Standard Operating Procedure	Lancaster University

Title: ICH GCP breach and protocol non-compliance procedure (non-CTIMP)

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Document History

Version	Date	Reasons for Change
1.0	**06/08/2025**	**Original document**

1.0 BACKGROUND

1.1 All research that falls under the remit of the Health Research Authority (HRA) or devolved administrations, must adhere to the UK Policy Framework for Health and Social Care research, and the International Council for Harmonisation Good Clinical Practice (ICH GCP) guidelines. Part of the guidelines include providing and adhering to a standardised study protocol.

1.2 Due to the nature of health and social care research, there may be times when researchers depart from the standardised protocol, or ICH GCP guidelines, either in error or where needed for the safety of participants.

1.3 It is important that in order to preserve the integrity and accountability of the research study and to ensure that the study results can be interpreted with all the relevant information relating to the conduct, those breaches and instances where researchers have had to break protocol are documented.

1.4 The sponsor is responsible for promoting and enforcing compliance where feasible and safe to do so and providing oversight by ensuring that robust systems and processes are in place to identify, monitor, categorise, document, and report both breaches of ICH GCP and deviations from the approved protocol.

1.5 It is the responsibility of the Chief Investigator (CI), along with the Principal Investigator (PI) at each site to ensure that the research study is run in accordance with ICH GCP, the approved study protocol and any other regulations applicable; and where breaches or deviations occur, following processes put in place by the sponsor to identify, document and report this.

2.0 PURPOSE AND SCOPE

2.1 This Standard Operating Procedure (SOP) describes the processes involved in identifying, documenting, managing, and reporting breaches of ICH GCP and/or failure to adhere to the approved protocol.

2.2 The process will allow Lancaster University to:

- Effectively oversee the management and conduct of the study at the host organisation and participating sites;
- ensure that where possible all regulations and best practice is upheld;
- document and report all breaches and non-compliance, to allow transparency around the conduct of research; and
- assess the impact of any breaches or non-compliance on the safety of participants and integrity of the research data.

3.0 PROCEDURE

3.1 Identification

3.1.1 ICH GCP Breaches and protocol non-compliance may be identified in several ways; this includes but is not limited to:

- Someone who is involved in the research identifies and reports the occurrences to the PI, CI, or sponsor;
- identified during scheduled or triggered monitoring visits;
- identified as a result of a regulatory inspection;
- identified as a result of an serious adverse event or adverse event report, that may have been a result of departure from the protocol or breach of ICH GCP; or
- identified during audit of the study by Lancaster University as the sponsor.

3.2 Documentation and Reporting

3.2.1 When identified, all breaches of ICH GCP or instances of protocol non-compliance must be clearly and systematically documented, using the ICH GCP and protocol non-compliance Report Form (HSCR-FORM07).

3.2.2 When identified, breaches and non-compliance reported to the chief investigator (CI) must also be reported to the Health and Social Care Research Sponsorship Committee (HSCRSC) via the Clinical Research Governance team (CRGT); notifications must be emailed to sponsorship@lancaster.ac.uk.

3.2.3 Documentation of a breach must include as a minimum:

- Full outline of the breach;
- the date, time and location of its occurrence;
- any corrective and preventative actions taken or planned (i.e. a CAPA plan); and
- a category, as determined by the CI, using the categorising GCP breaches and protocol non-compliance table (table 1, appendix 1).

3.3 Categorisation of ICH GCP breaches or protocol non-compliance

3.3.1 Once notified of a breach or non-compliance event, the CI must use table 1 (appendix 1) to categorise the event in relation to if the event impact the safety or physical or mental integrity of the subjects, or the scientific value of the trial as a whole to a significant degree; this must then be documented on the HSCR-FORM007 ICH GCP and protocol non-compliance report form.

3.3.2 The completed HSCR-FORM007 must be emailed to the CRGT for verification of the category and CAPA plan in line with the information outlined in table 1 and 2 (appendix 1).

3.3.3 Any events which fall within Category A will automatically amount to a "serious" breach and the procedure outlined in table 2 (appendix 1) will apply. Where there is a discrepancy between the CRGT and CI's categorisation, or where the CRGT feel escalation is required, the HSCRSC will be consulted and will determine the final category of the event.

3.3.4 The CRGT will document the outcome of their verification and any communication from the HSCRSC on the ICH GCP breach & protocol non-compliance report form (HSCR-FORM007) and return it to the CI.

3.3.5 The CRGT, in liaison with the CI and research team must consider whether a review of the risk assessment and/or amendment submission is required; in particular when a serious breach occurs, or where a pattern appears to develop.

3.3.6 The CI is responsible for implementing any CAPA plans, and notifying research sites of the event or any action required at site.

3.4 External Reporting Requirements for serious breaches or incidence of protocol non-compliance for non-CTIMPs (excluding Medical Device Trials)

3.4.1 Once categorized, serious breaches and non-compliance in non-CTIMP/non-medical device trials must be reported to the NHS REC who originally gave the study favorable opinion within, 7 days of the sponsor becoming aware of the incident.

- When the breach occurred.
- The location.
- Who was involved.
- The outcome.
- Any information given to participants.
- An explanation.
- What further action the sponsor plans to take.
- If the study is a CTIMP, a copy of the MHRA report form should be included.

The CI and research team are to work with the CRGT to notify the appropriate REC of any serious breaches.

3.4.2 There are no external reporting requirements for non-serious breaches or non-compliance for non-CTIMP/non-Medical Device trials however it is important that they are documented using the report form (HSCR-FORM007) and logged with the CRGT to be actioned as appropriate.

3.5 External Reporting Requirements for all breaches or incidence of protocol non-compliance for medical device trials

3.5.1 The Medical Device Regulations (2002) require the sponsor of a medical device trial to notify the MHRA in writing of any breach of the conditions and principles of ICH GCP or the approved protocol as soon as they become aware of the breach-regardless of seriousness. Breaches should be notified in line with MHRA guidance, and include the following as a minimum dataset:

- When the breach occurred;
- the location;
- who was involved;
- the outcome;
- any information given to participants;
- an explanation; and
- what further action the sponsor plans to take.

3.5.2 The CI and research team are to work with the CRGT to report any events to the MHRA.

3.5.3 The sponsor and CI must use the MHRA's protocol deviation tracker Excel template, maintain it as a live document, and email the completed spreadsheet to info@mhra.gov.uk as notification of the event.

3.5.4 Upon receipt of a medical device breach notification, the MHRA will log and review it and may take any number of actions depending on the nature of the breach and its potential impact.

3.5.5 Serious breach events must be referenced within all relevant publications pertaining to the study, and the MHRA may undertake audits to ensure publication transparency.

4 APPENDIX

4.1 Table 1 Categorisation of GCP Breaches and Protocol Deviations:

Minor (C): A deviation or non-compliance from the protocol, GCP or Sponsor procedures, that is not approved by the sponsor / REC / MHRA prior to its implementation that <u>does not</u> impact on subjects' safety or compromise the integrity of the study data. (Unlikely to affect). Example: The researcher has completed a measure a day later than planned on the study protocol, as this was the only time the participant was free.
Major (B): A major protocol violation or non-compliance is one that could potentially impact on the participant safety, legal or ethical rights, or affects the integrity of the study data. (Could affect) Example: The researcher has completed the study measures in the wrong order, but on the same visit. This could impact the integrity of the data.
Serious (A): A serious protocol violation or non-compliance is one that has impact on the participants' safety, legal or ethical rights, or significantly affects the data integrity of the study data. (Has affected) Example: The participant was randomised to the treatment arm of a study, where the study involved actively stopping an approved treatment in favour of the study intervention. Those not randomised to receive the intervention were expected to continue standard treatment. Due to a administration error, the participant has not been sent the study treatment, and has also not received standard care. This has impacted the participants safety, as they have been without treatment for several weeks.

4.2 Table 2 Actions to be taken for each category:

Deviation Category	**Actions**
Serious (A)	When the CI is made aware, the non-compliance issue will be logged on an *'HSCR-FORM007-ICH GCP and Protocol non-compliance form'* including any corrective and preventative action plans (CAPA), and then provisionally categorised by the CI. This should then be sent to the CRGT for verification and review.

Major (B)	The visit report and form will be jointly reviewed by clinical research governance team in collaboration with the HSCRSC or a delegate to discuss any further actions required or escalation/de-escalation of category. Based on the outcome of this review, the HSCRSC in liaison with the CI will determine the next appropriate action which could include: (i) The findings should be regarded as category C and handled accordingly (ii) Additional CAPAs should be implemented (iii) Recruitment should be temporarily halted until issues are resolved (iv) The research should be suspended (v) The research should be terminated Complex cases will be escalated to an appropriate committee. All cat A deviations will be reported to the relevant ethical and regulatory bodies.
Minor (C)	When the CI is made aware, the non-compliance or deviation issue must be logged on an *'HSCR-FORM007-ICH GCP and Protocol non-compliance form'* and categorised by the CI. This should be shared with the Clinical Research Governance Team and logged by them. If they deem escalation is required or disagree with the categorisation, they will escalate to the HSCRSC for input before reporting back to the CI. Where no escalation or input is required, the CAPAs will be implemented by the research team and no further HSCRSC input is required. The CRGT and research team must retain the documentation in the Trial Master File (TMF) and if identified at site in the Investigator Site File (ISF) at that site.

4.3 HSCR-FORM007 ICH GCP & Protocol Non-compliance Form:

Form Title:	ICH GCP & Protocol Non-compliance Report Form	Lancaster University
Form Ref.:	HSCR-FORM007	

This form is intended to be used for projects sponsored by Lancaster University that have discovered an incidence of GCP or Protocol non-compliance. It will be used in accordance with the procedure outlined in the GCP Breaches and Protocol non-compliance SOP (HSCR-SOP004).

This should be completed accurately, and in full, for the sponsor to review all breaches. Please send all forms to the Clinical Research Governance Team via email to **Sponsorship@lancaster.ac.uk** with high importance and noting 'ICH GCP Breach and Protocol Non-compliance and report form for review' and the study name in the subject line.

Details	
Study Title	
Chief Investigator Name	
Site where the breach occurred (Please state Lancaster University if the breach is a study wide breach)	
Site Principle Investigator Name (if a site issue)	
Date Non-compliance occurred	Click or tap to enter a date.
Date Non-compliance Identified	Click or tap to enter a date.
Name and Position of Person Completing Form	
Date Form Completed	Click or tap to enter a date.

Participants Affected					
Single Participant			**Multiple Participants**	**All Participants**	**None/Not Known**
☐	**Participant ID number**		☐	☐	☐
	Initials				

Description (Be as specific as possible about the deviation/breach, and include any references to GCP or protocol where necessary)

Does the PI or CI (If a study wide issue) think this is likely to affect to a significant degree any of the following:	
Scientific value of the study	☐
Safety, physical or mental integrity of the participant(s)	☐
None of the above	☐

Corrective and Preventative Actions Taken (please outline any actions you have undertaken to correct the breach or deviation, and any long-term actions to be undertaken to prevent this happening in the future)**:**

PI/CI Signatures (Please ensure the PI signs this if the issue is a single site issue, the CI should sign if this is a study wide or researcher issue)	
PI or CI Name	
Signature	
Date (DD/MM/YYYY)	

For sponsorship office Use (to be completed by the clinical research governance team upon receipt of the form)		
Name and Position		
Date Received (DD/MM/YYYY)		
Date Completed (DD/MM/YYYY)		
Category	**(A) Serious**	☐
	(B) Major	☐
	(C) Minor	☐
Initial Action Taken	**No further action, CAPA outlined is satisfactory**	☐
	Further action required, discussed CAPA with CI/PI	☐
	Escalated to HSCRSC/Sponsor Rep	☐
	Other (please outline)	☐

4.4 HSCR-FLOW007 GCP Breach and Protocol non-Compliance Flow Chart: