Workstream 6: Pharmacovigilance

1 Introduction

This document describes good practice and how to comply with the recording and processing of adverse events in clinical trials of investigational medicinal products (CTIMPs). 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 Medicines and Healthcare Products Regulatory Agency (MHRA) accepts that a risk-based approach to trial management and monitoring is appropriate for certain trials. 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.

The language used in this document reflects that used in the UK Regulations and the supporting EU guidance documents. The term '**competent authority**' refers to the licensing authority in each member state where a clinical trial is being conducted, which in the UK is the MHRA. Therefore for a trial run solely in the UK, the phrase 'reported to the competent authorities and ethics committees' will mean 'reported to the MHRA and the ethics committee that approved the trial'. A glossary and description of terms can be found in section 10.0 and Appendix 1.

1.1 Background

The EU Clinical Trials Directive (2001/20/EC) was published on the 4 April 2001. The Medicines for Human Use (Clinical Trials) Regulations (SI 2004/1031) transposed this EU Directive into UK law on 1 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. Since 2006, three further amendments have been made to the 2004 Regulations. The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, will be referred to as **the Clinical Trials Regulations** in the rest of this document. The Clinical Trials Regulations set out the legal requirements for pharmacovigilance in clinical trials involving UK participants. The Clinical Trials 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 competent authorities and ethics committees, including expedited reports of SUSARs and annual safety reports.

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

In addition to Directive (2001/20/EC)*, the European Commission has issued Commission Communication: 'Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use CT-3 2011' (referenced in this document as **Commission guidance CT-3 2011**). Their advice has been taken into account in this document. The safety reporting web pages produced by the MHRA and the National Research Ethics Service (NRES) should also be taken into account.

** The European Commission have published a proposal to repeal Directive (2001/20/EC) and to replace it with new legislation in the form of a European Regulation. However, the proposed*

Regulation is not imminent (due 2016) and the proposal is potentially subject to change so will not be considered further in this document.

1.2 Definitions

Directive 2001/20/EC, Article 2, lists definitions of terms for use across the EU.

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 Comment: 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 response to an investigational medicinal product related to any dose administered Comment: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product would 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 unauthorised investigational product or Summary of Product Characteristics (SmPC) for an authorised product). Comment: Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented adverse reactions constitute unexpected events.
Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any AE, AR or UAR 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 • consists of a congenital anomaly or birth defect Comment: 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. **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.*

2 Definition of Sponsor for Pharmacovigilance

The Clinical Trials 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; or
- Allocate the sponsorship responsibilities among the members of the group.

When a group allocates the sponsorship responsibilities, 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 responsibilities and functions as necessary to comply with the Clinical Trials Regulations, for example, to chief investigators or clinical trials units. Where the term '**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/functions have been delegated. The responsibilities and procedures for pharmacovigilance should be documented and agreed by all parties. This includes all parties to whom responsibilities have been delegated.

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

- Investigators "notify" the sponsor;
- Sponsors "report" to competent authorities and ethics committees.

3 General Considerations: Risk Adapted Approaches to Safety Reporting

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-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products has been published to help sponsors undertake this process. The risk to subjects varies considerably in clinical trials, depending on what is known about the investigational medicinal products (IMPs) and the risks of the extra interventions undertaken. 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' trials. At the other, there are large-scale phase IV trials of agents that have been used widely in routine practice.

The decision on the nature of the adverse events to be notified and reported depends both on the extent of knowledge of the benefit-risk 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, 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 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 annual 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 subjects should be asked at each trial visit about hospitalisations, consultations with other medical practitioners, disability or incapacity or whether other adverse events have occurred. Anything that is relevant to the clinical care of the subject should be recorded in their 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 competent authorities 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.

4 Adverse Events: Investigator Responsibilities

Regulation 32 of the Clinical Trials Regulations (SI 2004/1031) 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 evaluation of the safety of the trial (i.e. notable events) should be notified 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 Commission guidance CT-3 2011 specifies it should not exceed 24 hours following knowledge of the event.*

For each trial, the sponsor should specify in the protocol, 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. 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. SARs that come to the attention of the investigator after this time should continue to be notified to the sponsor and followed up until resolution.

Local safety reporting policies may also be in place and all investigators should be aware of any reporting requirements specified by their host organisation.

5 Assessment of Adverse Events

Adverse event undergo three main assessments:

5.1. Assessment of Seriousness

This is based on the regulatory definitions of seriousness defined in section 1.2. This definition should be included in the trial protocol. 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.

5.2 Assessment of Causality

This is a clinical assessment of whether the adverse event is likely to be related to an investigational medicinal product (IMP). All adverse events judged as having a reasonable suspected causal relationship to the IMP 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.

5.3 Assessment of Expectedness

The 'expectedness' of an adverse reaction to an IMP is assessed in the light of the **Reference Safety Information (RSI)** for that product which for clinical trials is contained in either:

- The summary of product characteristics (SmPC) for a product with a marketing authorisation; or
- The investigator's brochure (IB) for any other investigational medicinal product.

However, 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.

The Clinical Trials Regulations require that the sponsor shall ensure that the investigator's brochure is validated and updated at least annually.

Competent authority approval is required if the Reference Safety Information (i.e. IB or SmPC) on which expectedness is judged, is modified or changed. This constitutes a substantial amendment to the CTA. However, annual updates to the investigator's brochure which do not alter the benefit-risk assessment of the trial should not be submitted as substantial amendments.

Where a trial 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 appropriate with reference to subject safety) should be selected as the Reference Safety Information for all trial sites and this should be documented in the protocol. If the sponsor is not the Marketing Authorisation Holder for the IMP, a system to monitor whether there has been any update to the SmPC should be implemented. The electronic Medicines Compendium (eMC) contains up to date information about medicines licensed for use in the UK.

5.4 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 sponsor is responsible for the on-going safety evaluation of the IMP. However, the local investigator, the chief investigator (CI) coordinating the trial, and the sponsor share responsibility for the assessment and evaluation of adverse events with regard to seriousness, causality and expectedness.

The local investigator knows the patient's history, clinical signs and symptoms, laboratory findings and other investigations, and is 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 (made by the investigator and the sponsor), the causality assessment

made by the local investigator cannot be downgraded by the sponsor, but can be upgraded. In the case of a difference of opinion on causality, the opinion of both the investigator and the sponsor should be provided with any report made.

Assessment of expectedness is usually undertaken by the sponsor; however the local investigator may assess expectedness if they are equipped to do so. In a single site trial where the CI is undertaking pharmacovigilance responsibilities, they 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.

5.5 Assessment of Adverse Events in Blinded Trials

Blinded trials are complex to set up. Maintenance of the blind is 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 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 subjects. The safety of subjects in the trial always takes priority. It is important that the details of the unblinding process are included in the trial protocol/SOPs.

For blinded trials involving a placebo and an active drug, seriousness, causality and expectedness should be evaluated as though the subject 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 before they are reported to the competent authorities and ethics committees. 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 subject was 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.

An independent Data Monitoring Committee (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 (see Appendix 1). The committee's assessments are carried out without disclosure to the trial team. They may recommend protocol amendments, or termination of the trial, if they detect serious safety issues. In addition, the chairman of the 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).

6 Adverse Events: - Sponsor Responsibilities

The Clinical Trials Regulations require the sponsor to keep detailed records of all adverse events relating to a clinical trial which investigators have notified to them. The sponsor may be required to submit these records to competent authorities on request.

Responsibility for reporting to the relevant competent authorities and ethics committees rests with the sponsor. In some situations, pharmaceutical companies that provide IMP for non-commercial trials may be prepared to take on certain safety reporting responsibilities such as the assessment of expectedness of events and any required SUSAR reporting to competent authorities and ethics committees. The agreed responsibilities should be outlined clearly in contractual agreements. These agreements should also cover the exchange of safety information between parties.

Where companies have supplied devices for IMP/device trials, the exchange of safety information between parties would also be appropriate for any device incidents that occur.

6.1 Expedited Reporting to Competent Authorities

6.1.1 Timelines for SUSAR Reporting

The Clinical Trials Regulations set time limits for expedited reporting of SUSAR for all IMPs in a clinical trial (including comparators and placebos*): Sponsors should report:

Fatal or life threatening SUSARs:

- No later than **7 calendar days** after being made aware of the case**, with any follow-up information to be reported within a **further 8 calendar days**.

All other SUSARs:

- No later than **15 calendar days** after being made aware of the case.

**Events associated with placebo will usually not satisfy the criteria for a SUSAR. However, where they do occur, (for example a reaction due to an excipient or impurity) the sponsor should report such cases.*

**The clock for expedited initial reporting starts as soon as the information containing the minimum reporting criteria (see section 6.1.3) has been received by the sponsor (not when the sponsor first registers that a report has been sent by the local investigator). The definition of what constitutes Day 0 should be clearly described in local sponsor SOPs

If significant new information on an already reported case is received by the sponsor, the clock starts again at day zero, i.e. the date of receipt of new information. This information should be reported as a follow-up report within 15 days.

Any SUSARs identified after the end of the trial should also be reported

6.1.2 SUSARs Associated with Non IMP/IMP Interactions

A Non Investigational Medicinal Product (NIMP) is a medicinal product which is not classed as an IMP in a trial, but may be taken by subjects during the trial. Examples include concomitant or rescue/escape medication used for preventive, diagnostic or therapeutic reasons and/or medication given to ensure that adequate medical care is provided for the subject during a trial. See EU Guidance on Investigational Medicinal Products (IMPs) and Non Investigational Products (NIMPs). SUSARs that result from a possible interaction between an IMP and a NIMP, (i.e. the reaction cannot clearly be attributed to the NIMP alone) should be reported in accordance with section 6.1.1.

6.1.3 Minimum Reporting Requirements for 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 (set out in section 6.1.1) when 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 competent authorities and ethics committees as appropriate. Detail on what would be considered relevant follow-up information can be found in Volume 10 EC Guidance Document: Questions and Answers Specific to Adverse Reaction Reporting in Clinical Trials.

6.1.4 Format of a SUSAR Report:

The International Conference on Harmonisation (ICH) standard for adverse reaction reporting is ICH E2B (M) (Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports).

In the UK, SUSARs should be reported electronically to the MHRA using the MHRA's eSUSAR website. The eSUSAR website is the gateway into the EudraVigilance Clinical Trial Module (EVCTM). Before using the eSUSAR website for the first time, institutions will need to register with the MHRA. See MHRA Safety Reporting page for registration form and details.

For multi-site EU trials, sponsors may choose to report (indirectly to all relevant Member States) by populating The EudraVigilance Clinical Trial Module (EVCTM). This method of reporting enables the sponsor to send a single report (rather than a report in each member state).

6.1.5 SUSARs from Trials Run in Third Countries (i.e. Countries outside the European Economic Area)

In an international trial, reporting should follow the requirements of the countries in which the trial is taking place. For trials with sites within the EU, the sponsor must ensure that all SUSARs occurring in third countries are reported to the competent authorities of the EU countries in which the trial is taking place. For non-commercial sponsors, this may be achieved using the MHRA eSUSAR website (as described in section 6.1.4). If a sponsor is conducting a trial outside the EU (and has no other trial in the EU with the same active substance), there is no requirement to ensure reporting into the EudraVigilance Clinical Trial Module (EVCTM).

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

6.1.6 Other Safety Issues Requiring Expedited Reporting

Safety issues, which might materially alter the current benefit-risk assessment of the trial but which do not meet the definition of a SUSARs, may occur during a trial.

Examples include 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 serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial;
- A significant hazard to the patient population, such as 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 (such as carcinogenicity);
- A temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;
- Recommendations of the Data Monitoring Committee (DMC), if any, where relevant for the safety of the subject.

These events/observations are not to be reported as SUSARs, but they might require other action, such as urgent safety measures, substantial amendments or early termination. Where such actions are not taken, Commission guidance (CT-3 2011) recommends that the sponsor informs the competent authorities and ethics committees.

6.2 Expedited Reporting to Ethics Committees

SUSARs and other safety issues are reported to the ethics committees which approved the trial in the same timeframes as the reports to competent authorities (section 6.1.1). However, the UK ethics committee is only required to receive expedited reports of SUSARs occurring in the UK, in the trial.

All safety reports to the UK ethics committee should be accompanied by the covering form provided on the NRES 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. Reporting requirements are detailed on the NRES Safety Reporting pages.

6.3 Annual Safety Reports

An annual report for each trial must be submitted by the sponsor to the competent authorities and the ethics committees of the concerned Member States, taking into account all new available safety information received during the reporting period. It should be in the format of a **Developmental Safety Update Report (DSUR)**. The required format is detailed in the ICH guideline E2F Note for guidance on development safety update reports. The main points are summarised below:

6.3.1 Content and Format of a DSUR

The aim of the annual safety report is to describe concisely all new safety information **relevant to the IMP** providing information on comparators where required (separate DSURs for comparators and placebos not required). The DSUR should contain:

- Safety information obtained by the sponsor during the reporting period
- Analyses of any new information based on the previous knowledge of the IMP
- Changes to the safety profile of the IMP and any change in the benefit-risk ratio

To achieve these objectives, it is important to use the format provided in ICH guideline E2F which includes data presented in line listings and summary tabulations:

- Interval line listings of SARs for the reporting period
- Cumulative summary tabulations of SAEs since the DIBD (DIBD defined in Section 6.3.2)
- Subject exposure to the IMP (number of subjects treated in the reporting period)

The ICH guideline E2F requires the sponsor to produce one DSUR per IMP (covering all trials undertaken by the sponsor with that IMP). Therefore, when an unlicensed IMP is being

developed by a non-commercial sponsor, (for example a biomedical unit) one DSUR should be submitted covering the IMP and safety data from all trials being conducted within the reporting period.

For UK trials however, where the sponsor is not the Marketing Authorisation Holder, the MHRA recognize that it may be more appropriate to submit trial specific DSURs. In this instance, the sponsor should submit a covering letter with any justification for the approach taken with a specific point of contact for any queries.

The completion of a DSUR may be shared, for example between the chief investigator and sponsor and in this case, it is important to ensure that responsibilities are defined in any relevant SOP. Generally, the chief investigator completes the majority of sections in the DSUR report however; the sponsor's input is required in areas such as:

- Inclusion of any unblinded SUSAR/SARs for submission to competent authorities and ethics committees with a blinded version for the CI to file;
- Where a trial specific DSUR is completed, a list of all trials with the IMP sponsored by that organisation.

When completing a DSUR, a non-commercial sponsor who is not the Marketing Authorisation Holder for the IMP, may not have access to information relevant for the completion of some parts of the report (such manufacturing issues, non-clinical data, and marketing status). This should be made clear in the DSUR.

Where trial specific DSURs are completed, it would be good practice to ensure that all other investigators working with that IMP within the sponsor's organisation, are provided with appropriate information (e.g. The DSUR Executive Summary). General communication between investigators working with the same IMP can help advance understanding of the use and safety profile of that IMP. Any relevant safety information should also be provided to the Marketing Authorisation Holder, where applicable.

6.3.2 Timelines for Reporting DSURs and the Data Lock Point

For IMPs without a marketing authorisation, (unlicensed), the **Development International Birth Date (DIBD)** is the date of the first authorisation by the sponsor of a clinical trial in any country (worldwide) for the investigational product.

For IMPs with a marketing authorisation (licensed), the DIBD is the **(International Birth Date (IBD)** which is the date when the product was first given a marketing authorisation in any country worldwide.

For non-commercial trials in the UK, where the sponsor is not the Marketing Authorisation Holder, the formal IBD may not be known and it is usually acceptable for the DIBD to be defined as the date of MHRA approval or, for trials submitted through the clinical trial notification scheme, the date of the confirmation of receipt of the CTA by the MHRA.

The DIBD must be indicated within the DSUR or in the covering letter.

The **Data Lock Point (DLP)** of the DSUR is the last day of the one-year reporting period. The DSUR should be submitted to all concerned competent authorities and ethics committees, no later than 60 calendar days after the data lock point.

If a trial has not started by the DSUR reporting date then only a covering letter stating this, is required. A DSUR must be submitted during every 12 month reporting period until the End of Trial. If a clinical trial is completed within a time period shorter than 1 year, (for example a Phase I trial) a DSUR does not have to be produced.

6.3.3 DSURs for Combination Therapies

In general, a single DSUR should be prepared for clinical trials involving a fixed combination product (i.e., a product consisting of at least two active ingredients in a fixed dose that is administered in a single dosage form). For trials involving multi-drug therapy, i.e., combinations of drugs that are not fixed, the sponsor can prepare either:

(1) A DSUR for the multi-drug therapy, or
(2) DSUR(s) for one or more of the individual components; in this case information on the multidrug therapy trials can be included in the DSURs of one or all of the components.

The following table provides examples of strategies for preparation of DSURs for multi-drug therapies

Multi-drug therapy used in clinical trial(s)	**DSUR**
Investigational drug (A) + marketed drug(s) (X, Y, Z)	Either a single DSUR focusing on (A+X+Y+Z) or A single DSUR focusing on (A) including data on the multi-drug therapy
Two investigational drugs (A) + (B)	Either a single DSUR focusing on (A + B) or Two separate DSURs (A) and (B), each including data on the multi-drug therapy
Two (or more) marketed drugs as an investigational drug combination (X, Y, Z)	A single DSUR focusing on the multi-drug therapy (X + Y + Z)

6.3.4 Changes in the Reference Safety Information during the Reporting Period

The Reference Safety Information (IB or SmPC) in place at the start of DSUR reporting period should be appended to the DSUR, and should serve as the Reference Safety Information throughout the reporting period. The DSUR should the include date and version number of the IB or SmPC. For SUSAR reporting, expectedness should be assessed in line with the current approved IB or SmPC. When the IB or SmPC has been revised during the DSUR reporting period, the sponsor should also submit the current version with the DSUR.

6.4 Informing Investigators of Safety Issues

The Clinical Trials Regulations require the sponsor to ensure that local 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 information should be communicated immediately. In other cases information on SUSARs should be aggregated in a (blinded) line listing of SUSARs in periods warranted by the nature of the research project/clinical development project and the volume of SUSARs generated. This line listing should be accompanied by a concise summary of the evolving safety profile of the IMP. The protocol/SOPs should define this period.

6.5 Advanced Therapy Investigational Medicinal Products (ATIMPs)

The safety reporting requirements for ATIMPs are governed by the same legislation as other clinical trials on investigational medicinal products. However, sponsors should also refer to section 8 of EC Detailed Guidelines on Good Clinical Practice Specific to Advanced Therapy Medicinal Products, which lists specific considerations.

7 Urgent Safety Measures

The Clinical Trials Regulations allow the sponsor and investigator to take appropriate urgent safety measures to protect clinical trial subjects from any immediate hazard to their health and safety. The measures should be taken immediately. There is no requirement to wait for competent authority or ethics committee approval before implementing urgent safety measures. For UK trials, the MHRA advise the sponsor to phone the MHRA Clinical Trial Unit and discuss the event with a safety scientist prior to reporting if this is practicable. The sponsor must report the urgent safety measure in writing to competent authorities and ethics committees within 3 days* of the action being taken. Details for reporting can be found on the **MHRA web site.**

Note: For pandemic research, the 3 day timeline does not apply but the urgent safety measure should be reported as soon as possible.

8 Pregnancy Notification and Follow-Up (Foetal Exposure to an IMP)

Pregnancies that occur while a subject is on a clinical trial should be notified to the sponsor as specified in the protocol. The local investigator must also ensure that any pregnancy is followed-up until outcome. This follow-up ensures the detection of any congenital anomalies or birth defects that may occur when:

- Females participating in trials become pregnant; or
- The female partners of males participating in trials become pregnant.

Any events (including congenital anomalies/birth defects) that meet the definition of a SAE/R would need to be notified in accordance with the Clinical Trials Regulations (see section 1.2 SAE/R definition and section 4). In addition, if evidence exists to suggest foetal exposure to a particular IMP may cause a longer term safety issue, (for example, learning difficulties caused by exposure to methotrexate), then the follow up period should be defined appropriately and these timeframes and any follow-up requirements, made clear in the protocol.

A congenital anomaly would only need to be expedited to competent authorities and ethics committees if it met the definition of a SUSAR or if the requirement to report specific safety information is specified in the protocol (usually if it was known that the IMP posed a specific risk).

If it was suspected that a pregnancy occurred due to a drug interaction that reduced the efficacy of hormonal contraception (resulted in a healthy pregnancy and baby), this would be a drug interaction of note that should be considered in all future trials. Such information would also be relevant to report in the annual safety report (DSUR) for that trial/IMP.

9 Patient Safety Incidents

Although not a requirement of the Clinical Trials Regulations, local investigators should ensure their host organisations are notified of patient safety incidents that occur on that trial according to the organisation's incident reporting policy. Any adverse event occurring in a trial therefore, which meets the definition of a clinical incident must be reported through this route as well as in accordance with the protocol and local research reporting requirements.

10 Glossary of Terms

AE	Adverse Event
AR	Adverse Reaction
ATIMP	Advanced Therapy Investigational Medicinal Product
CI	Chief Investigator
CRF	Case Report Form (including electronic CRFs)
CTA	Clinical Trial Authorisation
CTCAE	Common Toxicity Criteria for Adverse Events
DIBD	Development International Birth Date
DLP	Data Lock Point
DMC	Data Monitoring Committee
DSUR	Developmental Safety Update Report
EVCTM	EudraVigilance Clinical Trial Module
IB	Investigator's Brochure
IBD	International Birth Date
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
NIMP	Non Investigational Medicinal Product
NRES	National Research Ethics Service
PI	Principal Investigator
PV	Pharmacovigilance
REC	Research Ethics Committee
RSI	Reference Safety Information
SAR	Serious Adverse Reactions
SAE	Serious Adverse Events
SmPC	Summary of Product Characteristics (also known as SPC)
SOPs	Standard Operating Procedures
SSAR	Suspected Serious Adverse Events
SUSAR	Suspected Unexpected Serious Adverse Reactions
TSC	Trial Steering Committee
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 Clinical Trials 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 (Regulation 3). In this document, 'sponsor' is used to describe the individual organisation or group members named in the CTA as sponsor for pharmacovigilance or the person(s) to whom these responsibilities/functions have been delegated.

Competent Authority: Refers to the licensing authority in each member state where a clinical trial is being conducted, which in the UK, is the MHRA

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/she is an investigator at any particular site, who takes primary responsibility for the conduct of the trial.

Principal investigator: The authorised health professional responsible for the conduct of that trial at a trial site, and if the trial is conducted by a team of authorised health professionals at a trial site, the Principal Investigator is the leader responsible for that team.

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): The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial. Ideally, the TSC should include members who are independent of the investigators, their employing organisations, funders and sponsors. The TSC should monitor trial progress and conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) or equivalent and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

See MRC Guidelines for GCP for Clinical Trials 1998 for terms of reference (Appendix 3)

Data monitoring committee (DMC):
A committee that is usually independent of the investigators, funders and sponsors 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 subject). It is recommended that appropriate reporting channels (normally via the sponsor) be established for each trial; for example, the sponsor should ensure that the DMC receives any information that may be relevant to their assessments, such as urgent safety measures (see Section 8.0).

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. 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.
- EMA Guidelines On Data Monitoring Committees

MHRA: The Medicines and Healthcare products Regulatory Agency. It is the competent authority for the UK in relation to the EU Directive and the Clinical Trials Regulations. A Clinical Trial Authorisation (CTA) from the MHRA is required before a clinical trial of an investigational medicinal product (CTIMP) 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 Clinical Trials 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 Clinical Trials Regulations do require that the REC is kept informed (within the same timelines as the MHRA) of all SUSARs that occur in a trial, and that the REC also receives a copy of the annual Safety Report.

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 Case Report Forms (CRFs).

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

- to record only serious adverse events; or
- to record only non-serious adverse reactions; 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 is usually 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.

Trials where non-serious adverse reactions of a particular clinical severity are collected: 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. Some drugs are expected to cause adverse reactions in a high proportion of subjects (e.g. with cytotoxic chemotherapy.) 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 subject.

In certain circumstances, it may be justifiable to restrict the collection of data on non-serious adverse reactions. The protocol might require that Case Report Forms record only adverse reactions or laboratory test abnormalities of a certain severity (for example, WHO grade 3 or 4 haematological toxicity). Less severe reactions may only be noted in the subject's medical records.

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 Case Report Form.

This might be appropriate in a trial comparing different treatment strategies based on licensed drugs used within 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 subjects with respiratory tract infections. In such trials, non-serious adverse reactions could be noted in subjects' medical records, and appropriate clinical action taken. However, it may be justifiable not to record non-serious adverse reactions on Case Report Forms 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 subject 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 Trial Steering Committee and sponsor to any major safety concerns. Consequently, this approach may impact upon the extent and frequency of DMC review.