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Curriculum Development of Human Clinical Trials for the Next Generation of PhD Students and Early Career Researchers in Medical, Science, Pharmacy and Health Professions

# CHAPTER 5

# PHARMACOVIGILANCE AND STUDY MEDICATION

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## Content



**Time required to complete this chapter**

| | |
|---|---|
| Core content: | 1h 10m |
| Additional/advanced content: | 0h 20m |
| Activities/practical exercises: | 1h 00m |
| **Total time:** | **2h 30m** |

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# 1 Introduction to the chapter

This chapter aims to give adequate information to describe the importance of pharmacovigilance, why we need to monitor drug safety, and how it fits with the lifecycle of a medicinal product. In other words, what should be done in particular safety situations in clinical trials? The lesson will also describe the issues around investigational medicinal products (IMPs) (study medication) and their handling, regulatory requirements, including responsibilities of team members. This chapter will also focus on the broader perspective of using unauthorized products.

# 2 Practical aspects of pharmacovigilance in clinical trials

## 2.1 General introduction, authorized and unauthorized products

Pharmacovigilance is the science and activities relating to the **detection** (identifying, collection), **assessment** (evaluation), **understanding**, **reporting,** and **prevention** of **adverse effects** (*Adverse drug reactions; ADRs*) or any other **medicine-related problem** (*Adverse Events; AEs*) during **the whole drug life cycle** (pharmacovigilance is a key part of the effective drug regulation systems, clinical trials, clinical practice and public health programs).[1] Being "vigilant regarding medicines" (generally, not only in clinical trials) is essential today because of the following:

- medicine overuse;
- polymorbidity;
- accelerated approval of some drugs;
- the increasing complexity of medicines, polypharmacy;
- population growth, diversity, and aging.

In practice, this means having in place a **well-organized and robust** pharmacovigilance system/arrangement, which provides the foundation for a national ethos of medicine **safety**, and for public **confidence** in medicines. To be effective, the remit of drug regulatory authorities needs to go further than the approval of new medicines to encompass a broader range of issues relating to the safety of medicines, namely:

- preclinical tests;
- clinical trials;
- the safety of 'Complementary and Alternative Medicines (CAM)', vaccines, and biological medicines;
- general public engagement;
- the development of effective lines of communication between all parties interested in medicine safety ensures that they can function efficiently and ethically, particularly in times of crisis.

Pharmacovigilance programs and drug regulatory authorities must collaborate to achieve their respective objectives. On the one hand, pharmacovigilance programs need to maintain strong links with the drug regulatory authorities to ensure that the latter are well briefed on safety issues in everyday clinical practice, whether these issues are relevant to future regulatory

[1] https://www.who.int/teams/regulation-prequalification/pharmacovigilance

action or to concerns that emerge in the public domain. On the other hand, regulators need to understand the specialized and pivotal role that pharmacovigilance plays in ensuring the ongoing safety of medicinal products.

A new medicine must comply with three essential requirements before the drug regulatory authority approves it. Sufficient evidence is required to show the new drug be:

- of good quality,
- effective, and
- safe for the purpose(s) for which it is proposed and has an adequate benefit-risk balance.

In other words, unlike the first two requirements, safety is not absolute and can be judged only in relation to efficacy, requiring judgment on the part of the regulators in deciding on acceptable safety limits and an acceptable benefit-risk balance. Rare serious adverse events (such as those occurring with an incidence rate of 0.001) are hardly detectable in the pre-registration clinical development phase of the drug. Therefore, benefit-risk must be continuously reassessed during the post-marketing setting within the drug's life cycle. More information on pre-registration and post-marketing pharmacovigilance settings is in part 2.4.

You may have noticed several specific terminologies in the previous paragraph – e.g., serious adverse event. Are you sure about handling these terms?

**Further explanation of the terminology and pharmacovigilance ecosystem**
Knowledge of pharmacovigilance terminology is extremely important for all stakeholders involved in clinical research and product life cycle. What terms should you be able to distinguish?

- Adverse Events (AEs) and Adverse Drug Reactions (ADRs).
- Serious Adverse Events (SAEs) and Serious Adverse Drug Reactions (SADRs), Unexpected Adverse Drug Reactions (UADRs), Suspected Unexpected Serious Adverse Reactions (SUSARs).

Need a deeper insight into pharmacovigilance theory? Remind yourself of its importance. Open lesson 13 of the CONSCIOUS project.[2]

You can, moreover, watch this short YouTube video "Adverse Drug Reaction (ADR) Vs Adverse Event (AE)".[3] An overview of the terminology can also be watched here (YouTube video "SUSAR in clinical trials - what is it? Clinical trials in short").[4]

Click here and watch this short 2-minute video explaining Pharmacovigilance (YouTube video "What is Pharmacovigilance").[5]

**Practical exercise: Adverse Event Scenario**
A randomized doubled blind Clinical Trial of an IMP "Wonderdrug" versus Humira (adalimumab) (marketed drug) in the treatment of psoriasis in adults. The active treatment period of 6 weeks: (Day 1 to Day 42), during which the patient gets weekly subcutaneous (SC) injections of "Wonderdrug" or Humira. Weekly visits to the Dermatology clinic (to take place on days 1,7,14,21,28, and 35 where the patient fills out a self-assessment of symptoms, the Principal Investigator (PI) of the study

[2] http://conscious.novaims.unl.pt/login/index.php
[3] https://youtu.be/z7C6Uc1G5kE
[4] https://youtu.be/DP8jNoZFtx8
[5] https://youtu.be/aaY7CMmcq-Q

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assesses psoriasis symptoms, and the study nurse delivers an SC injection of “Wonderdrug” or Humira (blinded). The patient stops study medication after 6 weeks. The final study visit on day 42 involves a psoriasis assessment by the PI and self-assessment by the patient.

**Day 0:** The patient is seen by the PI for assessment of suitability, inclusion/exclusion criteria, etc. The patient consents, is enrolled in the study, given the first injection of “Wonderdrug” or Humira.

**Day 8:** The patient slips on ice and suffers a broken arm and substantial grazes to their right knee. The patient attends the local A&E department, has the arm x-rayed and set, has the knee cleaned and dressed, and returns home on the same day.

**Day 14:** During the study visit, the patient complains of pain in the broken arm. The PI notes that the knee wound has become infected. The PI prescribes analgesics and cleans and dresses the knee.

**Day 17:** The patient is admitted to the hospital with a severe local infection in the knee wound. The patient is given IV antibiotics.

**Day 19:** The infection has not responded to the IV antibiotics, has become systemic, and is now life-threatening. The patient is unconscious.

**Day 21:** The patient begins to improve.

**Day 26:** The patient is discharged and goes home.

**Day 27:** Laboratory results come back to the PI. Based on lab test results, the investigator thinks it’s possible that the IMP may have compromised the patient’s immune system and that this has exacerbated the infection. This has not previously been reported with this IMP.

**Questions**

1. Which category does the broken arm fall into (AE, SAE, SUSAR, Not an AE)?
2. Which category does the knee injury on day 14 fall into?
3. Which category does the knee injury on day 17 fall into?
4. Which category does the knee injury on day 19 fall into?
5. Which category does the knee injury on day 27 fall into?

**Topics for further study, research, discussion board**

Answer the following questions.

1. What is the major problem in detecting AEs?
2. How could a GP/Physician/Principal investigator/Collaborating investigator detect if a patient has an AE?
3. What causes AEs?

## 2.2 Principles of the setting of the pharmacovigilance unit/team in a clinical trial

The key and patient-closest players involved in the pharmacovigilance system in a clinical trial are:

- **Investigator** – identifying, evaluating, and reporting any AE to Sponsor during the clinical trial.
- **Sponsor** – receiving the reports from investigators, creating the Development Safety Update Reports/Annual Safety Reports (DSURs/ASRs; see later), and submitting them to regulatory authorities and Ethics Committees/through CTIS. The sponsor may decide to terminate the trial in the event of any safety concerns also.

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- **Competent regulatory authority** – receiving the reports, DSURs/ASRs; decision making if a clinical trial may continue or must be terminated.
- **Ethics Committee** – receiving the reports, DSURs/ASRs; decision making if a clinical trial may continue or must be terminated.

In the case of an investigator-initiated clinical trial, the setting of responsibilities in the pharmacovigilance field can be misinterpreted. If the investigator is a sponsor at the same time, roles **must be clearly separated** for pharmacovigilance team members and investigator. **All reported AEs** must be independently revised and evaluated by a second person. In any case, it must not be the investigator himself/herself because of transparency ensuring and bias avoiding; usually, it is the responsibility of the **Safety manager** or **Medical advisor** at the Sponsor site – their **background must be human medicine,** but they must not be involved to study team members, reciprocally. **All reported SAEs** must be checked during monitoring visits without exception. The additional questions (queries) to the SAE reports done by an independent monitor/clinical research associate/safety manager must be answered by the investigator as soon as possible. It is clear that the monitoring of SAEs cannot be done by the investigator, irrespective of his/her (possible) role as a sponsor.

The human capacity and experience in pharmacovigilance or monitoring can be limited in some clinical trial sites, which are simultaneously the Sponsors of a clinical trial (especially in investigator-initiated clinical trials where the Sponsor is, e.g., a university or a hospital). Some of them can **outsource this service** to any experienced company. It is important to keep in mind that even though the Sponsor may outsource this service, the Sponsor continues to be fully responsible for pharmacovigilance and safety reporting obligations. Thus, the Sponsor needs to verify that the third party is performing the services effectively, in high quality, and according to delegated tasks, and an external audit by the Sponsor is a tool for verifying it.

## 2.3 Reporting in clinical trials generally, including case reports

The pharmacovigilance is an integral part of each clinical trial. The clear and predefined rules of all AEs, SAEs, SUSARs,… reporting are defined in the European legislation. Reporting in clinical trials is one of the main responsibilities of the investigator/sponsor.

For detailed information, visit the link Legal framework: Pharmacovigilance | European Medicines Agency (europa.eu).[6]

### 2.3.1 Key partners and pillars in pharmacovigilance

The **European Medicines Agency** (EMA) is a decentralized agency of the European Union. The Agency is responsible for the scientific evaluation, supervision, and safety monitoring of medicines in the EU. Please click here to find out more about the EMA.[7]

The **Pharmacovigilance Risk Assessment Committee** (PRAC) is the EMA committee responsible for assessing and monitoring the safety of human medicines. The committee

[6] https://www.ema.europa.eu/en/human-regulatory/overview/pharmacovigilance/legal-framework-pharmacovigilance
[7] https://www.ema.europa.eu/en

ensures that drugs **approved** for the EU market are optimally used by maximizing their benefits and minimizing risks. Please click here to find out more.[8]

**A safety signal** is an information on a new or known adverse event that may be caused by a medicine and requires further investigation. The EMA, together with the regulatory authorities in the Member States and Marketing Authorization Holders are responsible for detecting and managing safety signals. Safety signals can be detected from a wide range of sources, such as **spontaneous reports, clinical studies, and scientific literature**. The **EudraVigilance** database is an important source of information on suspected adverse reactions and signals.[9,10]

**EudraVigilance** is a system for monitoring the safety of medicines that are under development (clinical trials) or have been authorized in the European Economic Area (EEA). Its components facilitate electronic reporting of SAEs related to medicines and the effective analysis of data. This enables the early detection of potential safety issues. Please click here to find out more about the EudraVigilance.[11] EudraVigilance provides two reporting modules:

- The EudraVigilance Clinical Trial Module (EVCTM) to facilitate the electronic reporting of SUSARs as required by Directive 2001/20/EC and Reg. (EU) 536/2014.
- The EudraVigilance Post-Authorisation Module (EVPM) for post-authorization Individual Case Safety Reports (ICSRs) as required by Regulation (EC) No 726/2004, Directive 2001/83/EC as amended.

As a means of pooling existing data on ADRs, **WHO's Programme for International Drug Monitoring** was started in 1968. Currently, 131 countries participate in the program, which is coordinated by WHO together with its collaborating Centre in Uppsala, Sweden. The collaborating center is responsible for maintaining the global ADR database, Vigibase.

The **International Society of Pharmacovigilance** (ISoP) is a professional, independent, non-profit society open to anyone interested in the safe and effective use of medicinal products. ISoP aims to foster science and learning in pharmacovigilance in all countries by providing the following:

- Opportunities for networking in a friendly environment.
- Collegial and convivial support among fellow pharmacovigilance professionals.
- An open and impartial forum for sharing experience and knowledge.
- A platform for discussion and generation of new research and ideas.
- Meetings, education, and affordable training.

Please click here to find out more about ISoP.[12]

Please watch the video linked here to learn more about the WHO Programme for International Drug Monitoring (YouTube video "What does Uppsala Monitoring Centre do?").[13]

[8] https://www.ema.europa.eu/en/committees/pharmacovigilance-risk-assessment-committee-prac
[9] https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/signal-management
[10] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-ix-signal-management-rev-1_en.pdf
[11] https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance
[12] https://isoponline.org/
[13] https://youtu.be/1zTf78XU1sQ

Other pillars of pharmacovigilance are the **European Commission** (as the competent authority for medicinal products authorized centrally in the EU), **Marketing Authorization Holders**, **MedDRA** (Medical Dictionary for Regulatory Activities), and the regulatory framework. The key regulation is, of course, **Reg. (EU) 536/2014** ("Clinical Trial Regulation", CTR),[14] where the entire chapter VII focuses on Safety reporting in the context of a clinical trial, defines the responsibilities of the sponsor and the investigator, and refers to **ICH GCP E6(R2)** guidelines.[15,16] Moreover, Annex III summarizes reporting obligations. However, in some cases, **Dir. 2001/20/EC**[17] still applies ("Clinical Trial Directive", CTD). The cooperation of the EU Member States in the safety assessment of clinical trials is embedded here: **Commission Implementing Regulation (EU) 2022/20**.[18] On the other hand, this does not apply to you as potential investigators/sponsors/clinical trialists.

### 2.3.2 Reporting in clinical trials

We will focus on the **SAE Report Form**, the Council for International Organizations of Medical Sciences (**CIOMS**) Form – the two most important forms for the investigator regarding pharmacovigilance; and the Development Safety Update Report (**DSUR**) (replaced by the Annual Safety Report (**ASR**) according to the CTR). We will also outline the processes involved in reporting to the relevant authorities. But first, here is Table 1 outlining who is obliged to report and what they need to report, via which route, and within which period (via CTD/CTR – be aware of changes in recent years!). Regarding the "how" question in Table 1, it must be stressed that the way of reporting is specified in the protocol (not always all the mentioned ways are possible simultaneously). In other words, the investigator cannot select the method of reporting at his/her discretion.

**Table 1: Reporting in clinical trials**

| | Who? | To whom? | How? | Timelines |
|---|---|---|---|---|
| ADR | investigator | sponsor | ADR form or eCRF section or CIOMS form# | promptly but not specified in legislation, might be set in the protocol and local legislation |
| AE | investigator | sponsor## | AE form or an eCRF section | promptly but not specified in legislation, might be set in the protocol and local legislation |
| AESI### | investigator | sponsor | a specific form or an eCRF section | not specified in legislation, might be set in the protocol and local legislation |
| SADR | investigator | sponsor | SAE form or eCRF | within 24 hours from the moment when the investigator has learned about the fact |
| UADR | investigator | sponsor | | |
| SAE* | investigator | sponsor | | |
| SUSAR | investigator | sponsor | | |
| SUSAR | sponsor | EudraVigilance (under CTR and CTD) + (under CTD: CA in all concerned member states + ECs) + let investigators know | | within 7/15 days** (in the former case, follow-up information is communicated within following 8 calendar days) |

[14] https://eur-lex.europa.eu/eli/reg/2014/536/oj
[15] https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline
[16] A consultation on the proposed R3 version is running until September 26, 2023, so pay attention to the possible upgrades to the R3 version. https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline#revision-3-section
[17] http://data.europa.eu/eli/dir/2001/20/oj
[18] https://eur-lex.europa.eu/eli/reg_impl/2022/20/oj

| | Who? | To whom? | How? | Timelines |
|---|---|---|---|---|
| death as SAE | sponsor | under CTD, reported to the CA; under CTR, only when SUSAR – reported as SUSAR | | within 7 days (under CTD) |
| line listing*** | sponsor | multicenter EC + let investigators know | electronic or printed | every 6 months |
| DSUR[&] (under CTD)/ ASR (under CTR) | sponsor | CA and EC's under CTD; or to EudraVigilance under CTR | electronic or printed; format follows EMA guideline[19] (under CTD); CTIS (under CTR) | within one year of the date of first authorization of a clinical trial in any country worldwide (Development International Birth Date, DIBD) and annually. |

Abbreviations: CA – competent authority, EC – ethics committee (institutional review board)
[#] CIOMS form applicable, e.g., for trials having an authorized and on-label IMP, non-interventional or low-interventional trials.
[##] Sponsor must retain all AE reports and perform the evaluation.
[###] Adverse event of special interest (AESI)
* Except for those that the protocol or IB/SmPC identified as not requiring immediate reporting. Detailed, written reports shall follow the **immediate report**. The **immediate** and **follow-up reports** shall identify subjects by unique code numbers assigned to the letter.
** 7 days in case of outcome of death or life-threatening SUSAR; 15 days for the rest of SUSARs
*** Evaluation of the safety situation, whether it is necessary to adopt safety measures, and if so, which ones, including their justification. Line listing contains reports on SUSARs for the IMP, arising from the clinical trial.
[&] The DSUR/ASR might be supplemented with a line listing of AEs and/or SAEs.[20]

How does the SAE become a SUSAR? Why should the investigator use the SAE form for reporting?

Each AE must be assessed from different perspectives – seriousness, severity, expectedness, and causality by the investigator.

- The evaluation of the seriousness of AEs should follow the regulatory-defined seriousness criteria. The reporting investigator usually makes the judgment as to whether the event is serious.
- The assessment of whether there is a reasonable possibility of a causal relationship is usually made by the reporter who is approved for the notification, investigator, or collaborators. This task is mentioned in a delegation log. In the absence of information on causality from the reporting investigator, the sponsor should consult the reporting investigator and encourage him to express an opinion on this aspect. The clinical suspect provided by the first notifier is very important and is typically maintained by the sponsor, above all in investigator-driven clinical studies. The sponsor should not downgrade the causality assessment given by the investigator.
- The most important in the reception of an SAE is the suspicion to be related to the IMP, so to proceed to the expedited notification, it is clearly in dependence of the casualty reported by the notifier, so only this one is provided in the report.

[19] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-e2f-development-safety-update-report-step-5_en.pdf
[20] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-e2f-development-safety-update-report-step-5_en.pdf

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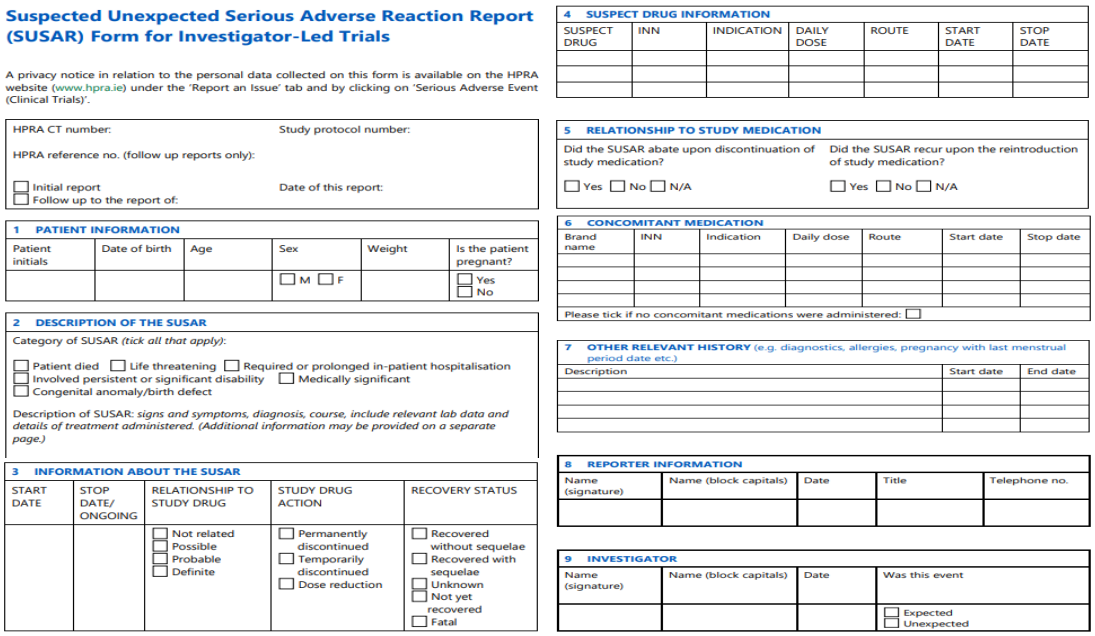
Let's look at the above-mentioned documents and start with the **SAE Report Form**. It is designed to allow for a proper case assessment and appropriate reporting in accordance with the applicable international standards. The available fields must be completed as much as possible with the relevant information available at the time of reporting. The minimal information to be reported includes:

- name or any identifier of a reporter (name of the, e.g., study nurse reporting the event);
- an identifier of the patient (e.g., patient study number);
- at least one suspected drug (study drug);
- at least one serious adverse event.

The SAE report form and SUSAR report form are the same. See here for an example through this reporting is all done online now (Figure 1).



**Suspected Unexpected Serious Adverse Reaction Report (SUSAR) Form for Investigator-Led Trials**

A privacy notice in relation to the personal data collected on this form is available on the HPRA website (www.hpra.ie) under the 'Report an Issue' tab and by clicking on 'Serious Adverse Event (Clinical Trials)'.

HPRA CT number: Study protocol number:
HPRA reference no. (follow up reports only):
☐ Initial report ☐ Follow up to the report of: Date of this report:

**1 PATIENT INFORMATION**

| Patient initials | Date of birth | Age | Sex | Weight | Is the patient pregnant? |
|---|---|---|---|---|---|
| | | | ☐ M ☐ F | | ☐ Yes ☐ No |

**2 DESCRIPTION OF THE SUSAR**

Category of SUSAR *(tick all that apply)*:
☐ Patient died ☐ Life threatening ☐ Required or prolonged in-patient hospitalisation ☐ Involved persistent or significant disability ☐ Medically significant ☐ Congenital anomaly/birth defect

Description of SUSAR: *signs and symptoms, diagnosis, course, include relevant lab data and details of treatment administered. (Additional information may be provided on a separate page.)*

**3 INFORMATION ABOUT THE SUSAR**

| START DATE | STOP DATE/ ONGOING | RELATIONSHIP TO STUDY DRUG | STUDY DRUG ACTION | RECOVERY STATUS |
|---|---|---|---|---|
| | | ☐ Not related ☐ Possible ☐ Probable ☐ Definite | ☐ Permanently discontinued ☐ Temporarily discontinued ☐ Dose reduction | ☐ Recovered without sequelae ☐ Recovered with sequelae ☐ Unknown ☐ Not yet recovered ☐ Fatal |

**4 SUSPECT DRUG INFORMATION**

| SUSPECT DRUG | INN | INDICATION | DAILY DOSE | ROUTE | START DATE | STOP DATE |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |
| | | | | | | |

**5 RELATIONSHIP TO STUDY MEDICATION**

Did the SUSAR abate upon discontinuation of study medication? ☐ Yes ☐ No ☐ N/A
Did the SUSAR recur upon the reintroduction of study medication? ☐ Yes ☐ No ☐ N/A

**6 CONCOMITANT MEDICATION**

| Brand name | INN | Indication | Daily dose | Route | Start date | Stop date |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

Please tick if no concomitant medications were administered: ☐

**7 OTHER RELEVANT HISTORY** (e.g. diagnostics, allergies, pregnancy with last menstrual period date etc.)

| Description | Start date | End date |
|---|---|---|
| | | |
| | | |
| | | |
| | | |

**8 REPORTER INFORMATION**

| Name (signature) | Name (block capitals) | Date | Title | Telephone no. |
|---|---|---|---|---|
| | | | | |

**9 INVESTIGATOR**

| Name (signature) | Name (block capitals) | Date | Was this event |
|---|---|---|---|
| | | | ☐ Expected ☐ Unexpected |

*Figure 1: Report form example*

Once the investigator fills in the SAE form, further processing is taken over by the sponsor pharmacovigilance team. Firstly, the pharmacovigilance team will conduct a validation check to ensure that minimum information for reporting is present. If a case is not valid, pharmacovigilance staff contact the sender and request the missing information. Any source documentation which is received is reviewed to ensure that it is anonymized.

The pharmacovigilance team then enters the data into a pharmacovigilance database in an expedited manner. All documents (SAE form, emails relating to the event, lab reports, etc.) relating to the case should be uploaded to the database. MedDRA coding of events and an expectedness assessment using the relevant reference safety information (RSI, see later) can be carried out as part of the process. A CIOMS form can then be generated. When this is complete, another member of the pharmacovigilance team carries out quality control of the case (e.g., MedDRA coding, expectedness assessment). A medical assessor is then requested to perform a sponsor causality assignment, i.e., definitely, probably, possibly, etc., and review of the case to determine if it is an SAE, SAR, SUSAR.

The case is updated when follow-up reports for new or amended information relating to the case are received from the site.

**The CIOMS form** provides a standardized format for the reporting of suspected ADR to any particular medical product (you can see that in standard healthcare practice to report ADR; however, obviously, it plays a role also in clinical trials).

For more information on the CIOMS 1 Form, please watch the YouTube video "CIOMS Form".[21]

If any SAEs occur during a clinical trial, this does not necessarily mean immediate termination of the clinical trial. For example, there can be predefined rules in the protocol in case of expected AEs and how to manage them. It can be ensured by dose reduction or IMP administration stopping, but the follow-up continues in each case.

If SUSARs occur, it is connected with unblinding and the termination of IMP administration, but the subject continues in the follow-up period, and data are collected from the participants.

**Let us add some important notes to unblinding:**

- Unblinding is never a decision of the pharmacovigilance team. This is a decision that must be taken by the Sponsor. The pharmacovigilance responsible can break the blind at the request of the Sponsor. But the decision must be taken by the Sponsor´s team.
- Caution must be taken with operational bias. Unblinding can be performed by the pharmacovigilance responsible or medical advisor, but the result of unblinding must never be communicated to the rest of the team to avoid breaking the study blind.
- The participant cannot continue with IMP after unblinding, but the safety data must be continuously collected. Specific SOPs must be in place describing the procedure.

**DSUR** is a key safety document released **by the sponsor annually** – as a potential investigator, you are outside of the pharmacovigilance team, and you have no direct obligations towards the creation of the DSUR, but the sponsor of a trial (including the investigator-initiated ones), must keep in mind this obligation.

DSUR is a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed, by:

- examining whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug's safety;
- describing new safety issues that could have an impact on the protection of clinical trial subjects;
- summarising the current understanding and management of identified and potential risks; and
- providing an update on the status of the clinical investigation/development program and study results.

DSUR can more comprehensively include critical information such as preclinical and epidemiological studies, as well as clinical trials that have been conducted. Additionally, non-interventional CTs conducted must also be reported, in terms of safety data.

[21] https://youtu.be/3g_v0BZMahM

All essential information on DSUR can be found in the ICH guideline E2F.[22] According to the CTR, the DSUR is replaced by the **Annual Safety Report (ASR)**.

Let us add one note to the difference between a DSUR and a PSUR (Periodic Safety Update Report). PSURs are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product at defined time points **after its authorization**.[23] The focus of the DSUR is on **investigational drugs**. However, there can be an overlap between the content of the DSUR and PSUR, and some repetition is expected. This issue is one of the differences between authorized and unauthorized products in terms of pharmacovigilance (further details are below in part 2.4). All essential information on PSUR can be found in the ICH guideline E2C. In this guideline, the PSUR is also named the periodic benefit-risk evaluation report (PBRER).[24]

For example, information from marketing experience (reported in the PSUR) might be relevant to clinical development and, therefore, reported in the DSUR. Safety findings from clinical trials conducted using marketed drugs would be included in the DSUR but would also be pertinent to post-marketing safety and would be reported in the PSUR. Both the DSUR and PSUR should be comprehensive and stand alone as they focus on different subject matter and have differing periodicities and recipients.[25]

## 2.4 Specific procedures in pharmacovigilance, authorized and unauthorized products

You may come across different usage options of an **unauthorized product and authorized product:**

In the case of an **unauthorized product**, two possibilities can be distinguished of its use:

1. In clinical trial – with the aim to get the authorization and to be marketed;
2. In compassionate use – see part 3.5.

In the case of **authorized product**, three possibilities can be distinguished of its use:

1. Standard use – in accordance with Summary product characteristic (SmPC);
2. “Off label use” – out of SmPC – unapproved use of an approved drug (e.g., age group, dosage, route of administration) but still in standard clinical practice;
3. In clinical trials – even though the product has received authorization, it can be used for clinical trial as an investigational medicinal product (IMP) (“study medication”, see part 3) (a test and/or a comparator).

**Pharmacovigilance** procedures **must be applied** in the whole drug lifecycle regardless of whether the product is already approved or not yet.

Based on the fact whether the product is already authorized or not yet, we distinguish some fundamental differences in the pharmacovigilance procedures:

[22] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-e2f-development-safety-update-report-step-5_en.pdf
[23] https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/periodic-safety-update-reports-psurs
[24] https://www.ema.europa.eu/en/ich-e2c-r2-periodic-benefit-risk-evaluation-report-scientific-guideline
[25] [25] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-e2f-development-safety-update-report-step-5_en.pdf

Let´s start with **terminology**:

A) AEs, SAEs, AESIs, SUSARs are used for **unauthorized products** during clinical trials.
B) ADRs, SADRs, UADRs are used for **authorized products.**

Note how ADR differs from AE (above). When we use the word “reaction”, we assign at least a reasonable possibility of a causal relationship, whereas the term AE does not imply a causal relationship, and we use it in the clinical trial setting.

The second crucial difference between authorized and unauthorized products regarding pharmacovigilance is the **Reference Safety Information** (RSI). RSI is used to assess the expectedness of all “suspected” serious adverse reactions (SUSARs) or UADRs.

A) In unauthorized products: The RSI is a list of expected serious adverse reactions, which are classified using Preferred Terms (PTs) according to the MedDRA. An expectedness assessment is required to be conducted by the study sponsor on each “suspected” SAR to determine expedited reporting of SUSARs. If the study sponsor prepares an **Investigator's Brochure** (IB) for the IMP in a trial, the RSI should be contained in the IB in a clearly-identified separate section titled “Reference safety information for the assessment of expectedness of serious adverse reactions”.
B) In authorized medicinal products: The RSI of an IMP with a marketing authorization in the EU can be the table or list of ARs in section 4.8 of the appropriate **Summary of Product Characteristics** (SmPC).

IB contains the results related to the safety or toxicity coming from preclinical tests. This type of safety information forms the basis for further **risk analysis and monitoring plans**. Besides that, different approaches can be suggested to increase the safety of clinical trial participants by the Regulatory authorities, e.g., **interim analysis**. The interim analysis is one of the reliable, rational approaches to clinical trials that incorporate what is learned during the course of a clinical study and how it is completed without compromising the validity or integrity of data. The interim analysis can call for potential termination or appropriate modification in sample size, study design and keeps the decision process free of conflict of interest. The **Data Safety Monitoring Board** (DSMB) is an independent group of experts that advises the Sponsor during clinical trial and can contribute to increasing safety monitoring.

The third essential distinction between clinical trials and standard use regarding pharmacovigilance procedures is **the different reports** submission:

A) DSUR/ASR is applied in clinical trials.
B) PSUR is applied to already authorized medicinal products.

Let´s summarize the topic:

A) Pre-authorization pharmacovigilance thus focuses on evaluating a drug's safety and efficacy during clinical development and includes **clinical trial monitoring** (following the monitoring plans)**, safety data collection (AE, SAE, AESI, SUSARs…), risk assessment, benefit-risk analysis, and DSUR/ASR submission**.
B) Post-authorization focuses on continuous monitoring of the drug's safety once it is available on the market and includes **ADR, SADR, and UADR** reporting, signal detection, case evaluation, risk management plan (RMP), **PSURs**, post-marketing surveillance studies.

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The marketing authorization applicants must submit a **risk-management plan** (RMP) to the EMA when applying for marketing authorization. To help applicants, guidance is available on how to submit RMPs.[26,27]

RMPs include information on:

- a medicine's safety profile;
- how its risks will be prevented or minimized in patients;
- plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine;
- measuring the effectiveness of risk-minimization measures.

For medicines that do not have an RMP, one may be required with any application involving a significant change to the marketing authorization. The RMP contains information on important risks (identified and potential) and missing information (populations not studied during the clinical development of the product; e.g., people of >75 years old and who are expected to receive the product and should, therefore, be monitored more closely). A continuous assessment will be conducted even after the market approval. The RMP should be updated based on the new information that impacts a risk-benefit balance.

## 2.5 Overview of phase IV clinical trials for post-market drug safety surveillance

The legal obligation to report serious or unexpected adverse drug reactions does not end after approval obtaining and marketing authorization. Efficacy in the clinical trial setting may not reflect the true effectiveness of the medicinal product in everyday medical practice, and so the risk-benefit balance of a medicinal product as assessed at the time of authorization will inevitably change post-authorization. The same issue concerns safety. Therefore, post-market drug safety surveillance is a crucial part of evaluating the real safety of a new drug in a real-world setting.

One interesting point: Onakpoya IJ et al showed in a previously published work that there are discrepancies in the patterns of withdrawal of medicinal products from the market when adverse reactions are suspected, and withdrawals are inconsistent across countries. Overall, 462 medicinal products were withdrawn from the market between 1953 and 2013, the most common reason being hepatotoxicity. The median interval between the first reported adverse reaction and the year of first withdrawal was 6 years (IQR, 1-15) and the interval did not consistently shorten over time.[28]

### 2.5.1 Phase IV clinical trials

The synonym for phase IV clinical trials is post-authorization safety study (PASS) or post-authorization safety and efficacy study (PAES). It is now generally accepted that part of the process of evaluating drug safety needs to happen in the post-marketing (approval) phase if important innovations are not to be lost in an unduly restrictive regulatory net. Judgment as to

[26] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf
[27] https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pharmacovigilance/risk-management/risk-management-plans
[28] Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. BMC Med. 2016 Feb 4;14:10. doi: 10.1186/s12916-016-0553-2. Erratum in: BMC Med. 2019 Mar 2;17(1):56.

whether and how this might happen lies with the regulators.
Especially in the case of accelerated assessment, the PASS or PAES are compulsory.

The stronger the national system of pharmacovigilance and ADR reporting, the more likely it is that reasonable regulatory decisions will be made for the early release of new drugs with the promise of therapeutic advances. Legislation governing the regulatory process in most countries allows for conditions to be placed on approvals, such as a requirement that there should be detailed pharmacovigilance in the early years after a drug's release.

Careful safety monitoring is not confined, however, to new drugs or to significant therapeutic advances. It has an important role to play in the introduction of generic and biosimilar medicines, and in the review of the safety profile of older medicines already available, where new safety issues may have arisen, especially rare and very rare adverse reactions.

### 2.5.2 Safety surveillance in standard clinical use out of the clinical trial

Available methods for communicating messages about the safety of medicines are listed in Table 2. Medical journals and websites maintained by national agencies are other methods of communication. The choice of method employed tends to depend on the urgency and seriousness of the issue in question. Guideline on communication methods of safety information can be found at Guideline on good pharmacovigilance practices (GVP) Module XV – Safety communication (Rev 1).[29]

**Table 2: Communicating messages about medicine safety**

| Vehicle | Issued by |
|---|---|
| 'Dear doctor'/Dear healthcare professional (DHPC) letters | pharmaceutical manufacturers |
| Medicine alerts | national health authorities |
| Media statements | national health authorities/pharmacovigilance centers |
| Patient information leaflets | pharmaceutical manufacturers/national health authorities/pharmacovigilance centers |
| Newsletters | national pharmacovigilance centers and WHO |
| Personal feedback to reporters | national pharmacovigilance centers |

While spontaneous reporting by healthcare professionals, patients remains a cornerstone of pharmacovigilance in the regulatory environment and is indispensable for signal detection, the need for more active surveillance has also become increasingly clear. Without information on utilization and the extent of consumption (denominator), spontaneous reports do not make it possible to determine the frequency/incidence of an ADR attributable to a product or its safety in relation to a comparator. More systematic and robust epidemiological methods that can take into account the limitations of spontaneous reporting are required to address these important safety questions (such as active pharmacovigilance studies, like sentinel sites, drug event monitoring, registries; comparative observational studies; stimulated reporting; or targeted Clinical investigations). They need to be incorporated into post-marketing surveillance programs. From a regulatory perspective, these studies are considered PASS, see Guideline

[29] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xv-safety-communication-rev-1_en.pdf

on Good Pharmacovigilance Practices (GVP) Module VIII – Post-authorisation safety studies (Rev 3)).[30]

There are other aspects of drug safety that have been rather neglected until now, which should be included in monitoring the latent and long-term effects of medicines. These include:

- detection of drug-drug interactions,
- measuring the environmental burden of medicines used in large populations (i.e., ecotoxicity),
- assessing the contribution of 'inactive' ingredients (excipients) to the safety profile,
- systems for comparing safety profiles of similar medicines,
- surveillance of the adverse effects on human health of drug residues in animals, e.g., antibiotics and hormones.

# 3 Study medication

The general aim of clinical trials is to refine the pharmacological profile of a drug. Retrospective studies that evaluate backward the effect of a drug, its specific dose, or treatment regimen can also lead to this goal. However, the use/prescription/indication of such a drug is not influenced by study participation due to the retrospective nature of the study, and the drug is not considered a study medication. Therefore, in this chapter, it will be covered what kind of medication use or regimen makes a drug become a **study medication**.

It will be trials evaluating a new drug, a new route of administration, a new dose of a known drug, a new formulation of a known drug, or trials comparing different combinations of drugs. **The drug thus plays a central role in the clinical trial and represents the main intervention**. Therefore, at a minimum, these trials will be prospective, defined by specific inclusion and exclusion criteria for participation, and trials with a well-defined administration schedule for the study medication and defined objectives. Study medication handling is also one of the many responsibilities of the principal investigator or sponsor. And since you may find yourself in this position, we would like to provide you with a basic overview of the proper handling of study medication in this chapter. Proper handling is a prerequisite for obtaining quality and reliable results.

## 3.1 What all can be a study medication?

As we have already indicated above, not every clinical study meets the requirement of a clinical trial on medicinal products. Indeed, a distinction should be made between the terms 'clinical study' and 'clinical trial'. Regulation (EU) 536/2014[31] defines both:

- 'Clinical study' means any investigation in relation to humans intended:
  a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;
  b) to identify any adverse reactions to one or more medicinal products; or

[30] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf
[31] http://data.europa.eu/eli/reg/2014/536/oj

c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products; with the objective of ascertaining the safety and/or efficacy of those medicinal products;

- 'Clinical trial' means a clinical study which fulfils any of the following conditions:
  a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;
  b) the decision to prescribe the IMP is taken together with the decision to include the subject in the clinical study; or
  c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

Thus, a clinical study can be conducted, for example, as a standard-of-care study where the deployment, dosage, and termination of therapy is the sole decision of the attending physician. This makes the handling of the drug no different from standard practice, and it does not have to become a study medication with all the formalities. In contrast, if a clinical study meets the conditions of a clinical trial (e.g., study comparing two antihypertensive medications where the patient is randomized and assigned via randomization to one of two drugs), the drug should also become a study medication. Some special precautions may be applied in so-called low-interventional clinical trials.

The term "study medication" itself does not exist in the legislation. Still, as we discuss it in the following text, its meaning most closely matches the definition of an **Investigational Medicinal Product (IMP)** - *a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial*.[32] The IMP is, therefore, defined by three separate definitions – the definition of a medicinal product, the intended use, and the definition of a *clinical trial*. Now, you may imagine an IMP as a completely new product that comes to testing in humans for the first time. But, it must be stressed that the medicinal products already having marketing authorization may also become IMPs when they are to be used as the test product, reference product (comparator), or placebo in a clinical trial. In the non-commercial (academic, investigator-initiated) clinical trials, a medicinal product with a marketing authorization or an individually compounded product are typically (but not exclusively) used; in the commercial trials, we can see an unapproved product as the IMP tested more frequently.

**Commercial clinical trials** typically lead to the registration/authorization of a new product. In other words, they compare an unapproved IMP with an approved IMP that is currently the gold standard treatment for the disease in question.

**Non-commercial clinical trials** tend to focus on new indications, new dosing regimens, new dosage forms of the registered/authorized product. These clinical trials also focus on comparative effectiveness and safety of registered/authorized products.

Current is also the use of generally called **drug repurposing**, or the search for new effects in drugs already in use.

[32] https://health.ec.europa.eu/system/files/2016-11/gl_2_consult_0.pdf

In clinical trials, you can meet another type of product – the generally called **Auxiliary medicinal product (AMP)**. Reg. (EU) 536/2014 defines AMP as *a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an IMP*.[33] Let's look at some practical examples of an AMP in a clinical trial design: some clinical protocols require medicinal products such as rescue medication, challenge agents, medicinal products used to assess end-points in the clinical trial, and background treatment.[34] Can you come up with any examples? In Practical exercise, you will soon be able to give them.

According to the definition, an AMP must also be a medicinal product. In other words, not all products used for the needs of a clinical trial are AMPs (e.g., some challenge agents are not defined as AMPs because they are not medicinal products). On the other hand, AMPs should not include concomitant medications, medications unrelated to the clinical trial, and not relevant to the design of the clinical trial. Quite complicated, right?

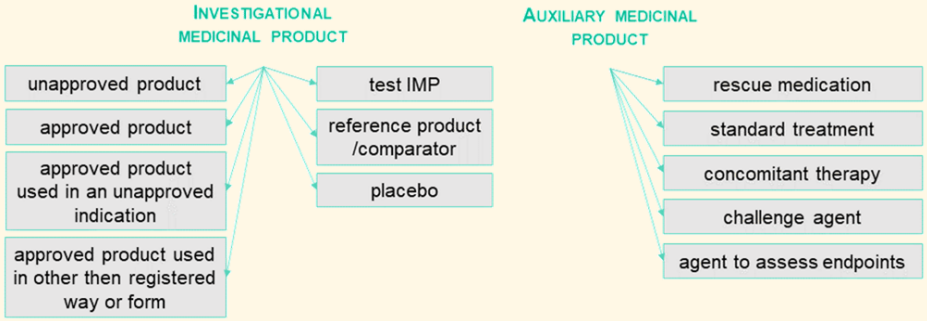
**Practical exercise**
Could you give me some real examples of auxiliary medicinal products?

Now let's try to give one example of an AMP to each category; please add the context of a trial design:

2.1 medicinal products as a rescue medication:
2.2 medicinal products as challenge agents:
2.3 medicinal products used to assess end-point in the clinical trial and background treatment:

Please, paraphrase the definitions of an IMP and an AMP; describe them in your words. It would be best to stress the limitations – when other than IMP is AMP and when not.

**Let's summarize the learning outputs of this subchapter in the following scheme:[35]**




## 3.2 Regulatory framework of the study medication, responsibilities

The regulatory framework for study medication is currently Regulation (EU) 536/2014 on clinical trials on medicinal products for human use (CTR).[36] This regulation contains the definition of IMP itself, resp. AMP. However, it also defines the content of the accompanying documents such as protocol, IB, Investigational Medicinal Product Dossier (IMPD) (Annex 1),

[33] http://data.europa.eu/eli/reg/2014/536/oj
[34] https://health.ec.europa.eu/system/files/2016-11/gl_2_consult_0.pdf
[35] Adapted from SVOBODNÍK, Adam, Regina DEMLOVÁ a Ladislav PECEN. *Klinické studie v praxi*. Brno: Facta Medica, 2014. ISBN 978-80-904731-8-8.
[36] http://data.europa.eu/eli/reg/2014/536/oj

imposes requirements for traceability, storage, return, and destruction (Preamble (55); Article 51), defines general rules for manufacturing and import of the IMP and AMP (Chapter IX), labelling (Chapter X). Moreover, Regulation (EU) 2017/1569 supplementing the above Regulation and specifying principles of and guidelines for good manufacturing practice for IMPs for human use and arrangements for inspections.[37]

This basic regulation is then supplemented by guidelines on:

- Good Manufacturing Practice:[38,39,40] IMPs should be produced in accordance with the principles and the detailed guidelines of Good Manufacturing Practice for Medicinal Products;
- Good Distribution Practice:[41] The 2013 Guidelines on Good Distribution Practice (2013/C 343/01) focus on the wholesale distribution of medicinal products. However, IMPs are not notably excluded. The Guideline may therefore give some guidance on how to supply clinical trial material. Generally, when it comes to transporting IMPs from the manufacturer to the distributor or investigator sites, the sponsor is responsible for controlling the distribution chain and assuring that IMPs are stored, transported, and handled properly.
- Good Clinical Practice:[42] IMP is mentioned in the part dedicated to the Investigator (part 4.6) and the Sponsor (parts 5.12, 5.13, and 5.14).

## 3.3 Accompanying documentation and labelling

With all that you already know about clinical trials and their conduct, it will be no surprise that the documentation related to study medication is quite extensive. Its purpose is to sufficiently document the entire journey of the drug from the manufacturer to the patient/participant of the clinical trial. What this pathway actually looks like? See part 3.4. Here we will focus on typical forms, their purpose and design, and an overview of the processes that must be considered in the documentation (part 3.3.1). Another subchapter will cover the label used to identify the study medication (part 3.3.2).

It is necessary to stress that standardizing the management of the IMP is to improve patient safety, improve efficiency, and provide robust clinical data that allow new and innovative medications to reach the patients who need them or to have improved safety or efficacy profiles.[43]

As the sponsor of a non-commercial clinical trial, it will be you who will prepare and provide this documentation to the centres; as the principal investigator, you will be responsible for adherence and correct completion of the forms by the study team members.

[37] http://data.europa.eu/eli/reg_del/2017/1569/oj
[38] https://health.ec.europa.eu/system/files/2017-12/guideline_adopted_1_en_act_part1_v3_0.pdf
[39] https://health.ec.europa.eu/system/files/2016-11/2009_06_annex13_0.pdf
[40] https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en#annexes
[41] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52013XC1123(01)
[42] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf
[43] https://www.ashp.org/-/media/assets/policy-guidelines/docs/guidelines/management-investigational-drug-products.ashx

Handling study medication is usually outsourced to pharmacists – trained experts who possess knowledge of the clinical research study process, human subject protection, and national and local (e.g., hospital) regulations governing drug research. The pharmacist can be responsible for providing information to the appropriate healthcare team members, including pharmacy staff who may be unfamiliar with the study medication. This enables them to correctly dispense it as described in the protocol and ensure its safe use.[44] When a pharmacist is involved in the study team, his/her name and role must be specified in the Delegation log. If applicable, the pharmacist or other pharmacy staff involved in dispensing the IMP should participate in the site initiation visit and pharmacy-specific training and be trained in GCP. Records of training must be maintained for auditors and sponsor. As a principal investigator, you are responsible for ensuring the pharmacist has the most up-to-date version of study documents (not all are mandatory; the below-mentioned list represents an example of the study documents set):

- contact list of the sponsor and members of the local study team,
- protocol,
- IB/SmPC/IMPD,
- pharmacy manual/IMP Handling Instructions,
- a sample request form based on which the drug will be dispensed from the pharmacy,
- logs applicable (described below),
- randomization sheet and instruction on unblinding (if applicable), and labels on the IMP.

All of them are gathered in the generally called Pharmacy Site File.

There is no legal requirement for pharmacy involvement, however, it is advisable to check if there is any local one in the specific facility where the study will be conducted. At the same time, pharmacy involvement may facilitate the keeping of all documents and drug accountability.

### 3.3.1 Accompanying documentation

The study medication accompanying documentation shall document the receipt, accountability, storage, handling, preparation, dispensing, or administration, and final disposal of the IMP to ensure inspection readiness and compliance with corresponding regulations and the approved study protocol.[45]

***Storage, temperature control, and monitoring***

According to the GCP guidelines, the IMP should be stored in a secured location and under specific, acceptable conditions as specified by SmPC or the IMPD (usually temperature, sometimes protection from light, humidity). Control and monitoring of IMP storage conditions are crucial for the integrity of the products. Temperature is manually documented in a Temperature log; or it can be replaced by an export of temperature curves for a certain period from temperature monitoring devices. Documentation that the proper storage condition of the IMP has been maintained must be available upon the sponsor's/monitor's or CRA's/auditor's request and is applicable for all locations where the study medication is stored (during transport to the pharmacy, in the pharmacy, at the outpatient clinic, at the department).

[44] https://www.ashp.org/-/media/assets/policy-guidelines/docs/guidelines/management-investigational-drug-products.ashx
[45] https://www.ashp.org/-/media/assets/policy-guidelines/docs/guidelines/management-investigational-drug-products.ashx

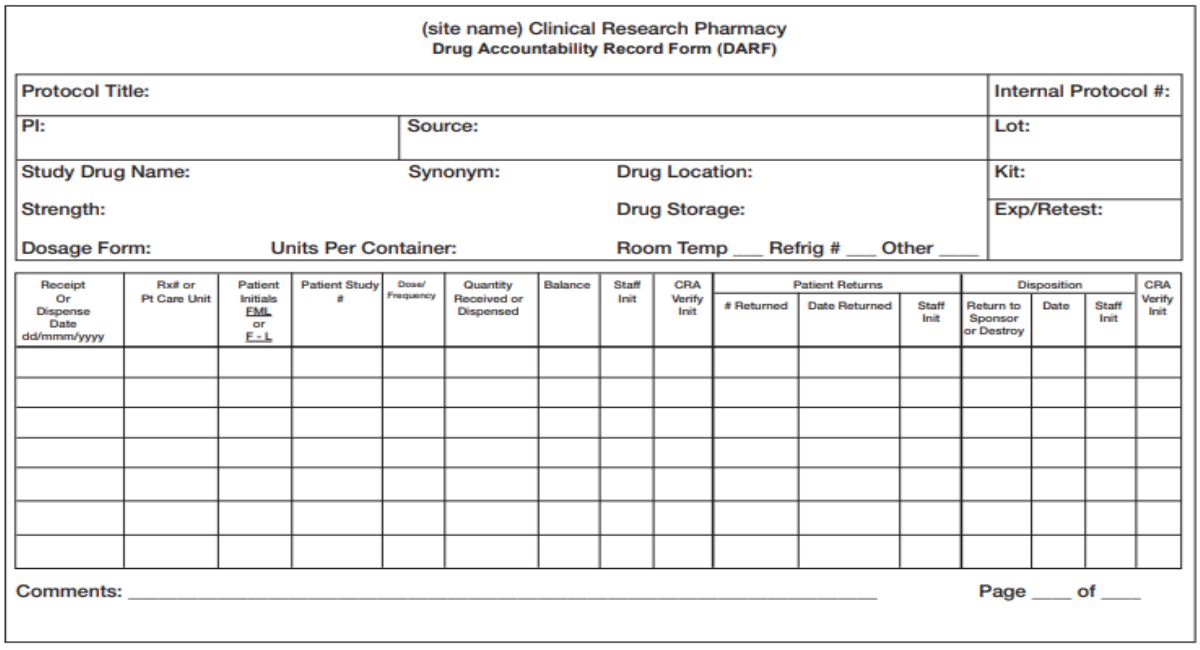
The temperature monitoring devices should be calibrated at the interval set by the national or local policy (e.g., annually); documentation of the calibration must also be available for the sponsor, monitor or auditor. For thermolabile products, the daily temperature record in the refrigerator or the freezer should be available, and those devices should be connected to a backup power supply.

The study medication can have set some acceptable excursions – deviations which can be assessed by the trained pharmacist independently of the sponsor/principal investigator and without quarantining of the product. Sometimes, the sponsor set up strict rules for communication of safety excursions.

***Accountability of the study medication***

Detailed records required to be kept by the sponsor must identify the investigator to whom the IMP is shipped as well as the date, quantity, and batch or code mark of such shipment (documents received with the IMP like packing slip, shipment temperature records should be stored). On the other side, the clinical site is required to maintain records detailing the participant to whom the IMP was dispensed, the date, the quantity, and the batch or code mark dispensed. According to the GCP guidelines, along with product receiving and dispensing, returns from the patients and disposal must also be tracked.

There could be only one form combining all of these records (e.g., Drug Accountability Record Form – please see an example in Figure 2), or there could be separate forms (see examples in Figure 3). The forms can be customized for different protocols and sites and may contain more information but always maintain an appearance that enables simply filling in and orientation.



(site name) Clinical Research Pharmacy
**Drug Accountability Record Form (DARF)**

| | | | |
|---|---|---|---|
| Protocol Title: | | | Internal Protocol #: |
| PI: | Source: | | Lot: |
| Study Drug Name: | Synonym: | Drug Location: | Kit: |
| Strength: | | Drug Storage: | Exp/Retest: |
| Dosage Form: | Units Per Container: | Room Temp ___ Refrig # ___ Other ___ | |

| Receipt Or Dispense Date dd/mmm/yyyy | Rx# or Pt Care Unit | Patient Initials FML or F-L | Patient Study # | Dose/ Frequency | Quantity Received or Dispensed | Balance | Staff Init | CRA Verify Init | Patient Returns | | | Disposition | | | CRA Verify Init |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | # Returned | Date Returned | Staff Init | Return to Sponsor or Destroy | Date | Staff Init | |
| | | | | | | | | | | | | | | | |
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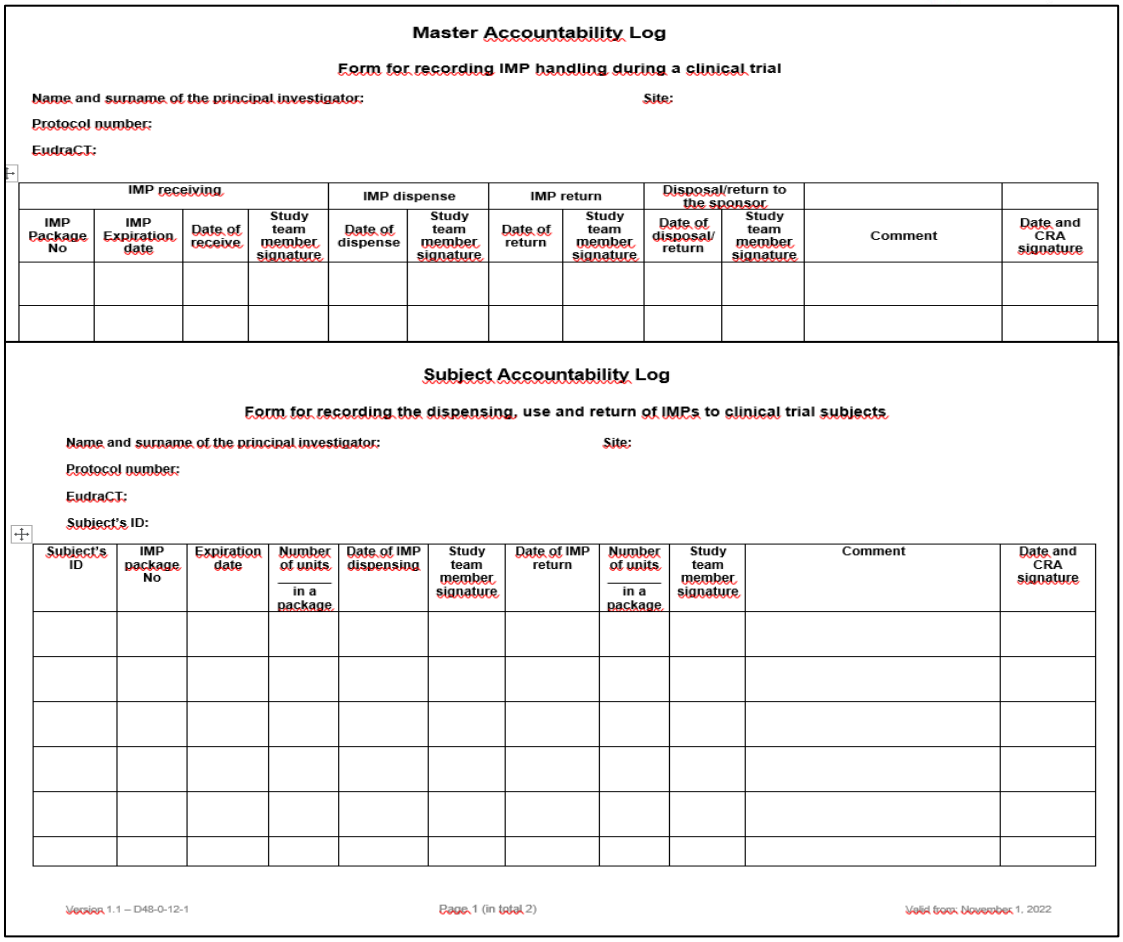
Comments: _____ Page ____ of ____

*Figure 2: Examples of a Drug Accountability Record Form/Log*[46]

[46] https://www.ashp.org/-/media/assets/policy-guidelines/docs/guidelines/management-investigational-drug-products.ashx



**Master Accountability Log**

**Form for recording IMP handling during a clinical trial**

Name and surname of the principal investigator: Site:

Protocol number:

EudraCT:

| IMP receiving | | | | IMP dispense | | IMP return | | Disposal/return to the sponsor | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| IMP Package No | IMP Expiration date | Date of receive | Study team member signature | Date of dispense | Study team member signature | Date of return | Study team member signature | Date of disposal/ return | Study team member signature | Comment | Date and CRA signature |
| | | | | | | | | | | | |
| | | | | | | | | | | | |

**Subject Accountability Log**

**Form for recording the dispensing, use and return of IMPs to clinical trial subjects**

Name and surname of the principal investigator: Site:

Protocol number:

EudraCT:

Subject's ID:

| Subject's ID | IMP package No | Expiration date | Number of units / in a package | Date of IMP dispensing | Study team member signature | Date of IMP return | Number of units / in a package | Study team member signature | Comment | Date and CRA signature |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | |
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*Figure 3: Example of Master Accountability Log and Subject Accountability Log; another equivalent terminology is possible (e.g., Site Inventory Log and Single Patient Log)*

It might also be helpful to set an interval in which the routine inventory counts should be performed for the IMP to ensure that the physical quantity on hand corresponds to the amounts recorded in the log.

Low-interventional trials are often of crucial importance for assessing standard treatments and diagnoses, thereby optimising the use of medicinal products and thus contributing to a high level of public health. Those clinical trials should be subject to less stringent rules, as regards monitoring, requirements for the contents of the master file and traceability of IMPs.[47]

### *IMP returned from the study subject*

**Practical exercise**
Before we start, what do you think – is it reasonable to follow the IMP product returned from the patients? Why?

According to the GCP guidelines, the principal investigator is responsible for ensuring and assessing adherence to the protocol, receiving, counting, and documenting IMP returned from the patients might be the tool. So, that is the answer to the previous Practical exercise question – it is reasonable because good adherence is the main precaution for high-quality results.

[47] http://data.europa.eu/eli/reg/2014/536/oj

In the above examples of the Drug Accountability Log in Figure 2 and Subject Accountability Log/Single Patient Log in Figure 3, a specific part is dedicated to the returned medication. The returned product needs to be stored in a separate area from the IMP available for dispensing.

***IMP final disposition***

For the IMP returned to the sponsor or destroyed onsite, the return or destruction must be documented – again Drug Accountability log displayed in Figure 2 can have a dedicated part to these activities, or separate forms – IMP Return Form and Onsite IMP Destruction Log (+ certificate of destruction) – should be filled in/collected. The procedures for returning the unused medication to the sponsor or destroying the IMP should follow the sponsor's instructions and the institutional policy.

***AMP handling***

AMP movements should be traceable too. At least a procedure documenting which patient received which AMP(s) during the trial with an evaluation of the compliance, where necessary. AMP may be supplied by the sponsor or by the investigator site.[48]

**Let's summarize the learning outputs of this subchapter in the Accompanying documentation:**

- The traceability of medicinal products that allow adequate reconstruction of IMP and AMP movements and administration should be ensured, considering the purpose of the trial and trial subjects' safety.
- The generally applicable logs are Temperature log, Drug accountability log or more or less complex equivalents (e.g., Master Accountability Log/ Site Inventory Log; Subject Accountability Log/ Single Patient Log; IMP Return Form and Onsite IMP Destruction Log).
- The traceability of the IMP is crucial, and any deviation must be solved; the exact requirements apply to AMPs with more flexibility in some aspects.

### 3.3.2 Labelling

A study medication label should be created to ensure that information required by the study protocol is included on the label and that the administration instructions are consistent with the protocol. A label must comply with all the regulatory and protocol requirements (the label is submitted to the national competent authority and other study documentation to be approved).

**Practical exercise**

Try to suggest a label for your IMP used in a proposed non-commercial clinical trial. What information do you expect should be included? What language should the label be given in?

Details on what kind of information should appear on the package of an IMP can be found in Chapter X – Labelling of Reg. (EU) 536/2014. For IMPs, the following are applicable:

- information to identify contact persons or persons involved in the clinical trial;
- information to identify the clinical trial;
- information to identify the medicinal product;
- information related to the use of the medicinal product.

[48] https://health.ec.europa.eu/system/files/2016-11/gl_2_consult_0.pdf

Are you still unsure on how to correctly design a label for the IMP? No problem, we will discuss this during the pilot teaching, including designing a real label for an IMP. Consider participation in the pilot lesson or find a recording on the project websites.

Maybe you are asking what about labelling in placebo-controlled trials. Active and placebo investigational drug products must be identical in appearance and labelling. The label of the placebo should also contain the expiration date. The same applies to products used in blinded trials – the blinding is protected, and the non-pharmacy-based study staff cannot determine the product's actual composition.

**Practical exercise**
Above, we have mentioned the difference between IMP and AMP – do you remember? What do you think about the labelling of AMP? Does the same apply as for the IMP? Or do you expect some differences? Are we interested in following the AMP?

## 3.4 Pathway of the study medication to the patient (and back)

The distribution of an IMP in a clinical trial is determined by the type of the IMP (approved product/having a marketing authorization or non-approved; being opioids/other drugs with extraordinary evidence required). The following scheme (Figure 4) summarizes the medication pathways for the patient. Always keep in mind the local (national, hospital) specifics of drug handling and check them before starting the trial.

The backward path of the unused IMP basically follows the opposite direction. The patient can return the IMP either directly to the study nurse, coordinator, or investigator or to the pharmacy. Once the returned amount is recorded, the IMP is then either directly disposed of or sent back to the sponsor.

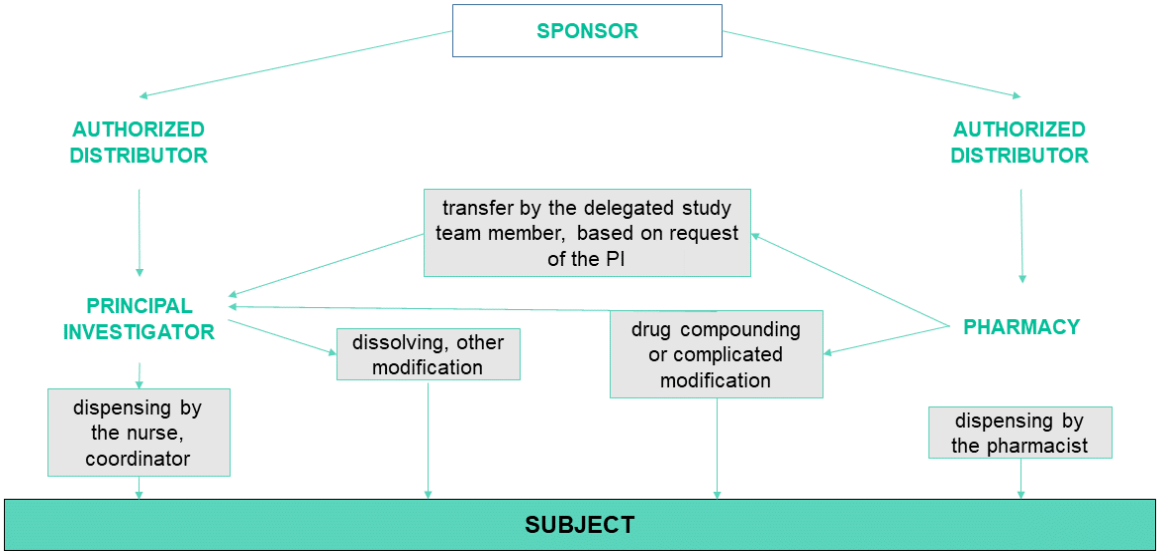


*Figure 4: Example of the pathway of an IMP from the sponsor to the patient*[49]

[49] Adapted from SVOBODNÍK, Adam, Regina DEMLOVÁ a Ladislav PECEN. *Klinické studie v praxi*. Brno: Facta Medica, 2014. ISBN 978-80-904731-8-8.

### 3.5 Compassionate use

Let us add one short note to the so-called **compassionate use**, which is simply staying between clinical trials and standard practice. What does it mean? Compassionate use is a treatment option that allows the use of unauthorized product (see part 2.4) under strict conditions. Product in development can be made available to group of patients who have a disease with no satisfactory authorized therapies and cannot enter clinical trial (more in Article 83 of Regulation (EC) No 726/2004).[50] In other words, the medicine must be undergoing clinical trials or have entered the marketing-authorisation application process and patients should always be considered for inclusion in trials **before** being offered compassionate use programmes. European Regulation 726/2004/EC is clear on the intentions of 'compassionate use' programmes and aimed to harmonise them in the European Union. However, some studies have pointed out that European countries have adopted different national requirements and that 'compassionate use' is not interpreted in the same way across Europe.[51] Please find more information on EMA websites dedicated to the compassionate use.[52]

## 4 Conclusion

Drug safety is a central motive of clinical trials of all phases and standard medical care. The concept of safety does not only include reporting by either the investigator or the sponsor. On the contrary, reporting is only the beginning of the whole process of handling safety data at the national and especially transnational level. Because it is only through broad collaboration and standardization of communication that we can identify rare adverse drug reactions, refine the drug profile, and better exploit its potential. All of this, of course, has far-reaching ethical and economic implications.

But the safety of medicines starts long before they are actually administered to the patient. Well-established processes for monitoring the movement of the drug and the conditions in which it is kept are key to ensuring the quality of the drug, which of course, goes hand in hand with its safety and efficacy.

These are all reasons why we have combined pharmacovigilance and study medication management issues in this chapter. As trialists of the future, we believe you can now better understand the entire ecosystem of safety assurance in clinical trials.

[50] http://data.europa.eu/eli/reg/2004/726/oj
[51] Whitfield, K., Huemer, KH., Winter, D. *et al.* Compassionate use of interventions: results of a European Clinical Research Infrastructures Network (ECRIN) survey of ten European countries. *Trials* **11**, 104 (2010). https://doi.org/10.1186/1745-6215-11-104
[52] https://www.ema.europa.eu/en/human-regulatory/research-development/compassionate-use