RD SOP 34 Development Safety Update Reporting.

Greater Manchester Mental Health NHS Foundation Trust
<table>
<thead>
<tr>
<th>Title of Standard Operating Procedure:</th>
<th>RD SOP 34 Development Safety Update Reporting</th>
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<tr>
<td>Document Summary:</td>
<td>The DSUR is intended to be specific to CTIMP’s. This SOP covers the requirements for annual DSUR reporting for Greater Manchester Mental Health Trust (GMMH) sponsored Clinical Trials of Investigational Medicinal Products</td>
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</table>
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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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<table>
<thead>
<tr>
<th>Minimum Monitoring Requirement</th>
<th>Frequency</th>
<th>Process for monitoring</th>
<th>Evidence</th>
<th>Responsible Individual(s)</th>
<th>Response Committee(s)</th>
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<tr>
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<td>Head of R &amp; I Office</td>
<td>Research &amp; Innovation Committee</td>
</tr>
</tbody>
</table>
Contents

1. Introduction........................................................................................................................................... 3
2. Purpose .................................................................................................................................................. 4
3. Roles and Responsibilities ................................................................................................................... 4
  3.1 Duties within the organisation ........................................................................................................ 4
  3.2 Specific to this SOP .......................................................................................................................... 4
4. Procedure ............................................................................................................................................. 5
  4.1 Submission ........................................................................................................................................ 6
  4.2 Storage .............................................................................................................................................. 7
5. Equality Impact Assessment ................................................................................................................. 7
6. Consultation, Approval and Ratification Process .................................................................................. 7
  6.1 Consultation and Communication with Stakeholders ..................................................................... 7
  6.2 SOP Approval Process ..................................................................................................................... 7
7. Dissemination and Implementation ..................................................................................................... 7
  7.1 Dissemination .................................................................................................................................. 7
  7.2 Implementation of Procedural Documents ...................................................................................... 8
8. Review, Monitoring Compliance With and the Effectiveness of Procedural Documents ....................... 8
  8.1 Process for Monitoring Compliance and Effectiveness .................................................................... 8
  8.2 Standards and Key Performance Indicators ‘KPIs’ .......................................................................... 8
9. References and Bibliography ............................................................................................................... 9
10. Associated Trust Documents ............................................................................................................ 10
1. Introduction

In addition to the expedited reporting required for Suspected Unexpected Serious Adverse Reactions (SUSAR's), sponsors of CTIMP's are required to submit annual safety reports (ASRs) to the MHRA and REC/HRA throughout the duration of the clinical trial, or on request. ASRs for CTIMP's should take the format of the Development Update Safety Report (DSUR) and must be submitted at yearly intervals from the date of the original Clinical Trial Authorisation (CTA). For trials with marketed products, the date is the first marketing authorisation granted in the EU.

DSUR's should be submitted annually up until completion of the trial. The format of Development Safety Update Reports (DSUR) is set out in the ICH E2F guideline (see section 9). This guideline was adopted by the European Medicines Agency's Committee for Medicinal Products for Human Use in September 2010 and came into effect September 2011. It establishes a common standard for periodic reporting on drugs under development among the ICH regions. It meets the standards required for annual safety reports on CTIMP's undertaken in the EU.

The Development Safety Update Report (DSUR) is intended to be a common standard for periodic reporting on drugs under development (including marketed drugs that are under further study) among the ICH regions. US and EU regulators consider that the DSUR, submitted annually, would meet national and regional requirements currently met by the US IND Annual Report and the EU Annual Safety Report, respectively, and will therefore take the place of existing safety reporting requirements reports.

The main objective of a DSUR is to present a comprehensive 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:

1. Examining whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug's safety.
2. Describing new safety issues that could have an impact on the protection of clinical trial subjects.
3. Summarising the current understanding and management of identified and potential risks; and providing an update on the status of the clinical investigation/development programme and study results.
4. The DSUR is intended to be specific to CTIMP's. This SOP covers the requirements for annual DSUR reporting for Greater Manchester Mental Health Trust (GMMH) sponsored Clinical Trials of Investigational Medicinal Products.
2. Purpose

This SOP provides information on preparing and submitting a Development Safety Update Reports (DSUR) for all Clinical Trials of Investigational Medicinal Products (CTIMP’s) where the GMMH acts as sponsor.

3. Roles and Responsibilities

3.1 Duties within the organisation

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

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 (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 Trust procedural documents.

3.2 Specific to this SOP

In studies where GMMH is the Sponsor the responsibility for completing and submitting ASR’s and DSUR’s is delegated to the Chief Investigator (CI). This delegation of responsibility must be formally documented in the investigator agreement as one of the delegated responsibilities. The Sponsor has responsibility for ensuring all reports are submitted by ensuring appropriate delegation, reviewing the reports and filing the paperwork. It is the responsibility of Chief Investigators (CIs), Co-investigators and research staff to ensure the appropriate recording and reporting of all adverse events.

Where GMMH is the Sponsor it is the responsibility of the CI to ensure all CTIMP’s which have a Clinical Trial Authorisation (CTA) have a DSUR completed. The DSUR must be submitted to the R & I Office and the CI must also ensure the DSUR is submitted to the MHRA and the main REC/HRA (the REC who provided favourable ethical opinion) annually.

For trials with marketed products the Trust as sponsor, or the CI, is advised to contact the marketing authorisation holder when the trial is being planned to investigate whether or not the marketing authorisation holder will submit a DSUR covering the GMMH-sponsored trial. If they agree, then there is no need for a separate DSUR.

Where the marketing authorisation holder declines to include a GMMH-sponsored CTIMP in their DSUR, the CI will be responsible for preparing a DSUR related to their
trial, and the CI must also ensure the DSUR is submitted to the MHRA and the main REC annually.

If a sponsor is conducting more than one clinical trial of the same Investigational Medicinal Product (IMP), a single annual report may be prepared covering those trials. If there is a valid reason for submitting separate reports this should be clearly explained on the DSUR. In the event of more than one Sponsored or Co- Sponsored trial involving the same IMP, the Sponsor or Co- Sponsor via the Research & Innovation Manager will liaise with the CIs to produce one report for the trials involving the same IMP. A separate DSUR for a comparator, placebo or Non IMP (NIMP) is not required, however, relevant safety information of the above mentioned drug types (comparator, NIMP or placebo) should necessarily be addressed in the DSUR’s of the investigational drugs.

4. Procedure

The DSUR should be submitted according to the format adopted by the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP). See section 9 for the link to an example DSUR. Under each heading information should be presented concisely. Where the Sponsor does not have access to the information to be included in the specific sections, this should be stated in the DSUR.

For trials involving multi-drug therapy the sponsor can prepare either:

• DSUR for the multi-drug therapy or
• DSUR(s) for one or more of the individual components; in this case information on the

multi-drug therapy trials can be included in the DSUR’s of one or all the components.

The following table provides examples of strategies for preparation of DSUR’s for multi-drug therapies:
<table>
<thead>
<tr>
<th>Multi-drug therapy used in clinical trial(s)</th>
<th>DSUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational drug (A) + marketed drug(s) (X, Y, Z)</td>
<td>Either a single DSUR focusing on (A+X+Y+Z) or A single DSUR focusing on (A) including data on the multi-drug therapy</td>
</tr>
<tr>
<td>Two investigational drugs (A) + (B)</td>
<td>Either a single DSUR focusing on (A+B) or Two separate DSURs (A) and (B), each including data on the multi-drug therapy</td>
</tr>
<tr>
<td>Two (or more) marketed drugs as an investigational drug combination (X,Y,Z)</td>
<td>A single DSUR focusing on the multi-drug therapy (X+Y+Z)</td>
</tr>
</tbody>
</table>

### 4.1 Submission

CI will submit the DSUR on behalf of the Sponsor to the MHRA and the main REC.

- The DSUR will be submitted to the MHRA through the Common European Submission Portal (CESP; see section 9) no later than 60 days from annual reporting date.

- A receipt of submission will be issued for submissions to the MHRA made via CESP.

- The DSUR will be sent to the main REC and should include a global list of all SSAR’s (Suspected Serious Adverse Reactions) related to the IMP that have occurred within the reporting period. If the Sponsor is conducting more than one trial in the UK, each responsible main REC should receive a copy.

- The co-ordinator of the main REC will acknowledge receipt of all safety reports within 30 days.

### 4.2 Storage

The original DSUR will be filed in the Trial Master File. Where the DSUR relates to multiple Clinical Trials copies will be placed in each TMF with a file note indicating the location of the original. A copy of the DSUR will be placed on Q-Pulse.

The CI must ensure that a copy of the DSUR receipt of submission from CESP and the REC is stored in the Trial Master File alongside any other communications with the Sponsor, Research Staff, R & I, MHRA and REC/HRA.
5. **Quality 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.

6. **Consultation, Approval and Ratification Process**

6.1 Consultation and Communication with Stakeholders

All Trust R & I 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 Research & Innovation Operational Group, R & I Committee, or external advisors, as necessary.

6.2 SOP Approval Process

All SOPs must be sent to the R & I Manager in order to start the SOP approval process.

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

7. **Dissemination and Implementation**

7.1 Dissemination

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.

7.2 Implementation of Procedural Documents

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

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Ref: RDSOP34  |  Issue date: 13/08/2018  |  Version number: 1.0
Status: Final  |  Next review date: 13/08/2021  |  Page 7 of 10
8 Review, Monitoring Compliance with and the Effectiveness of Procedural Documents

8.1 Purpose 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.

8.2 Standards and Key Performance Indicators ‘KPIs’

This SOP will be available on the Trust website.

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

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


ICH guideline E2F on Development Safety Update Report:


ICH E2F Example DSUR:


Questions and Answers to the Annual Safety Report: Frequently asked questions regarding the Development Safety Update Report (DSUR)


UK Policy Framework for Health and Social Care Research v3.3 07/11/17

10 Associated Trust Documents

RDSOP03 Definition and delegation of investigator responsibilities for CTIMPs
RDSOP8a Pharmacovigilance for Trust-Sponsored MHRA-regulated Clinical Trials
RD SOP33 R & I Committee Safety Oversight