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JOINT RESEARCH AND DEVELOPMENT OFFICE

Somers Clinical Research Facility

Recording and Reporting of AE/Rs that arise during Clinical Trials of Medicinal Products for human use

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Revision History			
Previous version	Comments	Reviewed by	Date archived
GOSH ICH/05/SO5/07	Amendment in line with the changes made to AE/R recording, removal of F43 and other minor clarifications	Emma Pendleton	09 August 2016

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GOSH ICH/05/SO5/06	Amendment in line with the major changes made to request SAEs from externally sponsored studies and the new email address for safety reporting	Emma Pendleton	04 September 2015
GOSH ICH/ 05/S05/05	Change in R&D department structure and staff and to minor changes to the format and content of OP	Dr Lorna Gibson	14 August 2013
GOSH ICH/05/SO5/04	Deletion/correction of telephone and fax number as requested in Independent GCP audit report	S Klager	26/01/2012
GOSH ICH/05/SO5/03	Amendment in line with the major changes made to OP 43 and the reporting forms	Dr Sabine Klager	25 FEB 2010
GOSH ICH/05/SO5/02	To make the procedure more clear for the investigator. In this first 11 months of using version 1 there were some misinterpretations. More definitions have been added. In addition, the responsibility of reporting SUSARs and other important safety issues has been removed from the PI and retained by the sponsor.	Emma Pendleton	30 July 2008
GOSH ICH/05/SO5/01	First Version	Prof D. Goldblatt	3rd April 2006

1. Scope /Background

This SOP applies to the procedures for the adequate recording, evaluation and reporting of AEs, ARs, SAEs, SARs and SUSARs in clinical trials of investigational medicinal products where GOSH/ICH is acting as a sponsor or as a hosting organisation. The safety reporting procedure applies to both single site and multi-site studies. It will further outline the Investigator's and sponsor's responsibilities to ensure oversight and management of pharmacovigilance systems in compliance to the UK Regulations. Annual Safety Reporting is not the scope of this SOP.

2. Legal basis

The legal basis for this OP is Council Directive 2001/20/EC[1] (Article 15). This Directive (published in 2001) is also known as the Clinical Trials Directive (CTD) and relates to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use. In the UK the CTD was transposed into law by the 'The Medicines for Human use (Clinical Trials) Regulations 2004: SI 2004 No 1031[2]. The UK Regulations took effect on 1 May 2004 and then further amendments.

Directive 2001/20/EC[1] published in 2001 (also known as Clinical Trials Directive: CTD) which establishes specific provisions regarding the conduct of clinical trials, in particular relating to the implementation of good clinical practice (GCP). In line with the CTD, the EU Commission published detailed guidance on how to collect, verify and present adverse events/reactions reports[2]. Articles 16 and 17 of the CTD outline the legal obligations for both the investigator and sponsor for the recording and reporting of all adverse events and reactions, be them expected, unexpected, serious, or critical to the safety evaluation of the trial. In the UK, Articles 16 and 17 of the Directive are implemented by Regulations 32, 33, 34 and 35 which constitute the Pharmacovigilance Part (Part 5) of Statutory Instrument 2004 No. 1031: 'The Medicines for Human Use (Clinical Trials) Regulations 2004' for the UK[3].

3. Purpose

The purpose of this SOP is to inform investigators – namely the Chief Investigator (CI) and Principal Investigator/s (PI) - on how to record and report adverse events/reactions (AE/Rs) that arise in clinical trials of a medicinal product (CTIMP).

4. Definitions

The definitions of Directive 2001/20/EC Article 2 are applicable throughout this document. These are as follows:

(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 (IMP) 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 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,
- a congenital anomaly or birth defect;
- other important medical events.

(e) Other important medical events are the 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 information about the medical 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 'Investigator's Brochure' (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.

5. Personnel responsible

The responsibilities of an investigator in relation to the notification of Adverse Events are set out in Article 16 of the Clinical Trials Directive. In summary, Article 16 places an obligation on the investigator to report all serious adverse events/reactions (expected or unexpected) to the sponsor of the trial. The CI and the individual investigators within a trial team at the site are responsible for keeping records of all adverse events that occur in trial subjects as per protocol.

The CI/PI may further delegate this duty to the investigators within the trial team. This delegation must be performed on whether trial members are qualified to perform the delegated task and this must be authorised in the delegation log.

6. Procedure

6.1 Evaluation of Adverse events/Reactions

The evaluation of the seriousness, causality and expectedness of adverse events is best done by the delegated member/s of the trials team closest to the trial subject, the Chief/Principal Investigator of the trial and/or other independent medical expertise. The Sponsor of the trial evaluates the expectedness of the event in line with available reference safety information like IB, Summary of Product Characteristics and study protocol. It might also be necessary to evaluate adverse events by the Data Safety Monitoring Board and/or Trial Steering Committee.

6.2 Recording Adverse events/Reactions

(a). Which are the AE/Rs you need to keep a record of?

According to Directive 2001/20/EC Article 16 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol. These may include non-serious, serious, expected and unexpected and also adverse events and/or laboratory abnormalities identified in the protocol as being critical to safety evaluations.

(b). Where do you record AE/Rs?

Investigator and/or suitably delegated trial team member will need to record all the Adverse Events/Reactions. According to the risk level of the study(MHRA Risk Adapted Approach), this can be reported in the medical records or CRF as below. The reporting procedures for the AE/Rs should be detailed in the study protocol. For GOSH sponsored CTIMPs, below guidelines are suggested to record the adverse events based on the trial's risk ratio.

Type A (No higher than the risk of standard medical care)

For Type A trial, AE/Rs can be recorded in the medical notes. There is no need to record all the AE/Rs in the CRF for these studies. However, if AE/Rs need to be included in the endpoint analysis then this can also be recorded in the CRF. But this should be specified in the protocol.

Type B(Somewhat higher than the risk of standard medical care)

Adverse Reactions (ARs- AEs related to the study drug) should be reported in the Case Report Form. All other Adverse Events not related to the study drug will need to be recorded in the patient's medical notes and/or source document.

Type C (Markedly higher than the risk of standard medical care)

All the AEs, regardless of their relatedness to the drug should be recorded in the Case Report Form and the Medical Records.

6.3 Reporting AE/Rs to your sponsor/hosting organisation R&D

6.3.1 Which are the AE/Rs you need to report?

In case the event is serious;

For GOSH/ICH sponsored research the investigator or suitably delegated trial team member need to complete **Form 44** – the Serious Adverse Event/Reaction Report Form (GOSH ICH/08/F44).

For **externally sponsored trials** investigators may provide a faxed copy of the **trial specific reporting form.**

When completing the SAE/R report form the subject confidentiality must be respected at all times. To comply with this requirement, you should never use hospital numbers or patient names, but use the patient trial number instead. This number is a code that will help your sponsor identify the trial and the subject number.

The investigator or suitably delegated trial team member need to report **all serious** events and reactions to your sponsor, expected and unexpected.

For GOSH Sponsored CTIMPs, the investigator or suitably delegated trial team member also need to report to the Joint GOSH/ICH R&D office all other safety issues outlined in section 7 above, using Form 20 identified as GOSH ICH/06/F20 (F20).

Article 16(4) of the Directive states that the Regulatory Authorities, such as the MHRA, expect your sponsor to keep a record of all SAE/Rs, and to make these reports available on request.

6.3.2 SAEs that do not need to be reported to your sponsor and hosting organisation.

Investigators are not required to report SAEs, which are listed as "not requiring reporting" in the CTIMP protocol.

Note: Investigators are still expected to keep a record of these events in the CRF.

6.3.3 When do you report SAE/Rs to the Joint GOSH/ICH R&D Office

The investigator or suitably delegated trial team member need to send the SAE/R form to the GOSH/ICH R&D office by fax or by mail within 24 hours of the awareness of the event, or within the timeframes specified for SAEs and SARs in your CTIMP protocol.

- Report any **expected** SAE/Rs to R&D/your sponsor within the time-frame specified in the protocol.

- Report any adverse events and/or laboratory abnormality that you would consider as critical to safety evaluations within the time-frame specified in the full protocol.

- Report all **SUSARs immediately as is practical** to the GOSH/ICH R&D/your sponsor (Article 16 (1) of the Directive requires the PI to report immediately). (This will be called the initial report).

Note: For the initial report of a SUSAR you might not yet have all the details that are requested in the form. In this case, the investigator will need to send a Follow-Up report (F44). The Follow-Up report needs to be reported as soon as all the relevant information is available, but no later than **8 days** of the initial report.

6.4 Other Safety Events

Other safety issues might arise during the course of a Clinical Trial that uses an Investigational Medicinal Product (CTIMP). These are defined as follows:

- SUSARs which are identified by spontaneous reports or a publication
- Safety issues where they might materially **alter** the current benefit-risk assessment of an IMP
- Safety issues that would be sufficient to consider changes in the IMP administration
- Safety issues that would be sufficient to consider changes in the overall conduct of the trial.
- SUSARs which are identified by spontaneous reports or a publication
- Recommendations of the Data Monitoring and Safety Committee, relevant for the safety of the trial subjects.

Examples of such safety issues might include:

- Single case reports of an expected serious adverse reaction with an unexpected outcome (e.g. a fatal outcome);

- An increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the subject has completed a clinical trial;
- A new event relating to the conduct or the development of the IMP likely to affect the safety of the subjects eg:
    - A serious event which could be associated with the **trial procedures** and which could modify the conduct of the clinical trial
    - lack of efficacy of an IMP used for the treatment of a life-threatening disease;
    - a major safety finding from a newly completed animal study.

Investigators should report all **other safety issues** described in section 6.4 above **immediately or as soon as is practical** to R&D/your sponsor.

6.5 How to report to the Joint R&D Office

(a). Reporting SUSARS,SAEs and other safety issues that require expedited (immediate) reporting

To report SAEs, SUSARs and other important safety issues as outlined in section 7 above, you will need to email a copy of the signed form to the GOSH/ICH R&D on CTIMP.safety@gosh.nhs.uk or alternatively you can fax a copy of the report

The fax number for the joint GOSH/ICH R&D office is: 020 7905 2201.

When sending a fax, you **need to call the office** to inform the relevant member of staff to expect to receive a safety report.

DO NOT USE the INTERNAL Mail for sending any safety events that need expedited reporting (The internal mail is slow and unreliable).

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

6.6 What to expect after sending a report to R&D office of GOSH/ICH

The R&D office will **always** acknowledge receipt of the report within 3 working days by sending the reporter of the report an email. Failing receipt of this acknowledgement, please contact the R&D office immediately on ext 2346 (direct number: 020 7905 2346).

6.7 Pregnancy Reporting Form

This form is identified as Form 45 (GOSH ICH/08/F45)

Any pregnancy that occurs in a female trial subject/ or female partner of male trial subject during the clinical trial should be followed up to termination or term. Pregnancy data provides vital data to the overall knowledge concerning the IMP. There might be special circumstances, that it might be necessary to monitor the development of the new-born, or to monitor the pregnancy of a woman whose male partner is the trial subject.

6.8 Reporting to the MHRA

There is no need to report SAE/Rs to MHRA but SUSAR should be reported and this is your Sponsor's responsibility. MHRA's electronic SUSAR (eSUSAR) reporting form is available for use by all sponsors and institutions responsible for safety reporting in clinical trials.

The reporting timeline for fatal or life-threatening SUSARs is as soon as possible, but no later than 7 days after the trials team is first aware of the reaction. Any additional relevant information must be sent within 8 days of the report. For non-fatal or non-life-threatening SUSARs, the event should be reported as soon as possible but no later than 15 days after the trials team is first aware of the reaction.

For GOSH sponsored CTIMPs, the Clinical Trials Manager will make specific arrangements with the CIs and PIs for timely reporting to the MHRA. For externally sponsored studies, the relevant sponsor shall be making arrangements for the reporting.

6.9 Reporting to Other Investigators

Reporting of significant safety events to other PIs (in a multi-centre trial) is a Sponsor responsibility. For trials sponsored by GOSH, this responsibility is delegated to the Chief/Principal Investigator. Investigator and/or trial team member will also need to inform the GOSH/ICH R&D office that you have done this.

For externally sponsored studies, the relevant sponsor shall be making arrangements for the reporting.

6.10 Reporting To Ethics

There is no need to report SAE/Rs to ethics but SUSAR should be reported to the relevant ethics committee. For trials sponsored by GOSH, the responsibility of reporting SUSAR to the Ethics Committee is delegated to the chief/principal investigator. You will also need to inform the GOSH/ICH R&D office that you have done this.

For externally sponsored studies, the relevant sponsor shall be making arrangements for the reporting.

6.11 Confidentiality And Data Protection of Trial Subjects

During recording and reporting of any AE/R subject confidentiality must be respected at all times according to the Data Protection Act 1998. During the trial the PI will keep a 'Subject Identification Code List'. This is a confidential list of names of all subjects allocated trial numbers on enrolling in the trial. This list will be kept in the Trial Master File (TMF).

6.12 Unblinding Treatment Codes

This is only applicable to the assessment of causality and expectedness of serious adverse event, which has occurred in trial subjects who are participating in a blinded trial.

In case of a blinded study, the case is assessed for seriousness, expectedness and causal relationship assuming that the tested investigational medicinal product caused the reaction. If the case appears to be a SUSAR, then the blinding should be broken.

GOSH Pharmacy procedures for un-blinding will be followed if this becomes necessary in relation to SUSAR reporting. It is important that the blind is being broken only for that specific patient. Blinding must be broken by the Pharmacy Department according to their procedure and/or study protocol and report back to 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 of non-clinical emergency situations where subject's safety is not at risk, the Investigator should complete the SAE form F44 for causality, relatedness and expectedness of SAE to study treatment without being un-blinded and Pharmacy to provide un-blinded information to Joint R&D Office who will make judgement if an SAE is SAR or SUSAR in conjunction with Investigator's initial assessment of SAE with IB/SmPC and/or study protocol. For multi-centre trials, the sponsor will inform the other site PIs.

7. Associated documents and SOPs*

Document Name	File Path	Author
F20: Report for Other Important Safety Issues	http://www.gosh.nhs.uk/research-and-innovation/information-researchers/joint-rd-office/clinical-trials/standard-operating-procedures-sops-and-forms	Joint R&D Office Clinical Trials Team
F44:SAE/R Reporting Form	http://www.gosh.nhs.uk/research-and-innovation/information-researchers/joint-rd-office/clinical-trials/standard-operating-procedures-sops-and-forms	Joint R&D Office Clinical Trials Team
F45:Pregnancy Reporting Form	http://www.gosh.nhs.uk/research-and-innovation/information-researchers/joint-rd-office/clinical-trials/standard-operating-procedures-sops-and-forms	Joint R&D Office Clinical Trials Team

8. Recommendations

NA

9. References

Detailed guidance on the collection, verification, and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use. Révision 1 April 2004. EU Commission, Brussels ENTR/ CT 3.

DIRECTIVE 2001/20/EC of the European Parliament and of The Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities; 1st May 2001, L121/34

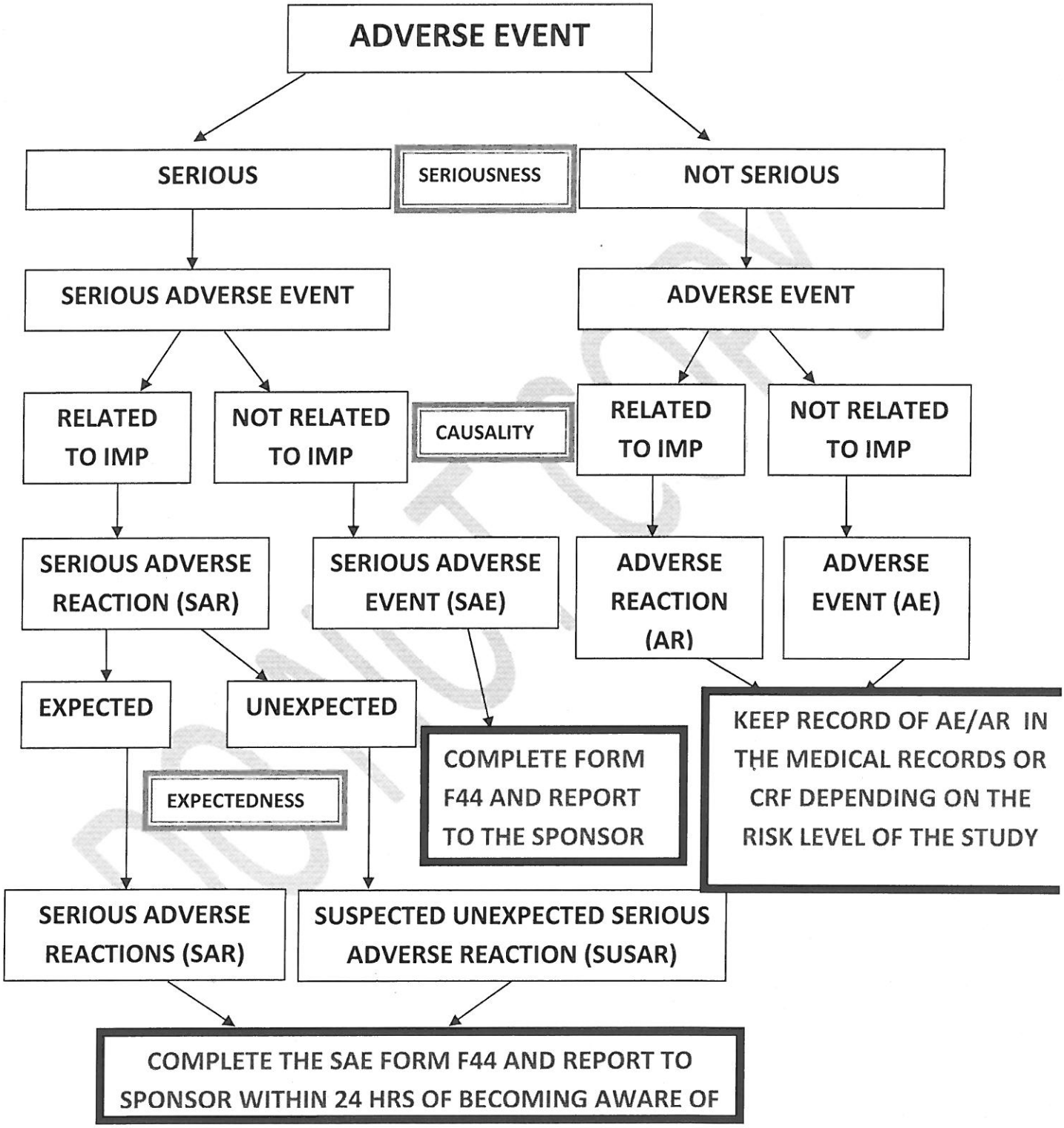
MHRA Risk Adapted Approach ;
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf

Statutory Instrument 2004 No. 1031. The Medicines for Human Use (Clinical Trials) Regulations 2004. The Stationery Office Limited. ISBN 0110490487.

10. Appendices

*all these documents are available electronically

APPENDIX 1: Safety Reporting Flowchart


ADVERSE EVENT
SERIOUS
SERIOUSNESS
NOT SERIOUS
SERIOUS ADVERSE EVENT
ADVERSE EVENT
RELATED TO IMP
NOT RELATED TO IMP
CAUSALITY
RELATED TO IMP
NOT RELATED TO IMP
SERIOUS ADVERSE REACTION (SAR)
SERIOUS ADVERSE EVENT (SAE)
ADVERSE REACTION (AR)
ADVERSE EVENT (AE)
EXPECTED
UNEXPECTED
EXPECTEDNESS
COMPLETE FORM F44 AND REPORT TO THE SPONSOR
KEEP RECORD OF AE/AR IN THE MEDICAL RECORDS OR CRF DEPENDING ON THE RISK LEVEL OF THE STUDY
SERIOUS ADVERSE REACTIONS (SAR)
SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR)
COMPLETE THE SAE FORM F44 AND REPORT TO SPONSOR WITHIN 24 HRS OF BECOMING AWARE OF