RDSOP41 Recording and Reporting Adverse Events for non-CTIMP’s

Greater Manchester Mental Health NHS Foundation Trust

Improving Lives
### Title of Standard Operating Procedure:
RDSOP41 Recording and Reporting Adverse Events for non-CTIMPs

### Document Summary:
To outline the process for recording and reporting adverse events for non-CTIMPs (Clinical Trials of Investigational Medicinal Products) sponsored by the Trust, e.g. trials of psychosocial interventions.

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### Target Audience:
All Researchers, R&I staff

### Consultation:
R&I Operations Group and R&I Committee

### Approval Committee:
R&I Committee

### Cross Reference Document(s):
Research Conduct Policy
RDSOP22, RDSOP34, RDSOP02, RSOP11
All Trust R&I SOPs

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1. Introduction

The UK Policy Framework for Health & Social Care Research 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 research studies (including clinical trials) where the Trust may or may not be the Research Governance Sponsor.

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 R&I Office to make Trust R&I SOPs available via the R&I pages of the Trust internet to all research active staff working on Trust-approved research studies.

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

It is the responsibility of the Chief Investigator (CI) or local Principal Investigator (PI) to distribute study-specific SOPs to appropriate members of the research team and to ensure that up-to-date copies are filed in the Investigator Site file and are available to research staff.

It is the personal responsibility of all staff to follow the research project’s procedural documents.
3.2 Specific to this SOP

Where the Trust is Sponsor, all of the Trust’s sponsor responsibilities in relation to adverse event recording and reporting are formally delegated to the Principal Investigator (PI); 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 responsibilities are being appropriately met, the R&I Office will periodically request information from researchers on their procedures for monitoring and reporting adverse events; it is the responsibility of the CI and PIs (or delegate) to respond to such requests in a timely manner.

At each study visit, 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 PI to another member of the research team such as the Research Assistant or Research Co-ordinator, this must be recorded in the delegation of duties log.

A suitably qualified member of the study team (usually the CI or PI) must be responsible for assessing the ‘relatedness’ of an event (also see 3.2.8 below).

It is the responsibility of the CI or PI to periodically (for example quarterly) 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 Annual Safety Report, 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 Case Report Form (CRF) as specified in section 6. The minimum required fields in the log should be: AER ref, contact name, participant ID, date of event, type of event, details, outcome, future actions, whether deemed related to study procedures, to whom reported and when.

Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) involving GMMH service users and/or occurring at all sites (including sites that do not belong to GMMH, but where GMMH is the sponsor or host) are reported to the GMMH R&I 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.
4. Definitions of Adverse Events

4.1 Adverse Event (AE)
Any untoward medical or psychological occurrence in a patient or trial subject receiving psychological therapy or other trial intervention and which does not necessarily have a causal relationship with this intervention. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease in any subject in a trial (including those in an untreated control group), whether or not considered related to the investigational psychological therapy/intervention.

4.2 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)
Unless exempted by the approved protocol, any untoward medical or psychological occurrence that:
- Results in death
- Is life-threatening (see 4.2.1)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity

Life-threatening in the definition of a Serious Adverse Event or Serious Adverse Reaction in section 4.2 above 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 SAEs 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 SAEs for the purposes of the trial.

Professional 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.

4.3 Adverse Reaction (AR)
All untoward and unintended responses to an investigational psychological therapy or other intervention. 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 psychological therapy/intervention qualify as adverse reactions.

Like for Investigational Medicinal Product (IMP), many terms and scales are in use to describe the degree of certainty in relation to causality between a psychological therapy/other intervention 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.

4.4 Unexpected Adverse Reaction
An adverse reaction, the nature or severity of which is not consistent with the effects or consequences of the psychological therapy/intervention being investigated.

4.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)
An adverse reaction that is judged to be both serious and unexpected, according to the definitions in 4.2–4.4.

Systems for SUSAR reporting should be detailed in the Protocol and, as far as possible, should maintain blinding of individual clinicians and of trial 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 unblinding. However, the safety of patients in the trial always takes priority and unblinding clinicians may be unavoidable if the information is necessary for clinical management purposes.

4.6 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 in Appendix 1, 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.
6. Recording and Reporting of Adverse Events

6.1 Adverse Event (AE)
Check whether the AE is classified in the Protocol as not requiring to be recorded. Otherwise, proceed as in 6.1.2-6.1.6.

Where appropriate, clearly document the following in the patient medical records (i.e. PARIS or Amigos if a GMMH patient):

- 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 (not to be confused with seriousness – see definitions)
- Any treatment/medication given for the event, including dates
- The outcome of the event

Enter the AE into the trial adverse event spreadsheet or log (see 3.2.6).

Take any other action as specified by the Protocol (for example, some AEs 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 as in 6.1.2 at each study visit until resolved, returned to baseline, stabilised, or as otherwise specified in the Protocol. AEs that are ongoing on completion of the study should be followed up as required by the Protocol and as clinically indicated.

AEs that result in the subject withdrawing, or being withdrawn, from the study must be recorded for inclusion in the annual progress report to the Ethics Committee.

6.2 Adverse Reaction (AR)
Where appropriate, clearly document the following in the patient medical records (i.e. 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 (not to be confused with seriousness – see definitions)
- Any action taken regarding the psychological therapy/intervention
- Any treatment/medication given for the reaction, including dates
- The outcome of the episode

Enter the AR into the trial adverse event spreadsheet or log (see 3.2.6).
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 6.2.1 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 Ethics Committee.

6.3 Serious Adverse Events (SAE)
Check whether the SAE is classified in the Protocol 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 SAEs, proceed as detailed in section 6.3.2-6.3.8.

Where appropriate, clearly document the following in the patient medical records (i.e. Amigos):

- 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)
- Any treatment/medication given for the event, including dates
- The outcome of the episode

Scan a copy of the SAE report to the R&I Office, quoting the Trust Project Reference Number and IRAS number.

Enter the SAE into research project’s adverse event spreadsheet.

If the event is ongoing at the time of completing the initial report, it should be followed up and documented via PARIS/Amigos (GMMH service users) at subsequent study visits until resolved, returned to baseline, or stabilised. At this point, and as relevant in the interim, a follow-up SAE report should be completed and emailed to the R&I Office.

SAEs should be reported to the Ethics Committee in an expedited fashion (i.e. according to the same timelines as for SUSARs, as outlined in sections 6.5 and 6.6) if they are associated with trial procedures and could modify the conduct of the trial.

SAEs 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 SAEs that result in the subject withdrawing, or being withdrawn, from the study must be kept for inclusion in the annual progress report to the Ethics Committee.

6.4
6.5 Serious Adverse Reaction (SAR)
Check whether the SAR is classified in the Protocol 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 6.2. For all other SARs, proceed as detailed in section 6.4.2-6.4.9.

Where appropriate, clearly document the following in the patient medical records (i.e. PARIS/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)
- Any action taken regarding the psychological therapy/intervention
- Any treatment/medication given for the reaction, including dates
- The outcome of the episode

Scan a copy of the SAR report to the R&I Office immediately, quoting the Trust Project Reference Number and IRAS number.

Enter the SAR into research project’s 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 patient medical records at subsequent study visits until resolved, returned to baseline, or stabilised. At this point, and as relevant in the interim, a follow-up report should be completed and emailed to the R&I Office.

SARs should be reported to the Ethics Committee in an expedited fashion (i.e. according to the same timelines as for SUSARS, as outlined in section 6.5) if they:

Have an unexpected outcome (such as death)
Increase in frequency
Are associated with qualitative changes that are judged to be clinically important
Are associated with trial procedures and could modify the conduct of the trial

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.

All SARs must be recorded in a line-listing format for inclusion in the Annual Safety Report.

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 Ethics Committee.

6.6 Suspected Unexpected Serious Adverse Reaction (SUSAR)
Where appropriate, clearly document the following in the patient medical records (i.e. Amigos):

- The date - and if possible the time - of the onset of the reaction
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- If completely resolved, the duration of the reaction
- The severity of the reaction (not to be confused with seriousness – see definitions)
- Any action taken regarding the psychological therapy/intervention
- Any treatment/medication given for the reaction, including dates
- The outcome of the episode

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

The R&I Office (researchoffice@gmmh.nhs.uk) quoting the Trust Project reference number and IRAS number.
The main Research Ethics Committee.

Enter the SUSAR into the research project’s 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 in the patient medical records and master file.

SUSARs 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 SUSARs must be recorded (a separate entry made for each SUSAR) and included in the Annual Safety Report.

A record of SUSARs that result in the subject withdrawing, or being withdrawn, from the study must be kept for inclusion in the annual progress report to the Ethics Committee.

7. Expedited Reporting

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

- A significant hazard to the subject population.
- A major safety finding from a newly completed study.
- Recommendations of R&I Committee and/or Trial Steering Committee, if any, where relevant for the safety of the subjects.

The Chief Investigator/Principal Investigator must ensure that any such events are identified and reported in an expedited manner.
8. Urgent Safety Measures

If necessary, appropriate urgent safety measures may be taken to protect participant subjects from any immediate hazard to their health and safety. The measures should be taken immediately, without waiting for ethics approval.

Where urgent safety measures have been implemented, the Principal Investigator must immediately:
Telephone the main REC to report the situation.
Prepare a substantial amendment, including a covering letter detailing the measures taken, the reason for them, a Notification of Amendment form and supporting documentation.

Within 3 days, the substantial amendment must be:

Sent by email to the main REC.
Sent by email to the R&I Office (researchoffice@gmmh.nhs.uk).

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 AEs or SAEs that occur to GMMH 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 Support 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 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)
- Any treatment/medication given for the event, including dates
- The outcome of the episode
- GMMH R&I project number and IRAS number
- A “patient identifier” such as patient number or randomisation number
10. Annual Progress Report

The Research Ethics Committee Annual Progress Report form appropriate to the type of study must be completed in typescript and signed by the Chief Investigator.

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.

An electronic copy of the Annual Progress Report should be sent by email to the main REC, with a copy to the R&I Office. For studies with HRA Approval that were not required to be reviewed by a REC, progress reports should be sent to hra.approval@nhs.net.

If in any doubt about any of the above sections, researchers should contact the R&I Office at researchoffice@gmmh.nhs.uk or the Research Ethics Committee.

11. Brief Summary of Key Steps for All Adverse Events

- Document all details of AR/AE/SAE/SAR/SUSAR (complete study ‘SAE’ form if required).
- Log all details on a ‘SAE’ spreadsheet, store in TMF and/or electronically.
- Report SAEs/SARs/SUSARs to: Sponsor, R&I Office of relevant Trusts, REC, HRA (as required by the Protocol).
- AEs and AR’s may not need to be reported – check Protocol and Study Procedures.
- Report on Trust DATIX system if a Trust patient and on Trust premises.
- Note all timelines for reporting.
- Note blinding procedures according to Protocol.
- Record in Trust electronic patient record system (PARIS/AMIGOS) if GMMH patient.
- Review by CI/PI, DMEC, TSC to determine relatedness and identify trends.
- Follow up actions from review and record in SAE Log, patient record, and DATIX where necessary.
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- Include details of withdrawals due to any adverse event in Annual Progress Report to REC (or HRA) annually.

- Report SUSARs in Annual Safety Report to REC.

- In particular, note sections 7 (Expedited Reporting) and 8 (Urgent Safety Measures) reporting arrangements and timelines.

Refer to all sections above for details and clarification.