

MRC/DH joint project

Work stream 6: Pharmacovigilance

1.0 Introduction.....	2
1.1 Background	2
1.2 Definitions	3
2.0 Definition of Sponsor for Pharmacovigilance	4
3.0 General Considerations	5
4.0 Assessment of Adverse Events	6
4.1. Assessment of Seriousness	6
4.2 Assessment of Causality	6
4.3 Assessment of Expectedness	7
4.4 Assessment of Adverse Events: Responsibilities	7
4.5 Assessment of Adverse Events in Blinded Trials.....	8
5.0 Adverse Events: - Sponsor Responsibilities.....	9
5.1 Expedited Reporting to Regulatory Authorities.....	9
5.1.1 How to report: SUSARs.....	10
5.1.2 Format of an expedited SUSAR report:.....	10
5.1.3 Format of the reports of other important safety issues	11
5.2 Expedited Reporting to Ethics Committees	11
5.3 Quarterly Safety Reports to Ethics Committees	11
5.4 Annual Safety Reports	11
5.5 Informing Investigators	12
5.6 Reporting of Safety Issues Following Completion of the Clinical Trial in the European Community.....	13
6.0 Clinical Trials in Third Countries	13
7.0 Role of the DMC.....	13
8.0 Patient Safety Incidents	13
8.1 Notifying NHS Trusts – Investigator Responsibilities	14
8.2 Reporting to the National Patient Safety Agency (NPSA) - Trust Responsibilities	14
9.0 Glossary of terms	14
Appendix 1: Individuals and organisations involved in pharmacovigilance.....	16
Appendix 2: Data recording and notification of non-serious adverse events	18
Appendix 3: Serious Adverse Events and Reactions that may not Require Immediate Notification to Sponsor	20

1.0 Introduction

This document describes good practice and how to comply with in the recording and processing of adverse events in clinical trials that assess the efficacy or safety of medicinal products. However, the principles may be applied to trials of other forms of intervention.

The UK Regulations require that all trials within their scope adhere to the principles of GCP. The MHRA accepts in principle that a risk-based approach to trial management and monitoring is appropriate. This includes the management of pharmacovigilance.

For each clinical trial, a risk assessment should generally be undertaken at the protocol development stage. This may be used to plan the details of the approach to pharmacovigilance taken for the trial. These plans should be documented, together with the risk assessment, so that the management strategy is both transparent and justified.

For further information on risk assessment can be found in the Joint Project document, [Clinical Trial Risk Assessment](#).

The language used in this document reflects that used in the UK regulations and the supporting EU guidance documents.

1.1 Background

The EU Clinical Trials Directive (2001/20/EC) was published on the 4th April 2001. The Medicines for Human Use (Clinical Trials) Regulations 2004/1031 transposed this EU Directive into UK law on 1st May 2004. The Medicines for Human Use (Clinical Trials) Amendment Regulations (SI 2006/1928) came into force on 29 August 2006. The Amendment Regulations principally implement EU Directive 2005/28/EC (the Good Clinical Practice (GCP) Directive) by amending the 2004 Regulations. The Medicines for Human Use (Clinical Trials) Regulations 2004 together with the 2006 amendment will be referred to as the Regulations in the rest of this document. The Regulations set out the legal requirements for pharmacovigilance in clinical trials involving UK participants that evaluate medicines.

The Regulations cover:

- Definitions of adverse events,
- The responsibilities of investigators for recording of adverse events and the notification of adverse events to sponsors
- The responsibilities of sponsors for reporting to regulatory authorities and RECs, including expedited reports of SUSARs and regular Safety Reports.

To comply with the Regulations, those taking on pharmacovigilance responsibilities must ensure that the necessary quality standards are observed in case documentation, data collection, validation, evaluation, archiving and reporting of adverse events in the clinical trial. This includes devising Standard Operating Procedures (SOPs) or equivalent written policies/guidelines.

In addition to the Clinical Trials Directive, the European Commission has issued guidance notes on the collection, verification and presentation of adverse reaction

reports (ENTR/CT3 Revision 2 April 2006)¹. Their advice has been taken into account in this document. COREC (Central Office for NHS Research Ethics Committees) has also issued guidance concerning the requirements for Safety Reporting to UK ethics committees². A useful summary can be found at:

[http://www.corec.org.uk/applicants/help/docs/Safety_and_Progress_Reports_Table_\(CTIMPs\).doc](http://www.corec.org.uk/applicants/help/docs/Safety_and_Progress_Reports_Table_(CTIMPs).doc)

1.2 Definitions

Directive 2001/20/EC, Article 2, lists definitions of terms for use across the EU. These definitions are also given in Annex 1 of the EC Guidance document ENTR/CT3 Revision 2 and in the Regulations.

Term	Definition
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 <i>Comment:</i> An adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease in any subject in a clinical trial (including those in an untreated control group), whether or not considered related to the investigational medicinal product.
Adverse Reaction (AR)	Any untoward and unintended responses to an investigational medicinal product related to any dose administered <i>Comment:</i> All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression “reasonable causal relationship” means to convey, in general, that there is evidence or argument to suggest a causal relationship.
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 unapproved investigational product or Summary of Product Characteristics (SmPC) for an authorised product) <i>Comment:</i> When the outcome of the adverse reaction is not consistent with the applicable product information, this adverse reaction should be considered as unexpected.

¹ ‘Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use. April 2006. Revision 2’ Available at: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2006/04_2006/susar_rev2_2006_04_11.pdf#search=%22entr%20ct3%20April%202006%22

² This can be found at: <http://www.corec.org.uk/applicants/apply/safety.htm>

<p>Definition of Seriousness: Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)</p>	<p>Any AE, AR or UAR that at any dose:</p> <ul style="list-style-type: none"> ▪ results in death ▪ is life-threatening* ▪ requires hospitalisation or prolongation of existing hospitalisation ▪ results in persistent or significant disability or incapacity ▪ consists of a congenital anomaly or birth defect <p><i>Comment:</i> Medical judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.</p> <p>*Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.</p> <p>The definition of seriousness above reflects the definition used in the EU Directive, and from EudraCT guidance. “Other important medical condition” is taken from ICH E2A and can also be used to define an SAE.</p>
---	---

2.0 Definition of Sponsor for Pharmacovigilance

Part 1 of the Regulations defines the “sponsor” role in the UK. It is possible for more than one entity (individuals or organisations) to be the sponsor for a trial.

A group may either:

- Arrange to take on the sponsorship responsibilities jointly (Regulation 3(2)(a)); or
- Allocate the sponsorship responsibilities among the members of the group (Regulation 3(2) (b)).

For further information on sponsorship: <Link to sponsorship section of toolkit>

When a group allocates the sponsorship responsibilities under Regulation 3, one “person” will be named as the sponsor for pharmacovigilance. Requests to the MHRA for a Clinical Trial Authorisation (CTA) must indicate who is taking on the role of sponsor for pharmacovigilance. The sponsor may then delegate the tasks and functions as necessary to comply with the Regulations - for example, to chief investigators, other investigators, NHS trusts or clinical trials units. Where “the sponsor” is used in this document, it refers to the individual, organisation or group member named in the CTA as the sponsor for pharmacovigilance or the person to whom these responsibilities have been delegated.

It is essential that the responsibilities and procedures for PV, which are usually decided upon in the risk assessment process, be documented and agreed by all parties. This

includes all parties to which these responsibilities have been discharged to. Responsibilities should be detailed in the trial protocol and/or SOPs as appropriate.

Please note: The terminology used in this document is as follows:

- Investigators “notify” the sponsor;
- Sponsors “report” to the regulatory authorities and ethics committees.

3.0 General Considerations

Before initiating a clinical trial the sponsor should give careful consideration to the following points:

- The specific requirements for recording and notifying adverse events in the trial;
- Which events should be recorded and where; and
- Which events should be notified to the sponsor and the timelines for notification.

In order to make these decisions, the sponsor should carry out an assessment of the risk associated with the clinical trial. The risk to patients varies considerably in clinical trials, depending on what is known about the medicines in the trial. Examples of factors that need to be taken into account include the phase of the trial and the level of clinical experience with the trial medication in the population under study. At one extreme, there are phase I "first in man" studies. At the other, there are large-scale phase IV studies of agents that have been used widely in routine practice.

The decision on the nature of the adverse events to be recorded, notified and reported depends both on the extent of knowledge of the risk/benefit profile of the drugs under study, particularly in the population to be studied in the trial, and on the aims of the trial.

Depending on the risk associated with the clinical trial (as defined above), it may be reasonable to collect one or more of the following:

- All AEs (serious and/or non-serious)
- Only SAEs (or, in certain circumstances, only specific types of SAE)
- All ARs (serious and/or non-serious)
- Only SARs
- All AEs/ARs of a certain grade of severity, graded using standard toxicity grading scales such as CTCAE, WHO or Division of AIDS.

The proposed procedures for assessing, recording, notifying and reporting adverse events should be detailed in the trial protocol and/or SOPs as appropriate and will be reviewed by the MHRA during the CTA assessment.

Non-serious adverse events do not have to be reported either as part of expedited or periodic reporting, unless they are defined during the risk assessment as being critical to the safety assessment in the trial. This type of event is often referred to as a “safety critical” or “notable” event.

It is recommended that the protocol states that patients should be asked at each trial visit about hospitalisations, consultations with other medical practitioners, disability or incapacity or whether other relevant adverse events have occurred. These may be recorded in the patient’s medical records. The protocol should specify which adverse event data are to be recorded on the trial Case Report Forms (CRFs). Where appropriate, data on non-serious adverse events may be recorded as part of the clinical

follow up on the relevant CRF. SAEs and notable AEs often require collection of additional information required for the assessment of the event and for reporting to the appropriate regulatory body and ethics committees. Information on SAEs may be recorded on a specific form.

Further guidance on the recording of non-serious and serious adverse events and reactions is given in Appendix 2.

Regulation 32 sets out the following responsibilities for the notification of adverse events to sponsors:

1. An investigator shall notify the sponsor of any SAE that occurs in a subject at a trial site immediately* (unless covered by point 2 below). This immediate report may be made either orally or in writing as long as a detailed written report follows the immediate report.
2. The sponsor may specify in the protocol certain SAEs that an investigator does not have to notify immediately. The protocol should state how and when these events should be notified.
3. Other AEs identified in the protocol as critical to evaluations of the safety of the trial (i.e. notable events) should be notified by the investigator to the sponsor in accordance with the requirements, including the time periods for notification, specified in the protocol.

*There is no legal definition of “immediate”, but this is usually within 24 to 48 hours of their becoming aware of the event.

For each trial, the sponsor should specify the period of time during which investigators should notify them of SAEs. This period of time will be dependent on the risks associated with the trial and should be specified in the protocol. For example it may be that investigators are required to notify the sponsor of all SAEs occurring from the time of randomisation until 30 days after the last protocol treatment administration, whereas SARs may be required to be notified whenever they occur.

4.0 Assessment of Adverse Events

The assessment of an adverse event includes three main aspects:

4.1. Assessment of Seriousness

This is based on the regulatory definitions of seriousness as defined in Section 1.2. These definitions should be included in the trial protocol. **Note:** The term “severe” is often used to describe the intensity (clinical severity) of a specific event. This is not the same as “serious”, which is a regulatory definition based on patient/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

4.2 Assessment of Causality

This is a clinical assessment of whether the adverse event is likely to be related to the trial drug. All adverse events judged as having a reasonable suspected causal relationship (e.g. definitely, probably or possibly related) to the study drug are considered to be adverse reactions. The expression “reasonable suspected causal relationship” is meant to

convey in general that there is reason (e.g. facts, evidence or arguments) to suggest a causal relationship.

Many terms and scales are in use to describe the degree of certainty in relation to causality between an IMP and an event, such as certainly, definitely, probably or possibly; or likely related or not related. Whichever system is used, this should be specified and explained in the protocol, and the events that qualify as SARs should be made clear.

4.3 Assessment of Expectedness

The evaluation of expectedness is based on knowledge of the adverse reaction and any relevant product information. The list of expected events should be based on:

- The Summary of Product Characteristics (SmPC) for the products under investigation for a licensed drug; or
- The investigator's brochure (IB) for a non-licensed drug.

The relevant product information (IB or SmPC) can either be included or referred to in the protocol. Note: Documentation of previous reports of an event in the SmPC or IB does not automatically qualify an event to be expected. For example, a particular event may be deemed more severe or occur more frequently than documented in the SmPC/IB.

Note:

- The MHRA's approval is required if the reference document (i.e. IB, SmPC) on which expectedness is judged, is modified or changed. This constitutes a substantial amendment to the CTA.
- Where a study is taking place in more than one country, using a licensed medicine with different SmPCs around the globe, a single SmPC and labelling information (the most comprehensive) should be selected as the reference document for all trial sites, and this should be documented in the protocol.

4.4 Assessment of Adverse Events: Responsibilities

Individual investigators at a site (i.e. the principal or other clinical investigators responsible for the patient's care - will be referred to as the local investigator throughout the rest of this document), the chief investigator (CI) coordinating the trial, and the sponsor (see Section 2.0) may share responsibility for the assessment and evaluation of adverse events with regard to seriousness, causality and expectedness. The sponsor is responsible for the ongoing safety evaluation of the IMP, however the Regulations allow the duties of sponsors to be delegated, including to investigators. Whatever decision is made for a given clinical trial it is vital that the arrangement be documented in the trial protocol and/or SOPs and in any agreements or contracts between the sponsor and the investigator.

The local investigator knows the patient's history, clinical signs and symptoms, laboratory findings and other investigations, and so may be best placed to make the immediate assessment of causality, distinguishing suspected adverse reactions from unrelated adverse events. Where there are two assessments of an event, the causality assessment made by the local investigator cannot be downgraded. The causality assessment can, however, be upgraded. In the case of a difference of opinion on

causality, both assessments are recorded, and the “worst case” assessment is used for reporting purposes.

Depending on the organisation of the trial, the local investigator may also assess expectedness if they are equipped to do it. In a single site trial where the CI is undertaking all the pharmacovigilance responsibilities of the sponsor, the CI will normally assess the expectedness of serious adverse events. In a multi-site trial coordinated by a clinical trial unit, the sponsor and the CI may delegate the assessment of expectedness to appropriately trained individuals in the co-ordinating unit. Whichever approach is taken, the same system should be adopted across the trial. However, it is advisable to have some arrangement for central review of adverse event and/or serious adverse event data in large multi-site trials. This can prevent misclassifications of safety data, may detect systematic non-compliance with the reporting requirements for SUSARs, and may also lead to the early detection of new safety issues or concerns.

There is no legal requirement for two independent assessments of an event. When the local investigator is responsible for assessing causality and expectedness, there may be only one assessment.

Depending on the level of risk associated with the trial it may be appropriate for sponsors to conduct some sample auditing and monitoring to ensure that the assessment of expectedness is properly conducted and that appropriate decisions are reached. This may be particularly appropriate if events are being assessed by more than one individual.

4.5 Assessment of Adverse Events in Blinded Trials

Blinded trials are complex to set up. Maintenance of blinding can be important for the integrity of a trial. Systems for SUSAR and SAR reporting should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. Unblinding clinicians may be unavoidable if the information is necessary for the medical management of particular patients. The safety of patients in the trial always takes priority. It is important that the details of the unblinding process are included in the trial protocol.

For blinded trials involving a placebo and an active drug, seriousness, causality and expectedness should be evaluated as though the patient was on active drug. Cases that are considered serious, unexpected and possibly, probably or definitely related (i.e. possible SUSARs) would have to be unblinded. Only those events occurring among patients on the active drug (unless thought to be due to the excipient in the placebo) should be considered to be SUSARs requiring reporting to the regulatory authority and ethics committee. It may be that individuals who are not directly involved in the management of the trial could perform unblinding (for example, in a trials unit, staff working on a separate trial might undertake the unblinding).

For blinded trials involving two active drugs, the evaluation is more complex. However, the person responsible for the evaluation for causality and expectedness might be able to state that if the patient were on drug A the event would be causal and/or unexpected, but if on drug B it would be expected. If the event were unexpected for either of the active drugs, the case should be unblinded by the individual charged with unblinding, who would then classify the event accordingly.

A DMC has access to semi-blinded or unblinded data and can oversee the assessment of emerging risks, such as an increase in frequency or severity of adverse events. The committee's assessments are carried out without disclosure to the trial team. They may recommend protocol amendments, or termination of the study, if they detect serious safety issues. In addition, the chairman of an independent Data Monitoring Committee (DMC) might be able to play a role in unblinding individual reports of SUSARs for expedited reporting (if this could be managed within the requisite timeframes) and serious expected adverse reactions for annual reports.

5.0 Adverse Events: - Sponsor Responsibilities

The Regulations require the sponsor to keep detailed records of all adverse events relating to a clinical trial which investigators in that trial have notified to them, unless they have been documented in the protocol as not required. The sponsor may be required to submit these records to the licensing authority (MHRA) on request.

Responsibility for reporting to the relevant competent authorities and to the Ethics committee rests with the sponsor. In some situations, pharmaceutical companies who provide drugs for a trial may take on responsibility for adverse reaction reporting. Reports would be sent to the relevant company and the company would take responsibility for the sponsor's assessment of expectedness (if appropriate) and reporting to the regulatory and ethics committees. The agreed responsibilities for each trial should be documented in the protocol and also in the SOPs for the trial.

5.1 Expedited Reporting to Regulatory Authorities

The Regulations set time limits for expedited reporting:

Fatal or life threatening SUSARs:

- Not later than **7 calendar days** after the sponsor is first aware of the reaction, with any follow-up information to be reported within a **further 8 calendar days**.

All other SUSARs:

- Not later than **15 calendar days** after the sponsor is first aware of the reaction.

The following safety issues are also recommended in EC Guidance document ENTR/CT3 Revision 2 to be reported in an expedited fashion:

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:
 - a. A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial;
 - b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
 - c. A major safety finding from a newly completed animal study (such as carcinogenicity);
 - d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;
- Recommendations of the DMC, if any, where relevant for the safety of the subjects.

5.1.1 Reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the following minimum criteria are met:

- A suspected investigational medicinal product;
- An identifiable subject (e.g. trial number);
- An adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship;
- An identifiable reporting source;

And, when available and applicable:

- A Eudract number (or, in the case of non-European community trials, the sponsor's trial protocol code number); and
- A unique case identification (i.e. sponsor's case identification number)
- Treatment assignment after unblinding and validation (or not) of the suspected causes.

The sponsor is responsible for ensuring that all relevant follow-up information is requested and submitted to the regulatory authorities and ethics committees as appropriate.

5.1.2 Format of an expedited SUSAR report:

Eventually, electronic reporting may be the expected method for expedited reporting of SUSARs to the competent authority. However, systems for electronic reporting are not yet available to all organisations in the non-commercial sector, and the costs and training involved with the use of the Eudravigilance database may mean that it will be sensible to coordinate this on a national basis. Arrangements for this are being explored with the MHRA. (This section of the present document will be updated when electronic reporting of SUSARs is more widely available.)

For the time being Safety Reports should be submitted to the MHRA on paper. Details can be found at:

http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=101

The ICH standard for adverse reaction reporting is ICH E2B (M) (Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports), which can be found at: <http://eudravigilance.emea.eu.int/human/docs/e2b.pdf>

The EudraCT number in the format YYYY-NNNNNN-CC# should be inserted at the start of the ICH E2B M2 message field, A.2.3.1 Study Name, until such time as a separate field is available in the E2B standard to accept the EudraCT number. The CIOMS 1 form is, however, acceptable for reporting in the UK and this can be found at: <http://www.cioms.ch/cioms.pdf>. The EudraCT number in the format YYYY-NNNNNN-CC# should be inserted at the start of the Study Name.

No matter what the form or format used, however, we recommend consideration of the basic information/data elements described in annexe 3 of the ENTR/CT 3 Revision 2 document which can be found at:

http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2006/04_2006/susar_rev2_2006_04_11.pdf#search=%22entr%20ct3%20April%202006%22

5.1.3 Format of the reports of other important safety issues

Other important safety issues should be reported to the competent authority by a letter entitled “Safety Report”. The first page of the report should reference the EudraCT number, the title and the sponsor’s protocol number of the trial to which it refers and the points of concern summarised in a short section.

5.2 Expedited Reporting to Ethics Committees

In accordance with national legislation, the ethics committee concerned (in the UK this is the ethics committee which approved the trial, and will be referred to here as the main REC) may only wish to receive expedited reports of SUSARs that occurred in subjects who have been recruited in that Member State. Further details on the expedited reporting of SUSARs to RECs in the UK can be found at: <http://www.corec.org.uk/applicants/apply/safety.htm> For multi-site studies with a favourable opinion from more than one REC prior to 1st March 2004, sponsors should nominate one of the RECs for appointment by COREC as the main REC for all further purposes, including safety monitoring.

All Safety Reports to the main REC should be accompanied by the covering form provided on the COREC website. The form should be signed by the person submitting the report and submitted on paper. All enclosures should be listed and referenced on the form. Forms should not normally be used to submit reports covering more than one trial. However, this may be permitted by the REC where two trials are very closely connected (for example a main study and an extension study with the same treatment regimen). The co-ordinator of the main REC will acknowledge receipt of all Safety Reports within 30 days by signing and returning a copy of the covering form. Reports sent without the covering form will not be acknowledged.

5.3 6-Monthly Safety Reports to Ethics Committees

6-monthly safety reports replace the quarterly reports required by COREC for international trials. However, non-commercial sponsors are not required to submit 6-monthly safety reports. This information is available in the updated COREC SOPs (Version 3.1, October 2006, page 173).

5.4 Annual Safety Reports

An annual report for each trial must be submitted to the competent authority and the main RECs of the concerned Member States (i.e. those Member States in which the trial is taking place), taking into account all new available safety information received during the reporting period. The aim of the annual safety report is to describe concisely all new safety information relevant for one or several clinical trial(s) and to assess the safety conditions of subjects included in the concerned trial(s). In a multi-site international trial, the annual report should include SUSARs and SARs from both UK and non-UK

sites. The same report should be sent to both the competent authorities and relevant ethics committees.

The annual Safety Report should have three parts:

- A report on the subjects' safety in the clinical trial;
- A line listing of all suspected SARs (including all SUSARs) that occurred in the trial, including those from third countries³; and
- An aggregate summary tabulation of suspected SARs that occurred in the trial.

The report should include a summary of any published literature relevant to the safety of subjects in the trial, or aggregated reports of any other relevant unpublished data known to the sponsor. It may also usefully include a summary of any concerns or recommendations from the DMC (see section 7.0) on safety of subjects in the trial. Further information on the annual Safety Report can be found in Section 5.2 of ENTR/CT 3 Revision 2 and on the COREC website.

Link to COREC website: <http://www.corec.org.uk/applicants/apply/safety.htm>

Link to ENTR/CT3 Revision 2:

http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2006/04_2006/susar_rev2_2006_04_11.pdf#search=%22entr%20ct3%20April%202006%22

The reporting time frame for annual reports starts from the date of the first authorisation of the clinical trial (CTA) by a competent authority in any member state (or from the first authorisation of the trial in a European Economic Area (EEA) state). The anniversary of this date is designated as the cut-off date for data to be included in the annual report. Unless agreed otherwise, the report should be submitted within 60 days of this cut-off date.

Reports can cover more than one trial of the same medicinal product. It has been suggested that an annual report by the non-commercial sponsor might not be required if a pharmaceutical company includes the trial data in its own annual report for the agent under study. In fact, that would not comply with the Regulations. In order to comply with the Regulations, sponsors must provide an annual report on the trial or trials for which they are responsible. It could, however, be documented in agreements that a pharmaceutical company will prepare an annual report on behalf of an academic sponsor. If the report covers two trials, then the annual report can be submitted on the anniversary of the first trial, or on a date pre-arranged with the MHRA.

In the case of short-term trials (less than 6 months), the Safety Report may be submitted within 90 days of the end of the trial together with the notification of the end of the trial (according to Directive 2001/20/EC, article 10).

5.5 Informing Investigators

The Regulations require the sponsor to ensure that the investigators responsible for the conduct of a trial are kept informed of any SUSARs that occur in relation to any IMP in that trial. If a significant new safety concern is identified, either upon receipt of an individual case report or upon review of aggregate data, then this should be done

³ A third country is defined in the Medicines for Human Use (Clinical Trials) Regulations 2004 as "a country or territory outside of the European Economic Area".

immediately. In other cases, the sponsor should determine how frequently and in what format (e.g. a line-listing) to send SUSAR information about SUSARs to all of the investigators involved in the trial. This decision should be based on a risk assessment (which should be documented) and the procedures to be used should be included in the protocol and the trial SOPs.

In the case of blinded trials data, a decision could be made to present all SUSARs, regardless of the medication administered (including those allocated placebo or no active drug) in order to avoid the risk of inadvertently informing the investigators of the identity of a patient's treatment.

5.6 Reporting of Safety Issues Following Completion of the Clinical Trial in the European Community

After termination of the clinical trial, any unexpected safety issue that changes the risk benefit analysis and is likely to have an impact on the subjects who have participated in it, should be reported as soon as possible to the competent authority(ies).

6.0 Clinical Trials in Third Countries

In an international trial, reporting should follow the requirements of the countries in which the trial is taking place. For trials within the EU, the sponsor must ensure that all SUSARs occurring in other countries are reported to all the competent authorities of the EU countries in which the trial is taking place.

The protocol should specify procedures for both the timing and format of reports of SUSARs in sites outside the EU.

If an international trial is taking place outside the EU only but has an EU sponsor, the sponsor has no obligations to report events to the MHRA or other EU equivalent.

The procedures for notifying events to the sponsor, and of reporting relevant events onwards to regulatory and ethics committees should be included in any agreements between international groups performing the trial.

7.0 Role of the DMC

Many large publicly funded trials have a DMC to oversee the safety of subjects in the trials. Normally the DMC reports to the Trial Steering Committee (TSC) or to the sponsor. If a DMC identifies safety issues which might materially alter the current benefit-risk assessment of an IMP or that would be sufficient to consider changes in the IMPs administration or in the overall conduct of the trial this would also need to be reported to the MHRA. It is recommended that appropriate reporting channels (normally via the sponsor) be established for each trial.

8.0 Patient Safety Incidents

A patient safety incident is defined as any unintended or unexpected incident, which could have or did lead to harm for one or more patients receiving NHS-funded healthcare. In other contexts these may be referred to as adverse incidents or clinical errors, and include near misses.

8.1 Notifying NHS Trusts – Investigator Responsibilities

Although not a requirement of the Regulations, the PI at each centre participating in a trial should ensure their NHS trust are notified of patient safety incidents that occur on that trial according to the trust incident reporting policy.

8.2 Reporting to the National Patient Safety Agency (NPSA) - Trust Responsibilities

All NHS organisations in England and Wales should report patient safety incidents to the NPSA. This reporting should be undertaken through the NPSA's National Reporting and Learning System (NRLS). The system is designed to draw together reports of patient safety errors and systems failures from health professionals across England and Wales to help the NHS to learn from things that go wrong.

NHS organisations have their own local reporting systems for patient safety incidents. Patient safety incidents that take place in the course of research should be reported in accordance with the local standard procedures. This reporting is to make sure incidents of interest to the NPSA are not missed when they occur during research. For example, a prescribed overdose or maladministration of a trial drug by a health care worker could be evidence of organisational failure with implications outside the study. More information on reporting to the NPSA is available at www.npsa.nhs.uk.

9.0 Glossary of terms

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form (including electronic CRFs)
CTA	Clinical Trial Authorisation
CTCAE	Common Toxicity Criteria for Adverse Events
DMC	Data Monitoring Committee
IB	Investigator's Brochure
IDMC	Independent data monitoring committee
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
NPSA	National Patient Safety Agency
NRLS	National Reporting and Learning System
PI	Principal Investigator
PV	Pharmacovigilance
REC	Research Ethics Committee
SAR	Serious Adverse Reactions
SAE	Serious Adverse Events
SmPC	Summary Product Characteristics
SSAR	Suspected Serious Adverse Events
SUSAR	Suspected Unexpected Serious Adverse Reactions
TSC	Trial Steering Committee

UKECA United Kingdom Ethics Committee Authority
WHO World Health Organisation

Appendix 1: Individuals and organisations involved in pharmacovigilance

Sponsor(s): Defined in EC Directive 2001/20/EC as an “individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial”. The Regulations specify that it is possible for more than one legal person, either in terms of individuals or organisations, to take on the role of sponsor. Also described in regulation 3 of the Regulations. In the present document, “sponsor” is used to describe the individual organisation or group members named in the CTA as sponsor for pharmacovigilance or the person to whom these responsibilities have been delegated.

Chief investigator: In relation to a clinical trial conducted at a single trial site, the investigator for that site; or in relation to a clinical trial conducted at more than one trial site, the authorised health professional, whether or not he is an investigator at any particular site, who takes primary responsibility for the conduct of the trial.

Comment: This will be the clinician named on the Clinical Trial Authorisation (CTA) as having overall responsibility for the conduct of the study in the UK.

Principal investigator: The clinical investigator at each research site who has responsibility for the conduct of the study at that site. (This definition is not taken from Regulations.)

Trial site: Hospital, health centre, surgery or other establishment or facility at or from which a clinical trial, or any part of such a trial, is conducted.

Trials unit/centre: Organisation responsible for running trials. Trials units typically have a co-ordinating office with expert staff responsible for communication and for data collection. They may be large units co-ordinating many trials, or they may be part of the office of the chief investigator co-ordinating a single site trial. A trials unit may have been delegated responsibility for pharmacovigilance. Alternatively, it may provide the systems that enable its parent organisation to be the sponsor. In this definition, a “trials unit” does not mean simply a site where a trial takes place.

Trial steering committee (TSC): A committee that may include both investigators and independent members. A TSC oversees the conduct and progress of a trial, particularly a large complex trial. The TSC will also consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) or equivalent.

Data monitoring committee (DMC): A committee that is usually independent of the investigators, funder and sponsor of a trial. A DMC reviews the accruing trial data on a regular basis to assess whether there are any safety issues that investigators or participants should be aware of. The DMC is the only body that routinely has access to semi-blinded or unblinded data (competent authorities might request unblinded data and, in emergency situations, unblinding might occur for an individual patient). The decision whether or not a DMC is required depends on the trial’s design and the potential risks and benefits to participants associated with the trial. (These issues are discussed in more detail in the notes on Monitoring Procedures.) A number of different titles are used for DMCs, for example: Independent Data Monitoring Committee (IDMC), Data and Safety Monitoring Board (DSMB), Independent Safety Monitoring Committee (ISMC) and

Data Monitoring and Ethics Committee (DMEC). The DAMOCLES project considered the role and function of DMCs. The following publications may be of interest:

- DAMOCLES study group. A proposed charter for clinical trial Data Monitoring Committees: helping them to do their job well. *The Lancet* 365:711-722, 2005.
- AM Grant, DG Altman, A. B. Babiker, MK Campbell, FJ Clemens, JH Darbyshire, DR Elbourne, SK McLeer, MKB Parmar, SJ Pocock, DJ Spiegelhalter, MR Sydes, AE Walker, SA Wallace, and the DAMOCLES group. Issues in data monitoring and interim analysis of trials. *Health Technology Assessment monograph series* 9 (7), 2005.

MHRA: The Medicines and Healthcare products Regulatory Agency. The Regulations make the MHRA the UK competent authority. A Clinical Trial Authorisation (CTA) from the MHRA is required before a clinical trial of an Investigational Medicinal Product (IMP) may begin. The MHRA has to be satisfied with the proposals for the sponsor's responsibilities, including pharmacovigilance. It has a legal duty to ensure that suspected unexpected serious adverse reactions (SUSARs) are recorded in the EudraVigilance database.

EMA: The European Medicines Agency does not authorise individual Clinical Trials, but maintains the EudraVigilance database. This database allows the competent authorities of all member states to share drug safety information.

Research Ethics Committee (REC): Under the Regulations, it is against the law to start a trial, or even advertise recruitment, before a REC has given a favourable opinion. Regulation 15 outlines what the REC has to consider when forming its view. This includes the trial design, risks and benefits, the protocol and investigator's brochure, and the suitability of the research team and facilities for the trial. There is no specific requirement for the REC to consider pharmacovigilance arrangements, but the Regulations do require that the relevant REC (see below) is kept informed of all SUSARs that occur in a trial, and that that REC also receives a copy of the annual Safety Report.

Relevant ethics committee: The Regulations require a single ethical opinion for multi-site trials; the Regulations call this the "relevant ethics committee". Directive 2001/20/EC calls it "the concerned ethics committee". In the UK, this is generally referred to as the main REC. This main REC is responsible for deciding whether to give a favourable opinion. Any other RECs are advising the main REC on locality issues, not giving a separate opinion.

UKECA: UK Ethics Committee Authority. The Regulations require that the positive opinion for a trial with medicines comes from an ethics committee recognised by the UKECA for that purpose.

Appendix 2: Data recording and notification of non-serious adverse events

There are several factors to consider when deciding what non-serious adverse events to record on trial CRFs (in addition to recording all, or in some special circumstances, only selected serious adverse events).

Depending on the risk of the clinical trial, it may be entirely reasonable

- to record only serious adverse events; or
- to record only those non-serious adverse events which are reactions to an investigational medicinal product; or
- to record only those adverse events which have led to modification of trial treatment; or
- to record only the more severe non-serious adverse reactions.

This decision should follow an appropriate risk analysis and should be agreed by the sponsor. The trial protocol should state the reasons for the decision.

Trials in which all non-serious adverse events are collected

In the following trial scenarios it may be necessary to collect information on all non-serious adverse events:

- Trials of a new drug (new molecular entity) where the safety profile of the drug is not yet established.
- Trials of a licensed drug being used in novel combinations or in a way that is very different from the licensed indication.

The trial protocols (and/or SOPs as appropriate) should specify the following:

- on which CRF details of the event should be recorded
- the timelines for notifying non-serious adverse events/reactions to the sponsor*

*If a given non-serious adverse event is deemed during the risk assessment process to be safety-critical then the event should usually be notified to the sponsor in an expedited manner.

Trials where non-serious adverse reactions of a particular clinical severity are collected

Some drugs are expected to cause adverse reactions in a high proportion of patients (e.g. with cytotoxic chemotherapy.) The Directive clearly asks for individual risk/benefit analyses for each trial; article 3.2(a) states that a clinical trial may only be undertaken if the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject.

The risk/benefit evaluation in the trial would be the balance of:

- the potential efficacy (often the impact on survival); and
- the risk of adverse reactions of a certain clinical severity for the trial population as a whole, as well as for the individual patient.

For example, the vast majority of patients may be expected to experience some degree of toxicity (such as anaemia), when taking a particular cytotoxic drug. The decision about the risk and benefits of the treatment would be based on the balance of effect on survival and the frequency of more severe toxicity. In this situation, it may be justifiable to restrict the collection of data on non-serious adverse reactions. The protocol might require that CRFs record only clinical reactions or laboratory test abnormalities of a certain severity. (For example, collect only WHO grade 3 or 4 haematological toxicity.) Less severe reactions could be noted only in the patients' medical records, and not on trial CRFs.

Trials where non-serious adverse reactions are not collected

The risk/benefit profile of the medicines under study may be very well established. The medicines may have been licensed in the UK, and may have been in clinical use here for many years. If so, it may be unnecessary to record data on every expected non-serious adverse event or reaction on trial CRF forms.

This might be appropriate in a trial comparing different treatment strategies based on licensed drugs used in their licensed indication. For example, there have been several trials conducted in primary care, comparing different approaches to antibiotic prescribing (immediate vs deferred or none) on the duration of symptoms in patients with respiratory tract infections. In such trials, non-serious adverse reactions could be noted in patients' medical records, and appropriate clinical action taken. However, it may be justifiable not to record non-serious adverse reactions on CRFs in such circumstances. The protocol should document how the approach is compatible with the safety and aims of the trial.

This approach needs justification case by case. It cannot be assumed there is never any need to record non-serious adverse events in trials with licensed products. In addition, it is recommended that an appropriate level of monitoring/auditing should take place in these cases, to ensure that the procedures specified in the protocol are being adhered to.

Appendix 3: Serious Adverse Events and Reactions that may not Require Immediate Notification to Sponsor

Some serious adverse events are expected. Examples could include:

- Death or hospitalisation of a patient due to the disease under study; or
- Events that are common in the type of people being studied (e.g. as a consequence of their age, medical condition or other circumstances).

The decision to exclude specific SAEs from immediate notification to the sponsor should be considered during the risk assessment process and specified in the protocol. If they are specified in the protocol and approved by the relevant ethics committee and the MHRA, these events need not be reported as part of safety monitoring. Such expected events would be recorded as outcome measures on CRFs, and included in the results of the trial.

In trials with a DMC, the DMC would monitor the frequency of such events, by treatment group if appropriate, and alert the TSC and sponsor to any major safety concerns. Consequently, this approach may impact upon the extent and frequency of DMC review.