Notification of Serious Breach of GCP or Trial Protocol

Policy Details	
Document Type	Standard Operating Procedure
Document name	KHP-CTO/CT/SOP 6.0 Notification of Serious Breach of Good Clinical Practice or Trial Protocol
Version	Final v6.0– 08 March 2023
Effective from	8th March 2023
Review date	28 February 2025
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Superseded documents	Final v5.0 – 12 March 2019
Relevant regulations/legislation/guidelines	Statutory Instrument 2004 no 1031 Statutory Instrument 2006 no 1928 As amended from time to time MHRA Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol

Change History			
Date	Version Number	Change details	Approved by
12/02/2010	2.0	Change to King's Health Partners Livery and amend MHRA notification contact details.	Jackie Powell
24/01/2012	2.0	Reviewed and no change required.	Jackie Powell
11/02/2013	3.0	Change to reflect rebranding of JCTO and to reflect new guidance issued by MHRA	Jackie Powell
24/02/2016	4.0	Scheduled review including consistency check of Glossary terms	Jackie Pullen
01/10/2018	4.1	Minor amendment to include trials managed by KHP-CTO and amend Jackie Pullen's title to Director KHP-CTO	Jackie Pullen
12/03/2019	5.0	Scheduled review, inclusion of requirement to notify Ethics Committee of serious breach at same time as MHRA	Jackie Pullen
08/03/2023	6.0	Scheduled review, minor revisions	Jackie Pullen

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1.0 GLOSSARY

Clinical Trial of an Investigational Medicinal Product (CTIMPs) - Any investigation in human subjects, other than a non-interventional trial, intended to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal product or to identify any adverse reactions to one or more such products and to study absorption, distribution, metabolism and excretion in one of more such products with the object of ascertaining the safety or efficacy of those products.

Good Clinical Practice (GCP) - as defined in the Regulations.

King's Health Partners - King's Health Partners Academic Health Science Center is a pioneering collaboration between one of the King's College London (University) and three of London's most successful NHS Foundation Trusts – Guy's & St Thomas'. King's College Hospital and the South London & Maudsley.

King's Health Partners Clinical Trials Office (KHP-CTO) – Established in 2006 by Kings College London, Guy's & St Thomas' NHS Foundation Trust and King's College Hospital NHS Foundation Trust to provide a streamlined approach for all aspects of trial administration since joined by the South London & Maudsley NHS Foundation Trust in 2009. Formerly known as the Joint Clinical Trials Office (JCTO).

KHP-CTO Quality Team – Comprises the Clinical Quality Manager, Clinical Research Associate(s), Clinical Trial Administrator(s), Systems Executive, Training Executive(s) and Training Assistant.

KHP-CTO Standard Operating Procedure (SOP) - "detailed, written instructions to achieve uniformity of the performance of a specific function," SOPs are the base on which Quality Systems and Processes are conducted and monitored against.

Quality Policy - Policy signed by the Medical Directors' of the Partner Organisations and the Vice Principal of the Health Schools of King's College London. The Quality Policy binds all relevant clinical research activity conducted or managed by the Partner Organisations to the KHP-CTO Clinical Trial SOPs.

Research Ethics Committee (REC) – The REC undertakes the review of the research protocol, including the content of the patient information sheet and consent form, rather than site specific approval for each centre.

Serious Breach of GCP - a "serious breach" of the principles of GCP that is likely to affect to a significant degree, the safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial.

Serious Breach of trial Protocol - a serious breach of trial protocol that is likely to affect to a significant degree, the safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial.

The Regulations - Medicines for Human Use (Clinical Trial) Regulations 2004 (as amended from time to time) transposed the EU Clinical Trials Directive into UK legislation, as Statutory Instrument 2004 no 1031. This became effective on the 1st May 2004**.** An amendment to implement Directive 2005/28/EC was made to the Regulations as Statutory Instrument 2006 no 1928.

2.0 BACKGROUND AND PURPOSE

Statutory Instrument 2004/1031 – the Medicines for Human Use (Clinical Trials) Regulations 2004 transposed the European Union Directive 2001/20/EC for Clinical Trials into UK law effective from the 1st May 2004. The original UK regulations were amended in August 2006 to incorporate the EU Good Clinical Practice Directive (2005/28/EC) as Statutory Instrument 2006/1928.

The Regulations state that Clinical Trials involving medicinal products MUST be authorised by the MHRA and conducted according to the Principles of GCP as defined in the Amended Regulations and any subsequent amendments.

Regulation 29A of the Regulations state that:

"The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of—
(a) The conditions and principles of good clinical practice 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."*

This SOP describes the process for the identification and notification of serious breaches of GCP or the approved trial protocol.

3.0 SCOPE

All clinical trials sponsored, co-sponsored, managed or hosted by the Partner Organisations as bound by the Quality Policy.

It is the responsibility of a trial Sponsor to ensure monitoring (which may be risk adapted) for compliance with GCP and the trial protocol is performed. All Clinical trials sponsored by one or more of the Partner Organisations will be monitored by the KHP-CTO CRAs or, if outsourced, the KHP-CTO will retain oversight of the monitoring. Trials sponsored by organisations other than the Partner Organisations may be monitored by KHP-CTO CRAs from time to time; however this responsibility lies with the Sponsor Organisation.

4.0 PROCEDURE

4.1 Responsibility

It is the responsibility of the trial Sponsor or a person legally authorised by the Sponsor to carry out the notification procedure within **7 days** of becoming aware of the breach.

4.2 Serious Breach or Minor Deviation?

Minor deviations from clinical trial protocols and GCP can occur in clinical trials. The majority of these instances are technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial.

These cases will be documented appropriately on the protocol deviation log, in the monitoring visit reports and/or explained in File Notes filed within the Trial Master File or Investigator Site File.Corrective and preventative actions (CAPA) will be taken where appropriate. In addition, these deviations will be included and considered when the clinical study report is produced, as they may have an impact on the analysis of the data.

Protocol "waivers" or deviations to inclusion/exclusion criteria are NOT permitted and are considered and assessed as a potential serious breach. However, not every deviation from the protocol needs to be reported to the MHRA/REC as a serious breach.

The MHRA define a serious breach as:

- Any serious breach of:

  (a) the conditions and principles of good clinical practice in connection with <u>that</u> trial *(as defined in UK legislation)*; or

  (b) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25.

For the purposes of this regulation, a "serious breach" is a breach which is likely to effect to a <u>significant</u> degree:

(a) the safety or physical or mental <u>integrity of the subjects</u> of the trial *(this should be relevant to trial subjects in the UK)*; or

(b) the <u>scientific value</u> of the trial.

The judgement on whether a breach is likely to have a significant impact on the scientific value of the trial depends on a variety of factors e.g. the design of the trial, the type and extent of the data affected by the breach, the overall contribution of the data to key analysis parameters, the impact of excluding the data from the analysis etc.

It is the responsibility of the Sponsor to assess the impact of the breach on the scientific value of the trial. If a potential serious breach is identified by KHP-CTO staff or if the KHP-CTO is alerted to a potential serious breach, the Sponsor Organisation will be notified as soon as possible by a member of the KHP-CTO Quality Team.

A potential serious breach occurring in a trial sponsored or co-sponsored by KHP-CTO Partner Organisations will be reported to the KHP-CTO Quality Manager or Director who will determine whether the incident constitutes a serious breach of GCP or protocol.

4.3 Procedure for Notification

The procedure for notification of serious breaches of GCP or the trial protocol can be divided in to 5 key areas:

1. Identifying and notifying the sponsor of a serious breach
2. Assessment of a serious breach
3. Initial notification to the MHRA/REC
4. Provision of additional information to the MHRA/REC
5. Planning and implementing corrective action

4.3.1 Identifying and Notifying Sponsor of a Serious Breach

Any suspected breaches identified in CTIMPs sponsored, co-sponsored or managed a KHP Partner Organisations either through monitoring, audit or by other means must be reported to the KHP-CTO Quality Manager or Director within 24 hours of the breach being identified and confirmed.

The following information is required for Initial reporting to the KHP-CTO: -

Name of Chief Investigator and Principal Investigator at the site where the suspected serious breach occurred and:-

- Full title and IRAS number of the clinical trial.
- Details of the suspected serious breach.
- Details of any initial corrective actions already implemented.

4.3.2 Assessment of a Serious Breach

Upon receipt of an initial breach of trial protocol report the KHP-CTO Quality Manager or Director will discuss the incident with the Chief/Principal Investigator or clinical “expert” to determine how the breach impacts on subject/participant safety and/or the scientific integrity of the trial.

The KHP-CTO Team will work with the Chief/Principal Investigator to identify the extent of the breach and to initiate any Urgent Safety Measures (see PV policy for process) or additional training or other actions that may be required.

If the breach is not considered a serious breach by KHP-CTO Quality Manager or Director, the CI should ensure the CAPA is implemented at all sites as repeated deviations may result in a serious breach.

4.3.3 Initial Notification of Breach to MHRA

The Quality Manager or delegate may initially contact the MHRA Inspectorate by telephone to discuss the breach. The Quality Manager or delegate will follow up with a written notification within 7 days of the Sponsor becoming aware of the breach.

The KHP-CTO Quality Team led by the Quality Manager will collate all available information and complete the Notification of Serious Breaches of GCP or the Trial Protocol form (see related templates).

The form will be submitted via e-mail to the MHRA within the 7 day reporting period defined in the regulations. The form will be sent to:

GCP.SeriousBreaches@mhra.gov.uk

The Quality Manager will be the contact person for all correspondence with the MHRA. Whilst the Chief investigator is responsible for communication for the Ethics Committee a copy of the report will be submitted to the relevant REC at the same time of sending to the MHRA to ensure consistent communication is maintained.

4.3.4 Provision of additional information to the MHRA

Once the initial notification has been submitted to the MHRA, the KHP-CTO will review the breach in full to identify the extent of the breach and any new information will be forwarded to the MHRA/REC.

The Chief/Principal Investigator will compile a project report for submission to the MHRA/REC if applicable. The project report will include:

1. Full title of trial, IRAS number, EudraCT number, version number, date of commencement
2. Name of Chief Investigator
3. List of Sites
4. Number of subjects recruited
5. Brief description of the trial
6. Summary of the breach including any rationale
7. Summary of actions taken

8. Assessment of impact of breach to subject/participant safety and/or scientific integrity of trial
9. Root Cause Investigation
10. CAPA plan
11. Statement from Chief Investigator (if not the person completing the report)

The KHP-CTO will review the project report and submit to the MHRA and REC if applicable.

4.3.5 Planning and Implementing Corrective Action

The KHP-CTO Quality Team will work with the Investigator team and Sponsor Organisation to devise a formal plan of corrective action to address the breach. The corrective action plan will be submitted to the MHRA/REC on their request.

4.3.6 Notification of Serious Breach to Sponsor Organisation

4.3.6.1 Partner Organisations Sponsored Trials

Where trials have a single sponsor the KHP-CTO Quality Manager or Director will notify the Sponsor Organisation R&D Manager of the serious breach.

Where trials are co-sponsored by one or more of the Partner Organisations, the R&D Manager in the co-sponsoring NHS Trust, the Vice Principal (Health Schools) and the Director of Research Management KCL *(if applicable)* will be informed.

4.3.6.2 Trials Sponsored by Non-Partner Organisations

The Sponsor contact person designated in the Clinical Trials Agreement or trial protocol will be informed of the breach of GCP or trial protocol in a timely fashion.

5.0 RELATED TEMPLATES

5.1 MHRA Serious Breach Notification Form

6.0 RELATED DOCUMENTS

6.1 Notification of Serious Breach of GCP - Protocol Examples

7.0 APPROVAL and SIGNATURE

08 March 2023

Jackie Pullen,
Director,
King's Health Partners Clinical Trials Office

Date