RDSOP8B Pharmacovigilance for MHRA-regulated Clinical Trials not sponsored by the Trust.

Greater Manchester Mental Health NHS Foundation Trust
**Title of Standard Operating Procedure:** RDSOP8B Pharmacovigilance for MHRA-regulated Clinical Trials not sponsored by the Trust.

**Document Summary:** This document describes the procedure for the pharmacovigilance for studies hosted by Greater Manchester Mental Health NHS Foundation Trust.

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**Target Audience:** Trust-wide, Research Community, Internal and External Researchers

**Consultation:** R & I Office, research community and R & I Committee members

**Approval Committee:** R & I Committee

**Cross Reference Document(s):** Research Approval Policy  
All Trust R & I SOPs

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1. Introduction

The Medicines for Human Use (Clinical Trials) Regulations 2004 set out specific requirements for the recording and reporting of adverse events relating to clinical trials.

The Department of Health Research Governance Framework for Health and Social Care 2005 requires that the principles of Good Clinical Practice (GCP) are applied to all NHS research involving patients and that the safety of research participants is given priority at all times.

2. Purpose

To describe the responsibilities and processes related to the identification, assessment, recording and reporting of adverse events occurring in clinical trials being conducted on Trust premises or other sites where GMMH is the host and/ or involving Trust service users.

Researchers should initially familiarise themselves with the entire contents of this SOP. However, the document is primarily designed as a practical reference guide to be used alongside the study protocol. As such, it is recommended that when an adverse event arises, rather than reading every page of the SOP, sections 4 and 5 should be used to identify the relevant paragraphs of section 6, where actions to be taken are given according to the type of event that has occurred.

3. Roles and Responsibilities

3.1 Duties within the organisation

It is the responsibility of the Research & Innovation Office to make Trust R & I SOPs available to all research active staff working on Trust-approved research studies.

It is the responsibility of the study Chief Investigator (CI) or local Principal Investigator (PI) to ensure that up-to-date copies of Trust R & I SOPs are available to research staff.

It is the responsibility of the study Chief Investigator or local Principal Investigator to ensure up-to-date SOPs relevant to the study are filed in the Investigator Site File and are available to research staff, and to inform the Research Support Co-ordinator of the names of all research staff involved on a study so that copies of SOPs can be distributed appropriately.

It is the responsibility of the study Chief Investigator or Principal Investigator to designate if the SOPs of another organisation are to be followed for a study. For example those of a Clinical Research Network or commercial sponsor. If there is significant conflict between the external SOP and the Trust R & I SOP it is the responsibility of the CI or PI to resolve these with the R & I Office prior to starting the study.
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It is the personal responsibility of all staff to follow Trust (or the designated alternative organisations) procedural documents.

The Research & Innovation Office is responsible for managing Trust R&I SOPs including their approval, dissemination and archiving. All Trust R & I SOPs must be made available via Q-Pulse and published on the Trust website.

### 3.2 Responsibilities Specific to this SOP

At each study visit by the participant, or as otherwise specified in the protocol, the CI, PI or delegate is responsible for eliciting details of any AEs that may have occurred since the previous study visit and ensuring that these are evaluated appropriately.

Where any tasks relating to assessing, recording or reporting adverse events are delegated by the CI or PI to another member of the research team such as a Co-Investigator, Research Nurse or Trial Co-ordinator, this must be recorded in the delegation of duties log.

A medically-qualified member of the study team must be responsible for assessing whether or not an event is drug-related.

If any Sponsor responsibilities for reporting adverse events to the MHRA or Ethics Committee, or for completing a Development Safety Update Report (DSUR) or Annual Progress Report have been delegated to staff working in the Trust, please refer to SOP 8A: Pharmacovigilance – Trust-sponsored Clinical Trials, where the procedures for meeting these responsibilities are detailed.

If not provided by the Sponsor, it is recommended that a study-specific adverse event reporting SOP is developed, incorporating or referencing the assessment and reporting requirements outlined in sections 4 - 7. The study-specific SOP should also allocate responsibilities for each stage of the process to named individuals and clearly map the lines of communication that should be followed when adverse events are identified during a trial.

### 4. Definitions of Adverse Events

**Adverse Event (AE):**

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease in any subject in a clinical trial (including those in an untreated control group), whether or not considered related to the investigational medicinal product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR): Unless exempted by the approved protocol, any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Life-threatening in the definition of a serious adverse event or serious adverse reaction in section 4.2 refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Depending upon the nature of the trial, the protocol may also define certain events that do not fall into the categories listed in 4.2, but that should be considered as SAE’s for the purposes of the trial. Conversely, the protocol may specify certain events that fall into the categories listed in 4.2 that should not be considered as SAE’s for the purposes of the trial (e.g. hospitalisation for elective surgery).

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

4.1 Adverse Reaction (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship (e.g. definitely, probably or possibly related) to a medicinal product qualify as adverse reactions.

Many terms and scales are in use to describe the degree of certainty in relation to causality between an IMP and an event, such as certainly, definitely, probably or possibly; or likely related or not related. Whichever system is used, this should be specified and explained in the protocol, and the events that qualify as SARs should be made clear.

Where there are two assessments of an event, the causality assessment made by the local investigator cannot be downgraded. In the case of a difference of opinion on causality, both assessments are recorded, and the “worst case” assessment is used for reporting purposes.

Unexpected Adverse Reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable medicine’s information (e.g. investigator's
Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is judged to be both serious and unexpected.

For blinded trials involving a placebo and active drug where there are grounds to believe that a serious adverse event may be a SUSAR, or otherwise subject to expedited reporting, treatment codes must be un-blinded for specific subjects according to the directions in the protocol. If the event is found to have occurred in the placebo arm, it will generally then only satisfy the criteria for an SAE (unless thought to be due to the excipient in the placebo) and as such should not be reported in an expedited manner.

Systems for SUSAR reporting should be detailed in the protocol and, as far as possible, should maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. However, the safety of patients in the trial always takes priority and un-blinding clinicians may be unavoidable if the information is necessary for clinical management purposes.

Severity: The term "severe" is often used to describe the intensity (clinical severity) of a specific event. This is not the same as "serious", as defined in 4.2, which is a regulatory definition based on patient/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

5. Classification of Adverse Events

With reference to the flow diagram below, the definitions given in section 4, and the protocol, determine the nature of the adverse event. You will then be directed to the appropriate paragraph in section 6, where the relevant actions are detailed. Note that for blinded studies, expectedness may be determined by the Sponsor in order to retain the blind at the local site. The Sponsor may also give an additional opinion on causality.
Adverse Event
Refer to definition in 4.1

Is it serious?
Refer to definition in 4.2

Yes  No

Is it possibly, probably or certainly related to the drug?
Refer to definition in 4.3

No

This is an Adverse Event (AE)
Go to paragraph 6.1

Yes

This is an Adverse Reaction (AR)
Go to paragraph 6.2

Is it possibly, probably or certainly related to the drug?
Refer to definition in 4.3

No

This is a Serious Adverse Event (SAE)
Go to paragraph 6.3

Yes

Don’t know – protocol states that the Sponsor will assess expectedness

Unless Sponsor advises that event is unexpected

This is a Serious Adverse Reaction (SAR)
Go to paragraph 6.4

Is it unexpected?
Refer to definition in 4.4

No

This is a Suspected Unexpected Serious Adverse Reaction (SUSAR)
Go to paragraph 6.5

Yes
6. Recording and Reporting Adverse Events

6.1 Adverse Event (AE)

Check whether the AE is classified in the protocol as not requiring to be recorded (for example, some pre-existing conditions identified at screening or certain laboratory findings may not need to be recorded as AEs).

Record the AE as specified in the protocol.

Where appropriate, clearly document the following in the patient medical records and/or Amigos / PARIS:

- Whether the event has been observed by the PI (or delegate), or reported by the subject;
- The date - and if possible the time - of the onset of the event;
- If completely resolved, the duration of the event;
- The severity of the event – mild, moderate, severe (not to be confused with seriousness – see definitions) – this may be graded by using the criteria in the protocol;
- Any treatment/ medication given for the event, including dates;
- The outcome of the event.

Check whether the AE is classified in the protocol as critical to evaluating the safety of the trial, with specific onward reporting requirements to the sponsor, and action appropriately.

Follow up any ongoing AE’s as specified in the protocol, documenting at each study visit. AE’s that are ongoing on completion of the study should be followed up as required by the protocol and as clinically indicated.

If a participant – or the partner of a participant - becomes pregnant while taking part in a clinical trial, or during a stage where the foetus could have been exposed to the IMP (in the case of the active substance or one of its metabolites having a long half-life), the pregnancy must be reported as an adverse event and must be followed up until delivery, or as specified in the protocol.

6.2 Adverse Reaction (AR)

Record the AR as specified in the protocol.

Where appropriate, clearly document the following in the patient medical records and/or Amigos:

- Whether the event has been observed by the PI (or delegate), or reported by the subject;
- The date - and if possible the time - of the onset of the reaction;
- If completely resolved, the duration of the reaction;
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- The severity of the reaction – **mild, moderate or severe** (not to be confused with seriousness – see definitions) – this may be graded by using the criteria in the protocol;
- Any action taken regarding study drug;
- Any treatment/medication given for the reaction, including dates;
- The outcome of the episode.

Check whether the AR is classified in the protocol as critical to evaluating the safety of the trial, with specific onward reporting requirements to the sponsor, and action appropriately.

Follow up any ongoing AR's as specified in the protocol, documenting at each study visit. AR's that are ongoing on completion of the study should be followed up as required by the protocol and as clinically indicated.

6.3 Serious Adverse Event (SAE)

Check whether the SAE is classified in the protocol or Investigator’s Brochure as not requiring immediate reporting. For such events, take action as specified in the protocol, or if this is not detailed, follow the guidelines. For all other SAE’s, proceed as detailed in section 6.3.2.

Where appropriate, clearly document the following in the patient medical records and/or Amigos / PARIS:

- The date - and if possible the time - of the onset of the event;
- If completely resolved, the duration of the event;
- The severity of the event – **mild, moderate, severe** (not to be confused with seriousness – see definitions) – this may be graded by using the criteria in the protocol;
- Any treatment/medication given for the event, including dates;
- The outcome of the episode.

Complete the SAE page in the case report form (CRF) as soon as possible after becoming aware of the event.

Report the event to the Sponsor in accordance with any timeframes given in the protocol, (generally, SAE’s should be reported to the sponsor within 24 hours of first knowledge) If the SAE involves a GMMH service user or took place on GMMH premises or other sites where GMMH is the host or sponsor, email the report to researchoffice@gmmh.nhs.uk quoting the Trust Project reference number. If the event is ongoing at the time of completing the initial report, it should be followed up as specified in the protocol, with full details recorded in the CRF and in the patient medical records (and/or Amigos / PARIS for GMMH service users) and a copy of any follow up reports emailed to the GMMH’s Research and Innovation Office.

SAE’s that are ongoing at the end of a participant’s involvement in the study should be followed up as detailed in the protocol, or for 30 days if this is not specified.
6.4 Serious Adverse Reaction (SAR)

Where appropriate, clearly document the following in the patient medical records and/or Amigos / PARIS:

- The date - and if possible the time - of the onset of the reaction;
- If completely resolved, the duration of the reaction;
- The severity of the reaction – mild, moderate, severe (not to be confused with seriousness – see definitions) – this may be graded by using the criteria in the protocol;
- Any action taken regarding study drug;
- Any treatment/ medication given for the reaction, including dates;
- The outcome of the episode.

Complete the SAR page in the CRF as soon as possible after becoming aware of the event.

Report the event to the Sponsor in accordance with any timeframes given in the protocol (generally within 24 hours of first knowledge).

If the SAR involves a GMMH patient or took place on GMMH premises, email a copy of the SAR report to the Research and Innovation Office quoting the Trust Project Reference Number to researchoffice@gmmh.nhs.uk.

If the event is ongoing at the time of completing the initial report, it should be followed up as specified in the protocol, with full details recorded in the CRF and in the patient medical records (and/or Amigos / PARIS for GMMH service users) and a copy of any follow up reports emailed to the Research and Innovation Office.

SARs that are ongoing at the end of a participant’s involvement in the study should be followed up as detailed in the protocol, or for 30 days if this is not specified.

6.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Where appropriate, clearly document the following in the patient medical records and/or Amigos / PARIS:

- The date - and if possible the time - of the onset of the reaction;
- If completely resolved, the duration of the reaction;
- The severity of the reaction – mild, moderate or severe (not to be confused with seriousness – see definitions) – this may be graded by using the criteria in the protocol;
- Any action taken regarding study drug;
- Any treatment/ medication given for the reaction, including dates;
- The outcome of the episode.

Complete the SUSAR page in the CRF as soon as possible after becoming aware of the event. If such a page has not been provided as part of the CRF, refer to the protocol on how to proceed or contact the Sponsor for an appropriate reporting form.
Unless other reporting procedures are specified in the protocol, report the event to the Sponsor immediately, with reference to any timeframes stated in the protocol.

If the SUSAR involves a GMMH service user or took place on GMMH premises, email a copy of the report to the Research and Innovation Office, quoting the Trust Project Reference Number to: researchoffice@gmmh.nhs.uk. If there is no paper reporting system contact GMMH Research and Innovation Office by telephone as soon as possible to pass on information about the SUSAR.

If the event is ongoing at the time of completing the initial report, it should be followed up as specified in the protocol, with full details recorded in the CRF and the patient medical records (and/or Amigos for GMMH service users) and a copy of any follow up reports to the Sponsor emailed to GMMH Research and Innovation Office.

SUSAR’s that are ongoing at the end of a participant’s involvement in the study should be followed up as detailed in the protocol, or for 30 days if this is not specified. Any SUSAR’s that are identified after the participant has completed a clinical trial should also be reported to the Sponsor (and to GMMH Research and Innovation Office for GMMH service users).

Where the Sponsor is responsible for assessing expectedness and has notified the local investigator that a SAE/SAR occurring on GMMH premises and/ or involving a GMMH service user has been assessed as a SUSAR by the Sponsor, details should be emailed to the Research and Innovation Office at: researchoffice@gmmh.nhs.uk

7. Urgent Safety Measures

If necessary, appropriate urgent safety measures may be taken to protect clinical trial subjects from any immediate hazard to their health and safety. The measures should be taken at once, but the Sponsor must be informed within the timelines given in the protocol. This will generally be immediately as the Sponsor has a responsibility for informing the MHRA and Ethics Committee within 3 days.

Where urgent safety measures have been taken on GMMH premises, or involve a GMMH service user, GMMH Research and Innovation Office must also be informed.

8. GMMH Incident Reporting System - DATIX

If a researcher is based at GMMH, they are responsible for reporting any incident on Datix in line with Trust policy (for example AEs or SAE’s that occur to GMMH CTIMP participants whilst on Trust premises).

If a researcher is not based at GMMH, and cannot access the Datix system directly, they should inform the Research Governance Officer who should complete a Datix incident form on behalf of the researcher.

The following information should also be recorded on Datix when an electronic incident form is being completed:

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- The date - and if possible the time - of the onset of the event;
- If completely resolved, the duration of the event;
- The severity of the event – mild, moderate, severe (not to be confused with seriousness – see definitions) – this may be graded by using the criteria in the protocol;
- Any treatment/ medication given for the event, including dates;
- The outcome of the episode;
- The EudraCT number of the CTIMP
- GMMH R&D Office Project Number
- A “patient identifier” such as patient number or randomisation number.

9. Communication with General Practitioners (GP’s)

If any service user (recruited to a clinical trial of an investigational medicinal produce experiences an adverse event or reaction, the investigator must inform the service user’s GP

10. Equality Impact Assessment

This SOP has been equality impact assessed by the author using the Trust’s Equality Impact Assessment (EQIA), which has been submitted to the Equality and Diversity Department for ‘Service Equality Team Sign Off’.

No significant issues in relation to equality, diversity, gender, colour, race or religion are identified as raising a concern.

11. Consultation, Approval and Ratification Process

11.1 Consultation and Communication with Stakeholders

All Trust R & I SOPs are written by a member of the Research & Innovation Office staff with relevant expertise and experience. Additional advice is sought from members of the research community within the Trust, including the R & I Committee, or external advisors, as necessary.
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### 11.2 SOP Approval Process

All Trust R & I SOPs are subject to approval by the R & I Committee.

### 11.3 Dissemination

When approved, this SOP will be posted on the Trust R & I Office Intranet site; only the current version will be available. A list of current versions will also be posted on the public Trust website; researchers who do not have access to the intranet should refer to this list and request copies from the R & I Office accordingly.

All researchers listed on the Research Office ‘active researcher’ mailing list will be notified by email when an updated version of a SOP is available.

### 11.4 Implementation of Procedural Documents

Support and advice on the implementation of this SOP can be obtained via the Research Office.

### 12. Review, Monitoring Compliance With and the Effectiveness of Procedural Documents

#### 12.1 Process for Monitoring Compliance and Effectiveness

Review will be undertaken by the Research Office Management. Compliance with the Trust R & I SOPs by researchers will be monitored via the Trust’s Research Governance Monitoring Programme where appropriate.

SOP contents will be reviewed against any changes to the applicable guidelines and regulations and consider any feedback received from researchers or via the Monitoring Programme.

Review and monitoring will be conducted based on an initial risk assessment.

### 13. Associated Trust Documents

RDSOP8A: Pharmacovigilance for Trust-Sponsored MHRA-regulated Clinical Trials
14. References and Bibliography

The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004/1031)

The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (Statutory Instrument 2006/1928)

The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006 (Statutory Instrument 2006:2984)

The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008 (Statutory Instrument 2008/941)

ENTR/ CT3: Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (April 2006):
https://ec.europa.eu/health/documents/eudralex/vol-10_en

Joint Project Guidance on Pharmacovigilance - Final version for Clinical Trials Tool Kit (12th Jan 2007):
http://www.ct-toolkit.ac.uk/routemap/safety-reporting/

EU Commission - Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials (2007):
https://ec.europa.eu/health/documents/eudralex/vol-10_en

For information on submissions to MHRA via the Common European Submission Portal (CESP) see Clinical trials for medicines: manage your authorisation, report safety issues: