University Hospitals Birmingham NHS Foundation Trust

CONTROLLED DOCUMENT

Reporting Research Incidents and Breaches Policy

CATEGORY:	Policy
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PURPOSE	To set out the framework and principles for reporting research incidents and breaches.
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Contents

1. Policy Statement

1.1 University Hospitals Birmingham NHS Foundation Trust (the 'Trust') has an established Policy for Reporting and Managing Incidents which provides general guidelines for reporting clinical and non-clinical incidents. However, in order to comply with legislation, and governmental policy on research governance there are some specific requirements for reporting and managing research related incidents. This policy is to be read in conjunction with the Trust Policy for Reporting and Managing Incidents and gives additional specific guidelines relating to research.

1.2 This policy aims to ensure that:

1.2.1 Arrangements are in place to protect patient safety in all research involving human subjects taking place within the Trust;

1.2.2 Investigators are aware of the safety implications of their research; and

1.2.3 The appropriate organisations are notified of safety information relating to research involving medicines and devices.

1.3 Key definitions are set out in the associated Research Governance Policy. Additional definitions are provided in Appendix B.

2. Scope

This policy specifically covers clinical incidents that may be related to a drug, device or procedure introduced as part of a clinical Research Study as well as to incidents that arise from deviations to the study protocol agreed with the ethics committee and regulatory authorities, or deviations from international standards in the conduct of research known as Good Clinical Practice (GCP).

3. Framework

3.1 An internationally recognised set of principles known as "Good Clinical Practice" (ICH-GCP) has been used to govern the conduct of industry sponsored trials of medicines for nearly 20 years These principles are incorporated into UK legislation covering clinical trials of medicines and include specific requirements for reporting safety issues to the regulatory authorities.

3.2 Under the GCP principles, in clinical trials of medicines or devices, the sponsor of the trial has a statutory duty to report Suspected Unexpected Serious Adverse Reactions (SUSARs) to the main Research Ethics Committee and the Medicines and Healthcare products Regulatory Authority (MHRA) within 15 days of becoming aware of the event, or 7

days if the event is fatal. SUSARs must be reported through the online eSUSAR system maintained by the MHRA.

3.3 Serious Breaches in Protocol or GCP must be reported by the Sponsor to the main Research Ethics Committee and Regulatory Authority within 7 days.

3.4 Sponsors of clinical trials of medicines are required to provides Annual Progress Reports to the main Research Ethics Committee and an annual safety report to the MHRA in the form of a Developmental Safety Update Report (DSUR), which includes a line-listing of all suspected serious adverse reactions.

3.5 The key points of this reporting mechanism are:

3.5.1 Clinical incident reporting

a) All Serious Adverse Events that are potentially related to an intervention specified in a research protocol must be reported as a research incident through the Trust's online incident reporting system. It must be reported as soon as possible after the incident has been detected;

b) The Principal Investigator (PI), or a suitably qualified alternate designated by the PI, must make an assessment of whether the incident is reasonably likely to be related to an intervention specified in the protocol, and if it is related whether the incident is a known risk of the intervention;

c) If the PI determines that the Serious incident is likely to be related to the research intervention and is unexpected (a so-called SUSAR) then they must notify the Sponsor and Chief Investigator (CI) immediately so that they in turn can notify the Research Ethics Committee and regulatory authorities in line with legislation.

3.5.2 Protocol breaches

a) All breaches of protocol must be recorded by the PI in the study file;

b) Repeated and persistent technical and minor breaches must be reviewed for a possible need to amend the protocol in consultation with the Sponsor and CI;

c) The PI must ensure that any Serious Breach of Protocol (see definition in Appendix B), is reported to the Sponsor and CI as soon as possible;

3.5.3 Breaches of GCP

a) Suspected Serious Breaches of GCP (see Appendix B) identified during the conduct of a study must be reported to the Trust's Head of R and D Governance as soon as possible.

b) The Head of Research and Development (R and D) Governance will ensure that the Sponsor and CI are notified of the breach and confirm with them actions to be taken to address the Serious Breach.

4. Duties

4.1 Divisional Directors and Clinical Service Leads

Divisional Directors and Clinical Service Leads will have systems and procedures to ensure they are aware of clinical research within their division and service and to ensure that clinical research incidents and breaches are recorded and reported according to this policy.

4.2 Chief Investigator

4.2.1 Where the Trust is acting as Sponsor for a clinical study, primary responsibility for handling safety reporting is delegated to the CI who will:

- have in place procedures to ensure they are notified of all Serious Adverse Events or breaches as soon as possible after they occur, wherever they occur, particularly for multi-site studies;
- be responsible for reporting SUSARs to the MHRA and main Research Ethics Committee within 15 days of becoming aware of the event (7 days if the event is a fatality). If all of the information is not available, an initial report must nevertheless be made within the statutory timescale; follow up reports can then be made when more information becomes available;
- For clinical trials of medicines, submit to the MHRA a DSUR on the anniversary of the first trial authorisation by the MHRA; and
- send copies of SUSAR notifications and DSUR reports to the Trust R and D Office.

4.3 Principal Investigator

4.3.1 The local PI must have in place procedures to ensure they are notified of all Adverse Events or breaches occurring in studies for which they are leading;

4.3.2 Where an Adverse Event is classed as serious, the PI must make an assessment of the causality and expectedness of the event to any intervention specified in the protocol. The PI may delegate this assessment to someone else who is suitably qualified;

4.3.3 The PI must ensure that all Serious Adverse Events are recorded in the study file and that Serious Adverse reactions are reported to the CI and Sponsor as soon as possible; and

4.3.4 The PI must ensure that all Serious Adverse Events are reported through the Trust's incident reporting procedure.

4.4 Head of Research and Development Governance

The Head of R and D Governance is required to:

4.4.1 Ensure that all Researchers are made aware of the Trust policies and procedures for safety reporting;

4.4.2 Check for patterns in Adverse Event reporting and to query with PI's unusual patterns; and

4.4.3 Oversee compliance with statutory reporting requirements for studies that the Trust is sponsoring.

5. Implementation and Monitoring

5.1 Implementation

This policy will be available on the Trust's Intranet Site. The policy will also be disseminated through the management structure within the Trust.

5.2 Monitoring

Appendix A provides full details on how the policy will be monitored by the Trust.

6. References

Department of Health	Research Governance Framework, second edition (2005)
European Medicines Agency	ICH Topic E 6 (R1) Guideline for

	Good Clinical Practice
HMSO	Statutory Instrument 2006/1928
WMA	Declaration of Helsinki (as amended at the 59th WMA General Assembly, Seoul, October 2008)

7. Associated Policy and Procedural Documentation

Chief Investigators and Principal Investigators in Research Policy

Policy for the Reporting and Management of Incidents Including Serious Incidents Requiring Investigation

Procedure for Reporting Research Incidents and Breaches

Research Governance Policy

Appendix A Monitoring Matrix

MONITORING OF IMPLEMENTATION	MONITORING LEAD	REPORTED TO PERSON/GROUP	MONITORING PROCESS	MONITORING FREQUENCY
Reporting incidents	Research Governance Manager	Head of R&D Governance	Download DATIX report of research-related incidents and cross-checking with study details	Fortnightly
PI reporting serious incidents and breaches to the sponsor	Research Governance Manager	PI and Head of R&D Governance	Review incidents reported through DATIX and confirm with PI that serious incidents and breaches have been reported to the sponsor	Fortnightly
CI reporting serious unexpected reactions and serious breaches to the NHS REC and regulatory authority	Research Governance Manager	Head of R&D Governance	Check that directly reported incidents and incidents identified from DATIX reports have been submitted to the NHS REC and regulatory authority.	Fortnightly
Annual submission of DSUR	Research Governance Manager	Research, Development and Innovation Management Group	Research Governance Database flags DSURs that are due. Submission of DSURs are recorded on the database.	Continuously
Conduct of research studies	Research Governance Manager	Head of R&D Governance	Random study audits. Information on potential incidents identified from an audit can be matched with information reported through DATIX and in annual progress reports.	Monthly

Compliance report	Head of R&D Governance	Research, Development and Innovation Management Group.	Governance report presented to each RD and I Management Group meeting. Includes summary of research incidents reported through DATIX, clinical study audits, and status of DSURs reported to NHS REC and regulatory authority.	Quarterly

Appendix B – Definitions and Explanations

1. Incidents and Breaches

1.1 Adverse Event

1.1.1 A research-related adverse event is any untoward medical occurrence in a patient during clinical research involving a pharmaceutical product, medical device, or clinical intervention.

1.1.2 Where the research involves a medical device, any event which gives rise to, or has the potential to produce, unexpected or unwanted effects involving the safety of patients, users or other persons is described as an adverse incident.

1.1.3 In either case, the event or incident does not necessarily have a causal relationship with the treatment under investigation.

1.1.4 In research, there is a standard categorisation of adverse events dependant on assessments of the seriousness of the event, how likely it is to be related to an intervention specified in the research protocol, and whether or not the event could be expected from known prior information about the intervention. There are statutory requirements for reporting certain categories of adverse events in clinical trials of medicines or medical devices.

1.2 Serious Adverse Event

1.2.1 An Adverse Event/Incident is defined as a Serious Adverse Event (SAE) if it:

- Is fatal;
- Is life-threatening (i.e. at risk of death at time of event);
- Results in persistent or significant disability/ incapacity;
- Requires in-patient hospitalisation or prolongs a current hospitalisation;
- Results in a congenital anomaly in offspring; or
- May jeopardise the patient or may require intervention to prevent one of the outcomes listed above.

1.2.2 In order to detect congenital anomalies, it is important for the researchers to have procedures in place to monitor any

pregnancies occurring in participants of clinical trials (and possibly the partners of male participants) to term.

1.2.3 Additional Requirements for Medical Devices/ Equipment

In addition to the above definition a serious adverse incident involving a device would include:

a) Any incident, that was possibly linked to the device or with shortcomings in the information supplied, that might lead to death or serious deterioration in health if it recurred;

b) Any malfunction of a device used in accordance with the manufacturer's instructions, for which the manufacturer has not made provision, e.g. an alarm, and which causes an injury or potential injury; and

c) Inaccuracies or omissions in the manufacturer's instructions which caused, or could cause, misuse or incorrect maintenance or adjustment.

1.2.4 Relatedness (Adverse Reactions)

a) An Adverse Event that is likely to be related to an intervention in the study is referred to as an Adverse Reaction (AR), an SAE that is likely to be related to the intervention is a Serious Adverse Reaction (SAR); and

b) The local PI, CI or a medical advisor appointed by the PI,CI or Sponsor must make an assessment of relatedness.

1.2.5 Expectedness

a) Because of the nature of the disease, disease progression, or known characteristics of the device or medicine many AEs, ARs SAEs and SARs may **not** be unexpected. Known information about the medicines or devices or interventions should be provided in the protocol, investigators brochure (IB), Summary of Product Characteristics (SmPC) for a marketed medicine, or technical brochure for a device. Any adverse event that is not consistent with the information in these documents, or with expected disease progression must be regarded as unexpected; and

b) The local CI, PI or a medical advisor appointed by the PI,CI or Sponsor must make an assessment of expectedness of the event to a protocol-specified intervention.

1.3 SUSAR

1.3.1 A Serious Adverse Event that is potentially related to an intervention and is unexpected is referred to as a **SUSAR** (Suspected Unexpected Serious Adverse Reaction). There are statutory reporting requirements for SUSARs.

1.3.2 Exemptions for disease-related events

a) The study protocol may have been written to exclude reporting of certain conditions of the disease under investigation. These events would not be classed as Serious Adverse Events provided they are recorded and the data included in the analysis to check there is no change in the frequency of the events.

1.4 Protocol Breach

In giving a favourable opinion for a Research Study, a research ethics committee will have reviewed the research protocol. Significant changes to the protocol must not be made without consideration and approval by the research ethics committee. A deviation from any of the conditions or procedures written in the protocol is technically a breach of protocol.

1.5 Breach of GCP

The principles of GCP (Good Clinical Practice) were originally set out by the International Committee on Harmonisation (ICH) and adopted into an EU Directive (the so-called GCP Directive) and subsequently into UK law through Statutory Instrument (SI 2006/1928). Conduct during a study that persistently fails to follow these principles is a breach of GCP.

1.6 Serious Breach

It is recognised that breaches of protocol or of GCP occur quite frequently in clinical studies. They may be inadvertent, technical breaches and have little consequence either to the research participants or to the outcome of the study. These should be recorded in the study file but usually do not need to be reported further. Persistent minor breaches may suggest a need to amend the protocol. However, some breaches may have more serious consequences. A Serious Breach of Protocol is defined in the Clinical Trials Regulations (SI

Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928) as one that is "*likely to affect the safety or physical or mental well-being of the research subject, or the scientific value of the study*".

1.7 Urgent Safety Measure

Urgent Safety Measures such as a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects can be made without prior approval/favourable opinion. However, the study Sponsor must be notified as soon possible so they in turn can notify the ethics committee and regulatory authority. Details should be provided of the implemented deviation or change, the reasons for it, and, if appropriate proposed amendments to the protocol.