NHS
Bradford District Care
NHS Foundation Trust

Recording and Reporting of Adverse Events for Research Studies.

SOP 03

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Recording and Reporting of Adverse Events for research studies

The key messages the reader should note about this document are:

1. It is the responsibility of all staff involved in research to be aware of the requirements of safety reporting for the studies in which they are involved.

2. Reporting of all adverse events should be in line with GCP guidelines, and any special instructions listed within the study protocol. https://www.nihr.ac.uk/our-faculty/clinical-research-staff/learning-and-development/national-directory/good-clinical-practice/gcp-resources/gcp.htm

3. All serious incidents will follow the 'Serious Incident (SI) Policy' (see corporate policies on Connect). Should the incident be serious then the serious incident procedure must be followed and Serious Incident Alert must be completed within 2 hours of the incident or knowledge of the incident.
http://connect.bdct.local/docs/policies/pubdocs/Incdnt_Rprtng_Mngmnt_Policy_10-03_Final__PDF_26-10-2015.pdf

4. Reporting may be required to several bodies including but not limited to:

    a) Trust
    b) Sponsor/Chief Investigator
    c) Medicines and Healthcare Products Regulatory Agency (as applicable)
    d) Research Ethics Committees

Recording and Reporting of Adverse Events for Research Studies

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Amendment Summary:	**Throughout:** a. BDCT changed to BDCFT to reflect Trust Foundation status. b. The UK Framework for Health & Social Care Research has replaced the Research Governance Framework (2005). c. Links have been updated where appropriate. **Key Messages:** a. point 2, information added to reflect new serious incident procedure. b. point 3, changed to reflect updated Trust Serious Incident Policy.

Contents

1 Introduction:

The UK Framework for Health & Social Care Research requires the Trust to ensure that arrangements are in place for monitoring and reporting on research, and places an obligation on researchers to report suspected serious adverse incidents promptly. Furthermore, ICH/GCP and the Medicines for Human Use (Clinical Trials) Regulations 2004 require certain adverse events and unexpected reactions to be reported to Research Ethics Committees and the Medicines and Healthcare Products Regulatory Agency.

The Trust's Risk Management Strategy and policies, including Incident management Policy and Serious Incident management procedures provide guidance and procedures for reporting clinical and non-clinical adverse events. However, they do not include all of the definitions or scenarios of adverse events/incidents that are described within a research context. Therefore the aim of this document is to outline the responsibilities of the Trust and research staff and the procedures for swift and accurate reporting of adverse events for research studies according to Good Clinical Practice for Research guidance.

2 Purpose

The purpose of this guidance is to provide information on the processes and systems in place for the management and reporting of all adverse events and reactions that may occur in research studies (in particularly clinical trials) in accordance with the Medicines for Human Use (Clinical Trials) Regulations and UK Framework for Health & Social Care Research.

Please note that this procedure is to be used along with the current Trust guidance for the management and reporting of adverse events and incidents. Links to the Trusts policies are obtained in the reference section (p16-17) and on the Trust intranet.

3 Type of document

This is a procedural document describing the “how”; and gives guidance about how to report adverse events for research in the Trust. It provides a step-by-step guide, which someone not familiar with the work can follow. Staff are required to follow the instructions given, and a breach of a procedure may have contractual consequences for the member of staff. The procedure will ensure research and development activity is carried out in accordance with national and statutory standards and guidance.

4 Definitions

Glossary of Definitions and terms used in Research

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product or intervention has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a service user to an investigational medicinal product which is related to any dose administered to that person.
Case report form/file (CRF)	Research participant's specific documents that relate to their participation in that study. This may include signed consent forms, records of data, transcripts of interviews etc. It should also contain specific reports of AEs as determined by the study protocol/GCP guidelines.
Chief Investigators (CI)	The designated lead for a research project, with overall responsibility for the conduct of that project. For multi-site projects, a CI may be based within another institution, with the responsibility for the local (Trust based) running of the project devolved to the Principal Investigator. They have responsibility for ensuring compliance with all monitoring and audit procedures.
Good Clinical Practice (GCP)	GCP is an international ethical and scientific quality standard for the design, conduct and record of research involving human participants: compliance with GCP is now a legal obligation in the UK/Europe for all trials of investigational medicinal products**.** All researchers and NHS staff wishing to participate in research are required to undertake certified GCP training every 2 years to maintain up to date awareness.
HEI	Higher Education Institutions' including Universities
ICH-GCP	International Committee on Harmonisation Good Clinical Practice Guideline.

Investigational medicinal product (IMP is known as a CTIMP if involved in a clinical trial)	"a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form."
MRC	Medical Research Council
Principal Investigator (PI)	The local (Trust based) lead in a multi-site project. They will report to the project Chief Investigator. They have responsibility for ensuring compliance with local monitoring and audit procedures.
Research Support Services (RSS) Framework	An initiative by the NIHR Research Support Services to provide a national framework for NHS research managers to offer a consistent professional service, using a risk approach to managing projects and governance. Within the framework there are a number of standards and procedures guiding the management of research governance in order for NHS R&D offices to provide an effective, streamlined service.
Serious Adverse Event/Reaction (SAE/SAR)	Any adverse event or adverse reaction that is an untoward and unintended response to an IMP (not a placebo or reference drug) at any dose, that: a. results in death b. is life threatening c. requires hospitalisation or prolongation of existing hospitalisation d. results in persistent or significant disability or incapacity e. consists of a congenital anomaly or birth defect. f. anything else as defined in the study protocol
Site File	Local investigator's file containing the generic documents relating to a study e.g. protocol, approval letters, study logs etc.
Source documents	Case notes/medical notes
Sponsor	The organisation providing assurance for the quality of a research project. It may be an NHS organisation, HEI or commercial.

Serious Adverse Reaction (SAR)	Any adverse reaction that is classed in nature as serious and which is consistent with the information given about the medicinal product : a. In the case of a licensed product, the summary of product characteristics (SmPC) for that product b. In the case of any other investigational medicinal product, the Investigators' Brochure (IB) relating to the trial in question.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reactions as a result of a drug (medicinal product) given in a clinical trial, that may or may not be dose related, but are unexpected, as they are not consistent with current information given by the manufacturers.
The Medicines and Healthcare Products Regulatory Agency (MHRA)	The government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe. The MHRA is an executive agency of the Department of Health.
UK Framework for Health & Social Care Research	The UK Framework for Health & Social Care Research (2017) is the key document, outlining the necessary regulation for research within the NHS. https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/

5 Duties

Chief Executive

Overall accountability for all R&D activities in the Trust lies with the Chief Executive. Responsibility for specific processes is delegated by the Chief Executive as set out below.

Medical Director & Caldicott Guardian

The Medical Director has overall delegated responsibility for R&D in the Trust. It is the responsibility of the Medical Director to ensure and give assurance to the Board of compliance with the systems and processes described in this procedure.

With support from the R&D Director and the Head of Research, the Medical Director's responsibilities also include the following:

- That Incidents are reported and managed using the appropriate systems as guided by the study protocol, MHRA legislation the Trust Risk management strategy and policies

- For the decision of the continuation of the study at BDCFT following an adverse event /reaction. The decision will be based on the identified risks.

Research & Development Director

It is the responsibility of the R&D Director, supported by the Head of Research BDCFT to ensure all relevant staff are aware of the Procedure, and to facilitate compliance with its contents.

Head of Research, Bradford District Care NHS Foundation Trust (BDCFT)

The Head of Research, BDCFT is responsible for the effective implementation and operation of the procedure. The Head of Research also has responsibility to ensure all researchers working at any Trust site are aware and compliant with the R&D policy and procedures.

That all events are reported and monitored appropriately according to Trust Risk management, and R&D policies, and MHRA legislation.

Sponsor:

The sponsor is responsible for:

- Information documented in the protocol on how to record adverse events/reactions in the Case Report Form (CRF), and the service user case notes and investigator Site file.
- Deciding if any events classed as serious should be excluded from immediate reporting for the disease area, and documents these in the study protocol.
- Keeping detailed records of all adverse events relating to a clinical trial which are reported by the investigators for that trial and reporting to the Licensing authority and research ethics.

For the full list of sponsorship responsibilities see UK Policy Framework for Health & Social Care Research and The Medicines for Human Use (Clinical Trials) Regulations (2004). See links below:

http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARsandASRs/index.htm#l4

Chief Investigator (CI):

This is the person with overall responsibility for the conduct of the research. As the lead researcher their relationship with the Sponsor (often the CI's employing organisation) puts them in a key role with regard to:

- Obtaining approvals for a project (e.g. HRA/REC, Trust Governance, obtaining Clinical Trials Authorisations [CTA] from the MHRA
- **Reporting to those organisations**. Reports to include annual updates safety/adverse event reporting.

They have specific responsibility for:

- Ensuring the project is conducted in accordance with the protocol, including all aspects of safety reporting
- Ensuring investigators are aware of their legal duties in respect of the conduct of the research
- Ensuring the study complies with all legal and ethical requirements.

Whilst some of these responsibilities can be delegated as duties of the local research teams/Principal Investigators, the Chief Investigator retains the responsibility for ensuing these duties are effectively undertaken.

For further details see UK Framework for Health & Social Care Research.

https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/

Principal investigator (PI) and research staff including Clinical Studies Officers (CSOs) and research nurses (RNs)

The PI is specifically responsible for:

- recording appropriately delegated responsibilities for reporting adverse events and reactions in the site file, to Sponsor, MHRA etc
- identifying causality, classification of the adverse event/reaction and subsequent management according to the study protocol and Trust Risk management policy
- ensuring the research team are aware of R&D procedures, and that they have received adequate training (GCP) in the reporting adverse events

All researchers and those with the delegated responsibilities must:

- ensure that information is available on electronic and medical records/case notes to 'alert' staff of Services Users/Patients who are participating in a research study
- ensure that the study protocol and study specific information is available and accessible for staff in the event of an adverse reaction/ event. Information should include study specific procedures on how to manage adverse reaction and events and contact details of research staff
- record and report adverse events and reactions to the sponsor as designated by the protocol and according to Good Clinical Practice , MHRA guidance and the Trust Risk Management strategy and Policy

A full list of PI and research staff responsibilities are provided in the UK Framework for Health & Social Care Research (2017)

Head Pharmacist or delegated representative

It is the responsibility of pharmacy staff to report adverse events in line with GCP for Pharmacy Staff, where appropriate.

Managers

It is the responsibility of all line managers to ensure that:

- staff participating in research within their areas of responsibility are aware of this procedure and Trust risk management policies
- any adverse events and reactions or concerns experienced, either reported by their staff, services users and or carers(related to a research project) are reported to the Principal Investigator and research staff as soon as possible and to follow further study specific adverse event procedures given.
- That all adverse events and reactions are reported according to the R&D and Trust Risk management strategy and policy

Clinical staff

Responsibility of clinical staff to know if any of their service users have been recruited onto a research study and;

- To know how to contact the study – specific researchers if they have any concerns or incidents in relation to a research project
- To report any adverse events and incidents or concerns described by services users and or carers to the principal investigator and researcher according to study specific instructions and Trust Risk management policy and incident reporting procedures. For example all serious events and reactions should be reported immediately to line manager and researcher and entered on the Risk register within 24 hours of the event – see procedures below section 0.

Clinical and non-clinical staff

Any member of staff who becomes aware of any practice that is not in accordance with this procedure, or where there are difficulties with implementing this procedure, has a responsibility to report this to their line manager who will assess the problem. If there is a problem specifically with this procedure, this should be reported to the Document Author, who will consider if immediate changes to the procedure are required or note for consideration at the next review of the procedure

Procedural Document Authors

It is the responsibility of procedural document authors to action the 'Procedure for the Development and Management of Procedural Documents' and ensure all procedural documents for which they have responsibility are developed, reviewed, authorised, ratified and implemented in accordance with the requirements of the procedure, and that they have been put onto the R&D Department web-site.

6 Procedures

It is important to note that this procedure for reporting adverse events will be in addition to the agreed Trust policy for the management and reporting of adverse events.

The reporting arrangement for adverse events in clinical trials will differ depending on the severity and categorisation of the event. See definitions in Section 4.

Prior to the study start the sponsor will decide on how to record adverse events and reactions in the research records. That will include the Case Report Form (CRF), the source document (case notes) and Investigator Site file. The sponsor documents these in the study protocol. The sponsor will decide if any events classed as 'serious' should be excluded from immediate reporting for the disease area and documents these in the study protocol.

For a Clinical Trial of Investigational Medicinal Products (CTIMP), the sponsor will then provide the PI with a 24 hour contact number, sometimes known as the 'safety desk', for reporting serious adverse events (SAEs). The contact number will be kept in the investigator and site file.

The PI will identify and document delegated responsibilities to other members of the research team these will be agreed in writing (delegation log) and stored in the site file.

Procedure for reporting Adverse Events and Adverse Reactions

The PI or delegate enquires with the participant at each study visit as to whether there have been any adverse events and records all details in the full Case Report Form (CRF) and source document (medical/case notes).

- The PI decides whether the reaction or event is due to the trial medicine or intervention (if appropriate).
- The PI or delegate follows the procedure outlined in the study protocol for the reporting of AE to the sponsor.

Procedure for reporting Serious Adverse Events, Serious Adverse Reactions and Suspected Unexpected Serous Adverse Reactions

1. The PI or delegate is notified of an SAE.
2. The PI or delegate, documents the event in the Case Report Form (CRF) and Clinical notes.
3. The PI or delegate, identifies the event to be serious, using ICH GCP definitions and study protocol. If the study is a CTIMP then this decision must be made by a doctor.
4. The PI or delegated qualified person, makes the decision on the event causality.
5. The PI or delegate completes the Serious Adverse Event Reporting Form (or equivalent) provided by the Sponsor, providing as much detailed information as known and relevant to the event. In some

cases, an initial oral report may be acceptable, to be followed by a fully detailed written report.

6. For CTIMP's the PI or delegate faxes the completed, signed SAE report to the Sponsor within 24 hours of discovery of the event. The SAE is sent to the 'Safety Desk' without the PI signature if it is not possible to complete before the 24 hour timeframe. The form is resent when the signature for the PI is added.

   The PI or delegate completes the IR-e form on the Trust's intranet (web based reporting).

   http://connect.bdct.local/docs/policies/pubdocs/Incdnt_Rprtng_Mngmnt__Policy_10-03_Final__PDF_26-10-2015.pdf

   The PI or delegate informs the Research Department of the SAE via email to the Senior Clinical Studies Officer.

   Guidance on how to report serious incidents within the Trust is located on 'Connect' Home page.

7. The Sponsor identifies the event status (SAE, SAR, SUSAR).
8. The Sponsor contacts the PI to request additional information if required.
9. The PI or delegate provides all requested information to the Sponsor relating to the event.
10. The PI or delegate files all SAE report forms and correspondence relating to the event in the Investigator Site File.
11. Where the event has been classified as a SUSAR:
    - The PI informs the Research Department of the event by e-mail within 24 hours of the event.
    - The Research Department informs the R&D Director who makes a decision on the continuation of the study at BDCFT based on the risk and details given on the adverse event/reaction.
    - The Research Department informs the PI and Sponsor if the study is to be discontinued at BDCFT.

(Note: SUSARs can be reported directly to MHRA via the e-SUSAR reporting system. This system is similar to the e-yellow card system and is E2B complaint. Link is available at https://esusar.mhra.gov.uk. This system may be used at stage 5 above – check with the sponsor/study protocol.

Procedure for receiving adverse event reports from the Sponsor

1. The Sponsor alerts the PI by fax of any SUSAR event occurrence that may put the safety of participants at risk.
2. The PI informs the Research Department of the event within 24 hours of receiving the alert: either by email or fax No: 01274 228621.
3. The PI files the report in the Investigator Site File.

4. The Head of Research or Senior CSO informs the R&D Director who makes a decision on the continuation of the study at BDCFT in relation to the reported event based on the risk.
5. The Research Department informs the PI and Sponsor if the study is to be discontinued at BDCFT.

Procedure for annual safety reporting by the Sponsor

1. Sponsors have a responsibility to update all investigators with regard to the safety aspects of the study, on an annual basis.
2. If the study is a CTIMP this will take place on the anniversary of the issue of the Clinical Trial Authorisation, and will include an update to the Investigators Brochure/Summary of Product Characteristics.
3. PIs are required to note the contents of such a report, and acknowledge its receipt to the Sponsor/CI.
4. Reports should then be filed in the relevant section of the project's Site File.

7 Consultation, Approval and Ratification Process

Consultation Process

Stakeholder	Level of involvement
Stakeholder	**Level of involvement**
Research Forum Risk Management Group R&D PPI RAG Clinical Studies Officers Pharmacy	Consultation
Research & Development Director Head of Research Clinical Studies Officer Risk Manager	Development
Research Forum	Approval and ratification

8 Review of the Procedural Document

This document will be reviewed every 2 years or when deemed necessary as a result of statutory or operational change in line with Trust policy

9 Dissemination of the Procedural Document

This document will be held in the R&D office and in the library services across the Trust. It will be available on the intranet once ratified. The policy will be disseminated to all service leads and all researchers and staff involved in research. The documents will be available on the research and development website.

10 Training and support for the implementation of the Procedure

The R&D department will provide support to individuals as and when required. This will be in a variety of means including:

- Guidance available on the intranet and internet web sites

Access to training e.g.

- Good Clinical Practice

Circulation of research courses available via the 'Comprehensive Local Research Network'

11 Monitoring Compliance and effectiveness of the Procedural Document

Criteria	Evidence identified to indicate compliance with policy	Method of monitoring i.e. how/where will this be gathered?	Frequency of Monitoring	Lead responsible for monitoring
Process for checking that staff are compliant with good clinical practice and research guidance as outlined by the NHIR RSS	Audit		As outlined by procedures and assessment of project – See RSS	BDCFT research manager and BIHR research governance manager

12 Consultation, Approval and Ratification Process

Consultation Process

Stakeholder	Level of involvement
Stakeholder	**Level of involvement**
Research Forum Risk Management	Consultation
Head of Research Clinical Studies Officers	Development
Research Forum	Approval and ratification

13 References:

European commission Definition of Investigational Medicinal Products (IMPs) http://ec.europa.eu/health/files/pharmacos/docs/doc2006/07_2006/def_imp_2006_07_27_en.pdf

Guideline for Good Cclinical Practice E6 (R1) web: www.icr-global.org

International Committee on Harmonisation Good Clinical Practice Guidelines (1996), http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/integrated-addendum-good-clinical-practice.html

UK Framework for Health & Social Care Research (2017) https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/

The Medicines for Human Use (Clinical Trials) Regulations 2004 http://www.legislation.gov.uk/uksi/2004/1031/contents/made

https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues

14 Associated Documentation

1. Trust R&D Policy
2. Research Passport Procedure
3. Research Project Monitoring and Audit Procedure
4. Recording of research in patient records keeping and site file management
5. Trust Data Protection Policies: see intranet
6. Records Management Policy: Procedural and Advice Guide:

   http://connect.bdct.local/docs/policies/pubdocs/Rcrd%20Mngmnt%20Policy%20v10-01%20Final%20PDF%2008-12-15.pdf
7. Research Finance Guidance
8. Model Clinical Trial Agreement - '*Clinical Trial Agreement For Pharmaceutical Industry Sponsored Research in NHS Trusts*'

   https://www.hra.nhs.uk/planning-and-improving-research/best-practice/model-agreements/
9. Trust Risk management strategy and policy: http://connect.bdct.local/docs/policies/pubdocs/Incdnt_Rprtng_Mngmnt_Policy_10-03_Final__PDF_26-10-2015.pdf
10. Procedure for Management of Serious Incidents: http://connect.bdct.local/docs/policies/pubdocs/Incdnt_Rprtng_Mngmnt_Policy_10-03_Final__PDF_26-10-2015.pdf