JOINT RESEARCH AND INNOVATION

Joint Research and Development Office

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Title: **PHARMACOVIGILANCE AND SAFETY REPORTING SOP**		
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	Name	Position
Authored by:	Ilyas Ali	Clinical Trials Manager
Approved by	Dr. Vanshree Patel	Head of Research Governance, Clinical Trials and Contracts

1. Scope

This SOP is applicable to all the clinical trials of Investigational Medicinal Product (IMP) and ATMP sponsored, co-sponsored and hosted by Great Ormond Street Hospital. This SOP applies to the procedures for the adequate recording, reporting and evaluation of AE, AR, SAE/SAR and SUSAR'.

Development Safety Update report and Annual Progress reports, which are also part of the Sponsor's pharmacovigilance responsibilities, are outside the scope of this SOP.

This SOP applies to both single centre and/or multi-centre trials.
In circumstances, where the GOSH/ICH Joint R&D Office has delegated the pharmacovigilance responsibilities to a trials co-ordinating unit, clinical trials unit or Clinical Research Organisation (CRO), the pharmacovigilance details are drawn up in an appropriate contract or a process document, which is not in the scope of this SOP.

2. Purpose

This SOP describes the process for recording, managing, reporting and follow up of adverse events for GOSH sponsored studies and hosted studies to ensure compliance with the regulation.

This SOP also describes the process how clinical trial team at R&D office (as a sponsor) manages SAE/SAR and any other important safety information related to subjects participating in a GOSH Sponsored trials.

Additionally this SOP covers the process involved in SAE reporting to R&D and the hosted sponsor for all hosted studies.

3. Definitions

a) Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

b) Adverse Reaction (AR): all untoward and unintended responses to an investigational medicinal product related to any dose administered.

Comment: All adverse events judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as an adverse reaction.

c) Unexpected Adverse Reaction (UAR): an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure (IB) for an unauthorised investigational product or summary of product characteristics for an authorised product).

Comment: Reports are also considered to be unexpected if they add significant information on the specificity or severity of an expected adverse reaction.

d) Serious Adverse Event or Serious Adverse Reaction (SAE/R): any untoward medical occurrence or effect that at any dose results in:

- death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- or is a congenital anomaly or birth defect.

e) Other medically important serious events: adverse events/reactions that may jeopardise the subjects or may require medical or surgical intervention to prevent one of the above 5 outcomes defining seriousness (d), from occurring should also be considered serious. Such events could be:

1. Overdose (accidental or intentional)
2. Pregnancy (of subject or partner)
3. An alarming adverse experience

4. Adverse events and/or laboratory abnormalities, which are listed in the trial protocol as critical to safety evaluation and requiring reporting.

f) Suspected Unexpected Serious Adverse Reaction (SUSAR): an adverse reaction which is both serious and unexpected.

g) Suspected Serious Adverse Reaction' (SSAR): An adverse reaction that is classed as serious and which is consistent with the information about the medicinal product listed in the relevant reference documentation. This is either the 'Summary of Product Characteristics'(SmPC) in the case of a licensed product being used within its licensed dosage and indication; or in the IB in case of any IMP or a licensed product being used outside its licensed dosage and indication.

h) Severe: The term severe is often used in clinical environment to describe the intensity of an event or reaction and should not be confused or interchanged with the term serious.

i) Blinding: A procedure in which one or more parties involved in the clinical trial are kept unaware of the trial treatment assigned. Single blinding usually refers to the subjects being unaware and double blinding usually refers to the subject, Investigator and Monitor being unaware of the trial treatment.

j) RSI – Reference Safety Information. This information is used for assessing whether an adverse reaction is expected. Normally this is listed in SmPC/IB

k) SmPC/IB – Summary of product characteristic /Investigator Brochure.

l) USM – Urgent Safety Measure - Where the sponsor and investigator may take appropriate action to protect a research participant from an immediate hazard to their health and safety without prior approval from regulatory and REC committee.

m) MHRA –Medicines and Healthcare Regulatory Agency

n) REC – Research Ethics Committee

o) IDMC – Independent Data Monitoring Committee

p) CTM – Clinical Trial Manager

q) CTC – Clinical Trial Co-ordinator

r) CI – Chief Investigator

s) PI – Principal Investigator

t) CTIMP – Clinical Trial of Investigational Medicinal Product

u) ATMP – Advance Therapy Medicinal Product

4. Responsibilities

The overall responsibility for recording and reporting AE/Rs in a clinical trial of a medicinal product is with the Sponsor of the clinical trial. At GOSH/ICH, the Sponsor is defined as the organisation GOSH: Great Ormond Street Hospital for Children NHS Trust. This responsibility is being usually delegated to the Chief Investigator of the GOSH/ICH Sponsored CTIMP in a Sponsor Agreement.

The CI has overall responsibility for the conduct of the study. The CI must liaise with the sponsor in reporting SUSAR to MHRA and REC.

4.1 – Investigator's responsibilities:

a. PI to report all SAEs and SUSARs within agreed timeline to Sponsor and cc CI.
b. CI to report all SAEs within agreed timelines to Sponsor
c. CI/PI to review all SAEs for casual relationship, seriousness and expectedness
d. CI to report SUSARs within agreed timelines to Sponsor
e. Provide the sponsor with details of all AEs identified in the protocol as critical to the evaluation of safety in timely manner.
f. Assess each event for causality and seriousness
g. Supply any supplementary information upon request by the sponsor

4.2 Sponsor's (Joint R&D Office) responsibilities:

a. Review SAE form and ensure all information is valid.
b. Ensuring all SAEs acknowledged
c. Report any SUSAR to MHRA and REC in collaboration with CI and inform other PI/sites in the trial.
d. Record all SAEs on the safety database
e. Review SAEs expectedness (This might be delegated to CI in some instance as per sponsor and CI agreement)
f. Ongoing safety evaluation of any IMP(s), including trend analysis.
g. Presenting all SAEs in Risk Action Group
h. Encourage to set up Data Monitoring Committee
i. Break treatment code before submitting expedited reports to MHRA and REC.

In addition, all members of the Joint R&D Office who are made aware of any AE/Rs that arise in a clinical trial will be responsible to ensure that the procedure outlined below is adhered to. A panel of medical experts have been set up to support the R&D Clinical Trials Team to review suspected adverse reactions (SARs) that need expedited reporting to the MHRA if required.

For externally sponsored studies - The sponsor shall make arrangements to support the recording, verification, reporting, analysis and management of adverse events. The Principal Investigator will be required to report to the R&D Office promptly of any individual SAEs or concerns regarding the safe conduct of the trial and/or any additional risks to the Trust. All SUSAR reports shall be copied to the R&D department.

5. Procedure

There should be clear information on SAE reporting procedure in the approved protocol. The CI can decide how to record and report adverse events. All adverse events must be recorded and all serious adverse events must be recorded and reported unless protocol specifies exemption. It is recommended that subject confidentiality is maintained at all times.

5.1 Adverse events

All adverse events that occur in trial subjects in a clinical trial from the point of informed consent should be recorded by the Principal Investigator or delegate in the participant's medical record irrespective of IMP being received or not. All adverse events must be assessed for seriousness, causality, expectedness and severity. Each adverse event must be recorded in the CRF. It is also recommended that a central/patient specific adverse event log is maintained for reporting purpose if required.

Non-serious adverse events which may include abnormal laboratory results may be identified as adverse events of interest or important to the evaluation of safety of clinical trial. These must be defined in the protocol and must be recorded and/or reported as per the requirements defined in the protocol.

Clinical trials of licenced IMP which falls in to type A or type B category of risk level defined in the MRC/DH/MHRA paper "Risk-adapted Approaches to the Management of clinical trials of Investigation Medicinal Products" it may be possible to state in the protocol that certain AE do not need to be reported by the investigator to the sponsor in a normal way (subject to MHRA approval). This is particularly applicable to licenced medication where extensive safety data already available.

It is expected that all AEs should be recorded in medical notes and CRF and these must be followed up until resolved.

5.2 Serious Adverse Events (SAE)

All AEs as defined in the protocol must be assessed by the principal investigator or other medically qualified person as per delegation log. The PI or delegate is

responsible for reporting this to the CI/sponsor in required timeframe as specified in the protocol. The PI/investigator will assess for:
Seriousness
Causality
Expectedness (only if delegated to CI)
Also see appendix 2.

5.2.1 Seriousness

An adverse event becomes serious if it:
Results in death
Is life- threatening*
Requires hospitalisation or prolongation of existing inpatient hospitalisation
Is significant disability or incapacity
Is congenital anomaly or birth defect

*Life threatening refers to an event where the participant's life was endangered at the time of the event not an event that could hypothetically cause death if it had been more severe.

5.2.2 Causality

Adverse events should be assessed for causality (relatedness) of the event to the IMP(s). The definition below can be used:

Relationship	Description
Not related	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the IMP). There is another reasonable explanation for the event e.g. patient clinical condition or other concomitant treatment
Possible*	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of IMP).However the influence of other factors may have contributed to the event (e.g. the patient clinical condition, other concomitant treatment)
Probable*	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely*	There is a clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

*If the AE is serious and causal relationship is probable, possible and definite then the event is considered as Serious Adverse Reaction. All SAR must be assessed for expectedness.

If the serious event is unlikely or not related, it is recommended that an explanation is provided on the SAE form where appropriate. There is no need to assess these events for expectedness.

If an event is “not assessable”, it is assumed that it is related to IMP until follow-up information is received.

5.2.3 Expectedness

All SAR which are considered probably, possibly and definitely must be assessed for expectedness. The assessment is made against the approved Reference Safety Information which is clearly stated in the protocol (examples, IB section or SmPC section 4.8). To be categorised as expected, the reaction must be clearly listed in the RSI. Events which are more specific or more severe than those listed in the RSI qualify as unexpected. All unexpected SAR, must be reported as SUSAR to MHRA and REC.

It is recommended that any SAR which are exempt from reporting because of various reasons must be listed in the RSI and clearly defined in the currently approved protocol. These type of events should still be reported to the sponsor within 24 hours.

Expectedness assessment is sponsor’s responsibility unless delegated and agreed with Chief Investigator.

5.3 Notification of SAE to GOSH R&D Office

5.3.1 Initial reporting

The principal investigator must assess all SAEs and reported to the sponsor within 24 hours of becoming aware of the event. SAE form provided by GOSH R&D form should be used for all GOSH sponsored studies OR sponsor’s provided SAE form for hosted studies. The initial report can be made verbally or in writing but must follow a full written report as soon as possible.

The minimum information provided in the initial report:

- Participant trial number, initials, date of birth, Gender
- The suspected IMP
- The reporting site (site number/name)
- The name of the serious event
- Onset date of event
- Causality assessment

The completed SAE form should be emailed/ via e-CRF to R&D Clinical Trial team at CTIMP.safety@gosh.nhs.uk and Chief Investigator who will review the form and either ask for additional information or acknowledge the receipt of the form within 3 days.

For GOSH sponsored trials, If IMP is provided by a pharma company/external organization, it is expected that SAE must be reported to them as per clinical trial agreement.

If GOSH is not the sponsor, report the serious adverse event to the sponsor and forward a copy to the R&D Department.

5.3.2 Follow up reports

All SAE reports which are ongoing must be followed up until full resolution. The follow up form should contain previous details and new information and signed by a delegated qualified medical doctor.

The PI is required to assess causality again on the follow up form. If the PI has change of opinion on causality after considering the additional follow-up information, the CI/sponsor then assess expectedness.

File the original signed SAE form in the safety section of the Investigator Site File.

R&D clinical trial team will review the SAE database on a regular basis to assess the status of all the unresolved SAEs to ensure they are followed by the trial team.

5.4 Reviewing and Reporting procedures at R&D

5.4.1 R&D office review/Sponsor's review – See appendix 1

The generic inbox CTIMP.safety@gosh.nhs.uk is checked on a daily basis. The Clinical Trials Coordinator is primarily responsible for managing the safety inbox. In the absence of the Clinical Trials Coordinator, the Clinical Trials Manager or Head of Governance, Contracts and Clinical Trials will be responsible for checking.

These reports can arrive in different formats: either on the SAE/R form, pregnancy form and 'other important safety issue' form. The hosted clinical trial reports are sent on the Sponsor's safety reporting template.

a) The reported SAE is quality control checked by ensuring it is reported within 24 hours of study team made aware of SAE and all fields reported are correct and complete.

b) The SAE form will be reviewed for completeness and assessment against the RSI to determine if the event constitute a SUSAR. The R&D office can not overrule the investigator's decision and any re-classification must notified to PI/CI. For hosted studies, the sponsor will be responsible for reviewing expectedness.

c) If any discrepancy arises this will be discussed with PI and/or CI as soon as possible to ensure reporting timelines are met. Where the CI opinion differs from that of PI, the PI's assessment will prevail, except where CI considers the event more serious. The sponsor will review both statements and document sponsor's decision.

d) If the expectedness determine that reported SAR is a SUSAR, follow the SUSAR reporting procedure section 5.4.2 below.

e) All SAEs will be recorded on the SAE database and event number is assigned. The same event number will be used for all follow up and final report correspondence.

f) For GOSH sponsored studies the reviewer will complete the "For sponsor/R&D office use only" section with all details and return to the study team as an acknowledgment.

g) The SAEs form will be filed in the corresponding study folder at "I" drive/electronic sponsor file

For Hosted CTIMPs

Upon receipt of serious adverse events from hosted CTIMPs at GOSH, the R&D Clinical Trials team will record the event on the controlled GOSH safety database on a excel sheet under Hosted CTIMPs tab. R&D office will send an acknowledgement of the receipt of the serious adverse event t by email to the reporting person. The actual form will be kept in in the CTIMP.safety@gosh.nhs.uk mail box only.

For GOSH sponsored CTIMPs external sites

For externally GOSH sponsored studies, the study team will follow the SAE reporting procedure in the protocol and report all SAEs to GOSH R&D accordingly. The site study team to follow points 5.3 of this procedure.

5.4.2 SUSAR recording and reporting

It is a legislative requirement that sponsor must report all relevant information about a SUSAR to competent authority in UK/EU and relevant REC in UK or equivalent if multi centre trial.

Fatal/Life threatening SUSARs must be reported to the MHRA within 7 days of the Sponsor (Joint R&D Office) being aware of the SUSAR. Non-fatal/non-life threatening SUSARs and safety issues need to be sent to the MHRA within 15 days of being aware of the report. Follow-up reports need to be sent to the MHRA within 8 days of the initial report.

Day 0 for reporting is when sponsor receive the SAE form.

The clinical trial coordinator will keep all relevant correspondence in the study folder on shared drive and/or electronic database. All SUSARs will be recorded on the safety database spreadsheet.

R&D Clinical Trials team may contact the Safety Panel to review suspected adverse reactions (SARs) that need expedited reporting to the competent authority, the Medicines and Healthcare Products Regulatory Agency (MHRA) if required.. These events need to be assessed carefully and proficiently by individuals with medical expertise. The committee can discuss cases virtually through emails if any safety events are reported

GOSH sponsored external sites and GOSH Hosted trials:

All SUSARs must be discussed with the sponsor first and the trial team should inform GOSH R&D for any SUSARs reported.

5.4.2.1 Electronic reporting of SUSAR to MHRA

SUSARs are reported to the MHRA electronically through e-SUSAR reporting. All the GOSH Sponsored CTIMP studies will be listed on e-SUSAR website by Clinical Trials Manager as soon as study has the relevant approvals. The e-SUSAR system administrators are CTM, CTC, Head of Governance at R&D who have access to GOSH trials portfolio on e-SUSAR website. It is expected that the R&D clinical trial team should have all details to report SUSAR, alternatively this task can be delegated to CI or dedicated trial team.

To report a SUSAR to the MHRA electronically open the https://esusar.mhra.gov.uk web link and log on using the e-mail address and password. Each user will only be given permission to access only trials they have responsible for. The trial details will be automatically populated in the report by first selecting the trial for which the report is to be made. Follow the series of steps to complete the report. Download the report at the end in PDF format and file in the Pharmacovigilance section of the Sponsor's R&D File on electronic TMF and/or shared drive. The PDF report shall be forwarded to the main REC along with safety report form.. In addition to this, the e-SUSAR website can be used to maintain a record of reports that have been submitted for each of the clinical trials.

Complete all fields in the report where possible. In the event of delay in receiving missing data, submit the report to MHRA with the missing data to meet the time line. Continuously follow up with the site for additional information and the missing data should be included in the follow-up report once available.

5.4.2.2 -Unblinding in double blinded trials

In double blind trials, unblinding should be done before reporting SUSAR. The protocol should have unblinding process.

For double blinded CTIMPs, the Sponsor needs to ensure that procedures are in place to maintain the blind for the investigator/s and other persons responsible for data-analysis and interpretation of results. Usually, Pharmacy keeps the un-blinding information in the CTIMP pharmacy file, and is specific for each double blinded CTIMP

GOSH Pharmacy procedures for un-blinding will be followed if this becomes necessary in relation to SUSAR reporting. Blinding must be broken by the Pharmacy department according to their procedure and/or study protocol and report back to the Investigator in case of clinical emergencies who will determine the causality and relatedness of the event. It is the Investigator's responsibility to report any SAE/SAR/SUSAR to Sponsor. In case regulatory reporting in non-clinical emergency situations where subject's safety is not at risk, Investigator should complete the SAE form for causality, relatedness and expectedness of SAE to study treatment without being un-blinded and Pharmacy to provide un-blinded information to the Joint R&D Office who will decide if a SAE is SAR or SUSAR in conjunction with Investigator's initial assessment of SAE with IB/SmPC and/or study protocol.

SUSAR reported for subjects receiving placebo will not be reported to MHRA or REC unless the opinion of the CI/PI or Sponsor for the event differs.

5.4.2.3 – How to inform reported SUSAR to other investigators in multi-centre trials

The Sponsor is responsible to inform all Investigators concerned at all sites of any findings that could adversely affect the safety of the study subjects. The Sponsor in liaison with the Chief Investigator can determine how, when and in which format this will be done. An acknowledgement is expected from each PI for receipt of report.

5.5 Safety reporting of hosted studies

Clinical trial study teams at GOSH must report all hosted studies SAE to R&D office on the sponsor's provided SAE form. The GOSHR&D will review these form and add event on the safety database and assign an event number. The event should be followed until resolved.

Any SUSAR reported to GOSH as a site must be recorded on the Safety database at R&D.
Any SUSAR occurring in hosted studies at GOSH site must be reported to R&D office.

5.6 Pregnancy reporting

The pregnancy criteria must be specified in the protocol. If a study patient or the partner of a study patient, falls pregnant when participating in a trial, the patient should be withdrawn unless CI/PI decide that the risk is not clinically significant.
R&D form 'Pregnancy report form' should be completed and reported to the sponsor. The pregnancy should be followed until the pregnancy end with either live birth, termination or spontaneous abortion. The final outcome should be recorded on the form.

5.7 ATMP long term follow up safety reporting

There is a requirement for long term safety follow up in the ATMP trials. The investigator should include the long term safety follow up in the protocol or any other MHRA approved document for e.g cover letter or safety plan. It is normally expected that long term safety reporting is followed for up to 15 years based on the risk assessment of the trial either in the same protocol or in a separate protocol. The protocol should also include the types of events need reporting.

It is also possible to define some SAEs in the protocol that do not require reporting to the sponsor even though they meet SAE criteria which may include conditioning regimen and/or ATMP.

5.8 Urgent Safety Measure

The chief investigator or principal investigator have authority to deviate from the protocol if there is an immediate safety risk to participants where continuous protocol follow up would harm health and safety of subjects.

Once a potential hazard is identified, the PI must contact sponsor immediately with full decision making process that lead to the implementation of urgent safety measure. The CI must also contact the CTU at MHRA and discuss the issue with medical assessor immediately.

The investigator does not need to wait for competent authority approval before implementing urgent safety measures; however they must inform the MHRA, REC and sponsor within 3 calendar days of implementation.
The sponsor must submit a substantial amendment as USM within 3 calendar days detailing measures taken, the reason for them and supporting documents.
For multi site trial, sponsor will inform all sites about the USM.

For hosted studies, the PI must inform the sponsor within 3 days; the external sponsor should submit the amendment to MHRA and REC.

5.9 Any other safety events

A report on 'any other important safety issue () deals with safety issues that need to be reported to the MHRA in an expedited manner. The Clinical Trials Directive has not stated what timeframe this should take. In light of this, these reports should be dealt with in a timely manner by the member of clinical trials team and sent to the MHRA as soon as possible and is practical.

5.10 Independent Data Monitoring Committee and ongoing safety evaluation

It is recommended that an IDMC is appointed to oversight safety of the trial and review safety data regularly through the trial and when necessary recommend to the sponsor whether to continue or modify or terminate the trial. Any significant recommendation made by IDMC should be actioned and notify to the MHRA and REC. It is up to the sponsor to act on IDMC recommendations.

5.11 Any changes to RSI is a substantial amendment to MHRA and REC

The CI or IMP provider must inform the sponsor for any changes to RSI. The CI or delegated team member/sponsor should review RSI at least annually using the RSI review form. If there are no changes to RSI, update the document once the review is fully signed. Record this review in the amendment log as well.

5.12 Trend analysis

A trend analysis of GOSH sponsored trial SAEs reported to R&D will be performed every 6 months by the R&D clinical trial team, unless concerns are raised by the investigator or R&D office about the type and number of SAEs. Any significant signals will be discussed with PI/CI.

Additionally, the CI in conjunction with the pharmaceutical company providing the IMP for the study may conduct regular trend analysis and signal detection to determine the continued safety of the drug within the study. The trend analysis report is stored in pharmacovigilance folder at R&D office shared drive i.e. I Drive.

5.13 – Outsourcing safety reporting to third parties

If any pharmacovigilance activities are delegated to third parties such as CRO or CTU this must be covered under the clinical trial agreement. If there is a significant difference to our normal reporting process, the process of safety reporting to the sponsor must be outline in the protocol/safety manual or study manual.

When the safety reporting task is delegated to a third party the 24 hours timeline starts when the third party is made aware of the event. The delegated third party may report all SAE in one of the following format:

a. Each individual SAE
b. Access to a database where all SAEs are recorded
c. Provide a weekly or monthly report with all SAEs

5.14 Governance review of reported SAE/SARs

The Clinical Trials Manager compiles a list of all received SAE/SARs which have occurred to subjects in GOSH Sponsored and other hosted CTIMPs every month and will report these events to the Research and Innovation Risk Action Group Meeting to discuss the serious incidents across the division. The Committee will discuss the occurred events and their outcomes, and decide if further investigations are required.

6. Associated documents and SOPs*

SAE reporting form
Pregnancy reporting form
Other Important safety issues reporting form
RSI assessment form
Reference to Amendment SOP for GOSH sponsored and hosted studies
Reference to DSUR and APR report
Pharmacy unblinding SOP
Monitoring SOP for IDMC

7. References

a) Directive 2001/20/Ec Of The European Parliament And Of The Council. (2001). [ebook] Official Journal of the European Communities. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF

b) *The Medicines for Human Use (Clinical Trials) Regulations 2004*. [online] Available at: https://www.legislation.gov.uk/uksi/2004/1031/part/5/made

c) Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use. https://eudravigilance.ema.europa.eu/human/docs/CT3.pdf

d) MHRA GCP guide (Grey Guide)

e) NHS R&D forum website https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf

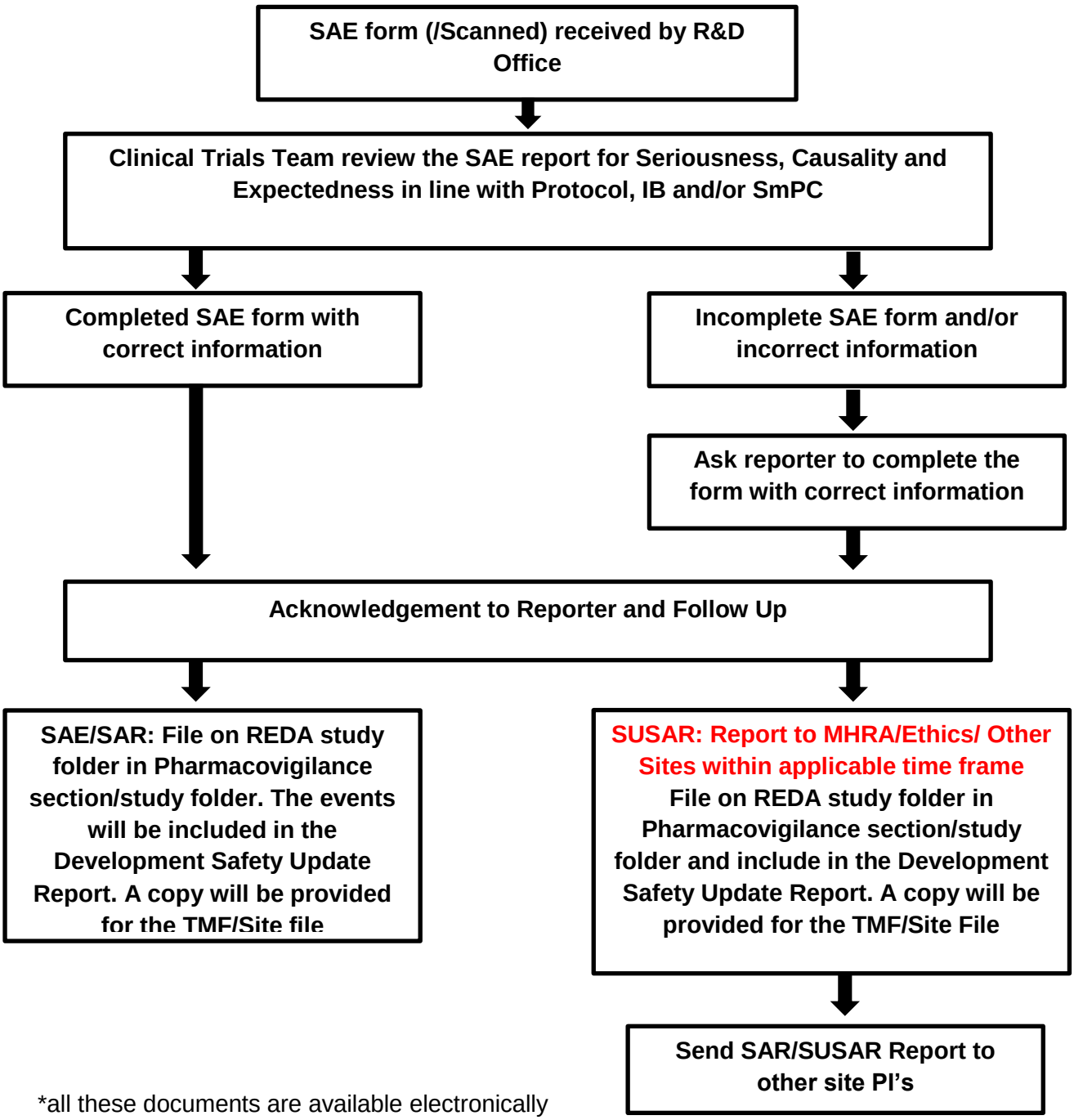
f) https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

g) https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/atmp_guidelines_en.pdf

8. Appendices

APPENDIX 1

R&D Office procedure Flow chart for receiving and reporting safety forms:



*all these documents are available electronically

Appendix 2 – Safety reporting flow chart