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

CHAPTER 7

EARLY PHASE TRIALS

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Content

Time required to complete this chapter

Core content:	50m
Additional/advanced content (yellow boxes):	1h 10m
Activities/practical exercises (blue framed boxes):	40m
Total time:	**2h 40m**

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1 Introduction

Clinical trials testing potential medical products are commonly classified into four phases. Investigational products go through Phases I, II, and III, after which they can be approved by regulatory authorities for use in the general population. When investigational products are on the market, Phase IV trials can be conducted. The main objective of the phase IV trial is to check the drug's performance in real-life scenarios, to study the long-term risks and benefits of using the drug and to discover any rare side effects. **For more information on different phases of clinical trials see Lesson 7 of CONSCIOUS project.**[1]

Early phase trials (usually Phase I/II) are the first step in testing new treatments that have been developed in the lab. The major intent of early phase studies is to establish how the particular treatment will act and to define its safety limits. At later phases efficacy also has an important role, however, in all phases evaluation of safety and tolerability constitutes an important element.

The aim of this lesson is to discuss the specialities of early phase trials, namely the difficulties of determining the first human dose, dose concepts, study design, risk minimization, the roles and tasks of study participants, and the role of volunteers. Throughout the practical examples at the end of this lesson, you can also study the complex process of trial design through the examples of a COVID-19 trial and the specialities of oncology trials.

This chapter focuses mainly on trials with investigational medical products (IMPs), leaving the special attributes of medical devices, cosmetic products, cell, tissue and gene therapy products etc. for other chapters.

2 Trends of early phase trials

In a research of the industry lobby group BIO, along with BioMedTracker and Amplion,[2] researchers analysed 7,455 drug development programmes that moved through the clinic between 2006 and 2015. They found that the probability of success was 63% in Phase I trials, 31% in Phase II trials, while 58% in Phase III trials. After ending all these phases, 15% of projects fail at the regulatory review process, resulting in an overall success rate of 9.6%.

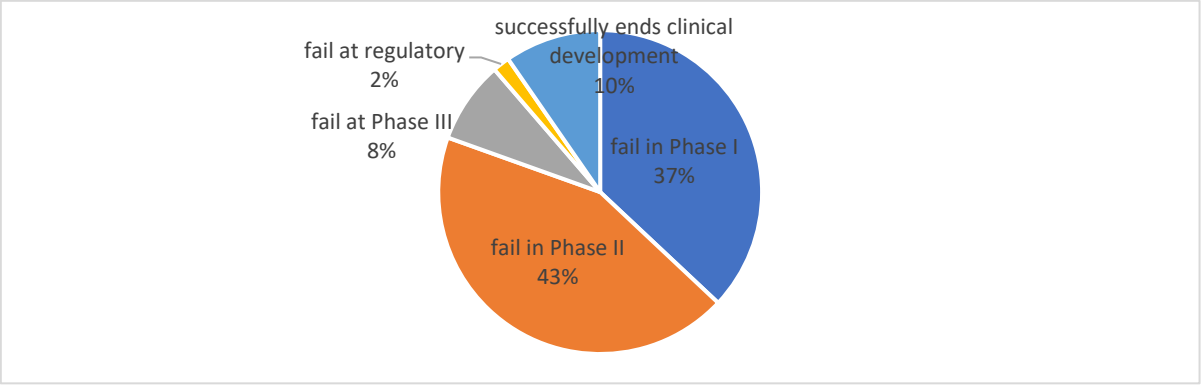

Figure 1: Probability of failure at different steps of clinical development

[1] CONSCIOUS: Chapter 7, Clinical Trial Phases; http://conscious.novaims.unl.pt/my/
[2] https://www.nature.com/articles/nrd.2016.136

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This means that more than 90% of investigational products starting clinical trials finish their career early at some point in the steps of drug development. Researchers also analysed the data by therapeutic area showing that overall success rates ranged widely from 26% for haematology projects to 5% for oncology projects, so there is also a relevant difference of the success rates of clinical trials by therapeutic areas.

As for the number of clinical trials of different phases, we can get an idea if we look at the data on EU Clinical Trials Register. There it can be found that among those trials that can be categorized into phases, only 5% are Phase I trials, 41% are Phase II and 32% are Phase III trials, and 21% are Phase IV clinical trials. Therefore, it can be said that early phase trials represent a huge amount of the overall number of registered clinical trials.

Regarding the cost of early phase trials, we can get an insight looking into a study from 2016,[3] which examined different factors, such as therapeutic area, patient recruitment, administrative staff, and clinical procedure expenditures, and their contribution to pharmaceutical clinical trial costs in the United States by clinical trial phase. Data showed that the average cost of a Phase I study conducted at a US site ranged from US$1.4 million to US$6.6 million, including estimated site overhead and monitoring costs of the sponsoring organization. Phase II study cost from US$7.0 million to US$19.6 million, whereas a Phase III study cost ranged from US$11.5 million to US$52.9 on average (see Figure 2).

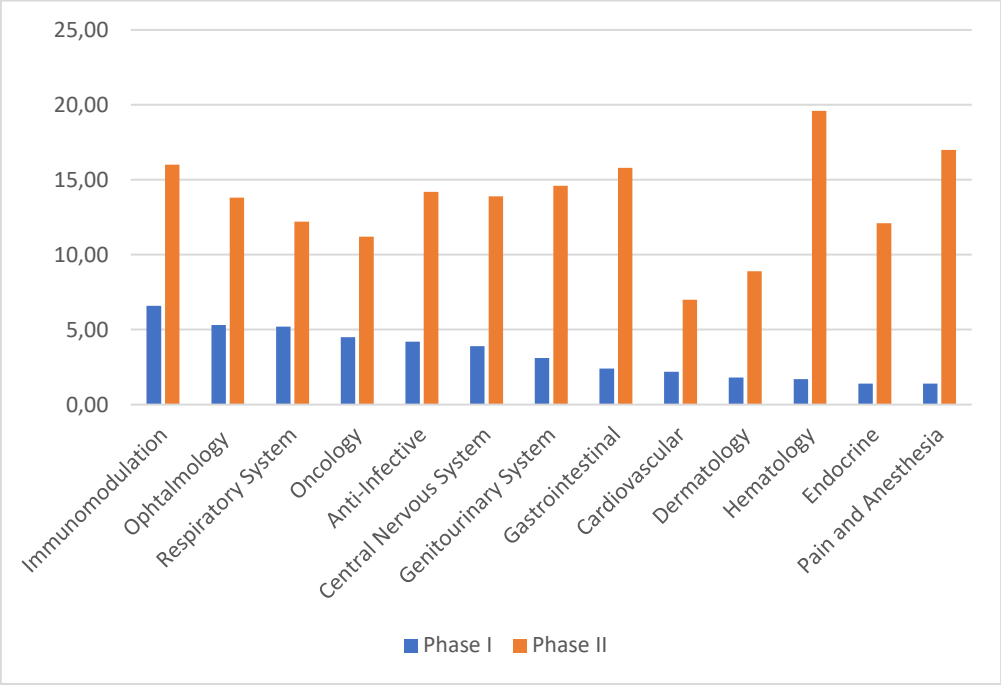


Figure 2: Average cost of trials at Phase I and II (dollars)

The study also showed that there are huge differences between clinical trial cost components by trial phases. While in all phases clinical procedure costs represent a huge portion (19-22%), in Phase I trials these are followed by source data verification costs (15%) and central laboratory costs (12%). In Phase II-III, however, administrative site costs play an important

[3] https://journals.sagepub.com/doi/10.1177/1740774515625964

component (18% and 20%). Site retention costs in Phase II trials (15%) and site monitoring costs in Phase III trials (14%) are also among the top three cost drivers.

As expected, study costs were highly dependent on the therapeutic area and the total number of planned patients as well. Immunomodulation per-study costs were the highest in Phase I with costs of studies in ophthalmology, respiratory system and oncology ranking next, respectively. In Phase II, hematology trial costs ranked first, followed by pain and anesthesia and immunomodulation trials. These differences are most likely due to differences in site procedure costs per therapeutic area.

As the above examples might show, there are several differences between clinical trial phases. Since early phase trials represent almost two third of clinical trials next chapters concentrate on explaining those in detail.

3 Types of early phase trials

To understand early phase trials more thoroughly, first, we should take a look at the specialities of their different types. In the followings Phase 0-II trials, pilot trials and bioequivalence studies are also introduced.

3.1 Phase 0 studies

Trials of this type examine whether the agent behaves in humans as expected from preclinical animal studies, gather preliminary data on pharmacodynamics (PD) or pharmacokinetics (PK), select promising lead candidates, thus helping go/no-go decisions for researchers. Phase 0 studies are the first step to find out whether the IMPs do what they are expected to do, therefore, can help save time and money that would have been spent on later phase trials.

Phase 0 studies use only a few small, usually subtherapeutic but pharmacologically active doses where IMP is administered for a short time in a few study participants. Because the doses and drug exposures are low, significant drug-related adverse events are not anticipated, and because of the modest amount of study drug needed, full-scale, clinical good manufacturing practice (GMP) – grade commercial manufacturing is not required either. Thus, phase 0 trials can be initiated earlier than traditional phase I studies, providing a valuable opportunity to study PK and drug target effects much earlier in the clinical development of an agent.[4] However, they are not a required part of testing a new drug and they give no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect.

In oncology, phase 0 trials are more common since they might answer at the very earliest opportunity – before large numbers of patients have been accrued and exposed to potential drug-associated toxicity – whether an agent is modulating its target in a tumor, and consequently whether further clinical development is justified.

[4] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7185299/

3.2 Phase I studies

Since Phase I trials were also introduced in Chapter 7 of CONSCIOUS program[5], there is only a quick revision here. In phase I trials the main purpose is to assess safety and tolerance: researchers are looking at what the IMP does to the body and what the body does with the IMP. The research team keeps a close eye on the people and watches for any severe side effects. Phase I trials most often include 20-100 healthy volunteers,[6] however, there are some circumstances when clinical patients are used (for more information on this look at section 4.1 Considerations on participants of this chapter). Because of the smaller numbers of people in phase I studies, rare side effects may not be seen until later phases of trials when more people receive the treatment. While some people may benefit from being in such a trial, disease response is not the main purpose of a phase I trial.

The operational complexity of phase I trials compared to later phases is due to the need of monitoring the safety of volunteers/patients very closely. Since the IMP being tested is new, and toxicity is the main concern, patients have to be supervised more exhaustively, and this implies the dedication of additional resources. These studies are usually conducted in tightly controlled Phase I Clinical Trial Units where participants receive 24-hour medical attention and oversight.

3.3 Phase II studies

Since Phase II trials were also introduced in Lesson 7 of CONSCIOUS I program,[7] there is only a quick revision here. In a phase II study, the main aim is to determine the safety and efficacy of the therapeutic intervention by administering the IMP to a group of a few hundred patients with the same type of disease. Patients are treated using the dose and method found to be the safest and most effective in phase I studies.

In phase II clinical trials, in order to find the optimal treatment regimen, everyone can get the same dose or be assigned to different treatment groups: these groups may get different doses or get the treatment in different ways to see which provides the best balance of safety and response. Phase II clinical programs historically have experienced the lowest success rate of the four development phases.

3.4 Pilot studies

Beyond the classical phases of trials, early phase trials include pilot studies as well, which are one of the important stages in clinical development and are conducted to identify potential problem areas and deficiencies in the IMP and protocol prior to implementation during the full study. It is to decide how and whether to launch a full-scale clinical research. It may be used in attempt to predict an appropriate sample size for next phases and/or to improve upon various aspects of the study design (for example to test the appropriateness of data collection, subjects' willingness to participate in the study). As clinical trials require a lot of time and money to be carried out, it is crucial that the researchers eliminate some problems before wasting time

[5] CONSCIOUS: Chapter 7, Clinical Trial Phases; http://conscious.novaims.unl.pt/my/
[6] https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#Clinical_Research_Phase_Studies
[7] CONSCIOUS: Chapter 7, Clinical Trial Phases; http://conscious.novaims.unl.pt/my/

and resources, however, similar to Phase 0 trials, pilot trials are not a required part of the development process of new IMPs.

3.5 Bioequivalence studies

Two medical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their effects (with respect to both efficacy and safety), are essentially the same after administration of the same molar dose. A bioequivalence study is designed to establish equivalence between IMP and reference products (e.g., already authorized product of the same therapeutic area), and should be designed in such a way that the formulation effect can be distinguished from other effects. If the number of formulations to be compared is two, a two-period, two-sequence crossover design is often considered to be the design of choice.

The subjects for bioequivalence studies should be selected with the aim to minimise variability and permit the detection of differences between pharmaceutical products. Therefore, the studies should usually be performed with healthy volunteers of normal values for Body Mass Index. For safety reasons, they should be screened for suitability by clinical laboratory tests, review of medical history and comprehensive medical examination. Standardization of diet, fluid intake, exercise is usually recommended to minimise the variability of all factors except that of the products being tested.[8]

Self-test quiz
Which clinical trial phase can be best characterised by the followings?

1. A special care unit is usually needed to conduct the trial:
2. It can be used to estimate the sample size for next phases:
3. It can be used to determine the appropriate dosage of the IMP:
4. Usually healthy volunteers take part in it:
5. GMP manufacturing of the IMP is not needed for the trial:
6. It has the lowest success rate of the four development phases:
7. It is the most expensive phase of clinical trials:

4 Design of early phase trials

"*Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products*"[9] by European Medicinal Agency (EMA) emphasises that due to the uncertainty in relation to both the possible benefits and risks of a novel IMP candidate, sponsors and investigators should identify, a priori for each clinical study, the potential risks that might arise and apply appropriate risk mitigation strategies. These include the following non-clinical and clinical steps according to the guideline:

- Ensuring adequate quality of the IMP (non-clinical step).

[8] https://www.ema.europa.eu/en/documents/scientific-guideline/draft-note-guidance-investigation-bioavailability-bioequivalence_en.pdf
[9] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf

- Conducting additional non-clinical testing, to obtain data of relevance for the risk assessment, which may include data to support assessment of relevance of animal models, e.g. by using human-derived material (non-clinical step).
- Applying a scientific rationale in the selection of the starting dose, for dose escalation and when defining the maximum exposure to be achieved (clinical step).
- Applying appropriate risk mitigating measures in the design and conduct of early clinical trials (clinical step).

In the following sections, we concentrate on the precautions that the guideline highlights regarding the clinical step of IMP development.

4.1 Considerations on participants

When planning clinical trials one of the crucial aspects that they should be designed in a way that optimises the knowledge to be gained from the study without exposing excessive numbers of participants. To reach this complex goal, choice of subjects, number of subjects per cohort (a group of subjects getting the same type of intervention), subject safety assessments and stopping rules should be thoroughly considered and explained in the protocol.

As for the **participants of clinical trials** we differentiate between healthy volunteers and patients. Healthy volunteer is a well (generally healthy, not sick) person who agrees to participate in a clinical trial for reasons other than medical purposes and receives no direct health benefit from participating. With respect to the choice between normal volunteers versus patients, there are certain indications where the particular absorption and metabolic properties may necessitate or merit using patients rather than healthy volunteers. When making this choice the decision is also based on the relative presence of the target in healthy subjects or in patients; the potential differences between the targeted patient group and healthy subjects; a patient's ability to benefit from other products or interventions; etc. It is also important to state that the protection of study participants should always be the first priority when designing early clinical studies, especially for the initial administration of an investigational product to humans (usually referred to as phase I).[10]

In the earlier phases of IMP development, the choice of subjects for a clinical trial may be heavily influenced by the wish to maximise the chance of observing specific clinical effects of interest, and hence they may come from a very narrow subgroup of the total patient population for which the IMP may eventually be indicated. An excessively heterogeneous patient population (patients with too different characteristics) is not the best strategy either, since heterogenity will decrease the meaning of certain endpoints. Even if the participants of early phase trials are usually more homogeneous, by the time the confirmatory trials are undertaken, the subjects in the trials should more closely mirror the target population.[11]

In early phases of clinical trials when the aim is to test a new research hypothesis, smaller **number of subjects** take part. This allows minimizing risks for study participants as well as spending too many resources (e.g. subjects, time and financial costs) on finding an association

[10] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ich-guideline-e8-r1-general-considerations-clinical-studies_en.pdf
[11] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf

between a factor and a disorder when there really is no effect.
However, if an association is found it is important to make it clear in the conclusions that it was from a hypothesis-generating study and a larger confirmatory study is needed.

Regarding the **design of cohorts**, it is considered appropriate to design the administration of the first dose in any cohort so that a single subject receives a single dose of the active IMP (called sentinel dosing). There should be an adequate period of time between the administration of IMP to these first subjects in a cohort and the remaining subjects in the cohort to observe for any reactions and adverse events. Between cohorts, administration of IMP (or from Phase II, the administration of placebo in case of placebo-controlled trials) to the next cohort should not occur before participants in the immediately preceding cohort has been treated and PK, PD and clinical safety data are reviewed in accordance with the protocol. Flexibility can be allowed for the number of cohorts to be investigated but any plan to include additional cohorts should be clearly pre-defined and the underlying rationale provided in the protocol.

Protocol should also detail the subject **safety assessment methods**: what will be routinely conducted, their timing and any additional monitoring actions or interventions. In early phase trials there should also be routine general monitoring (e.g. vital signs, ECG, respiratory signs and symptoms, clinical laboratory values or general neurological assessment, physical examination and interview) to detect potential unexpected adverse effects that are not related to known properties of the IMP. The length of follow-up of subjects should also be specified within the protocol (e.g. for possible delayed adverse reactions) as well as details on how safety monitoring should be extended until parameters return to within the normal range or to baseline.

In first in human trials protocol should define unambiguous **stopping rules** which result in an immediate stop to dosing. Stopping rules should be defined for final stop to dosing, stopping for an individual subject, stopping within a cohort. For example, healthy volunteer trials should stop at any serious adverse reaction in one subject, or at any “severe” non-serious adverse reaction in two subjects in the same cohort.

It should further be specified in the rule if the stop is a final end of dosing or a temporary halt. Restart is possible without a substantial amendment if review leads to a conclusion which is fully within predefined conditions for the relevant stopping criterion.

4.2 Dose finding in early trials

Careful dosing selection of an IMP is a vital element to safeguard the subjects participating in first-in-human and early clinical trials. The starting dose (for healthy volunteers and patients) and a maximum exposure, as well as dose escalation steps during the clinical trial, should be thoroughly planned and justified in the protocol.

Several early phase trials apply an **adaptive design**: it means a dynamic clinical trial in which the outcomes are observed by sponsor and its representatives during the trial and the parameters of the trial protocol are modified accordingly. This is in contrast to traditional randomized clinical trials that are static in their protocol and do not modify any parameters until the trial is completed. In adaptive trials the adaptation process generally continues throughout

the trial, as prescribed in the trial protocol. Adaptions may include modifications to dosage, sample size, IMP undergoing trial, patient selection criteria.

Beyond adaptive design, modifications to the planned dose-finding steps should be described and justified in all trials. Deviations from the prespecified dose escalation and decision-making criteria would warrant the submission of substantial amendments to competent authorities for protocol approval. Substantial amendments to the protocol will also be needed where the dose escalation has reached a pre-defined maximum exposure and an integrated analysis of available data leads to the sponsor's conclusion that further careful escalation is warranted.

The optimal dose is the dose that is high enough to demonstrate efficacy in the target population, yet low enough to minimize safety concerns and adverse events. There are a number of strategies to determine the optimal dose, here we will look at the four most common dose finding study designs.

4.2.1 Single-dose/Multiple dose escalation studies

Single-dose/multiple dose escalation design is typical in first-in-human studies. They are most often randomized, placebo-controlled with healthy volunteers (or patients, in certain cases). Usually, a small number of study subjects are recruited, and the dosage is increased in a stepwise fashion starting with the lowest dose while monitoring any occurrence of adverse events. In dose-escalation trials, the concentration of the IMP and its metabolites are measured in blood repeatedly.

The main difference between a multiple ascending dose study and a single ascending dose study is the number of doses given to individual study subjects. In single-dose escalation trials, each subject will be given a single dose of IMP on one occasion, while subjects in a multiple ascending dose study receive multiple doses of the IMP. Single dose studies are almost always performed first in order to obtain a rough understanding of the single dose pharmacokinetics of IMP.

In order to evaluate the relationship between dosage and pharmacokinetic parameters, several doses should be used, including the estimated clinical dose and a dose higher than the estimated highest clinical dose. An appropriate number of subjects should be used to determine the inter-individual variability of IMP effects. A sufficient number of samples should be obtained at appropriate time points to estimate blood concentrations of the IMP. However, consideration should be given to ethical and medical concerns regarding excessive blood collection. Urine samples should be collected until the unchanged IMP and its metabolites are no longer detectable.

Traditionally dose finding trials can apply a rule-based design, for example the 3+3 design. The process of finding the Maximum Tolerated Dose (MTD) using this basic design starts with the selection of a pre-specified set of doses among which the first dose will be determined based on animal trials or previous clinical trial data. Suppose we have a set of pre-defined doses, {…, i-1, i, i+1, i+2, …}. A dose, say 'i' will be assigned to a cohort of 3 subjects and the outcome of interest is whether the patient will experience a Dose Limiting Toxicity (DLT) which is pre-defined serious AE depending on the indication.

As the next figure shows if no subjects in that cohort are experiencing any toxicities, the same cohort will be administered by the drug with the next immediate higher dose level, 'i+1' which

has been fixed in advance, by adding three more subjects. If one subject out of three is experiencing DLT, three more subjects will be added to this cohort, and the drug with the same dose, 'i' will be administered for these six subjects. If only one subject is experiencing DLT out of these six subjects, the dose will be escalated to the next immediate dose, 'i+1'. If at least two subjects out of these six are experiencing a DLT in 'i' dose, the dose level will be de-escalated to 'i-1'. If more than one subject out of the three in the first cohort are experiencing DLT, the dose level is de-escalated to 'i-1' and will be treated for a total of six subjects. If a maximum of one subject out of these 6 is getting a DLT, 'i-1' will be selected as MTD.

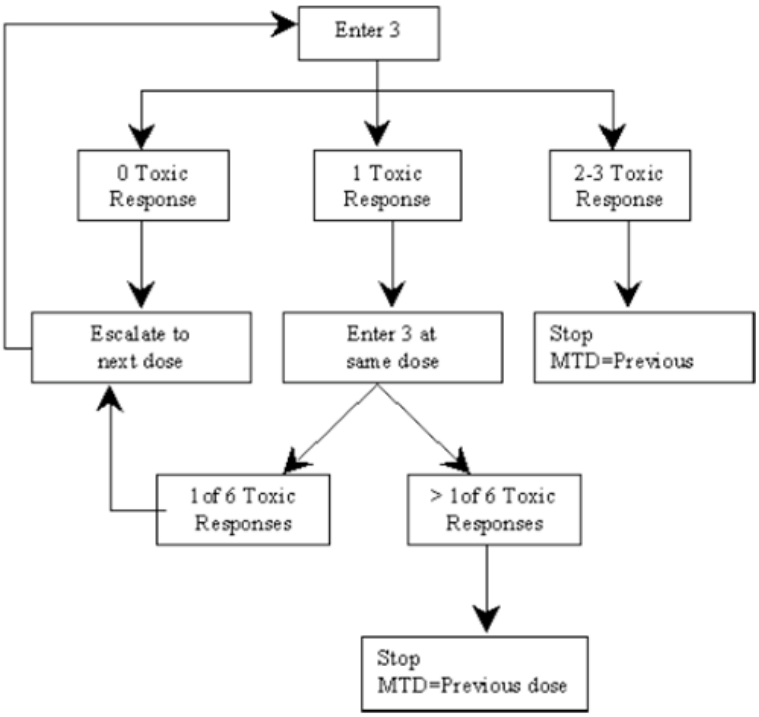


Figure 3: 3+3 design

Beyond rule-based dose-finding designs, as the 3+3 design described above, several researchers emphasise the importance of new designs such as the model-based design and the model-assisted design in dose finding early phase trials. If you are interested in these, read the recent article "Kurzrock R, Lin CC, Wu TC et al. (2021): *Moving Beyond 3+3: The Future of Clinical Trial Design.* American Society of Clinical Oncology Educational Book. 2021: 41, e133-e144."[12]

4.2.2 Parallel dose-response trials

Among dose finding trials, the randomized parallel dose-response design is one of the most widely used. In these trials participants are usually randomized to several fixed dose groups. This study design is best suited for situations where you have a good idea about the safety profile before the study starts. This design is simple in concept, widely used and has considerable success.[13]

[12] https://ascopubs.org/doi/full/10.1200/EDBK_319783
[13] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-4-dose-response-information-support-drug-registration-step-5_en.pdf

A widely used, successful and acceptable design, but not the only study design for obtaining population average dose-response data, is the parallel, randomized dose-response study with three or more dosage levels, one of which may be zero (placebo). From such a trial, if dose levels are well chosen, the relationship of IMP dosage, or IMP concentration, to clinical beneficial or undesirable effects can be defined.

Although including a placebo group in dose-response studies is desirable, it is not theoretically necessary in all cases; a positive slope, even without a placebo group, provides evidence of an IMP effect. To measure the absolute size of the IMP effect, however, a placebo or comparator with very limited effect on the endpoint of interest is usually needed.

It is all too common to discover, however, at the end of a parallel dose-response study, that all doses were too high (on the plateau of the dose-response curve), or that doses did not go high enough. A formally planned interim analysis (or other multi-stage design) might detect such a problem and allow study of the proper dose range.

4.2.3 Crossover trials

In crossover trials participants do not only receive one intervention, but multiple, and the effect of the interventions are measured on the same individuals. The value of crossover studies is they can determine efficacy of a dose within a subject because subjects act as their own control. This reduces the variability and can therefore reduce the number of subjects you need to study.

A randomized multiple cross-over study of different doses can be successful if IMP effect develops rapidly and patients return to baseline conditions quickly after finishing the therapy, in other words, if the IMP is quickly eliminated from the body. It can only work if responses are not irreversible (cure, death), and if patients have reasonably stable disease. Moreover, this design can only be applied if the IMP is designed to be used multiple times.

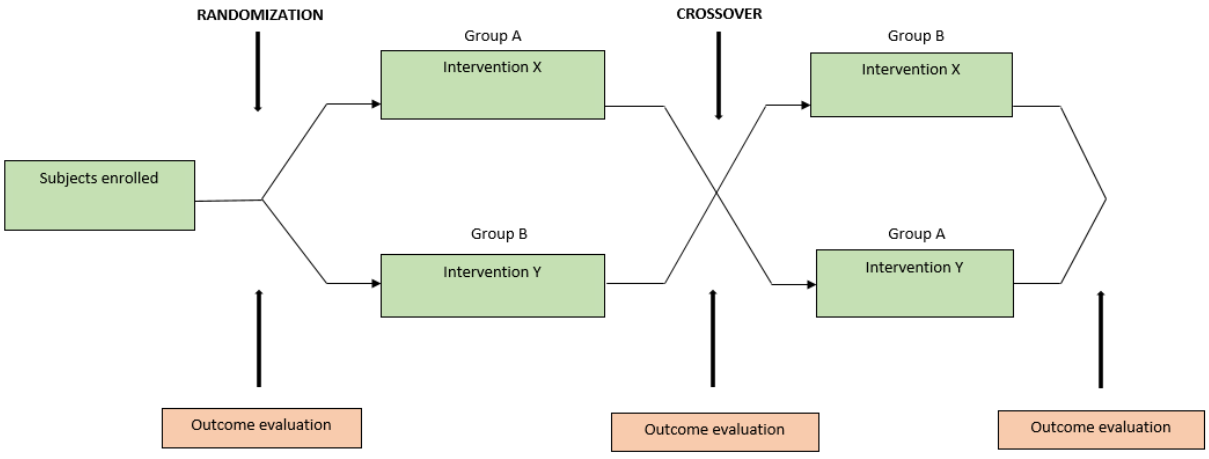


Figure 4: Crossover study design

4.2.4 Dose titration

In dose titration studies each subject will start at a low dose and receive a higher dose until the maximum dose is reached without adverse events. In this type of trials patients most often

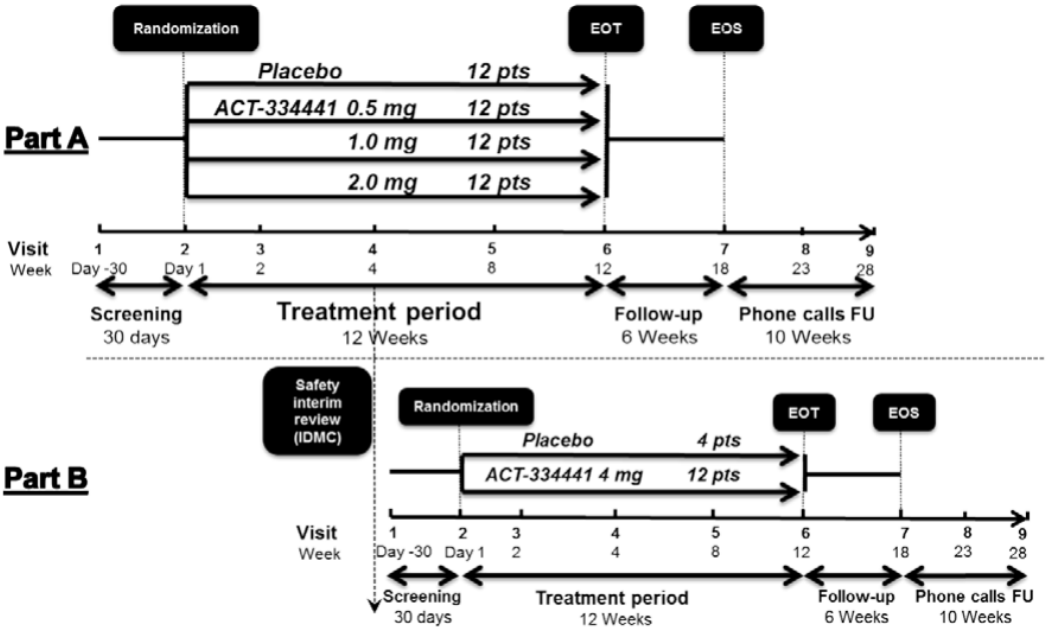
receive escalating doses of IMP/placebo and the trial is performed in a double-blind design, where patients and investigators will be blinded to treatment assignment and only other personnel (e.g. qualified back-up pharmacists) who are authorized to verify dose and dose assignment will be unblinded to the treatment.

Dose titration studies work well for treatments of chronic conditions where an IMP will be used for a long period of time. This design is also good for situations where it is likely that you will see significant differences in the way each subject reacts. However, a critical disadvantage is that this study design cannot distinguish the response to increased dose from the response to increased time on drug therapy or a cumulative drug dosage effect, therefore, may give inadequate information on adverse events.

Compared to a parallel dose-response study, this design may use fewer patients, and can, by extending the study duration, be used to investigate a wide range of doses, again making it a reasonable first study. With a concurrent placebo group, this design can provide clear evidence of effectiveness and may be especially valuable in helping choose doses for a parallel dose-response study.[14]

Discussion board

Look at the following two early phase trial designs taken from the protocols of completed clinical trials and find similarities and differences between them.



EOT = End-of-Treatment; EOS = End-of-Study; FU = follow-up; IDMC= Independent Data Monitoring Committee.

Figure 5: AC-064A201 study design

[14] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-4-dose-response-information-support-drug-registration-step-5_en.pdf

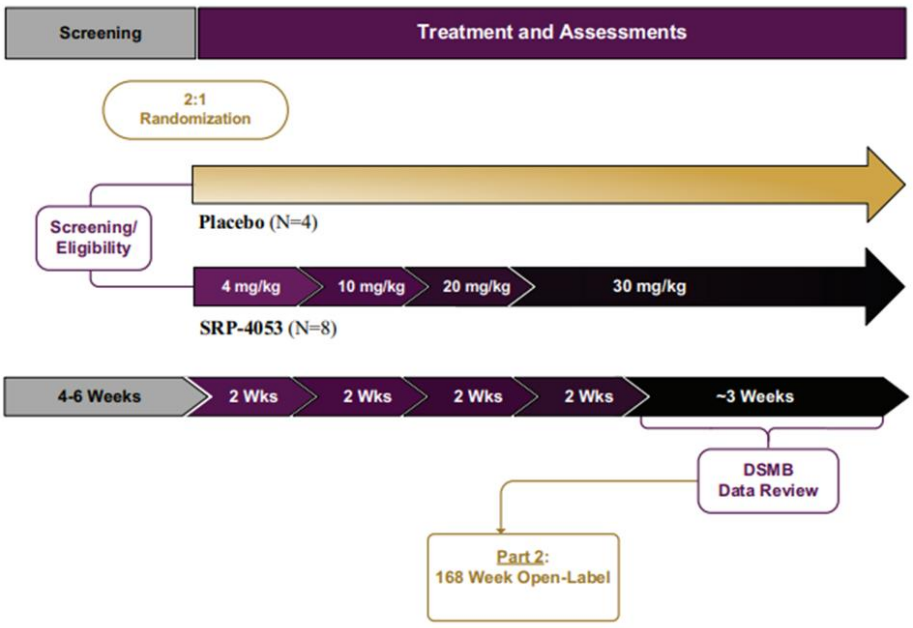


Figure 6: 4053-101 study design

5 Endpoints of early phase trials

In clinical trials we measure the pharmacokinetics, pharmacodynamics, tolerability, safety and efficacy of an IMP. Endpoints are the specific variables/outcomes that can be assessed throughout the clinical trial in order to measure, in an objective way, whether we reach the planned goals of the clinical trial. In practice, each goal we would like to achieve must be translated to a measurable endpoint. These endpoints must be relevant for the patient, clinically meaningful, and objectively measured without bias.

By watching the video "Endpoint in Clinical Trial"[15] you can get an insight into the different kinds of endpoints: primary and secondary endpoints, direct and surrogate endpoints, hard and soft endpoints and composite endpoints.

In the followings sections some typical endpoints of early phase trials are described to give an idea of the measured outcomes of these trials.

Pharmacokinetics: Pharmacokinetics defines what the body does to the IMP. It refers to the examination of the movement of IMP into, through, and out of the body: the time course of its absorption, distribution, metabolism, and excretion. Among many other factors, pharmacokinetics can examine, for example:

- the rate and extent to which the active substance is absorbed,

[15] https://www.youtube.com/watch?v=DfsOVSaA53Y

- data on substance concentration at peak (c_{max}), time to reach peak (t_{max}) and area under the concentration/time curve (AUC),
- percentage and characteristics of binding to serum proteins/red blood cells or other blood components,
- elimination rate for the parent compound (e.g. total body clearance (CL), elimination half-life ($t_{1/2}$),
- total cumulated amounts of unchanged and metabolised substance found in the urine following a single dose,
- renal clearance of the substance.

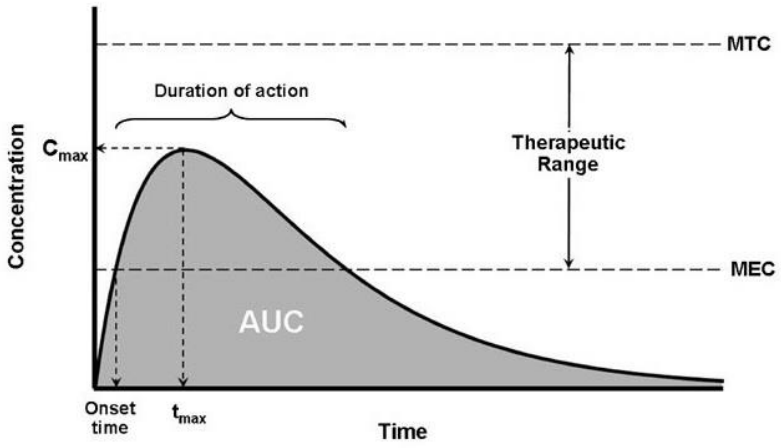


Figure 7: Pharmacokinetic parameters[16]

If you would like to know more on pharmacokinetics, look at the video "Pharmacokinetics - Part 1: Topical and Systemic Drugs".[17]

Pharmacodynamics: Pharmacodynamics define what the IMP does to the body. It is the examination of the biochemical, physiologic, and molecular effects of IMPs on the body. All IMPs produce their effects by interacting with biological structures or targets at the molecular level to induce a change in how the target molecule functions. There are several key variables to describe the extent and duration of the actions of IMP, for example:

- E_{max}, the maximal effect of an IMP on a parameter being measured,
- Half maximal effective concentration (EC_{50}), the concentration of the IMP at a steady state that produces half of the maximum effect,
- Hill coefficient, the slope of the relationship between IMP concentration and IMP effect.

[16] https://www.nature.com/articles/3901522
[17] https://www.youtube.com/watch?v=x_JaFhWlOZo&t=105s

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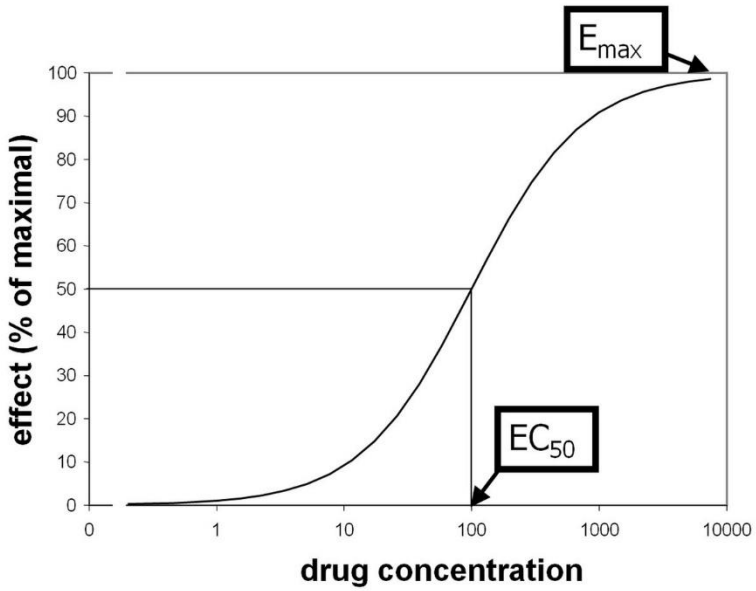

Figure 8: Pharmacodynamic parameters[18]

If you would like to know more on pharmacodynamics, look at the video "Pharmacodynamics - Part 1: How Drugs Act on the Body".[19]

Safety: In clinical trials safety means the anticipation, prevention, and assessment of any type of event that can have an unfavourable impact on the volunteers/patients who have been enrolled. Early clinical trials highly concentrate on measuring safety parameters, protect participants from rare, severe adverse reactions. Typical safety endpoints of early phase trials could be the followings:

- incidence of adverse events (AEs),
- incidence of serious AEs (SAEs),
- incidence of Treatment-emergent adverse events (TEAEs),
- incidence of Treatment-emergent serious AEs (TESAEs),
- vital signs (blood pressure, heart rate, body temperature, SpO_2 and respiratory rate),
- clinical laboratory tests (clinical chemistry, haematology, and urinalysis),
- physical examination findings.

During clinical investigations, adverse events may occur which, if suspected to be medicinal product-related (adverse IMP reactions), might be significant enough to lead to important changes in the way the medicinal product is developed (e.g., change in dose, population, needed monitoring, consent forms).

Efficacy: Efficacy endpoints in clinical trials mean whether the intervention produces a desired therapeutic effect on the disease or condition under investigation. Endpoints should be clinically meaningful which means that they must be direct measures of how patients feel,

[18] https://peerj.com/articles/117/
[19] https://www.youtube.com/watch?v=PhfhMBO-w9Q&t=139s

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function and survive. Efficacy endpoints can be objective (e.g., survival, clinical events), or subjective, such as validated measurements of symptom scores or quality of life.

For example, efficacy endpoints could be the followings:

- time to clinical recovery up to Day X,
- proportion of patients with clinical recovery up to Day X, Y, Z,
- proportion of patients with intensive care unit transfer up to Day X, Y, Z,
- proportion of patients with all-cause mortality up to Day X, Y, Z,
- proportion of patients with hospital admission up to Day X, Y, Z,
- time to “Clinical Worsening”: may include categorical decline in functioning, worsening symptoms, addition of a new medication, hospitalization due to the disease, death, etc.,
- complete remission of Disease X.

6 Safety results of early phase trials

When researchers start a clinical trial, they make a commitment to conduct the trial and to report the findings in accordance with basic ethical principles. This includes preserving the accuracy of the results and making both positive and negative results publicly available. These results should be part of the final report on the trial, and sent to ethics committee(s) and regulatory authority(ies) as required. In this section we concentrate on the results of early phase trials, giving some ideas on what should be reported regarding safety which is the most important aim of early phase trials.

Analysis of safety-related data can be considered at three levels.[20] First, the extent of exposure (dose, duration, number of patients) should be examined to determine the degree to which safety can be assessed from the study. Second, the more common adverse events, laboratory test changes, etc. should be identified, classified in some reasonable way, compared for treatment groups, and analysed, as appropriate, for factors that may affect the frequency of adverse reactions/events, such as time dependence, relation to demographic characteristics, relation to dose or drug concentration, etc. Finally, serious adverse events and other significant adverse events should be identified. This usually means the close examination of patients who left the study prematurely because of an adverse event, whether or not identified as drug related, or who died.

Safety data should be displayed at the following formats:

1. **summarised data,** often using tables and graphical presentations presented in the main body of the report: beyond the extent of exposure the basic display of adverse events should be displayed to compare rates in treatment and control groups. For this analysis it may be helpful to combine the event severity categories and the causality categories as in Figure 9.

[20] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-3-structure-content-clinical-study-reports-step-5_en.pdf

ADVERSE EVENTS: NUMBER OBSERVED AND RATE, WITH PATIENT IDENTIFICATIONS

Treatment Group X **N=50**

	Mild		Moderate		Severe		Total		Total
	Related*	NR*	Related	NR	Related	NR	Related	NR	R+NR
Body System A									
Event 1	6 (12%)	2 (4%)	3 (6%)	1 (2%)	3 (6%)	1 (2%)	12 (24%)	4 (8%)	
	N11**	N21	N31	N41	N51	N61			
	N12	N22	N32		N52				
	N13		N33		N53				
	N14								
	N15								
	N16								
Event 2									

* *NR = not related; related could be expanded, e.g., as definite, probable, possible*
** *Patient identification number*

Figure 9: Summary of adverse events in clinical reports

2. **listings of individual patient data**: all adverse events for each patient, including the same event on several occasions should be listed in appendix as well as all abnormal laboratory values.

Patient ID						
Description of AE	**Treatment**	**Severity**	**Relation to drug**	**Day of onset**	**Duration**	**Drug discontinued (Yes/No)**
Event 1	Treatment 1	Mild	No	2	1	Yes
Event 2	Treatment 2	Mild	No	4	1	Yes
Event 3	Treatment 3	Moderate	No	10	1	Yes
Event 4	Treatment 4	Moderate	No	17	3	Yes
Event 5	Treatment 5	Severe	Yes	25	4	No

Figure 10: Example of individual adverse event listings for one participant in a study[21]

3. **narrative statements of events of particular interests**: e.g., deaths or other serious adverse events resulting in any kind of intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy; laboratory abnormalities considered as serious adverse events.

Safety problems can stop clinical trials from going on at any point of the conduction of the trial. Beyond safety issues, early phase trials answer several questions that help go/no-go decisions

[21] https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002101

of researchers. For an IMP to get to further phases it should be proved that the IMP reached the target; affects the target; and there is a correlation between IMP and clinical signal.

Go/No-go decisions should be based on statistical analyses such as dual-criterion design and confidence interval-based approaches. In making statistically relevant decisions sponsors should define their levels of confidence regarding go/no-go decisions. Phase II studies are typically sized with (a) = 2.5% and (b) = 20% meaning, there is a 97.5% chance of a correct 'No-go' decision that drug is ineffective and an 80% chance of a correct 'Go' decision when the drug is effective (decision is correct). Varying these levels of confidence regarding decision making also affects the sample size and the Go/No-go criteria, which is defined from the primary endpoint(s).

Implementation of such quantitative decision approach requires close collaboration of clinical team members including clinicians and statisticians and complex understanding and interaction of statistics and clinical significance.

7 COVID-19 trials

The urgency of the COVID-19 pandemic required rapid development of COVID-19 vaccines without delay. By devoting more resources, funds, and efforts than ever before, and by testing more vaccine candidates than ever before, COVID-19 vaccine development became the top priority for many countries, companies, research groups, and health organizations.

In this chapter our aim is to give you an idea on the accelerated clinical trial processes and through a case study to demonstrate how different clinical trial phases are built on one another and follow each other.

Discussion board
Let's look at the number of clinical trials related to COVID-19. Based on the clinicaltrials.gov listings on COVID-19 trials[22] try to answer the following questions.

1) How many COVID-19 trials were started so far?
2) How many of these COVID-19 clinical trials were conducted in your country?
3) Are there more drug or vaccine studies related to COVID-19?
4) How many vaccine studies completed phase III?

7.1 Case study of Regkirona

In the following sections we are going to look at how COVID-19 treatment/vaccine trials were conducted, through the example of Regkirona, a treatment for COVID-19.

Discussion board
Regkirona is a medicine used for treating COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of their disease becoming severe. It contains the active

[22] https://clinicaltrials.gov/ct2/covid_view

substance regdanvimab, which is a monoclonal antibody with activity against SARS-CoV-2, the virus that causes COVID-19. A monoclonal antibody is a type of protein that has been designed to attach to a specific structure (called an antigen).

1. Try to find all clinical trials on Regkirona on clinicaltrials.gov. Fill in the yellow boxes of the following table with the missing information.

	Phase I		Phase II/III	
Location	Korea		Global	
Study population	Healthy volunteers	Mild patients		
Sample size	32	18		Part 2: 1 315
Statistical hypothesis	no, The proposed number of 8 subjects (6 subjects for CT-P59 and 2 subjects for placebo) in each cohort is set empirically based on sample sizes in other Phase 1 studies.	no, The proposed number of 6 subjects (5 subjects for CT-P59 and 1 subject for placebo) in each cohort is set empirically based on sample sizes in other Phase 1 studies.	yes	
Primary endpoint(s)	Safety and tolerability up to Day 14 of the last enrolled patient	Safety and tolerability up to Day 14 of the last enrolled patient	Efficacy by proportion of patients with clinical symptom requring hospitalization, oxygen therapy or experiencing mortality up to Day 28	Efficacy by proportion of patients with clinical symptom requring hospitalization, oxygen therapy or experiencing mortality up to Day 28 in high-risk patients
Secondary endpoint(s)	Additional safety, PK parameters		Additional efficacy parameters	
Study design		Double-blind, Placebo-controlled, Parallel Group, Single Ascending Dose Study	Double-Blind, Placebo-controlled, Parallel-group Study	
Study completion	18/07/2020-5/11/2020	04/09/2020 - 5/04/2020	25/09/2020 - 20/10/2021	

2. Compare the sample size, study population, endpoints of these phases.
   Why do you think there were only healthy volunteers in the first Phase I trial?
   In many clinical trials in Phase I there is no statistical hypothesis for the number of subjects involved. Why do you think it is possible?
   How does endpoints change throughout the clinical trial phases?
   If you take a look at the duration of clinical trials, you can see that 15 month were enough to get from the start of Phase I to the end of clinical phases. How do you think it was possible?

Researchers and clinicians can do a lot to help accelerate the clinical trial phases of treatments and vaccines. If they maintain transparency, the key results can be made available through public statements, and fuller details can be published as preprints, and with data sharing the

data from different trials can be pooled to answer meaningful public health questions, rather than staying inconclusive in isolation.

Beyond the accelerating efforts of researchers and clinicians, authorities also have applied special rules, for example the rolling review, for the clinical trials of special interests such as potential treatments and vaccines of COVID-19. In a rolling review, EMA reviews data as they become available from ongoing studies before a formal application is submitted. By reviewing the data as they become available, EMA can reach its opinion sooner on whether or not the medicine or vaccine can be authorised and help investigators/drug developers to streamline further clinical development and inform in protocol design.

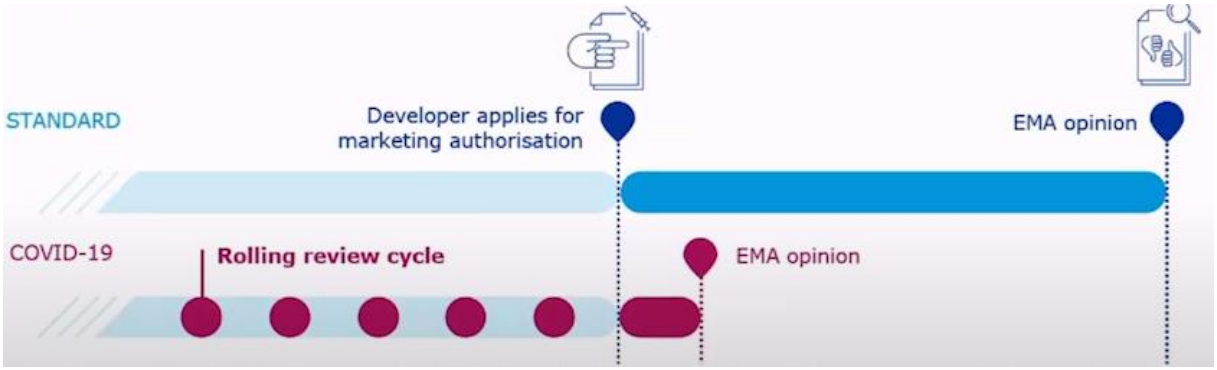

Figure 11: Rolling review of EMA[23]

In case of Regkirona the rolling review made it possible that the treatment got its **marketing authorization one month after the end of Phase II/III clinical trial**. The processes on behalf of EMA were the followings:

1. EMA started rolling review of Celltrion antibody regdanvimab for COVID-19 in 2021 February,
2. EMA supports national decisions on its early use 2nd March, 2021,
3. EMA issues advice on use of regdanvimab for treating COVID-19 on 26 March, 2021,
4. EMA receives application for marketing authorisation for Regkirona for treating patients with COVID-19 on 4 October, 2021,
5. EMA issues marketing authorisation valid throughout the European Union on 12 November 2021.

8 Early phase oncology trials

The number of novel anticancer drugs development has grown exponentially over the past decade. More than 750 drugs are presently under development for the treatment of cancer, but a **very low percentage of these will ultimately demonstrate sufficient efficacy** for regulatory approval and clinical use. In oncology, the likelihood of eventual approval for drugs tested in phase I trials is 6.7%, which is the lowest of all diseases.

The drug development process in oncology **is estimated to take 1.5 years longer** than in other diseases, which may be related to the slow recruitment rates because patients with

[23] https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-development-evaluation-approval-monitoring

advanced cancer are often too ill to enrol in clinical trials, as well as the long periods of follow-up needed to assess survival endpoints.

The development of a successful anticancer drug **from first-in-human study to approval normally takes about 7 years**, during which the safety and efficacy of the drug are thoroughly and rigorously evaluated. A typical endpoint in oncology studies is overall survival, the time from patient enrolment until death. This means a long process of study conduct. However, when an IMP has a well-defined biological mechanism backed by proof-of-concept studies, unprecedented clinical responses with minimal toxicity, and the availability of a strong predictive biomarker, many argue that the approval process should be accelerated, especially when promising results are observed in early phase trials.

Advances in our knowledge of the molecular pathogenesis of cancer have led to increased interest in **molecularly targeted agents** (MTAs), which target specific oncogenic drivers and are now a major focus of cancer drug development. MTAs differ from traditional cytotoxic agents in various aspects, including their toxicity profiles and the potential availability of predictive biomarkers of response. The landscape of phase I oncology trials is evolving to adapt to these novel therapies and to improve the efficiency of drug development.[24] These novel therapies resulted in a significant change in the number of patients as well.

8.1 Design of early oncology trials

Traditionally, IMPs were tested in Phase I trials with a small, heterogeneous patient population to establish safety and tolerability, to define the maximum tolerated dose (MTD), and to identify a safe dose. Dose-finding methods in oncology, similarly to other therapeutic areas, follow mostly rule-based designs, such as the previously explained 3 + 3 method. A review of 1235 cancer phase 1 trials conducted between 1991 and 2006 showed that over 98% used traditional up-and-down methods (where a discrete set of doses are used rather than vary the dose continuously) while only 1.6% of trials used adaptive Bayesian designs.[25] The development of Bayesian designs is fairly recent, and their usage requires planning clinical trials more thoroughly and differently than traditional methods. For example, in adaptive Bayesian designs there is a need for short-term endpoints instead of traditional oncology endpoints such as overall survival, since adaptive design requires updating information on accrued data.

If you are interested in Bayesian design, read the following article:
Alessandra Giovagnoli (2021): *The Bayesian Design of Adaptive Clinical Trials. Int J Environ Res Public Health*. 2021 Jan; 18(2): 530.[26]

In traditional Phase I trials the patient has no chance of potentially benefiting therapeutically from the study, as the dose is far below the theoretically planned effective dose due to safety concerns. Patients' voluntary decision to participate serves only altruistic purposes, trusting that they may provide therapeutic benefits for future patients. It also makes the decision harder

[24] Kit Man Wong, Anna Capasso and S. Gail Eckhardt (2016): *The changing landscape of phase I trials in oncology*. Nat Rev Clin Oncol 2016 Feb;13(2):106-17.
[25] Rogatko A, Schoeneck D, Jonas W, Tighiouart M, Khuri FR, Porter A (2007): *Translation of innovative designs into phase I trials*. J Clin Oncol 25(31):4982–4986.
[26] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7826635/

since severe side effects are more common in oncology studies, as the therapeutic window for cytotoxic compounds in particular is very narrow.

If you are interested in a patient's perspective in taking part in oncology trials, look at the video "Being recruited and accepted onto the Early Phase Clinical Trials Unit".[27]

However, the advances in the understanding of cancer biology in the past decade have led to the development of more effective drugs, more improved patient selection and therefore, an increased desire for early access to transformative new anticancer drugs. These processes have let to expediting the drug development and approval process, so the distinct sequential phases of drug development have therefore become increasingly blurred.[28]

Today Phase I protocols are incorporating preliminary evaluation of anti-tumour activities of the IMP, moreover, some first-in-human trial protocols use a seamless approach of adding cohorts with rapidly increasing number of patients in them to investigate doses and activity in a variety of cancers. This kind of trial design can be an effective way to accelerate the clinical phase of drug development, however, many experts have expressed concerns about the rapid proliferation of first-in-human trials enrolling hundreds or even thousands of patients as detailed in the last cited article. In order to design such first-in-human cancer trials with rapidly increasing cohorts and patient population, researchers should make sure that the protocol has a rationale for its multiple expansion cohorts, that the sample-size range is consistent with the stated objectives and endpoints, that there is an appropriate statistical analysis plan for all stated endpoints, etc.

9 Conclusion

The aim of this chapter was to give you an idea on the characteristics of early phase trials which are a crucial and essential stage in the drug development process. As presented in this chapter, early phase trials are special in their design, patient population and endpoints, however, just as in later phases, their planning must be the result of an active collaboration of a research team in order to be able to execute the trial with rationale and with a constant focus on patients.

Nowadays, due to fast developments in some therapeutic areas and the increased expectations of patients, researchers and authorities, traditional phases can be accelerated and new types of clinical trial designs appear. The last two subchapters on COVID-19 and oncology trials were meant to give a taste of these recent trends.

[27] https://www.youtube.com/watch?v=Zl94VBlFrtY
[28] Prowell TM, Theoret MR, Pazdur R (2016): *Seamless oncology-drug development*. N Engl J Med 74(21):2001–2003.

End of chapter quiz

1. Sentinel dosing means that
   A. investigators should thoroughly monitor the dose-escalation steps
   B. one person in the cohort of participants is dosed in advance of others
   C. one person in the cohort is getting a higher dose than others
   D. none of the above

2. In which of the following trial designs can a patient get several different doses of IMP?
   A. Multiple-dose escalation trial
   B. Dose titration trial
   C. Parallel dose-response trial
   D. Crossover trial

3. Which of the following trial designs can have a placebo group?
   A. Dose titration trial
   B. Parallel dose-response trial
   C. Crossover trial
   D. All the above

4. Dose titration can be an option for study design:
   A. when patients have an acute disease
   B. when it is likely to be differences in response of patients
   C. when researchers would like to compare two dose levels
   D. none of the above

5. Which of these can be a soft endpoint in a cancer trial?
   A. Incidences of adverse events
   B. Shrinkage of the tumour
   C. Improved quality of life
   D. Longer survival

6. Which of these should be explained in the safety part of the clinical report of a trial?
   A. Summarized data on adverse events
   B. Individual laboratory data on patients
   C. Narrative statements of special events
   D. All the above

7. In rolling review:
   A. EMA reviews clinical trial data between phases
   B. EMA applies a fix number of review circles
   C. Both of the above
   D. None of the above

8. In oncology trials clinical trial development phase is typically long because of the
   A. Long treatment periods
   B. Difficulties in patients recruitment
   C. Both of the above
   D. None of the above

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