General Principles of Pharmacovigilance in Clinical Development

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Abstract

Pharmacovigilance is a broad field that spans across all stages of the life cycle from preclinical drug development, clinical development, marketing approval, and post-marketing use. This chapter will focus on the pharmacovigilance aspects of interventional clinical trials. It provides a brief overview over the key elements of protecting patients in clinical trials as well as collecting and reporting safety information for the purposes of developing the safety profile of an investigational medicinal product. Regulations and requirements across the globe are complex and national, while certain international standards through the ICH guideleines form a common basic platform through which multinational clinical trials can harmonise.

Introduction and Scope

Pharmacovigilance / Drug safety is a broad field that spans across all stages of the life cycle from preclinical drug development, clinical development, marketing approval, and post-marketing use. This chapter will focus on the drug safety aspects of interventional clinical trials; other studies such as observational or epidemiological studies and non-study pharmacovigilance of drug use after marketing approval are beyond the scope.

The following pages will initially look at the regulatory requirements – taking the ICH guidelines (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, ICH) first and then adding a brief view on the legal framework and guidance in three major regions in the world: the US Food and Drug Administration (FDA), the European Union's European Medicines Agency (EMA), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA).

Thereafter key definitions and terminology are introduced to provide the basis for understanding of the following discussions around planning a clinical trial, the collection and reporting of adverse events and the tools and requirements for monitoring of patient safety in clinical trials, and, lastly, actions to take to actively protect patients.

The rules and regulations that govern drug safety in clinical trials are complex and, as they are within the jurisdiction of each individual country's health authority, differ across the world. Therefore, this chapter will focus on the underlying fundamental principles and rely on the definitions and basic rules agreed in the ICH guidelines, which form the basis from which individual country regulations have further evolved. Wherever and whenever an actual clinical trial is being planned, it is critical to ensure that the specific rules of the country or countries where this clinical trial will be conducted are followed.

When designing a clinical trial, a clear research question needs to translate into defined objectives for the study and specific data collected to meet the primary (and secondary) objectives of the trial. In the typical efficacy clinical trial, these will be a small and very well-defined set of data points. However, the purpose of drug safety in clinical trials is broader and beyond the narrowly defined efficacy data set, and the vast majority of data collected is in support of the drug safety requirements.

Drug safety in clinical trials has a twofold purpose and in the order listed firstly to protect the subject/patient who is participating in the clinical trial and secondly to understand the general drug safety and tolerability of the drug being studied for the protection of patients who would be exposed to the drug after its approval in general use and under less well-controlled conditions than those within a clinical trial. The purpose and

priorities have their origin in the Declaration of Helsinki and form the fundamental basis for clinical trials and the ethics governing scientific research.

The Interests of the Individual Patient in the Study Have Precedence over the Interests of Society at Large

This principle is taken forward in the practical guidelines on GCP (ICH E6) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 2016).

Regulatory Requirements

ICH

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline E6 "Good Clinical Practice" (GCP) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 2016) was finalized in 1996. It is the international basis describing the responsibilities and expectations of all stakeholders in the conduct of clinical trials in Europe, Japan, the USA, and beyond.

The clinical safety-related guidelines (as opposed to the ICH safety guidelines, which concern preclinical requirements) are presented in ICH E2A-F and the Medical Dictionary for Regulatory Affairs (MedDRA) under the ICH multidisciplinary guidelines. Those specific to safety in clinical trials are:

- E2A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 1994)
- E2B(R3) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 2013a) and E2B(R3) IWG (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 2013b) – Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (ICSR) and Implementation: Electronic Transmission of ICSRs
- E2F – Developmental Safety Update Report (DSUR) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 2010)

USA

The Food and Drug Administration (FDA) is the supervising authority for investigational new drugs and interventional clinical trials in the USA.

Interventional clinical trials performed in the USA are regulated by the code of federal regulations CFR (Code of Federal Regulations (CFR) – Title 21 food and drugs – Chapter I food and drug administration (FDA), Department of health and human services – Subchapter D – Drugs for human use – Part 312 – Investigational new drug application (n.d.)). In CFR Title 21, Chapter I, subchapter D, part 312 "Investigational New Drug Application," the general rules and detailed requirements are described, from setup and application until the closure of a clinical trial.

Definitions and specifics about the collection, ongoing analysis, and reporting of safety information are outlined in §312.32 "IND safety reporting."

Additional information can be found in the "Final rule" guidance document on 21 CFR Parts 312 and 320 "Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans."

EU

The regulations that currently govern interventional clinical trials in the EU are complex. EU Directive 2001/20/EC is the underlying basis, but legally binding is its adoption into local legislation in the individual EU member

states (e.g., German "Arzneimittelgesetz"), which in parts vary from country to country.

Details on the collection and reporting of safety information can be found in EU "CT-3" guidance document "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use" (2011/C 172/01) (European Commission 2011).

EU Clinical Trial Regulation 536/2014 was adopted and entered into force in 2014 and will replace in the second half of 2019 the existing EU Clinical Trial Directive 2001/20/EC and all national legislation that was put in place to implement this Directive. But there will be an interim period of 3 years, where clinical trials can still be run according to the national legislation.

Japan

The Pharmaceuticals and Medical Devices Agency (PMDA) is the supervising authority for the conduct of interventional clinical trials in Japan.

Clinical trials in Japan are carried out in accordance with the Japanese Ordinance on Standards for Conduct of Clinical Trials (GCP) (Enforcement Regulations of the Law on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics 1961; Pharmaceutical Administration and Regulations in Japan 2017; J-GCP Ordinance of the Ministry of Health and Welfare 1997).

Key Definitions (ICH E2A)

Adverse Event or Adverse Experience (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., there are facts (evidence) or arguments to suggest a causal relationship.

Unexpected Adverse Drug Reaction

An unexpected adverse reaction is one, the nature or severity of which is not consistent with the applicable investigator's brochure.

Serious Adverse Event (SAE)

Any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Serious Unexpected Suspected Adverse Reactions (SUSARs)

Any adverse event that is serious, is unexpected, and is suspected to be causally related to the investigational drug.

Planning of a Clinical Trial

The Investigator's Brochure (IB) is the Reference

This is the key document for any clinical trial; it forms the core of the submission package when applying for approval to conduct the clinical trial and as a living document will evolve during the conduct of a clinical trial program, as more information becomes available over time.

Each clinical trial is supported by the IB, containing all information on the study drug available at the time and providing a broad overview of the known safety and tolerability of the investigational medicinal product (IMP). The majority of the IB will be taken up by detailed descriptions of studies and research results available and displaying both the growing knowledge of the targeted efficacy and the gained safety information to inform the investigators, ethics committees (ECs)/institutional review boards (IRBs), and authorities approving the trial. The safety information will be further summarized in a concise section of the IB of a highly technical nature, known as the Reference Safety Information (RSI).

The RSI presents a list of any events identified in previous clinical trials as expected serious adverse drug reactions (SADR). Of note, this means that events which are **not** listed in the RSI are "unexpected" and therefore potentially reportable: the RSI guides the selection of individual safety reports that have to be reported to authorities, other investigators, and ethics committees during the conduct of the trial – because they are new information that has not previously been observed. The requirements for selecting appropriate events for the RSI is guided by detailed rules, particularly clearly laid out within the European regulations.

The Informed Consent Form to Include All Relevant Safety Information

While the IB is a technical, scientific document that is used for reviewing authorities, ethics committees, and investigators, the subject/patient in the study also needs to receive transparent and comprehensive information about the clinical trial, the demands of the protocol, and what is known about the study drug. The relevant safety information available – and what is not yet known about the drug – needs to be summarized in a concise, readable fashion that allows a layperson to understand the possible benefits but importantly the possible risks of participation in the clinical trial.

Routine Safety Data Collection: Adverse Events/Serious Adverse Events

As part of the planning/designing of a clinical trial, the protocol will have to define very clearly what data will be collected in the context of the trial. For interventional clinical trials, the standard set of data to be collected in (almost) all instances are adverse events and serious adverse events, regardless of causality – furthermore, the investigator and study sponsor are required to make an assessment as to whether or not an event observed in a study subject is possibly related to the study drug or not. Where the investigator – or the receiving sponsor of the clinical trial – considers an event possibly related to the study drug, the adverse event is considered a possible adverse drug reaction (ADR).

The study protocol defines not only what safety data will be collected, but it will also define timelines by which the investigator has to communicate with the sponsor and send certain reports in a more expedited manner than simply collecting the information in the case report form (CRF) of the trial subject. Typically events that have to be sent faster to the sponsor of the clinical trial are those that may require onward reporting in a quick turnaround to authorities, ethics committees, and other investigators – these will be the SAEs but may also include certain events of special interest and some so-called special situation reports (SSRs) like pregnancies, or medication errors (see below).

Outcome Events/Unblinding of Data

The adverse event information collected in certain clinical trials may serve a purpose beyond the general understanding of the safety of study subjects, but specific events may also constitute part of the data collected for answering the efficacy objective of the clinical trial. Such trials are named clinical outcome trials and study the impact of an intervention (in most cases the administration of a drug) on defined clinical outcomes. For example, cardiovascular outcome trials investigate strokes, heart attacks, and death – all of

such events would clearly be collected as adverse event safety data but at the same time are the key "endpoint events" for answering the efficacy question whether a certain medical intervention may prevent or reduce such cardiovascular outcomes.

In such clinical outcome trials, the planning of collection, data handling, assessment, and adjudication of defined "outcome events" is a key point and requires a complex system setup to standardize events as much as possible. Beyond the investigator reporting an event, such events routinely go to a separate adjudication committee, who reviews the available information and applies preset definitions and algorithms to maximize homogeneity of diagnosis.

In case of clinical outcome trials, the outcome events often constitute serious unexpected events In case of a suspected causal association these events would meet the definition of a SUSAR and require unblinding and reporting to Authorities and Ethics Commitees. It is therefore important in a clinical outcome trial protocol, that the protocol clearly identifies the specific outcome events. The study sponsor will have to obtain agreement with the supervising authorities and ethics committees for special conditions for the reporting or unblinding of outcome events. Global guidelines allow for clearly defined, case-by-case agreements on reporting conditions for outcome events to avoid routine and systematic unblinding of such events, which may threaten the data integrity of the clinical trial.

Definition of Expected Events/ Adverse Events of Special Interest

A primary part of the planning for a clinical trial and indeed a whole clinical development program is to determine (and update regularly) the RSI in the IB but also consider whether there are any adverse events of special interest (AESI). These AESIs may be nonserious in nature, but perhaps the preclinical program suggested that there may be a possible issue with a certain type of event (e.g., skin reactions or diarrhea) or they are part of the symptons of the treated disease but may be of particular importance to determine whether the study drug is a contributing factor or modifies the event in any way and requires an intensive additional diagnostic pathway to ensure full understanding (e.g., hepatic or neurologic events of a certain nature). Adverse events of special interests are then identified in the IB and the specific study protocol and require the investigator to perform more detailed data collection, possibly perform a set of predefined mandatory additional diagnostic tests and also expedited communication to the study sponsor – often aligned with the timelines for reporting SAEs. Therefore AESIs will undergo special and fast scrutiny by both investigators and sponsors, and the information on such events will be maximized – this may over the course of a development program disprove a preclinical concern or elucidate specific treatment pathways that may be helpful for later use of the drug in the post-approval era (such as effective treatment of drug-induced diarrhea).

Standardized Data Collection for Later Pooling

When planning a drug development program, the overall aim is to develop clinical data to the purpose of marketing authorization. From the very outset, the different clinical trials to be conducted need to be designed in a fashion that will allow them to be used not just in isolation, but the data should be standardized so that pooling of data from multiple studies becomes possible. In order to support analysis and understanding of emerging safety profiles, the data from different studies should be combinable as well as separating different subgroups and populations from across studies.

Data and Safety Monitoring Boards (DSMB)

When planning a clinical trial or a whole program, the setting up of a DSMB is a complex and important task to ensure effective oversight over the

clinical szudy or program. It requires the identification of the appropriate membership and development of communication routes and mechanisms to supply data, charters, and rules of communication among the members as well as with the sponsor, meeting frequency, review principles, and standards of assessment. The DSMB is set up independently from the conduct or sponsor of a clinical trial with the aim to perform ongoing unblinded data monitoring while the study is ongoing. DSMBs are often set up to support a number of studies in the same program and provide ongoing guidance to the study sponsor as to whether the trial may continue as it is, requires modification, or should be terminated. The sponsor remains blind and will not receive the detailed reviews of the DSMB, but only the final recommendation. The full DSMB materials, minutes, analyses and documentation will be added to the Trial Master File after end of study.

Endpoint Adjudication Committee

Where an endpoint of a clinical trial is not an objective measure (such as a blood pressure or a particular laboratory value) it is important to ensure standardization of the measure and remove subjectivity and variance as much as possible. Particularly for clinical outcome trials, where the endpoints may be composites of multiple adverse events – the standardization of diagnosis of each of the contributing events is critical and should be agreed upon beyond the individual investigator. An endpoint adjudication committee is a way to ensure that the defined endpoint events are diagnosed to a common standard and context independent, based on preset data elements, clinical tests, and diagnostics that allow a central diagnosis to be made.

Collection and Reporting of Adverse Events/Serious Adverse Events

Collection of Adverse Events

Adverse Events and Serious Adverse Events are actively collected by the investigator and sponsor starting from the moment a participant signs the informed consent and until leaving the clinical trial (protocol defined end of data collection).

All AEs experienced by a patient at a certain point in time form an adverse event case report, an ICSR (individual case safety report). The ICSR forms the smallest unit of reporting – it may contain more than one event in the patient.

The investigator uses an AE/SAE form, paper or electronic, to document the AE(s) the study participant has experienced. The AE/SAE form can be integrated into the electronic Case Report Form (eCRF) of the trial or be a separate, loose form.

All adverse events have to be evaluated by the investigator and sponsor concerning seriousness, causal relationship, and expectedness. The assessments given by the investigator should not be downgraded by the sponsor.

Usually all nonserious AEs are entered into the clinical trial database and all serious AEs into the clinical trial and safety database. Consistency of the two databases has to be ensured by either the way of collecting AEs (simultaneously and electronically into both databases) or later reconciliation between the databases.

Case reports containing a serious unexpected suspected adverse reaction (SUSAR) event are usually unblinded, unless they are defined as exempted outcome events by the clinical trial protocol. The investigational drug given (verum, comparator, or placebo) is then documented in the case report in the safety database.

Adverse events are coded using the Medical Dictionary for Regulatory Affairs (MedDRA).

Special situation reports without an associated adverse event (e.g., pregnancy, overdose, medication error, etc.) might not qualify for individual

case reporting but nevertheless need to be recorded by the sponsor for continuous and cumulative safety analysis and presentation and discussion in periodic aggregate safety reports such as the Development Safety Update Report.

Reporting of Serious Adverse Events

The obligations on the collection and reporting of safety information of a clinical trial are directly conferred with the approval to perform a clinical trial and lie with the study sponsor (the applicant for the clinical trial authorization).

The safety information collected in the clinical trial is reported by the investigators to the study sponsor – in the (e)CRF or on special forms and there is a subset of data that requires prompt (expedited) reporting to the sponsor – these are mainly serious events. Case reports containing a serious unexpected adverse reaction then have to be reported further by the sponsor.

When a case is initially reported to a sponsor, the report may be incomplete – for reasons where there is still a lack of knowledge, as the situation of the patient is still evolving or because a form has not been effectively completed. Only cases that contain a minimum set of data should be reported onward – these are considered "valid" cases for the purposes of reporting.

For the purpose of reporting cases of suspected adverse reactions, the minimum data elements for a valid case are:

- An identifiable reporter
- An identifiable patient
- An adverse reaction
- A suspect medicinal product (see Annex IV, ICH-E2D Guideline (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 2003))

If any of these elements are missing, the case is considered "nonvalid" for expedited reporting purposes, and while at that time therefore not reportable, it is incumbent on the sponsor of the clinical trial to follow up the case intensively and urgently to ensure that at least the minimal criteria are all met. In the setting of a clinical trial, there should not really be any nonvalid cases, as the structured and tight control over the treatment and data collection on all patients should ensure that all four minimal criteria are always available even at the first instance.

Depending on national legislation, the individual case reports have to be as a minimum reported in an expedited manner to national competent authorities. There are strict timelines defined for the reporting, usually 7 calendar days after first awareness, if the case report is classified as fatal or life-threatening, and 15 days for all other serious case reports. Based on the applicable legislation, these case reports might have to be reported, if the adverse reaction not only is causally associated to verum, but to a comparator drug or even placebo (although this is rare, if there is a suspicion of the ADR being related to an excipient).

The identification of potentially reportable cases in a timely manner as they are received by the sponsor of the clinical trial is a key activity in the ongoing support of a clinical trial. Particularly where a clinical trial is conducted in a double-blind fashion, the regulatory requirements of the EU require unblinding of the treatment code for the patient, unless there is a prior documented agreement with the authority who approved the clinical trial that certain events do not require unblinding (such as in the case of endpoint events in a clinical outcome trial). In the context of international clinical trials conducted in several countries worldwide, the sponsor will usually apply a common standard to reporting to authorities – so that all authorities receive the same information and therefore may report cases in an unblinded manner to authorities who do not require it.

Figure 1 presents an algorithmic decision tree to determine whether a case requires unblinding and potentially reporting. This is taking general principles only and would need to be adjusted and supported by detailed reporting requirements for each country, ethics committee and site, as any of these may have additional requirements for other events to be reported than SUSARs.

The challenge with unblinding of SUSARs for the purposes of expedited reporting is to ensure

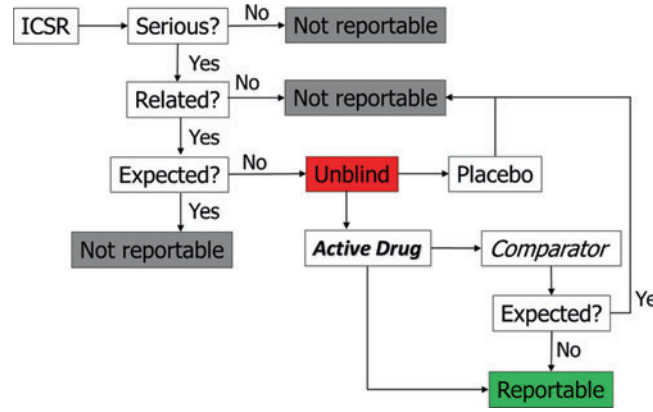

Fig. 1 Assessing reportability in blinded clinical trials (by ARvanTroostenburg)

that only a few select individuals in the sponsor responsible for reporting the event (typically a part of the drug safety personnel) receive the information on the treatment allocation of a patient and that this information is not shared with personnel otherwise involved in the conduct of the clinical trial or investigators.

In addition to reporting of SUSARs to supervising national competent authorities, individual countries may require reporting of individual case reports to ethics committees and to participating investigators. Timelines and report format vary from 7/15 days individual case reports to, e.g., quarterly batch reports with cases included in form of a line listing. Also, while reports to ethics committees will be of the same standard as the reports going to the national competent authority – i.e., in an unblinded fashion, reporting to investigators is done blinded, so as not to affect the integrity of the blinded study design and bias the investigators. Only in the case of a major safety concern arising from received safety information is consideration given to unblinding investigators at the same time as all other personnel – this is in general only when major actions for the safety of the patients in the clinical trial may have to be considered (see further below for Urgent Safety Measures).

If required or possible, expedited reporting can be done electronically using the ICH defined E2B standard.

Reporting requirements for serious unexpected adverse reactions continue even after the end of the clinical trial. Therefore collection, processing (only in the safety database), and reporting of respective case reports received after the end of the trial continue.

Events relevant for patient safety may occur during a clinical trial which do not fall within the definition of a serious unexpected adverse reaction and thus are not subject to the reporting requirements described above, e.g. a major safety finding from a newly completed animal study, such as carcinogenicity. Sponsors are also obliged to inform the national competent authority, ethics committee, and investigators of findings that could adversely affect the safety of subjects, impact the conduct of the trial, and might materially alter the current benefit-risk assessment for an investigational drug.

Monitoring of Patient's Safety and Actions

Continuous Monitoring of Patient's Safety

The sponsor is responsible for the ongoing safety evaluation of the investigational drug. Ongoing safety evaluation consists of various layers of safety monitoring activities.

Evaluation and assessment of individual case reports are performed during case processing. An important aspect is the causality assessment. To decide about a potential causal association between drug treatment and adverse event a variety of aspects can be taken into account, e.g.,

timely relationship, pharmacological plausibility, de-challenge and rechallenge, concurrent diseases, and concomitant medication.

Cumulative interim safety analyses are performed at specified time points. It may include a comparison of adverse event rates for verum against comparator/placebo or a comparison of adverse event rates against predefined expected rates based on epidemiological data, or identification of trigger events to detect cases of interest, e.g. Hy's Law cases and drug-induced liver injury.

In case of blinded clinical trials, the support of an external Data and Safety Monitoring Board for unblinded analysis is needed to keep staff of the sponsor involved in the conduct of the clinical trial blind.

Another tool for a cumulative safety evaluation is the Development Safety Update Report.

Development Safety Update Report

The ICH E2F Guideline (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 2010) defines format and content of the Development Safety Update Report (DSUR). It provides periodic (typically annually) analysis of clinical trial safety for an investigational drug. The DSUR summarizes identified and potential risks, describes new safety issues that arose during the period of the report, determines if reporting period safety information is in accordance with prior product safety knowledge, and provides an update on the clinical development program. The main focus is on interventional clinical trials, ongoing or completed during the reporting interval. The investigator's brochure is the reference document for the DSUR.

Included in the DSUR is a line listing of serious adverse reactions arising in the reporting interval and a cumulative tabulation of all serious adverse events organized by MedDRA System Organ Class, from the start of development to date, for verum, comparator, placebo, and still blinded cases.

Actions and Measures

New relevant safety information, such as newly identified safety issues, changed product safety knowledge, or DSMB recommendations, may warrant actions to be taken in a clinical trial or even across a whole clinical program.

A basic measure is the update of the investigator's brochure. New product safety knowledge is included and newly identified side effects added to the Reference Safety Information (RSI). Updates of the IB are usually performed on a frequent basis (e.g., yearly) to include and summarize the increasing knowledge about the developmental drug.

Safety issues having a significant impact on the safety of the subjects may require a substantial protocol amendment, e.g. changing exclusion criteria or introducing a new monitoring procedure and need to be submitted to national competent authorities and ethics committees for approval.

Safety issues requiring urgent safety measures to protect subjects against any immediate hazard, such as temporarily halting of the clinical trial, may be taken immediately without prior authorization from the competent authority in form of an urgent amendment. The sponsor must inform the competent authority and the ethics committee concerned as soon as possible. Some countries have strict timelines in place for the reporting of Urgent Safety Measures, and there may be only a few hours from the information being available to the study sponsor to the need to inform competent authorities. Therefore a rapid assessment and decision-making system needs to be in place at the sponsor to be able to respond to major safety issues with all due haste for the protection of patients in the clinical trial – or also possibly a whole development program of many clinical trials.

References and Further Reading

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