Products (CTIMPs), Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [SI 2004/1031], as amended by SI 2006/1928, contains a requirement for the notification of "serious breaches" of GCP or the trial protocol to the Medicines and Healthcare products Regulatory Agency (MHRA). See section 4.3.4 for further details.

The University of Warwick's Research Code of Practice 2019 provides guiding principles and standards of good practice in research across all subject disciplines and fields of study in the University. It applies to all those undertaking research on the University's premises using its facilities, or on behalf of the University, including staff, students, visiting or emeritus staff, associates, honorary or clinical contract holders, contractors and consultants. Research staff should be aware of and comply with the Code.

4. Procedure

4.1 Responsibilities

Chief Investigator (CI) or delegate	• Understanding of terminology used to identify and assess non-compliances • Completion of investigations and assessments of suspected or reported non-compliances and determination of suitable actions • Regular review of non-compliance reports at Trial Management Group (TMG) meetings • Onward reporting to sponsor and/or regulatory authorities as required
All research staff/students	• Adherence to the University's research code of practice • Reporting concerns or suspicions of misconduct to the appropriate authority
Sponsors Office	• Investigate any reports of research misconduct and take appropriate actions • Onward reporting of serious breaches for non-WCTU managed studies as applicable

4.2 When?

4.2.1 Reporting non-compliances

Timescales for the reporting of non-compliances are set out in the table below.

Non-compliance	Report to WCTU QA Team (WCTU managed studies)	Report to Sponsor's Office (sponsorship@warwick.ac.uk)	Report to REC (& MHRA where applicable)	Reviewed by
Deviation	N/A	N/A	N/A	TMG/SMG
Violation	As soon as is practicable	As soon as is practicable	N/A	TMG/SMG, WCTU QA Team (for WCTU managed studies), Sponsor's Office, University Sponsorship & Oversight Committee
Serious breach	Immediately	Immediately	Within 7 days	TMG/SMG, WCTU QA Team (WCTU managed studies), Sponsor's Office, MHRA (where applicable), REC, University Sponsorship & Oversight Committee, Director of WCTU (or delegate)

N.B. For any data breaches/non-compliances e.g., data being sent in error to the research team, the University's Security and Information Management team must also be informed. Details of the procedure and form to use can be found here:
https://warwick.ac.uk/services/sim/dataprotection/breaches
Please refer to SOP 36 'Data Breach Incident Management Procedure' for full details.

4.2.2 Reporting an Allegation of Misconduct

Allegations, or other evidence of possible misconduct in research, should be made formally in writing (where possible) as soon as possible to the Registrar (**Email:** RegistrarPA@warwick.ac.uk) and should include any supporting evidence available to the complainant. See section 4.3.8 for details of the University of Warwick's Code of Practice for the Investigation of Research Misconduct.

4.3 How?

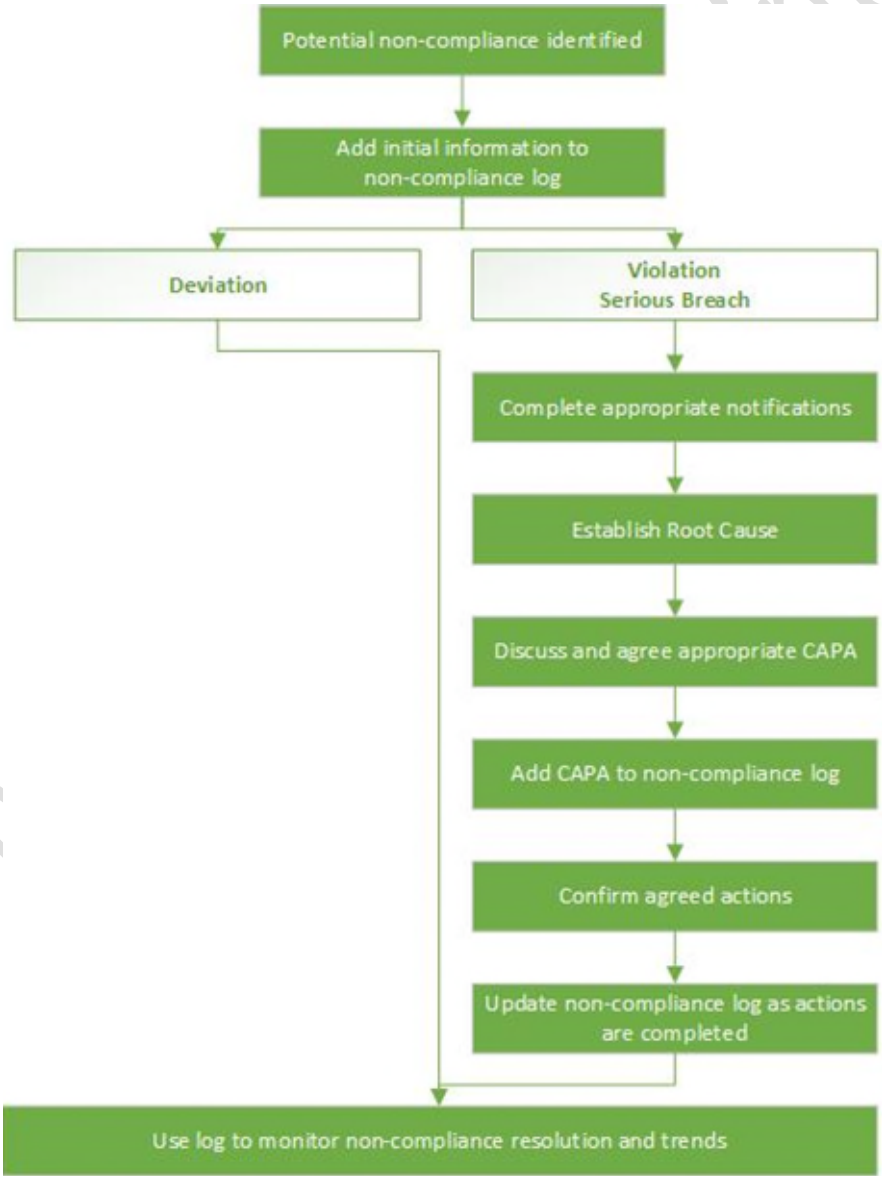
All studies should have a documented procedure in place for identifying, assessing, and reporting non-compliances. The procedure should be approved by the TMG/SMG stating the review procedure, personnel involved, and timeline requirements. This process should reflect the reporting timescales and pathways detailed in this SOP.

For research managed outside of WCTU, prior to each study opening to recruitment a working instruction should be written and approved to detail the flow of communication between all relevant parties. The Template Corrective and Preventative Action (CAPA) Report can be used to assist with

writing the working instruction (see Templates – T13). Following receipt of information concerning a non-compliance there should be an audit trail of when the information was received, how it was assessed, by whom it was assessed, and when the report was submitted to the Sponsor's Office and relevant bodies.

For WCTU managed studies, a non-compliance log will be set up for each study and held in the relevant Trial Master File (TMF). All non-compliances must be recorded onto the spreadsheet, following the instructions provided in the WCTU Non-Compliance Log Working Instruction (G25). The TMG should regularly review non-compliances to ensure appropriate corrective and preventative actions have been put in place and to look for any trends across recruitment sites. Any issues identified should also be reported to the trial oversight committees.

Process flow for WCTU managed studies:



For studies managed outside of WCTU, the template CAPA form should be completed, reviewed and followed up until resolution by the study management group to ensure all appropriate corrective and preventative actions are completed. The non-compliance can then be considered closed.

4.3.1 Non-compliance

Consideration should be made at the protocol development and risk assessment stages in collaboration with the trial statistician and any other relevant stakeholder(s), to identify and clarify examples of non-compliance. These should be reviewed periodically by the TMG and may lead to updates to the protocol and risk assessment.

4.3.2 Deviation

A deviation is a change or departure from the protocol and/or GCP that does not result in harm to the participants or significantly affect the scientific value of the reported results of the study. There is no requirement to report a deviation to the Sponsor's Office.

Examples include (but are not limited to):

- Study procedure/visit conducted out of timeframe (as determined by the statistician)
- Copy of consent form not given to participant during informed consent process
- Missing original signed consent form, but have a copy of the participant signed consent form
- Amended dose of IMP, planned in advance, or changed due to participant needs

A protocol deviation is usually a non-serious or minor non-compliance, or unintended departure from the expected conduct of the study, generally to deal with unforeseen circumstances.

The deviation documentation should include:

- The title of the research study
- The name of the Principal Investigator (PI) if applicable
- Details of the deviation and an explanation of how the deviation was identified
- Corrective actions
- An assessment on the impact on the study participants/data

For WCTU managed studies, all relevant details will be captured in the study specific non-compliance log. If required, a non-compliance report can be exported from the log to be able to communicate with stakeholders about the actions taken and status of the non-compliance.

Studies managed outside of WCTU should complete a CAPA form and file a copy in the SMF.

4.3.3 Violations

A violation is a failure to comply with or variance from GCP and/or the protocol, other key trial documents or applicable regulations as approved by the sponsor, REC, MHRA (where applicable) and NHS Trust Research & Development (R&D) departments.

A violation is a serious non-compliance resulting from error, fraud, or misconduct.

Examples of potential violations include (but are not limited to):

- Failure to obtain informed consent
- Enrolment of subjects that do not meet the inclusion/exclusion criteria

- Undertaking a study procedure not approved by the REC and/or the MHRA (unless for immediate safety reasons)
- Investigational Medicinal Product (IMP) dispensing/dosing error
- Sending documentation from research sites to the study team which contains confidential or personal data (if not consented to by the participant). (See also SOP 36 'Data Breach Incident Management Procedure').
- Persistent occurrence of a deviation

For WCTU managed studies, the details of any violation should be recorded in the non-compliance log as per the working instruction document (G25) and should be available for regular evaluation by the TMG. A copy of the non-compliance report can be generated for filing/onward reporting.

The Sponsor's Office in Research & Impact Services (R&IS) should be notified of protocol violations as soon as is practicable by the study team via sponsorship@warwick.ac.uk. The WCTU QA Team should also be notified for WCTU managed studies, with completed violation reports being sent to WCTUQA@warwick.ac.uk as soon as possible after the initial notification.

Studies managed outside of WCTU should complete a CAPA form, send on to the relevant sponsor's office and file a copy in the SMF.

4.3.4 Serious Breaches

A serious breach is a non-compliance that is likely to affect to a significant degree either the safety or physical or mental integrity of the participants of the study, or the scientific value of the study.

In order to report a serious breach to the MHRA and/or REC, the CAPA Report Form and, in the case of CTIMPs, the MHRA Serious Breaches Notification Form (see links below), should be completed by the study team and reviewed and approved by the Sponsor's Office, WCTU QA Team and the Director of WCTU or their delegate.

A report of any potential serious breach should be investigated and assess/consider the following in relation to findings, for example:

- A non-critical finding where evidence exists that a significant and unjustified departure from applicable legislative requirements has occurred that has not developed into a critical issue, but may have the potential to do so unless addressed and/or:
- Where evidence exists that a number of departures from applicable legislative requirements and/or established GCP guidelines have occurred within a single area of responsibility, indicating a systemic quality assurance failure.
- Where inappropriate, insufficient or untimely corrective action has taken place regarding previously reported violation(s).

The report should detail where/if significant and unjustified departure(s) from applicable legislative requirements have occurred, with evidence that:

- The safety, well-being or confidentiality of study participants either have been, or have significant potential to be, jeopardised, and/or
- The research study data are unreliable and/or
- There are a number of major non-compliances across areas of responsibility, indicating a systemic quality assurance failure

Identifying and investigating a potential serious breach will require the Sponsor and the CI (and PI if applicable) to work together as an Investigation Team to identify the extent of the breach and to initiate appropriate actions. For WCTU-managed studies, see Associated Documents G04 for further details.

Action(s) may include:

- Alerting the investigator (CI and/or PI) and asking for further explanation or data verification
- A triggered/for-cause audit of an investigator site or the study database, as applicable
- Examination of data from the site by a statistician, to estimate the likelihood that any anomalies could have occurred by chance
- Review of other data from the site (and other sites if applicable)

For WCTU managed studies a report can be generated via the non-compliance system. The report should include an assessment on behalf of the Sponsor of the impact on the safety of the participants and scientific integrity of the study, and the agreed corrective and preventative actions.

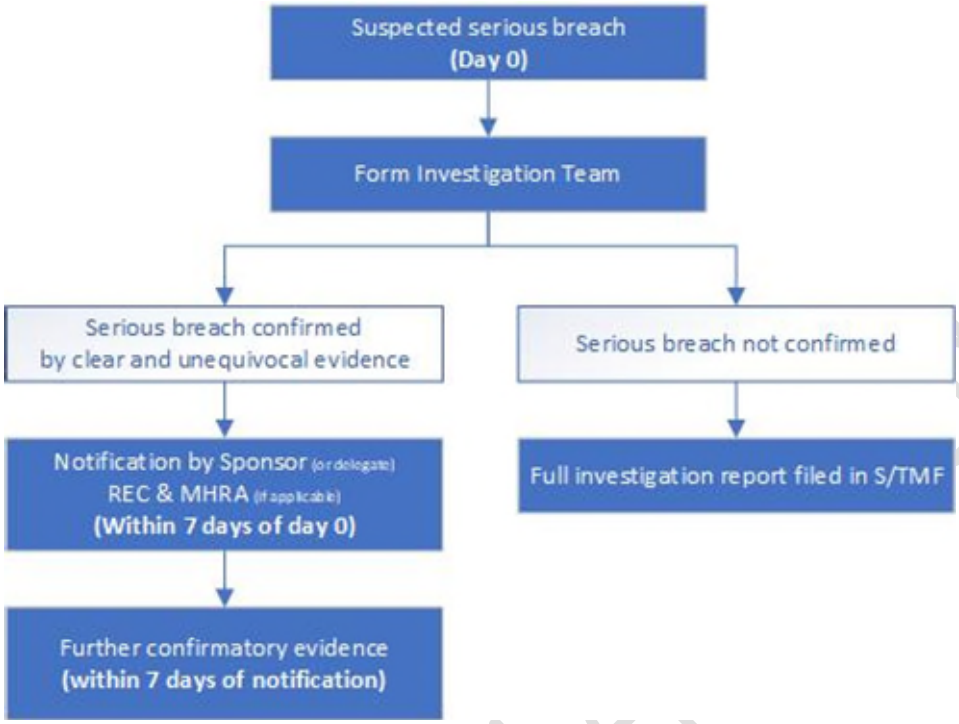
For other Warwick sponsored studies, findings should be agreed and documented by the Investigation Team using a CAPA Report.

This report should be provided to all relevant organisations in a timely manner as applicable. Depending on the nature of the event and the specifics of the study, these may include, but not limited to:

- Sponsor
- MHRA
- Relevant REC (NHS/BSREC)
- Organisation responsible for a clinical site (e.g., NHS Trust R&D office) and the site PI
- Funder
- Trial/Study Steering Committee (T/SSC)
- Data Monitoring Committee (DMC)
- Clinical study report writers (for assessment on any impact on the data analysis).

The decision for reporting to other third-party organisations e.g., professional body or employing organisation will be determined and undertaken by the Sponsor.

Process flowchart:



Failure to comply with the regulatory timelines for reporting serious breaches in CTIMPs is a criminal offence.

Full guidance from the MHRA and the form to be used to report to both the MHRA and REC can be found at:
https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials#report-a-serious-breach

Following review and approval by the Sponsor's Office, WCTU QA Team and the Director of WCTU (or delegate), reports for CTIMPs must be submitted to the MHRA via:
GCP.SeriousBreaches@mhra.gov.ukI

4.3.5 Corrective and Preventative Actions (CAPA)

An effective CAPA report should include an initial report, corrective action plan and preventative actions/processes in place. Considerations for each section are listed below.

Initial report

- Clear description of the finding
- Assessment of the implications of the finding
- Investigation and assessment of whether the finding is an isolated incident or part of a systematic non-compliance.
- Assessment of the impact of the finding (potential and actual impact on safety, integrity, rights and reputation)
- The root cause(s) of the finding (e.g., processes too complex, lack of resource, no formal procedures in place. Avoid use of 'human error')

Corrective actions

- Involvement of the right personnel, assigning actions as appropriate

- Ascertain and fully explain which retrospective actions are necessary to rectify/minimise impact
- Consider if approval is required from relevant bodies.
- Consider whether the corrective actions have impact on other areas
- Stipulate timelines

Preventative actions

- Ensure the preventative actions relate to the root cause(s)
- Address updates to related Quality Assurance/Quality Control processes
- Explain how the actions are to be implemented, ensuring they are measurable
- Stipulate timelines (with details of any interim measures)
- Avoid 'training' as a stand-alone preventative action

For WCTU managed studies, all actions should be followed up to resolution and documented within the non-compliance log. Other researcher teams should document the resolution of all actions on the CAPA form.

4.3.6 Oversight of non-compliances

Consideration should be given to whether an issue may be systematic within or across studies, and/or across sites in a particular study. The WCTU QA Team will have oversight of all study non-compliances entered onto the WCTU non-compliance log and will periodically review the data across the portfolio and run reports to identify any potential trends within and across trials. Escalation procedures will be implemented where repeated violations may constitute a serious breach as a systematic failure to take appropriate preventative actions. WCTU QA team will provide regular reports to the University's Sponsorship and Oversight Committee and the WCTU Governance Committee and ensure any required actions are taken.

For other research, the relevant sponsor must be informed, and they will be responsible for highlighting any trends.

4.3.7 Communications with recruiting sites in relation to non-compliance reports

When dealing with non-compliances identified and reported to the study coordinating centre by research sites, or where the coordinating centre has noticed a non-compliance, consideration should be made to ensure sensitive handling of any such reports.

The classifications used internally for Warwick sponsored or WCTU managed studies as detailed in this SOP, do not necessarily have to be shared with recruiting sites if there is any concern that distress or upset may be caused. It may be more appropriate to only use the over-arching term of 'non-compliance' when communicating with recruiting sites. We appreciate that site staff are extremely busy, and mistakes will inevitably occur, but we should avoid creating an atmosphere of negative feelings between coordinating centre and recruitment teams when dealing with these situations. It is good practice to work collaboratively with site teams to get input from and discuss potential areas of non-compliance and to ensure they are aware of when and to whom reports should be sent.

4.3.8 Research Misconduct

The University has a 'Code of Practice for the Investigation of Research Misconduct' https://warwick.ac.uk/services/ris/research_integrity/research_misconduct/codeofpractice_researchmisconduct/

Research Misconduct which could be investigated under this Code of Practice, may include, but not be limited to:

- Fabrication
- Falsification
- Misinterpretation of data and/or interests and or involvement
- Plagiarism; and
- Failures to follow accepted procedures or to exercise due care in carrying out responsibilities for:
    - Avoiding unreasonable harm or risk to humans, animals used in research, and the environment; and
    - The proper handling of privileged or private information on individuals collected during the research.

Anyone who has concerns over the conduct of a study, or the quality of the collected data, should immediately report these e.g., to their line manager or CI as appropriate and complete documentation to explain the concern(s).

Allegations will be dealt with in confidence, in accordance with the University's Code of Practice for the Investigation of Research Misconduct. Staff should not take any actions independently. All written material should be confined to factual observations and must not include opinions and preliminary conclusions. The line manager (or other person to whom the concern had been notified) will then escalate these details to the Investigation Team and an investigation will be instigated (if appropriate).

Investigations will be conducted in line with the University's Code of Practice for the Investigation of Research Misconduct, the University's general Code of Practice on 'Whistle blowing' and the University's Statute 24 (part III; Discipline, Dismissal and Removal from Office) and related ordinances. Further information is available on the University's Research Governance web pages: https://warwick.ac.uk/services/ris/research_integrity

An Investigation Panel will be set up and will produce a report which will:

- summarise the conduct of the investigation
- state whether the allegation of research misconduct has been upheld in whole or in part, giving reasons for its decision and recording any differing views
- make recommendations in relation to any matters relating to any other misconduct identified during the investigations
- address any procedural matters that the investigation has brought to light within the University and/or for example, any partner organisations and/or funding bodies.

The Chair shall then send the final report to the Registrar, Complainant and Respondent (including their representatives, by agreement), and inform all relevant parties of the reasons for reaching that conclusion in a final report.

If an allegation of research misconduct is upheld after appropriate investigation by clear and unequivocal evidence, it is the responsibility of the sponsor (or their designee) to notify the relevant REC and MHRA (if required) as soon as possible. Notification to an employee's professional body (where applicable) may also be considered.

Other actions may also be undertaken as appropriate which may include:

- Retraction/correction of articles in journals
- Withdrawal of payment/funding
- Notifying other employing organisations
- Notifying patients/doctors of any potential issues that may arise
- Notifying other organisations involved in the research
- Review internal management and/or training and/or supervisory procedures for research.

Misconduct may also constitute a potential serious breach of the protocol and/or GCP, and if confirmed, will require a report to be forwarded to the authorities as a serious breach (see section 4.3.4).

If research misconduct **is not confirmed**, a report documenting the enquiries made and an explanation of the reasons for the finding should be written and filed in the Trial/Study Master File (T/SMF).

List of Abbreviations

BSREC	Biological and Scientific Research Ethics Committee
CAPA	Corrective and Preventative Action
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMC	Data Monitoring Committee
DPA	Data Protection Act
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
QA	Quality Assurance
R&D	Research & Development
REC	Research Ethics Committee
R&IS	Research and Impact Services
SI	Statutory Instrument
SMF	Study Master File
SOP	Standard Operating Procedure
T/SMG	Trial/Study Management Group
T/SSC	Trial/Study Steering Committee
WCTU	Warwick Clinical Trials Unit

Templates

Template Corrective and Preventative Action (CAPA) Report (T13)

Associated Documents

Investigation Team to Assess/Report Potential Serious Breaches of GCP and/or Protocol (G04)
Non-compliance Log Working Instructions (G25)