York and Scarborough Teaching Hospitals NHS Foundation Trust R&D Unit
Standard Operating Procedure
R&D/S06

Reporting Requirements During Research Studies

IT IS THE RESPONSIBILITY OF ALL USERS OF THIS SOP TO ENSURE THAT THE CORRECT VERSION IS BEING USED

All staff should regularly check the R&D Unit's website and/or Q-Pulse for information relating to the implementation of new or revised versions. Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded versions are promptly withdrawn from use unless notified otherwise by the SOP Controller.

The definitive versions of all R&D Unit SOPs appear online. If you are reading this in printed form check that the version number and date below is the most recent one as shown on the R&D Unit website: www.research.yorkhospitals.nhs.uk/sops-and-guidance-/ and/or Q-Pulse

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	Date:	20th March 2019

This SOP will normally be reviewed every 3 years unless changes to the legislation require otherwise

Version History Log

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of significant changes
1.0	12th November 2009	
2.0	21st November 2011	Scheduled review. Inclusion of DSUR. Amended to be applicable to non-CTIMP studies.
3.0	15th July 2013	Removal of references to the North and East Yorkshire Alliance. Change of fax number.
4.0	15th August 2017	Change of title and removal of safety aspects to alternative SOPs as existing title confusing
5.0	20th March 2019	Change in procedure for quarterly reporting of Trust Sponsored Studies. Update to link for R&D website

Contents

1 Introduction, Background and Purpose

Clinical Trials of Investigational Medicinal Products (CTIMPs) are legally regulated by the Medicines for Human Use Act 2004 and regulations made by statutory instrument under that Act. [1] This legal framework imposes a number of reporting requirements in addition to those relating to specific adverse events. These reports must be made to the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Research Ethics Committee that gave the favourable ethical opinion for the study (REC).

For non-CTIMPs there are requirements to report various matters to RECs.

In addition to this external reporting investigators are required to inform R&D Offices responsible for care organisations in which research is conducted of any significant matters relating to the research of which these organisations should be aware. This SOP details how these responsibilities should be discharged.

2 Who Should Use This SOP

This SOP should be used by all staff involved in research studies sponsored or co-sponsored by the Trust and by personnel in the R&D Unit

3 When this SOP Should be Used

This SOP should be used when the Trust is the sponsor or co-sponsor of a research study where reporting requirements will exist throughout and at the end of that study. This SOP details those requirements and whilst this document is reviewed and updated regularly all users are strongly advised to refer to the relevant sections of the HRA website to ensure that the correct procedure is being followed.

4 Procedure(s)

4.1 Development Safety Update Report (DSUR) for CTIMPs only

For all CTIMP studies, sponsors are required to submit a safety report to the MHRA and REC, once a year or on request. Preparation of the DSUR is delegated to the CI but the Sponsor must review and approve the report prior to the submission being made. Enough time must be allowed for this when considering the timescales of the submission.

NOTE: For type A trials, authorised under the Notification Scheme, a full DSUR is no longer required and the Health Research Authority Annual Progress Report (APR) form may be submitted instead. For Type A trials using the APR Form in

[1] The Medicines for Human Use (Clinical Trial) Regulations 2004 and the Medicines for Human Use (Clinical Trial) Amendment Regulations 2006, the Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006, the Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008, and the Medicines for Human Use (Miscellaneous Amendments) Regulations 2009.

lieu of the DSUR this must be indicated in the covering and the EudraCT number and CTA reference number must be included. A list of all Serious Adverse Reactions must be included in section 6 of the APR.

4.1.1 Background to the DSUR

Required from 1st September 2011, this is intended to be a common standard for periodic reporting on drugs under development (including marketed drugs that are under further study) among the International Conference on Harmonisation (ICH) regions.

The DSUR is intended to present a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period 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 (4) providing an update on the status of the clinical investigation/development programme and study results.

A DSUR should be concise and provide information to assure regulators that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational drug. All safety issues discovered during the reporting period should be discussed in the text of the DSUR; however, it should not be used to provide the initial notification of significant new safety information or provide the means by which new safety issues are detected.

4.1.2 Responsibility and timelines for submission of DSUR

Responsibility for preparation and submission of the DSUR within the specified timescales is delegated to the CI. Reports must be provided at yearly intervals for the duration of the trial, from trial authorisation until termination.

The 'Development International Birth Date' (DIBD) determines the start of the annual reporting period for the DSUR. This date is the Sponsor's first authorisation to conduct a clinical trial in any country worldwide. The data lock point of the DSUR should therefore be the last day of the one-year reporting period.

The DSUR must be submitted to all concerned regulatory authorities **no later than 60 calendar days** after the DSUR data lock point.

The due date of the DSUR must be clearly documented in the ISF/TMF.

4.1.3 DSURs for Combination Therapies

In general, a single DSUR should be prepared for clinical trials involving a fixed combination product (i.e. a product consisting of at least two active ingredients in a fixed dose that is administered in a single dosage form). If the sponsor is also conducting clinical trials with individual component(s) of the fixed combination product, separate DSUR(s) should be submitted for each component.

4.1.4 Reference Safety Information

The Investigator's Brochure (IB) in effect at the start of the reporting period is the reference document to determine whether the information received during the reporting period remains consistent with previous knowledge of the investigational drug's safety profile. The IB version number and date must be stated in the DSUR. When an IB is not required for a study, the Summary of Product Characteristics (SmPC) should serve as the reference safety information and version information given similarly.

The IB should contain a discrete section, which is the Reference Safety Information (RSI), allowing the IB to be updated independently of the RSI.

The IB in place at the beginning of the reporting period should be appended to the DSUR, regardless of whether the IB or SmPC was altered during the period of the DSUR. The RSI in place at the beginning of the reporting period should be the reference for the expectedness assessments in the DSUR line listings, regardless of whether the RSI was updated during that reporting period. If the IB or SmPC was updated during the reporting period the current version should also be submitted.

The DSUR should include the date and version number of the IB or SmPC used as the RSI.

4.1.5 Completing the DSUR

The DSUR has a standard format and must be submitted using the Common European Submission Portal (CESP)[select regulatory activity G0042 - Development Safety Update Reports]. It is important to allow sufficient time to check the latest instructions for completion and submission of the DSUR on the MHRA website before the due date in the event of any changes to this process.

The DSUR should include:

- a cover letter listing all EudraCT numbers of trials covered by the DSUR, including any trials approved via the Voluntary Harmonisation Procedure (VHP). An email address should be included for correspondence.
- an analysis of the subjects' safety in the concerned clinical trial(s) with an appraisal of its ongoing risk/benefit
- a line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the trial(s), including all SUSARs from third countries
- an aggregate summary tabulation of SUSARs that occurred in the concerned trial(s)

Full details of what to include in a DSUR are found on the European Commission website.

In case of a first-in-man trial and subsequent short term metabolism or pharmacokinetic studies the DSUR should be notified within 90 days of the end of trial together with the notification of the end of the trial.

4.1.6 Submitting the DSUR

The CI should ensure that the DSUR is reviewed and approved by the Sponsor Representative in the R&D Unit prior to submission. The CI is responsible for submitting the DSUR.

MHRA are no longer sending acknowledgements for DSUR. In order to be able to demonstrate compliance with GCP the CESP submission details must be filed as evidence that the DSUR submission has been made.

At the end of the DSUR reporting period the sponsor should assess the new safety information that has been generated and submit any proposed safety changes to the investigator's brochure as a substantial amendment. This amendment should be supported by the DSUR and approved before the reference safety information (RSI) is changed.

4.2 Annual Progress Report (APR) (all studies with REC approval)

One year from obtaining REC approval, and annually thereafter, the CI must submit an Annual Progress Report (APR) to the Research Ethics Committee (REC) within 30 days of the end of the reporting period. For guidance on this refer to the HRA website. There are separate forms for submitting progress reports, depending on the type of research. Please use the form that is applicable to your type of research.

A copy of the signed APR must be retained in the ISF/TMF together with evidence of submission. An acknowledgement should always be requested and followed up if not received then filed in the ISF.

The CI is responsible for making the submission directly to the REC but a copy should be submitted to the R&D Unit at the same time.

4.3 Quarterly Study Review Report (QSR) (all studies)

To ensure adequate sponsor oversight a quarterly report must be submitted for all Trust Sponsored studies for consideration at the quarterly R&D Quality Assurance meetings. Reports are required quarterly, in January, April, July and October, unless specified otherwise by the R&D Unit and should be submitted on the template referenced in Section 5 R&D/F22 Quarterly Study Review (QSR) Form for Trust Sponsored Studies. The report should be submitted to the R&D Unit via the Research Quality Assurance email, Research.QA@york.nhs.uk no later than 7 working days before the due date of the designated review meeting.

4.4 Notification of End of Study (all studies)

The CI must notify the R&D Unit of the end date as soon as a study has ended.

The CI must then complete the correct Form (available to download from the HRA website) and submit within 90 days. Investigators must ensure that the correct form is used for CTIMP, non-CTIMP or device studies.

Final analysis of the data (following 'lock' of the study database) and report writing is normally considered to occur after formal declaration of the end of the study.

Before the declaration of the end of the study is completed, the plans that have been approved by the REC for use of tissue and data collected in the course of the study, providing information to participants, and dissemination of results must be reviewed. If any changes need to be made to these approved arrangements consideration must be given as to whether a substantial amendment is required before submitting the end of study notification.

Where a project has HRA Approval and has been reviewed by a REC you need only inform the REC when your study has ended. Where a project has HRA Approval and was not reviewed by an NHS REC, you will need to tell HRA when the project has ended. You should send this notification by email to hra.approval@nhs.net including your IRAS ID and your contact information (phone and email).

Submission must be made to the MHRA, REC and/or HRA as appropriate. Refer to the HRA website for information or seek advice from the R&D Unit.

A copy of the signed completed notification must be retained in the ISF/TMF together with evidence of submission.

If a CTIMP is terminated before the date specified in the protocol for its conclusion the CI must notify the R&D Unit immediately and is responsible for notifying the MHRA and the REC as soon as possible and within 15 days of the date of termination by submitting the declaration as described above. This must be undertaken in an expedited fashion.

4.5 End of Study report (all studies)

The CI should send a summary of the final research report to the REC (and MHRA for clinical trials of investigational medicinal products) within 12 months of the end of the study. MHRA (devices) may request a copy of the final report of a clinical investigation of a device. Where the study may be multi-national this is the end of study in all participating countries and not just in the UK.

Final report preparation and submission for CTIMPs is described in R&D/S27.

For non-CTIMPS there is no standard format for the final report. As a minimum, investigators should inform the REC whether the study achieved its objectives, the main findings, and arrangements for publication or dissemination of the research, including any feedback to participants. Final reports should be emailed to the REC.

Copies of all final reports should be submitted to the R&D Unit also. These will be shared with the Trust's R&D Group.

5 Related SOPs and Documents

R&D/S05 Research Related Adverse Event Reporting Procedure for CTIMP studies (Including reporting a Pregnancy)

R&D/S07 Implementing Amendments for Research Studies NOT Sponsored by the Trust

R&D S74 Making Amendments to Trust Sponsored Research Studies

R&D/F21 Developmental Safety Update Report (DSUR) Form

R&D/F22 Quarterly Study Review Form for Trust Sponsored Studies