Gloucestershire Hospitals
NHS Foundation Trust

Pharmacovigilance 01: Periodic reporting to Research Ethics Committee and MHRA

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 Research & Development Webpage 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 Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded version are promptly withdrawn from use unless notified otherwise by the SOP Controller.

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http://www.gloshospitals.nhs.uk/en/About-Us/Research--Development/

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Author:	Janet Forkes	signature
Reviewed by Associate Director of R&D	Julie Hapeshi	signature J. Hapeshi
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Version History Log

This area will be updated with details of all changes made to the SOP whether due for full review or not.

Version	Details of Change	Date Implemented
1.0	Original SOP	09/02/2017
2.0	Rebranding to GHNHSFT, updating of contact details and reference documents	31/03/2018

This SOP will be reviewed every two years unless changes to any relevant legislation require otherwise

Contents

1 Introduction, Background and Purpose

Pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information on the adverse effects of medicines, with a view to identifying information about potential new hazards and preventing harm to subjects. Pharmacovigilance is of the utmost importance in clinical trials to ensure both the safety of the trial subjects and the safety of current and future patients.

Effective pharmacovigilance facilitates an ongoing assessment of the risk-benefit ratio of a trial in relation to the IMP and the trial procedures. Emerging safety data allow the sponsor to safely manage the trial by introducing amendments to the protocol and providing updated information to the investigators and subjects where necessary and allows them to assess whether it continues to be safe to conduct the trial.

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 the 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 Trust R&D Office.

Section 5 describes how and when elements of this SOP may also be applicable to externally-sponsored studies hosted by the Trust.

3 When this SOP should be used

This SOP should be used when the Trust is the sponsor or co-sponsor. In addition, see Section 5 for applicability to externally-sponsored studies hosted by the Trust.

The 'sponsor representative' for the Trust is a member of the R&D Department.

4 Urgent Safety Measures (USMs)

During the course of a study, new safety information may necessitate an immediate change in study procedures or a temporary halt to the study to protect clinical trial subjects from any immediate hazard.

If time does not allow for an amendment to be authorised by the MHRA (CTIMP studies only), REC (CTIMP and non-CTIMP studies) and sponsor (CTIMP and non-CTIMP studies), this change in procedure can be implemented as an Urgent Safety Measure (USM), by the Chief Investigator (CI), Principal Investigator at a site (PI) or Sponsor.

Where the CI or a PI implements a USM responsibility for notifying MHRA and/or the REC is delegated to the CI. In exceptional circumstances this may be done by a PI. For a sponsor implemented USM, notification will be done by the R&D Department as sponsor representative.

Immediately following implementation USMs must be notified to:

- MHRA (CTIMP studies only)
- REC (CTIMP and non-CTIMP studies)
- R&D Department (CTIMP and non-CTIMP studies)
- CI (if PI is making notification).

The Investigator or sponsor representative must immediately telephone:

(i) The Clinical Trial Department at the MHRA, Telephone the Central Enquiry Point (http://www.mhra.gov.uk/Contactus/index.htm) and request transfer to the Clinical Trial Department to discuss an urgent safety measure with a Medical Assessor.

(ii) The REC. (http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/)

Details of the telephone conversation(s) must be documented in the Investigator Site File / Trial Master File (ISF/TMF).

If the reporting has been done by an Investigator s/he must then immediately fax a Notification of Urgent Safety Measure Report Form (See Appendix 1) to the R&D Department (fax: 0300 422 5469 or email ghn-tr.glos@nhs.net). The R&D Department will acknowledge receipt to the fax machine or email account from which the report was sent by noon of the next working day. It is the responsibility of the Investigator reporting the USM to ensure a receipt is received and to contact the R&D Department immediately by telephone (Tel: 0300 422 5463) if a receipt is not received within this timescale.

The R&D Department will contact the Investigator reporting the USM on the next working day. If the reporting Investigator will be unavailable s/he must discuss the matter fully with a delegated individual and give that person's contact details on the USM report form. Such delegation should only be done in exceptional circumstances - the reporting Investigator should make him/herself available to discuss the matter if at all possible.

The Investigator or sponsor representative implementing the USM shall then immediately, and no later than 3 days from the date the measures are taken, give

written notice to MHRA and/or the REC detailing the measures taken and the circumstances giving rise to them, including the name of the medical assessor contacted and any supporting documents.

The Notification of Urgent Safety Measure Report Form (Appendix 1)to fax notification to the R&D Department (see above) may also be used for this purpose.

The written notification should be:

- Sent by e-mail to clintrialhelpline@mhra.gsi.gov.uk) marked 'Urgent Safety Measure'
- Sent as PDF documents on disk to: Information Processing Department, Area 6, Medicines & Healthcare products Regulatory Agency, 151 Buckingham Palace Road, Victoria, London. SW1W 9SZ
- Sent to the main REC – details will be held in the ISF/TMF.
- Copied to the CI if the USM is reported by a PI or sponsor representative.
- Copied to the hosting Trust's own R&D Office
- An acknowledgement of USM notification should always be requested and followed up if not received. This acknowledgement and any other correspondence relating to the USM should be filed in the ISF/TMF.
- If the USM warrants submission of a substantial amendment then this should be submitted in as soon as possible.

5. Temporary Halt to a Research Study

When a study is halted temporarily for a reason involving risk to participants' health or safety, the halt should be reported as a USM (see Section 4.1).

Where a study is halted temporarily for any other reason the CI or sponsor representative must notify the MHRA (CTIMP studies) and/or REC (CTIMP and non-CTIMP studies) immediately and within 15 days from the date of the temporary halt. The notification should be made as a substantial amendment and should clearly explain exactly what has been halted (e.g. stopping recruitment and/or interrupting treatment of subjects already included) and the reasons for this action.

If the sponsor needs to halt a study temporarily (e.g. in light of issues highlighted in a monitoring report) the sponsor representative will notify the necessary regulatory authorities.

Substantial amendments relating to temporary halts should be:

- Submitted as PDF documents on disk to Information Processing Department, Area 6, Medicines and Healthcare products Regulatory Agency, 151 Buckingham Palace Road, Victoria, London SW1W 9SZ
- Submitted to the REC
- Notification to HRA
- Sent to the R&D Department by email (glos.rdsu@glos.nhs.uk)
- Copied to the CI if the temporary halt is submitted on behalf of the sponsor
- Copied to the hosting Trust's R&D Office by email.

- A copy of the complete application must be retained in the ISF/TMF together with evidence of posting (recorded delivery is recommended). An acknowledgement should always be requested and followed up if not received. To facilitate acknowledgement by regulatory authorities, it is good practice to include with the submission a stamped addressed return envelope enclosing a card, letter or form to be signed and dated by the receiving party. Any correspondence relating to the temporary halt from the MHRA, REC and/or sponsor must be retained in the ISF/TMF. Correspondence from the MHRA and/or REC must be copied to the R&D Department

5.1 Restarting a Halted Study

Restarting a halted study is a substantial amendment. As with any substantial amendment it must be approved by the sponsor before submission to the necessary regulatory authorities. The application made by the CI should include evidence that it is safe to restart the study.

If the sponsor decides not to recommence a temporarily halted study responsibility will be delegated to the CI to notify the MHRA and/or REC within 15 days of this decision, using the End of Trial Declaration form Appendix 2).

6. 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.

6.1 Background to the DSUR

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:

- 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.

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.(See appendix 3)

6.2 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.

6.3 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(See appendix 3).

6.4 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 DSUR 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.

6.5 Completing the DSUR

The DSUR has a standard format and a template is available (see Appendix 3). It is necessary to complete ALL sections, leaving no section blank – enter 'no information available' or 'not applicable' where necessary.

6.6 Submitting the DSUR

The CI should submit the DSUR to:

- MHRA: by using the Common European Submission Portal (CESP) https://cespportal.hma.eu/Account/Login?ReturnUrl=%2f .
- The REC: http://www.hra.nhs.uk/resources/during-and-after-your-study/nhs-research-ethics-committee-rec-ctimp-safety-report-form
- the R&D Department of the Sponsoring Trust

The MHRA and HRA websites must be checked for up to date submission requirements prior to the time of DSUR submission. A copy of the submitted DSUR must also be provided to the Trust R&D Office.

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

7. Annual Progress Report (APR) (all studies)

The REC has a duty to monitor research that has been granted a favourable ethical opinion by it. In order to do so, periodic progress reports are required to be submitted. Progress reports must be submitted to the REC which granted the favourable opinion. The due date for reports is 12 months after the date on which the favourable opinion was given and each year thereafter until the end of the trial.

Where a REC regards a trial as particularly high-risk, they may require quarterly or even monthly reports to be submitted. This will be detailed in the approval letter and must be adhered to.

The HRA has produced templates which must be used, available via the HRA website:
www.hra.nhs.uk/resources/during-and-after-your-study/nhs-rec-annual-progress-report-forms/.
Separate forms are available for CTIMP and non-CTIMP studies.

A copy of the signed APR must be retained in the ISF/TMF together and an electronic copy should be emailed to the REC within 30 days of the end of the reporting period.

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

8. Notification of End of Study

8.1 CTIMP Studies

The regulatory bodies need to be notified in the following manner:

- MHRA

  A declaration of the end of a clinical trial should be sent to MHRA within 90 days of the global end of the trial. More information can be found at : http://www.hra.nhs.uk/research-community/end-of-study-and-beyond/notifying-the-end-of-study

  Any trial activities (i.e. follow-ups, visits) should be completed before the submission of the end of trial declaration form.

  It is not possible to submit amendments to the trial once the declaration form has been received.

  The end of trial declarations must be submitted via Common European Submission Portal (CESP).

- Research Ethics Committee
  The REC which gave a favourable opinion of the research must be notified of its conclusion, in writing, using the appropriate form. There are separate forms for use in clinical trials of investigational medicinal products (CTIMPs) and all other research.

  You should email the appropriate form to the REC within 90 days of the end of the study.

  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.

  All details can be found at: http://www.hra.nhs.uk/research-community/end-of-study-and-beyond/notifying-the-end-of-study/

- End of study under HRA Approval
  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).

  A copy of the signed completed notification must be retained in the ISF/TMF together with evidence of submission to the various systems. An acknowledgement should be requested where possible and followed up if

not received. This acknowledgement and any other correspondence should be filed in the ISF/TMF.

- Trials terminated early
  If a trial is terminated before the date specified in the protocol for its conclusion the CI must notify the R&D Department immediately and is responsible for notifying the MHRA and the REC within 15 days of the date of termination by submitting a CT End of Trial Form available from the EudraCT website as described above.

- R&D Department
  The CI must notify the R&D Department of the end date as soon as a study has ended and provide copies of the notifications to the REC and MHRA.

8.2 Non-CTIMP Studies

For non-CTIMP studies an End of Study Declaration Form (available from the National Research Ethics Service website) should be submitted to the REC within 90 days of the end of the study. A copy of the signed completed notification must be retained in the ISF/TMF together with evidence of submission. A copy should be submitted to the R&D Department.

- End of study under HRA Approval
  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).

  For research studies terminated before the conclusion date specified in the protocol the CI must notify the R&D Department immediately and notify the REC within 15 days of the date of termination by submitting an End of Study Declaration Form as described above.

9.0 Final report on the research

The Researcher 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. It is likely that a copy would particularly be requested under certain circumstances, e.g. where a serious adverse event has occurred associated with a CE-marked device which had undergone clinical investigation authorised by the UK Competent Authority, or where a novel technology has been investigated.

Where this is a multi-national study this is the end of study in all participating countries and not just in the UK.

There is no standard format for final reports. As a minimum, you 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.

See more at: http://www.hra.nhs.uk/research-community/end-of-study-and-beyond/notifying-the-end-of-study

10. Other SOPs and Documents

www.hra.nhs.uk/resources/during-and-after-your-study/nhs-rec-annual-progress-report-forms/

http://www.hra.nhs.uk/research-community/end-of-study-and-beyond/notifying-the-end-of-study

http://www.hra.nhs.uk/documents/2015/06/safety-progress-reports-procedural-table-ctimps.pdf

https://cespportal.hma.eu/

http://www.hra.nhs.uk/resources/during-and-after-your-study/end-of-study-notification-studies-other-than-clinical-trials-of-investigational-medicinal-products

Appendix 1 Notification of Urgent Safety Measures Reporting Form

Fax to R&D Department <u>IMMEDIATELY</u> upon implementing an urgent safety measure
(Fax: 0300 422 5469)

A faxed receipt will be sent by noon of the next working day – if this is NOT received the reporting investigator must contact the R&D Department by telephone on 0300 422 5463 immediately.

1. Details of Chief Investigator

Name:		Telephone:	
Address:		Email:	
		Fax:	
Contact details where Investigator can be contacted to discuss urgent safety measure:			

2. Details of study

Full title of study:			
Sponsor:		R&D number:	
Name of main REC:		EudraCT Number:	

3. Details of Urgent Safety Measure

Details of urgent safety measure implemented::	
Circumstances giving rise to the urgent safety measure: :	
Measures taken: :	
Date urgent safety measure implemented:	

Name of MHRA Medical assessor contacted:	
Additional notes: :	

Continue on a separate sheet if necessary

Signature of person making report:_____

Date: DD-MMM-YY

Name (please print):_____

Appendix 2 https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/ending-your-project/

Declaration of the End of Trial Form (cf. Section 4.2.1 of the *Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial*[1])

NOTIFICATION OF THE END OF A CLINICAL TRIAL OF A MEDICINE FOR HUMAN USE TO THE COMPETENT AUTHORITY AND THE ETHICS COMMITTEE

For official use

Date of receipt :	Competent authority registration number : Ethics committee registration number:

To be filled in by the applicant

A MEMBER STATE IN WHICH THE DECLARATION IS BEING MADE :

B TRIAL IDENTIFICATION

B.1 EudraCT number :	**(..)**
B.2 Sponsor's protocol code number:	**(..)**
B.3 Full title of the trial :	

C APPLICANT IDENTIFICATION (please tick the appropriate box)

C.1	**DECLARATION FOR THE COMPETENT AUTHORITY**	☐
C.1.1	Sponsor	☐
C.1.2	Legal representative of the sponsor	☐
C.1.3	Person or organisation authorised by the sponsor to make the application.	☐
C.1.4	**Complete below:**	
C.1.4.1	Organisation :	
C.1.4.2	Name of person to contact :	
C.1.4.3	Address :	
C.1.4.4	Telephone number :	
C.1.4.5	Fax number :	
C.1.4.6	E-mail	

C.2	**DECLARATION FOR THE ETHICS COMMITTEE**	☐
C.2.1	Sponsor	☐
C.2.2	Legal representative of the sponsor	☐
C.2.3	Person or organisation authorised by the sponsor to make the application.	☐
C.2.4	Investigator in charge of the application if applicable[2]:	
	• Co-ordinating investigator (for multicentre trial):	☐
	• Principal investigator (for single centre trial):	☐
C.2.5	**Complete below** :	
C.2.5.1	Organisation:	
C.2.5.2	Name :	
C.2.5.3	Address :	
C.2.5.4	Telephone number :	
C.2.5.5	Fax number :	
C.2.5.6	E-mail :	

D END OF TRIAL

1 OJ, C82, 30.3.2010, p. 1; hereinafter referred to as 'detailed guidance CT-1'.

2 According to national legislation.

D.1	**Date of the end of the complete trial in all countries concerned by the trial?**
D.1.1	(YYYY/MM/DD):

D.2	**Is it an early termination?**[3]	yes ☐ no ☐
D.2.1	If yes, give date (YYYY/MM/DD):	
D.2.2	Briefly describe in an annex (free text):	
D.2.2.1	The justification for early termination of the trial;	
D.2.2.2	Number of patients still receiving treatment at time of early termination in the MS concerned by the declaration and their proposed management;	
D.2.2.3	The consequences of early termination for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product.	

E SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

E.1	I hereby confirm that/confirm on behalf of the sponsor that (delete which is not applicable): • The above information given on this declaration is correct; and • That the clinical trial summary report will be submitted within the applicable deadlines in accordance with the applicable guidance by the Commission.[4]

E.2	**APPLICANT TO THE COMPETENT AUTHORITY** (as stated in C.1) ☐
E.2.1	Date :
E.2.2	Signature :
E.2.3	Print name:

E.3	**APPLICANT TO THE ETHICS COMMITTEE** (as stated in C.2) : ☐
E.3.1	Date :
E.3.2	Signature :
E.3.3	Print name:

[3] Cf. Section 4.2. of the detailed guidance CT-1.

[4] Section 4.3. of the detailed guidance CT-1.

Appendix 3 Development Safety Update Report

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002827.pdf

Appendix 4 **ANNUAL PROGRESS REPORT TO MAIN RESEARCH ETHICS COMMITTEE**

4a CTIMPS

https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/progress-reports/

CLINICAL TRIAL OF AN INVESTIGATIONAL MEDICINAL PRODUCT (CTIMP)

ANNUAL PROGRESS REPORT TO MAIN RESEARCH ETHICS COMMITTEE

To be completed in typescript and submitted by the Chief Investigator. Please send this report only to the main REC. For questions with Yes/No options please indicate answer in bold type.

1. Details of Chief Investigator

Name:	
Address:	
Telephone:	
E-mail:	
Fax:	

2. Details of study

Full title of study:	
Name of main REC:	
REC reference number:	
Date of favourable ethical opinion:	
Sponsor:	
EudraCT Number:	

3. Commencement and termination dates

Has the study started in the UK?	**Yes / No**
If yes, what was the actual start date in the UK?	
If no, what are the reasons for the study not commencing in the UK? What is the expected start date?	

Has the study finished? ***If yes, complete and submit EudraCT "Declaration of end of trial" form at Annex 3 to ENTR/CT1, available at: https://eudract.emea.europa.eu/document.html***	***Yes / No***
If no, what is the expected completion date? **1** ***If you expect the study to overrun the planned completion date this should be notified to the main REC for information.***	
If you do not expect the study to be completed, give reason(s)	

4. Site information

Number of UK research sites proposed in original application: **Number of UK research sites recruited to date:**	
Do you plan to increase the total number of UK sites proposed for the study? ***The addition of any new sites not listed in the original applications to the REC and the MHRA should be notified to both bodies by submitting a substantial amendment using the form at Annex 2 to ENTR/CT1, available at https://eudract.emea.europa.eu/document.html***	***Yes / No***

5. Recruitment of participants

*** Number of participants recruited:**	***Proposed in original application:*** ***Actual number recruited to date:***
*** Number of participants completing trial:**	***Actual number completed to date:***
*** Number of withdrawals from trial to date due to:** **(a) withdrawal of consent** **(b) loss to follow-up** **(c) death (where not the primary outcome)** **Total study withdrawals:**	
***Number of treatment failures to date (prior to reaching primary outcome) due to:** **(a) adverse events** **(b) lack of efficacy** **Total treatment failures:**	

** In the case of international trials, please provide separate figures for UK and non-UK participants.*

Have there been any serious difficulties in recruiting participants?	***Yes / No***
If yes, give details:	
Do you plan to increase the planned recruitment of participants into the study? ***Any increase in planned recruitment should be notified to the main REC as a substantial amendment for ethical review.***	***Yes / No***

6. Safety reports

2 Have there been any Suspected Unexpected Serious Adverse Reactions (SUSARs) in this trial in the UK?	***Yes / No***
Have these SUSARs been notified to the Committee within 7/15 days under Article 17 of EU Directive? ***If no, please arrange urgently and give reasons for late notification.***	***Yes / No***
What is the reporting date for periodic safety reports to the main REC during this trial? ***This is the date of first authorisation of the trial in any EU member state or, if the sponsor is the Marketing Authorisation Holder, the International Birth Date for the product.***	
Has a 6 monthly safety report been submitted? ***Applies only to commercial sponsors undertaking this trial or other trials of the IMP outside the UK.***	***Yes / No / Not applicable***
Has the Annual Safety Report been submitted?	***Yes / No / Not yet due***
When is the next ASR due?	

7. Amendments

Have any substantial amendments been made to the trial during the year?	***Yes / No***
If yes, please give the date and amendment number for each substantial amendment made.	

8. Serious breaches of the protocol or Good Clinical Practice

Have any serious breaches of the protocol or GCP occurred in relation to this trial during the year? *Under the Clinical Trials Regulations, all serious breaches must be notified to the MHRA GCP inspectors within 7 days of the matter coming to the sponsor's attention.*	*Yes / No*
If yes, please give the date of each notification to the MHRA. *Please provide the REC with a copy of each notification for information (unless previously notified).*	

9. Other issues

Are there any other developments in the trial that you wish to report to the Committee?	*Yes / No*
Are there any ethical issues on which further advice is required? *If yes to either, please attach separate statement with details.*	*Yes / No*

10. Declaration

Signature of Chief Investigator:	
Print name:	
Date of submission:	

4b Non-CTIMP
https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/progress-reports/

ANNUAL PROGRESS REPORT TO MAIN RESEARCH ETHICS COMMITTEE
(For all studies except clinical trials of investigational medicinal products)

To be completed in typescript and submitted to the main REC by the Chief Investigator. For questions with Yes/No options please indicate answer in bold type.

1. Details of Chief Investigator

3 Name:	
Address:	
Telephone:	
E-mail:	
Fax:	

2. Details of study

Full title of study:	
Name of main REC:	
REC reference number:	
Date of favourable ethical opinion:	
Sponsor:	

3. Commencement and termination dates

Has the study started?	*Yes / No*
If yes, what was the actual start date?	
If no, what are the reasons for the study not commencing? What is the expected start date?	
Has the study finished? *If yes, complete and submit "Declaration of end of study" form, available at http://www.nres.npsa.nhs.uk/applications/after-ethical-review/endofstudy/*	*Yes / No*

If no, what is the expected completion date? *If you expect the study to overrun the planned completion date this should be notified to the main REC for information.*	
If you do not expect the study to be completed, give reason(s)	

4. Registration

Is the study a 'clinical trial'? (Defined as first 4 categories on the IRAS filter page) (For CTIMP please use CTIMP progress reporting template)	*Yes / No*
Is the study registered on a publically accessible database? (Registration of clinical trials is a condition of approval for studies approved after 30 September 2013)	Yes / No
If yes, please provide the name of the database and the registration number Database: Registration number:	
If no: a. What is the reason for non-registration? b. What are your intentions for registration?	

5. Site information

Do you plan to increase the total number of sites proposed for the study? If yes, how many sites do you plan to recruit?	*Yes / No*

6. Recruitment of participants

In this section, "participants" includes those who will not be approached but whose samples/data will be studied.

Number of participants recruited:	*Proposed in original application:* *Actual number recruited to date:*
Number of participants completing trial:	*Actual number completed to date:*
Number of withdrawals from study to date due to: (a) withdrawal of consent (b) loss to follow-up (c) death (where not the primary outcome) Total study withdrawals:	
*Number of treatment failures to date (prior to reaching primary outcome) due to: (a) adverse events (b) lack of efficacy Total treatment failures: * Applies to studies involving clinical treatment only	
Have there been any serious difficulties in recruiting participants?	Yes / No
If Yes, give details:	
Do you plan to increase the planned recruitment of participants into the study? *Any increase in planned recruitment should be notified to the main REC as a substantial amendment for ethical review.*	Yes / No

7. Safety of participants

Have there been any related and unexpected serious adverse events (SAEs) in this study? 4	*Yes / No*
Have these SAEs been notified to the Committee? *If no, please submit details with this report and give reasons for late notification.*	*Yes / No /Not applicable*
Have any concerns arisen about the safety of participants in this study? *If yes, give details and say how the concerns have been addressed.*	*Yes / No*

8. Amendments

Have any substantial amendments been made to the trial during the year?	*Yes / No*
If yes, please give the date and amendment number for each substantial amendment made.	

9. Serious breaches of the protocol

Have any serious breaches of the protocol occurred during the year? *If Yes, please enclose a report of any serious breaches not already notified to the REC.*	*Yes / No* *Yes / No*

10. Other issues

Are there any other developments in the study that you wish to report to the Committee? Are there any ethical issues on which further advice is required? *If yes to either, please attach separate statement with details.*	*Yes / No* *Yes / No*

11. Declaration

Signature of Chief Investigator:	
Print name:	
Date of submission:	