Phase 1 Clinical Trials in Psychopharmacology

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Phase 1 trials are an important step in drug development and are usually the first that involve human participants. Their main objective is most often to determine a safe and effective dose range for further clinical development of the drug. Specific guidelines and regulations apply to these type of trials and have been laid down by health authorities. These guidelines are aimed at minimizing the risks and maximizing the benefits and concern the trial's objective, design, methodology, and organization. To obtain approval for a clinical trial, a Clinical Trial Application, outlining how these guidelines are implemented, has to be reviewed and approved by competent authorities and an ethical committee.

In this chapter, an overview is given of the unique features of phase 1 trials, and the specific guidelines that apply to setting up, submitting, and conducting phase 1 trials in the European Union.

Learning Objectives

- To learn what phase 1 trials are in the process of drug development.
- To get familiar with the specific guidelines for submitting a phase 1 clinical trial application.
- To learn which guidelines and rules of conduct apply to performing a phase 1 study.

16.1 Introduction

Clinical development, or drug development, refers to the whole process of bringing a new drug (or device) onto the market. That is, before a drug or device is suitable for patients, it has to go through an extensive process of research and development. The sponsor, usually the pharmaceutical company, will have to determine the safety and efficacy of the product, to receive a marketing authorization ("license") from the relevant regulatory health authorities (EMA or FDA, see below). First, preclinical research conducted in animals will answer elementary questions about the drug's safety. Next, *clinical research* in human participants has the purpose of testing whether the drug is effective and safe in humans. Typically, these trials aim to test new drugs treating or preventing a disease or a condition. In order to bring a new compound to the market, clinical trials follow a typical series of studies starting from small-scale, phase 1 studies to post-marketing phase 4 studies (Friedman et al. 2010; European Medicines Agency 1998b; Derhaschnig and Jilma 2010).

Definition

The term "drug" used in this chapter, is considered synonymous with "investigational medicinal product."

Investigational medicinal product or IMP is "a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already having a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form." (European Parliament and Council of the European Union 2001).

Phase 1 trials are the first stage of testing an investigational medicinal product (IMP) in human participants. This phase involves testing multiple doses in a relatively small sample (10–200 participants) of healthy volunteers. The primary aims are to determine effective dose range, safety and tolerability, pharmacokinetics, and pharmacodynamics of the drug.

Phase 2 trials aim at evaluating the efficacy of the IMP in the target patient group. This is typically done in a much larger sample (100–300 participants). This level of trial is usually randomized, double-blinded, and placebo-controlled and is intended to identify further side effects. Approximately 30% of phase 2 trials progress to the next phase (Thomas et al. 2016), which is in fact the lowest transition success rate of all four stages.

Phase 3 trials are subsequently set up to confirm effectiveness shown in the previous

phase. In this stage, an even larger sample is used to augment statistical reliability and to identify less common side effects. In these trials, the IMP will often be compared to a known effective treatment (i.e., active comparator). Phase 3 trials are usually the longest and most expensive to conduct (Thomas et al. 2016).

Phase 4 trials take place after a drug has been marketed for sale. These post-marketing studies concentrate on long-term safety and effectiveness following use of the drug in the real world. These studies provide additional information on the drug's risks and benefits, and can identify any side effects resulting from long-term use or interactions with other drugs. Thousands of participants are typically included in phase 4 studies.

The European Medicines Agency (*EMA*) and the local Ethical Committee (EC) (or the Food and Drug Administration (*FDA*) and Investigational Review Boards (IRB) in the USA) ensure that drug experiments in humans are done in accordance with internationally agreed ethical standards and rules of conduct. Phase 1 trials are an important milestone in the development of new medicines, as this is when they are administered to humans for the first time (hence also called a *first-in-humans* trial, previously known as "first-in-men" trial).

Specific guidelines that apply to setting up and conducting phase 1 trials will be discussed in this chapter. This chapter will provide a starting point to familiarize researchers with some of the most prominent aspects that have to be taken into account when setting up, submitting, and conducting a phase 1 study in the European Union. For complete and up-to-date guidelines and instructions, consult the EMA or contact your local EC.

16.2 Regulations and Guidelines

A trial needs to comply with the appropriate national legislation and regulations of its country. Next to that, all clinical trials performed in the EU have to comply with the guidelines of the Clinical Trials Directive (*Directive 2001/20/EC*). This concerns the implementation of the *Good Clinical Practice* (GCP). The purpose of the GCP guideline is to protect the rights of human participants taking part in clinical trials and to warrant the scientific validity and reliability of the collected data. The rights, safety, and well-being of the trial participant, as formulated by the principles of the Declaration of Helsinki (World Medical Association 2001), are the most important considerations of this guideline and should prevail over the interests of science and society (Dixon 1999).

Definition

The *Clinical Trials Directive 2001/20/EC* is a European legal act, aimed at simplifying and harmonizing the administrative requirements for clinical trials in Europe. It harmonizes the rules for the approval of a clinical trial and sets rules on safety reporting in the context of a clinical trial. Volume 10 of Eudralex, the collection of rules and regulations governing medicinal products in the European Union, contains the guidelines and recommendations on the application of the Clinical Trials Directive (European Parliament and Council of the European Union 2001).

The Clinical Trials Directive will be replaced by the Clinical Trials Regulation in 2020 (Official Journal of the European Union 2014).

It is also essential that the quality and safety of medicines and drugs for human use is assured. Therefore, clinical trials also have to comply with the guidelines of *Good Manufacturing Practice* (GMP), which have been laid down by the *Commission Directive 2003/94/EC*. These guidelines govern the production, distribution, and supply of a drug to make sure that the medicinal product is of consistent and high quality, is appropriate for the intended use, and meets the requirements of the marketing authorization or clinical trial organization (Gouveia et al. 2015; European Commission 2003).

Declaration of Helsinki

The World Medical Association (WMA) developed a set of ethical principles for experiments with human participants. The Declaration was originally adopted in June 1964 in Helsinki, and has undergone 7 major revisions, the most recent in 2013 (Fortaleza). It was an answer in trying to find a balance between the need for knowledge concerning the efficacy and safety of interventions on the one hand, and the risk of harming human participants with untested drugs on the other hand (World Medical Association 2001).

16.3 Ethical Approval

To obtain approval to conduct a clinical trial, a *Clinical Trial Application* (CTA) has to be submitted to a competent authority (CA) and ethics committee (EC). The EC, also known as Institutional Review Board (IRB), reviews whether the clinical trial will be performed according to Good Clinical Practice (GCP) and the appropriate legal requirements. Besides submitting the application to the EC, a valid request for authorization also has to be submitted to the CA of the country in which the trial is planned. A trial may start only if the ethics committee and the competent authority conclude that the anticipated therapeutic benefits justify the risks. Compliance with this prerequisite should be monitored permanently. The requirements for the CTA are described in Directive 2001/20/EC, and additional documents may be required depending on the individual member state (European Parliament and Council of the European Union 2001). The main documents to be submitted are the trial protocol, the Investigator's Brochure (IB), the Investigational Medicinal Product Dossier (IMPD), and the EudraCT application form.

Study protocol: A trial's **objective, design, methodology**, statistical analyses, and **organization** are described in a study protocol.

Investigator's Brochure: The IB summarizes the information of an investigational medicinal product. It contains background information on the properties and history of the IMP, information on the sponsor's name, and the identity of the product (e.g., trade and generic names), and a summary of relevant non-clinical and clinical data (European Parliament and Council of the European Union 2001).

Investigational Medicinal Product Dossier (IMPD): The IMPD contains available information about the IMP and includes summaries of information related to the quality (chemistry, manufacturing, and controls), data from non-clinical studies and clinical trials and experience, as well as an overall risk and benefit assessment (Wood 2009).

The preclinical and clinical information thus can be supplied in the IB but also in the IMPD. By cross referencing between the two documents, overlap can be avoided.

EudraCT form is the application form used for Clinical Trial Applications in the EU. Information on the clinical trial, the investigational medicinal product, the study design, and the different parties involved (e.g., sponsor, applicant, investigators). For most clinical trials, the EudraCT form is uploaded to the EU clinical trials register, making certain information on the trial available to the general public (European Commission n.d.).

Definition

Ethics committee (EC): an independent body in a Member State, consisting of healthcare professionals and nonmedical members, whose responsibility it is to protect the rights, safety, and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent (European Parliament and Council of the European Union 2001).

Definition

Competent Authority (CA): The competent authority of each member state is responsible for the regulation of human medicines and the authorization of clinical trials. The authorization and oversight of a clinical trial is the responsibility of the competent authority of the country where the trial is taking place. Each trial must be approved by the competent authority country where the protocol was submitted (European Medicines Agency n.d.).

16.3.1 Objectives

The primary objectives of any study should be clear and explicitly stated. Phase 1 trials typically involve one or a combination of the following objectives:

Safety and Tolerability

The safety of a medical product concerns the medical risk to the participant, usually assessed by laboratory tests (e.g., clinical chemistry and hematology), vital signs, adverse events, and other specific safety tests (e.g., ECGs). The tolerability of the medical product is the degree to which evident adverse effects are acceptable for the participant. Safety and tolerability are studied for the expected therapeutic dose range and are typically done by using both single and multiple dose administration (European Medicines Agency 1998a).

Pharmacokinetics (PK)

A drug's pharmacokinetics (i.e., the drug's absorption, distribution, metabolism, and excretion) provide a lot of information even when the study sample is still relatively small. These analyses provide valuable information to determine the appropriate dose and dose intervals, which is essential for the next phase in the drug's development. In addition, pharmacokinetics are important to be able to assess the clearance of the drug and to predict possible accumulation of the drug and potential drug-drug interactions (Dunnington et al. 2018).

Pharmacodynamics (PD)

How the drug affects the body is studied in pharmacodynamics, providing information on the relationship between the concentration of the drug and biological and physiological effect. This knowledge on the activity, efficacy, and potential side effects of the drug can subsequently be used in deciding on the therapeutic dosage and dose regimen (Pacey et al. 2011).

Therapeutic Effect

In phase 1 studies, the therapeutic benefit, i.e., is the intended beneficial effect of the drug, is not the primary objective but can occasionally be studied as a secondary objective. Whether or not it is possible to study the therapeutic effect is dependent of the population and the drug target being studied (European Medicines Agency 1998b).

To achieve their objectives, researchers should first of all ask the relevant questions, and subsequently try to answer these by designing, conducting, and analyzing their clinical trial according to sound scientific principles.

Phase 1 clinical trials typically aim to determine safety and tolerability, pharmacokinetics, and pharmacodynamics of the expected therapeutic dose range of the drug, and occasionally also study the intended therapeutic effect.

16.3.2 Study Designs

The general rule for any study is that the trial is designed in such a way that it will provide the requested data, using as little participants as needed and ensuring the safety of these participants. This also means that all available information on PK, PD, level of risk, and the

number of doses of the IMP to be studied is taken into account in determining the appropriate study design (The Association of the British Pharmaceutical Industry 2018).

Some typical study designs in phase 1 trials are as follows:

- *Sentinel dosing*: To reduce the risk of exposing all participants in a cohort simultaneously, an important advice for phase 1 studies is that the administration of the first dose is given to a limited number of participants (often only one with the active compound) at a time (European Medicines Agency 2017).
- *Single ascending dose trials*: These are trials in which a single dose of the drug is given to a limited number of participants (usually three), in a sequential way, so one by one. After drug administration, participants are monitored and tested for a certain amount of time in order to investigate tolerability, safety, pharmacokinetics, and sometimes pharmacodynamics. If there are no side effects and the outcome data are as predicted, a new batch of participants is subsequently given an increased dose.
- *Multiple Ascending Dose Studies*: This type of study is usually performed after successful completion of single ascending dose trials. In these studies, each subject receives multiple doses of the study drug. The goal of these studies is to determine the pharmacokinetics and its metabolites at steady-state level, to identify if drug accumulation occurs, and to determine maximum tolerated dose (Norfleet and Cox Gad 2010).

It has become also more common to combine the single-dose and multiple-dose trials of an IMP, and even add a trial on the effect of food or age, in order to reduce the cost and time of drug development (European Medicines Agency 2017).

Phase 1 clinical trials typically use as little participants as needed. Therefore, they often apply sentinel dosing and choose a single or multiple ascending dose set-up.

16.3.3 Methodology

16.3.3.1 Participants

The *sample size*, or number of participants, should be determined and justified in the protocol. Whereas studies in later phases of drug development base their sample size on formal hypotheses and sample size calculations, the guidelines for phase 1 studies are less clear. As the focus of phase 1 studies lies on safety, the sample size should limit unneeded exposure to possible harmful treatments. Sample size will be dependent on PK and PD of the IMP, the study objectives as well as previous comparable studies (Shen et al. 2019; European Medicines Agency 2017).

The *type of participants* should also be determined beforehand. Most phase 1 studies are conducted in healthy participants. This has the advantage that participants are easy to recruit, and it avoids difficulties interpreting the results due to concomitant medication or interfering diseases. However, certain research questions can only be answered in a patient population, or it is more appropriate to include patients, due to the risk-benefit balance, e.g., with highly experimental drugs for life-threatening diseases or when an invasive administration route is essential (Shen et al. 2019; European Medicines Agency 2017; The Association of the British Pharmaceutical Industry 2018).

16.3.3.2 Determining the Dose

An important aspect in a phase 1 trial is deciding on the starting dose. Typically, the dose is determined by using all available preclinical data on pharmacology, toxicology, PK and PD. Data from clinical studies with a drug that has a similar mechanism of action can also be taken into account. For the starting dose, it is again important to find a balance between minimizing the risks (e.g., toxicity) and maximizing the benefits (eliciting a pharmacological response). For determining the dose range studied in a trial, the protocol needs to justify and outline the dose range that will be used, the dose escalation steps, and the maximum exposure. Available

data from previous doses (e.g., from previous cohorts) should be carefully taken into account before deciding on increasing a dose and the magnitude of the increase (Shen et al. 2019; European Medicines Agency 2017; The Association of the British Pharmaceutical Industry 2018).

16.3.3.3 Organization

Safety

Whether the study is done in healthy participants or in patients, safety of the participants has to be guaranteed (European Parliament and Council of the European Union 2001). To limit the risks and to minimize the variability in participants, clear *in- and exclusion criteria* have to be specified in the protocol and should be checked carefully when participants enter the study. In addition, the protocol should describe and define how and at what time points the participant's health is assessed before, during, and after participation in the trial.

Before study inclusion, the investigator checks the eligibility of a participant by performing a *screening*. This includes checking medical history (including use of medication and drugs of abuse), a physical examination (including an electrocardiogram), safety tests in blood and urine samples (hematology, blood chemistry, and urinalysis), and including drug and pregnancy screening (The Association of the British Pharmaceutical Industry 2018).

During a trial, the participant's health and safety is *monitored* via routine assessments, such as checking for adverse events, physical exam, vital signs, safety tests of blood and urine, ECG, and saturation measurements, but it can also include trial-specific tests (European Medicines Agency 2017; The Association of the British Pharmaceutical Industry 2018).

Participants who complete the trial, but also those who drop out prematurely, are required to have a *follow-up*, which usually includes the same assessments as before and during the study trial. In case some parameters are not within the normal ranges as defined in the protocol, the follow-up should be extended until these values return to normal.

Risk Assessment and Management

Each phase I trial should provide for a strategy to minimize any risk during the study. Again, this needs to be described clearly in the protocol.

Equipment

Phase 1 trials should take place in an appropriate facility with access to relevant medical equipment, including specific antidotes (if they exist). The facility should enable close supervision of the participants during and after administration of the IMP.

Staff

All investigators should be trained regarding the relevant procedures of the study. Medical supervision should be done by a medical doctor who is familiar with the specifics of the IMP and phase 1 trials. All staff should be GCP trained (European Medicines Agency 2017).

Reporting Adverse Events

Adverse events (AEs) are defined as any undesirable experience occurring to a participant during the study, whether or not they are considered related to the IMP or the experimental intervention. All AEs reported spontaneously by the subject or observed by researchers have to be recorded. With regard to serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs), the protocol should define a plan for a rapid communication between the investigators, IRB, competent authority, and participants (European Medicines Agency 2017).

Safety procedures should be in place so that all researchers involved know how to respond in case of adverse events. The medical doctor will determine the grade (severity) of the adverse event and on what action should be taken. An emergency procedure should be in place, describing how transfer of the participant to the nearest hospital is arranged, in case of life-threatening adverse events (European Medicines Agency 2017).

Data and Safety Monitoring Board (DSMB)

A DSMB is not always required for a phase 1 study, but is relevant in trials where interim

data analysis is needed to ensure the safety of research participants. A DSMB consists of independent experts who review the clinical study data for incidental events, and clinical study performance at predefined intervals. The DSMB subsequently advices the researchers whether the trial can continue, should be adjusted, or should be terminated (European Medicines Agency 2005).

Stop Rules

Clear stop rules, indicating under which circumstances the trial or the administration of the IMP should be stopped prematurely, have to be defined in the protocol. These rules are set in place to maximize the benefit and minimize the harm for the participants, and are based on the principles of safety (e.g., unexpected severe adverse event), benefit (interim analyses prove the hypothesis early), and futility (successful termination of the study does not seem possible) (European Medicines Agency 2017).

Emergency Unblinding

For double-blind studies, the protocol should foresee a clear procedure for rapid unblinding of a participant's treatment allocation in case of an emergency. All researchers involved should be able to perform this unbinding, in order to avoid any time delay (European Medicines Agency 2017).

Phase 1 trials' methodology and organization should apply the guidelines which are aimed at minimizing the risks and maximizing the benefits. This applies to selecting the right number and type of participants, determining a safe dose range, monitoring the participants safety, and assessing and managing risks during the trial.

Case Study

Novel Psychoactive Substances in Phase 1 Trials

Around 2010, massive amounts of novel psychoactive substances (NPS) flooded the recreational drug market. NPS consist of earlier developed pharmaceutical compounds and newly synthesized substances which mimic the effects of traditional drugs, such as cocaine, XTC, or cannabis. Yet, they are not controlled by the United Nations drug conventions, and when individual substances are banned, the clandestine producers modify the chemical structures to circumvent this regulation (European Monitoring Centre for Drugs and Drug Addiction and Eurojust 2016).

Usually, little is known about the PK, PD, or adverse effects of these NPS. Most of what we know comes from users' self-reports, hospital reports, and survey studies (Logan et al. 2017; Wood and Dargan 2012). Systematic toxicological and pharmacological studies with NPS in humans are virtually missing, but absolutely needed to define the health risk profiles.

In 2017, our group successfully completed the first controlled experimental study with a popular NPS (a synthetic cannabinoid) (Theunissen et al. 2018). Although the drug in question was not under investigation for drug development, and there was no therapeutic benefit to be expected, the study was technically a first-in-human study. Even though millions on the street had used the drug before, no controlled experiment had been performed in humans. Therefore, the study was set up and conducted according to the phase 1 guidelines.

Conclusion

Phase 1 trials are an important step in clinical drug development as they are the first introduction of the new drug to humans. They are focused on the safety aspects of the drug rather than the efficacy in treating a disease. This chapter provides an overview of the most important rules and regulations set by the European Union, in order to minimize the risks for participants taking part in the trial and maximizes the benefits, i.e., the resulting knowledge that is needed for further development of the drug.

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