RDSOP8A Pharmacovigilance for Trust-Sponsored MHRA-regulated Clinical Trials

Greater Manchester Mental Health NHS Foundation Trust

Improving Lives
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<th>RDSOP8A Pharmacovigilance for Trust-Sponsored MHRA-regulated Clinical Trials</th>
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<td>Document Summary:</td>
<td>This document describes the procedure for the pharmacovigilance of studies sponsored by Greater Manchester Mental Health NHS Foundation Trust.</td>
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<td>Research Approval Policy All Trust R &amp; I SOPs</td>
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1. Introduction

The Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments 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 where the Trust is the Research Governance Sponsor.

This SOP does not cover reporting responsibilities where the Trust is the co-ordinating site for an international, multi-centre trial; if your trial falls into this category, please contact the Research and Innovation Office for advice.

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.

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

All of the Trust’s sponsor responsibilities in relation to adverse event recording and reporting are formally delegated to the Chief Investigator (CI) and Principal Investigators (PIs); a signed copy of the Clinical Trials agreement and agreement of the HRA statement of activities provided prior to the start of the study should be kept in the Trial Master File.

For audit purposes, and to ensure that the Trust’s delegated sponsor responsibilities are being appropriately met, the Research and Innovation Office will periodically request information from researchers on their pharmacovigilance procedures; it is the responsibility of the CI and PIs (or delegate) to respond to such requests in a timely manner.

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 adverse events (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 the ‘relatedness’ of an event.

To help ensure that all members of the team are aware of their responsibilities, adverse event reporting will be discussed at the study initiation meeting. This will refer to the adverse event reporting procedures in the trial protocol and sponsor SOPs.

It is the responsibility of the CI and PI, or for a multi-centre trial the national Chief Investigator, to periodically perform and document a review of all adverse events occurring on the study, in order to identify any trends such as an increase in numbers or severity of events. To facilitate this exercise and completion of the Development
Safety Update Report (see section 10), a central spreadsheet or log of all events in a line-listing format should be maintained, in addition to recording details in the medical records and patient CRF as specified in section 6. A template adverse event log is available from the Trust Research and Innovation Office.

The outcome of the Adverse Event trend analyses should be reported to the sponsor and Data Monitoring Committee (DMC)/ Trial Steering Committee (TSC) as appropriate. The DMC/ TSC can advise on any safety issues raised by these analyses and actions required to address them.

The PI and CI should ensure that the current version of the Summary of Product Characteristics (SPC) or Investigator Brochure (IB) is circulated to all members of the study team, clinical trials pharmacy and participating centres. Regular checks should be completed to confirm if an update has been made to a SPC. These checks can be delegated to another member of the research team.

For multi-centre trials, it is the responsibility of the CI to ensure that:

All participating sites are provided with adequate instructions within the protocol, for the assessing, recording and reporting of adverse events.

Those responsible for assessing, recording or reporting adverse events at participating sites are identified in the site Delegation of Duties log, with a copy of the log stored in the local Site File.

Serious Adverse Events (SAE’s), Serious Adverse Reactions (SARs), Unexpected Adverse Reactions (UAR’s) and Suspected Unexpected Serious Adverse Reactions (SUSAR’s) occurring at all sites are reported to the GMMH Research and Innovation Office by the CI. The CI may delegate this role to another member of the research team e.g. trial coordinator.

Events requiring onward reporting to the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC) and Research Office are reported to the CI immediately, to allow him/ her to meet the reporting deadlines defined by the Regulations.

4. Definitions of Adverse Events

All of the Trust’s sponsor responsibilities in relation to adverse event recording and reporting are formally delegated to the Chief Investigator (CI) and Principal Investigators (PIs); a signed copy of the Clinical Trials agreement and agreement of the HRA statement of activities provided prior to the start of the study should be kept in the Trial Master File.

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All participating sites are provided with adequate instructions within the protocol, for the assessing, recording and reporting of adverse events.

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Serious Adverse Events (SAE’s), Serious Adverse Reactions (SAR’s), Unexpected Adverse Reactions (UAR’s) and Suspected Unexpected Serious Adverse Reactions (SUSAR’s) occurring at **all sites** are reported to the GMMH Research and Innovation Office by the CI. The CI may delegate this role to another member of the research team e.g. trial coordinator.

Events requiring onward reporting to the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC) and Research Office are reported to the CI immediately, to allow him/her to meet the reporting deadlines defined by the Regulations.

### 4.1 Definitions of Adverse Reactions

All untoward and unintended responses to an IMP 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 medicines information (e.g. investigator's brochure (IB) for an unlicensed medicine or summary of product characteristics (SPC) for a licensed medicine).

**Suspected Unexpected Serious Adverse Reaction (SUSAR):**

An adverse reaction that is judged to be both serious and unexpected, according to the definitions in **Error! Reference source not found.** - 0

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 (see criteria in section 7), 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 subject to expedited reporting (as outlined in sections 6.1).
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. For example, the sponsor, or staff working on a separate trial might undertake the un-blinding. 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. Criteria for grading severity should be included in the protocol. The following is an example:

**Mild:** Asymptomatic or mild symptoms, diagnostic observations only, no intervention indicated. Not interfering with everyday activities / functioning.

**Moderate:** an event that is sufficiently discomforting to interfere with normal everyday activities. Minimal, local or non-invasive intervention indicated.

**Severe:** an event that prevents normal everyday activities. Medically significant but not immediately life-threatening. Hospital or prolongation of hospitalisation indicated.

5. **Classification of Adverse Events**

With reference to the flow diagram on the next page, the definitions given in 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.
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

Yes No

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

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

This is a Serious Adverse Event (SAE)
Go to paragraph 6.3
Note expedited reporting requirements in 6.3.7

This is a Serious Adverse Reaction (SAR)
Go to paragraph 6.4
Note expedited reporting requirements in 6.4.7

This is a Suspected Unexpected Serious Adverse Reaction (SUSAR)
Go to paragraph 6.5
Note expedited reporting requirements in 6.5.3

This is a fatal/life-threatening SUSAR
Go to paragraph 6.6
Note expedited reporting requirements in 6.6.3 and 6.6.6
6. Recording and Reporting Adverse Events

6.1 Adverse Events (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 AE’s). Otherwise, proceed as in 0 - 0

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.

Complete the Adverse Event page in the Case Report Form (CRF). For Trust sponsored CTIMP’s, a standard Trust AE reporting form will be provided and should be used to record events.

Enter the AE into the trial adverse event spreadsheet or adverse event log.

Take any other action as specified by the protocol (for example, some AE’s may be identified in the protocol as critical to evaluating the safety of the trial and will have specific reporting requirements).

Follow up any ongoing AEs, documenting at each study visit until resolved, returned to baseline, stabilised, or as otherwise specified in the protocol. 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 to the sponsor and followed up until delivery, or as specified in the protocol. Any occurrences that result in a Serious Adverse Event should be reported to the sponsor.

AE’s that result in the subject withdrawing – or being withdrawn - from the study must be recorded for inclusion in the annual progress report to the REC by the Chief Investigator for that trial.

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6.2 Adverse Reaction (AR)

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;
- 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 Adverse Event page in the Case Report Form (CRF). For Trust sponsored CTIMP’s, a standard Trust AE reporting form will be provide and should be used to record events.

Enter the AR into the trial adverse event spreadsheet or adverse event log.

Take any other action as specified by the protocol (for example, some AR’s may be identified in the protocol as critical to evaluating the safety of the trial and will have specific reporting requirements).

Follow up any ongoing AR’s, documenting as in 0 at each study visit until resolved, returned to baseline, stabilised, or as otherwise specified in the protocol. AR’s that are ongoing on completion of the study should be followed up as required by the protocol and as clinically indicated.

AR’s that result in the subject withdrawing – or being withdrawn - from the study must be recorded for inclusion in the annual progress report to the REC.
6.3 Serious Adverse Event (SAE)

Check whether the SAE is classified in the protocol or Investigator’s Brochure (if applicable) as not requiring immediate reporting. For such events, take action as specified in the protocol, or if this is not detailed, follow the guidelines in section 6.1. For all other SAE’s, proceed as detailed in section 0–0.

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 CRF as soon as possible after becoming aware of the event. For Trust sponsored CTIMP’s, a standard Trust SAE reporting form will be provided and should be used to record and report events to the sponsor. **Email a copy of the initial SAE report to the Research and Innovation Office quoting Trust Project Reference Number to researchoffice@gmmh.nhs.uk.** For multi-site trials, this must be completed for SAE’s occurring at all sites.

Enter the SAE into the trial adverse event spreadsheet or adverse event log.

If the event is ongoing at the time of completing the initial report, it should be followed up and documented in the CRF and patient medical records (paper medical records and Amigos / PARIS (GMMH service users)) at subsequent study visits until resolved, returned to baseline, or stabilised. The standard Trust SAE form should be used and a copy faxed or emailed to the Research and Innovation Office. Follow up reports should continue until the event is resolved.

**SAE’s should be reported to the sponsor within 24 hours of first knowledge.**

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.

A record of SAE’s must be kept for inclusion in the DSUR (see section 10).

A record of SAE’s that result in the subject withdrawing, or being withdrawn from the study, must be kept for inclusion in the annual progress report to the REC.
6.4 Serious Adverse Reaction (SAR)

Check whether the SAR is classified in the protocol or Investigator’s Brochure as not requiring immediate reporting. For such events, take action as specified in the protocol. For all other SARs, proceed as detailed in section 0 - 0.

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

- 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. For Trust sponsored CTIMP’s, a standard Trust SAE reporting form will be provided and should be used to record and report events to the sponsor.

*Email a copy of the initial SAE report to the Research and Innovation Office on quoting the Trust Project Reference Number to* researchoffice@gmmh.nhs.uk. For multi-site trials, this must be completed for SAE’s occurring at all sites

Enter the SAR into the trial adverse event spreadsheet.

If the event is ongoing at the time of completing the initial report, it should be followed up and documented in the CRF and patient medical records (**paper medical records and Amigos or PARIS (GMMH service users)**) at subsequent study visits until resolved, returned to baseline, or stabilised. The standard Trust SAE form should be used and a copy faxed or emailed to the Research and Innovation Office. Follow up reports should continue until an event is resolved.

**SAR’s should be reported to the sponsor within 24 hours of first knowledge.**

SAR’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.

All SARs must be recorded in a line-listing format for inclusion in the DSUR (see section 10).

A record of SARs that result in the subject withdrawing – or being withdrawn - from the study must be kept for inclusion in the annual progress report to the REC.
6.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

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

- 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 (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.

If a SUSAR has been suspected to have occurred, the standard Trust SAE report form should be completed. The standard form has been designed to capture all the information required by the eSUSAR system. The form should be faxed to quoting the Trust Project Reference Number. Alternatively the report can be emailed The Research and Innovation Office (sponsor) will contact the research team to discuss expedited reporting via the eSUSAR system. The initial registration of a CTIMP on the eSUSAR system must be completed by the sponsor. For Trust sponsored CTIMP’s this will be completed by the Research Governance Co-ordinator or R&D Pharmacist. The Research Governance Co-ordinator or R&D Pharmacist will also instruct members of the research team (who have been delegated that role) on how to complete and submit an eSUSAR report.

For all SUSAR’s – except fatal or life threatening:

As soon as possible, and no later than 15 calendar days after first knowledge of the event, report the SUSAR to ALL of the following:

The MHRA, by completing an eSUSAR report (see https://esusar.mhra.gov.uk/).

The Research Ethics Committee, by posting a copy of the eSUSAR report and a covering letter.

If full details are not available at the time of initial reporting, the eSUSAR form should be completed as far as possible, saved, and further relevant information should be added as soon as possible. The form should then be submitted within the 15 day timeframe.

Retain a copy of the eSUSAR report in the CRF and trial master file.

For multi-centre trials, inform all local investigators of the SUSAR at the earliest possible opportunity.

Enter the SUSAR into the trial adverse event spreadsheet or log

Where indicated in the protocol, or as clinically appropriate, follow-up of the long term outcome of a particular reaction may be performed. In such cases, full details should be recorded on the follow-up SAE form and log, patient medical records, CRF and master file. The organisations listed in 6.5.3 should also be informed of any relevant information using a follow-up eSUSAR report.
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. An eSUSAR follow-up report should then be submitted.

SUSAR’s that are identified after the patient has completed a clinical trial should be reported as outlined in section 6.5.3.

All SUSAR’s must be recorded in a line-listing format for inclusion in the Development Safety Update Report (see section 10).

A record of SUSAR’s that result in the subject withdrawing – or being withdrawn from the study must be kept for inclusion in the annual progress report to the REC.

### 6.6 Fatal/Life-threatening 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 (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.

If a SUSAR has been suspected to have occurred, the standard Trust SAE report form should be completed. The standard form has been designed to capture all the information required by the eSUSAR system. The form should be faxed to quoting the Trust Project Reference Number (0161 798 6657). Alternatively the report can be emailed to. The Research and Innovation Office (sponsor) will contact the research team to discuss expedited reporting via the eSUSAR system

As soon as possible, and no later than 7 calendar days after first knowledge of the event, report the SUSAR to ALL of the following:

The **MHRA**, by completing an eSUSAR report (see [https://esusar.mhra.gov.uk/](https://esusar.mhra.gov.uk/)).

The **Research Ethics Committee**, by posting a copy of the eSUSAR report and a covering letter.

If full details are not available at the time of initial reporting, further relevant follow-up information should be provided on a follow-up eSUSAR report to the organisations listed in 6.6.3 within an additional 8 calendar days.

Retain a copy of the eSUSAR report in the CRF and trial master file.

For multi-centre trials, inform all local investigators of the SUSAR at the earliest possible opportunity.
Enter the SUSAR into the trial adverse event spreadsheet or log (see 3.2.7).

Where indicated in the protocol, or as clinically appropriate, follow-up of the long-term outcome of a particular reaction may be performed. In such cases, full details should be recorded on the SAE form and log, patient medical records, CRF and master file. The organisations listed in 6.5.3 should also be informed of any relevant information using a follow-up eSUSAR report.

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. An eSUSAR follow-up report should then be submitted.

SUSAR’s that are identified after the patient has completed a clinical trial should be reported as outlined in section 6.6.3.

All SUSAR’s must be recorded in a line-listing format for inclusion in the Development Safety Update Report (see section 10).

A record of SUSAR’s that result in the subject withdrawing, or being withdrawn from the study, must be kept for inclusion in the annual progress report to the REC.

7 Expedited Reporting

In addition to the reporting requirements outlined in section 6, safety issues also qualify for expedited reporting to the MHRA and REC (i.e. within the same timelines as a SUSAR, as outlined in sections 6.5 and 6.6) where they might materially alter the current risk-benefit assessment of an IMP, or are sufficient to consider changes in the IMP administration or in the overall conduct of the trial. Such events include:

An increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important.

Post-study SUSAR’s that occur after the patient has completed a trial.

A new event, related to the conduct of the trial or the development of the investigational medicinal product (IMP) that is likely to affect the safety of subjects, such as:

- A serious adverse event that could be associated with the trial procedures and which could modify the conduct of the trial;
- A significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
- A major safety finding (for example, carcinogenicity) from a newly completed animal study;
8. **Urgent Safety Measures**

If necessary, the sponsor and investigator may take appropriate urgent safety measures to protect clinical trial subjects from any immediate hazard to their health and safety. The measures should be taken immediately, without waiting for MHRA/REC approval.

Where urgent safety measures have been implemented, the CI/ PI must immediately:

- Telephone the Clinical Trial Unit at the MHRA (020 3080 6456) to discuss the issue with a Medical Assessor.
- Telephone the REC to report the situation.
- In discussion with the sponsor, prepare a substantial amendment including a covering letter detailing the measures taken, the reason for them and the MHRA Medical Assessor contacted, an Annex II Notification of Amendment form and supporting documentation.
- Within 3 days, the documents must be submitted to the MHRA through the Common European Submission Portal (CESP; see section 18) and:
  - Sent by post to the REC.
  - Sent by fax (0161 798 6657) to the Research and Innovation Office (sponsor).

9. **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 AE’s 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 Co-ordinator 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:
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 (not to be confused with seriousness – see definitions) – this may be graded by using the toxicity 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.

10. Development Safety Update Report (DSUR)

The DSUR replaced the Annual Safety Report (ASR) in September 2011. It must be completed by the CI/PI in conjunction with the sponsor and describe all new, relevant safety information, and assess the safety conditions of the trial subjects.

The sponsor of a clinical trial is considered responsible for the preparation, content and submission of a DSUR. The sponsor can delegate the preparation of the DSUR to a third party (for example, a contract research organisation).

See RD SOP34 Development Safety Update Reporting (DSUR) for further information on preparing and submitting a DSUR.

The DSUR is intended to be the common standard for periodic reporting on drugs under development (including marketed drugs that are under further study) among the ICH (International Conference on Harmonisation) regions. European Union and US regulators consider that the DSUR will meet national and regional requirements previously met by the ASR and IND Annual Report (US).

The DSUR should present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed, by:

- Examining whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug's safety;
- Describing new safety issues that could have an impact on the protection of clinical trial subjects;
- Summarising the current understanding and management of identified and potential risks;
- Providing an update on the status of the clinical investigation/development programme and study results.

Further guidance and information regarding the timing, content and format is available from the Research and Innovation Office.
The DSUR should be submitted following the Data Lock Point (DLP). The DLP is the last day of the one year reporting period.

For CTIMP’s that have not recruited any patients since the last DSUR submission, a DSUR must still be submitted stating that no recruitment has taken place.

The DSUR must be reviewed and authorised for submission by the sponsor prior to sending to the MHRA and REC.

The DSUR must be submitted to the MHRA within 60 days of the DLP through the Common European Submission Portal (CESP; see section 18) and to: The REC by posting a paper copy of the DSUR and a completed CTIMP Safety Report form, available from https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

11. Annual Progress Report

An Annual Progress report must be completed by the Chief Investigator using the Annual Progress report for Clinical Trials form available from https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/progress-reports/

The Annual Progress Report must be submitted within 30 days of each anniversary of the date of the favourable ethical opinion for the study.

If the study has not started within 12 months of receiving a favourable ethical opinion, an Annual Progress Report must still be sent, and should include an explanation for the delay.

The Annual Progress Report must be reviewed and authorised for submission by the sponsor prior to sending to the REC.

The Annual Progress Report should be sent by post to the REC which provided the initial ethical opinion. A copy should also be sent to the Research and Innovation Office.

12. Communication with General Practitioners (GP’s)

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

13. 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’.
14. Equality Impact Assessment

14.1 Consultation and Communication with Stakeholders

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

14.2 SOP Approval Process

All Trust R&D SOPs are subject to approval by the R&D Committee. The SOP will then be sent to the Trust Management Board for ratification.

15 Dissemination and Implementation

When approved, this SOP will be made available through Q-Pulse. Q-Pulse will publish approved SOPs to the Trust Research Office website. The Trust intranet will contain a link to direct staff to the approved SOPs on the external website. Only the current version will be available.

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

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

16 Review, Monitoring Compliance With and the Effectiveness of Procedural Documents

16.1 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 taking into account any feedback received from researchers or via the Monitoring Programme.
Review and monitoring will be conducted based on an initial risk assessment of the project. This process may change based on results on any monitoring visit.

The outcome of the review – and any resulting amendments - will be reported to the R & I Committee and the MMC.

16.2 Standards and Key Performance Indicators “KPI’s”

This SOP will be available on the Trust website and via Q-Pulse.

This SOP must be reviewed at least every two years or when there are significant changes to the document.

17 Associated Trust Documents

RD SOP34 Development Safety Update Reporting (DSUR)
18 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: