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Introduction to Clinical Trials *Handout*

Made by Wendy Boschloo (6437427)

Clinical trials are research studies performed in human to evaluate a medical intervention. The participants in these trials should represent the patients that will eventually use the medical products. However, some clinical trials rely exclusively on white male participants. This leads to knowledge gaps about disease development and treatment effectiveness in underrepresented populations. Therefore, researchers should enhance the diversity of populations in their clinical trials to better reflect the population most likely using the medical product. In this handout, the most important aspects of clinical trials will be explained, to be able to understand and critically evaluate various ethical and diversity-related issues in clinical trials.

Note: Most information is retrieved from the *Fundamentals of Clinical Trials* (2014) by Lawrence M. Friedman and others[1].

Content

1 INTRODUCTION

A well-designed and properly conducted clinical trial is considered to be the most rigorous research method for evaluating the effectiveness of health care interventions[2]. In a clinical trial one or more human subjects are prospectively assigned to one or more interventions to evaluate the effect of those interventions on health-related biomedical or behavioural outcomes[3]. Interventions may be single or combinations of diagnostic, preventative, or therapeutic drugs, biologics, devices, regimens, procedures or educational approaches.

A typical clinical trial assessing a new drug may be divided into four phases. Phase I studies aim to investigate the pharmacodynamics and pharmacokinetics of a drug. This will clarify which dose and which regimen should be used. Generally, these studies are undertaken in healthy volunteers and require relatively few subjects. Phase II trials occur in patients and are generally conducted to investigate any clinical benefit and to shed light on side effects. Patient groups used for phase II trials are highly defined to minimize extraneous variation. Both phase I and phase II trials are exploratory and often do not have a randomized comparison group. The phase III trial is a therapeutic confirmatory study, which demonstrates clinical usefulness and examines adverse effects. The new treatment is given to a large group of patients and is compared with a control treatment. If the new drug is found to be safe and effective, the drug will be approved and made available to the public. Now, phase IV trials start, focussed on tracking efficacy, safety and optimal use of the drug in the general population[1].

2 DESIGN

Good knowledge about clinical trial design is essential to ensure usefulness of the generated data for clinicians and decision makers in healthcare. The following considerations in trial design are focussed on confirmatory phase III clinical trials.

2.1 STUDY POPULATION

A study population is defined by unambiguous inclusion and exclusion criteria, called eligibility criteria. A person meeting the criteria can voluntary decide to participate in the trial. The group of participants actually enrolled in the trial are therefore a selection of the study population. Eligibility criteria can be set up using the following five categories:

- Potential for benefit: It is important to include participants that potentially benefit from the intervention. This can result in a homogeneous or a heterogeneous study population. Including participants with a really specific condition, creating a homogenous population, improves the precision of treatment effect estimates, but the opportunity to observe a possible effect might be missed, because the intervention might be effective in a different subgroup. Broader eligibility criteria lead to a heterogenous population, which might shed light on specific characteristics of patients that influence the effectiveness of an intervention. In addition, a more heterogeneous population leads to greater generalisation. However, the likelihood of showing a benefit is reduced.
- High likelihood of showing benefit: For an investigator it is similarly important to obtain results in a short time, given a reasonable number of participants and a limited amount of funding. Therefore, including participants that are most likely to show a positive response to the intervention, for example only including patients with a high-risk disease, increases the likelihood of showing a benefit of the intervention. This concept is called enrichment.

- Avoiding adverse effects: It is important to exclude any participants for whom the intervention is known to be harmful. For example, pregnant women are often excluded from clinical trials.
- Competing risk: Participants at high risk of developing conditions which prevent measuring the main outcome of interest should also be excluded from participation. For example, a patient that is at high risk of dying should not be included in a long-term trial.
- Avoiding poor adherence: Nonadherence by participants reduces the opportunity to observe the true effect of an intervention. Therefore, investigators prefer to enrol only participants who are likely to adhere to the study protocol. One way to achieve this is by including a run-in phase, in which patients are getting placebo or active treatment for a while, to select only the patients who adhere. However, including patients who show poor adherence is also an option. These trials are called 'pragmatic' clinical trials and resemble the real-world practice. 'Pragmatic' clinical trials have increased generalisability of the study results.

Clearly, these eligibility criteria can influence the feasibility of the study, but also generalisation of the study results to the general population. Firstly, the impact of eligibility criteria on the recruitment of participants should be considered when determining these criteria, since reaching a sufficient number of participants is a common problem for clinical trials. Therefore, it is recommended to use the five above-mentioned categories to set-up eligibility criteria that have a clear rationale. Changing criteria during the study, for example to increase the sample size, might have impact on participant safety and study design. Changes to the eligibility criteria should therefore carefully be considered. More about participant recruitment can be found in chapter *2.8 Recruitment of participants*. Secondly, the inclusion of participants in a clinical trial greatly influences the generalisation of the study results to the study population and the population with the condition, called external validity. Firstly, participants of a clinical trial must not be seen as truly representative of the study population, since they are selected from the study population by voluntary enrolment. Often it is difficult to account for the differences between the trial participants and the study population. However, sometimes a comparison of certain characteristics can be made between the actual enrolled participants and the participants that were not enrolled. In these special cases, a judgment about the external validity of the clinical trial can be made. Secondly, the study population does not always resemble the population most likely using the medical intervention, because eligibility criteria and recruitment strategies might disproportionately exclude certain subpopulations.

2.2 TYPES OF STUDY DESIGNS

In the most common parallel design, each participant is assigned to one of multiple arms to receive just one treatment and outcomes are measured and compared across groups. In contrast, a crossover design entails the randomisation of participants to one group for a set period and after a washout period, they will be assigned to the other study arm. Outcomes are compared within patients and differences are aggregated across all patients. A cross-over design increases the power to detect a treatment effect by eliminating differences in baseline characteristics between the study arms.

In addition, there are superiority and non-inferiority study designs. A superiority design demonstrates if an intervention is superior to no treatment, a placebo or the standard of care. However, it is also possible to investigate whether a certain formulation of a treatment is as effective as another treatment or even better. This non-inferiority design is especially useful when there is already an effective treatment available, but a new treatment might have other advantages, for example preferable pharmacokinetics or fewer adverse events.

2.3 Response variable

Response variables are outcomes measured during the trial in order to answer the research question. Examples may be total mortality, death from a specific cause, incidence of disease, quality of life, symptomatic relief or a laboratory measurement. A primary response variable depends on the objectives of the trial, while secondary response variables can be incorporated to explore other probably significant changes. Additionally, a composite outcome can be used when one response involves two kinds of events. Decisions about appropriate response variables should be based on knowledge of the disease, the kind of intervention and the expectations of how the intervention will work.

2.4 Comparator

In most clinical trials, the outcomes of participants receiving the intervention is compared to those of a 'control' group. Including a control arm allows evaluation of the attribution of the intervention on the observed effect. Furthermore, a control group allows to study if the new intervention is superior or non-inferior to that control, which can for example be a standard treatment or placebo. Occasionally, incorporating a control group is unethical, for example in case of a highly promising drug for a fatal disease. In addition, it is debatable if investigators have the responsibility to ensure that all participants receive the best proven therapy as a control or background care, even if the usual care is not up to that standard.

2.5 Randomisation

Observed differences between the outcome in the intervention and comparator group may occur because of a true effect of the treatment, but it might also be a consequence of a confounding factor. A confounder is a variable that influences both the independent variable, in this case the two different groups, and the dependent variable, the outcome. For example, systematically different baseline characteristics between the two groups might influence the observed results. Therefore, minimizing confounding increases the reliability of the results. Randomisation is a process by which all participants are equally likely to be assigned to either the intervention or the control group, preventing influence of any confounding factors. In addition, randomisation ensures the formation of comparable groups, creating similar magnitude of variation within each group.

2.6 Blinding

Preventing investigators and/or study participants from knowing which treatment the study participant receives, reduces the risk of measurement bias. This process of blinding or masking individuals involved in the clinical trial can be implemented on different levels, including single-blinding, double-blinding and triple-blinding. It is recommended to have at least double-blinding in your study design, so neither the participants nor the investigators know the intervention assignment.

2.7 Sample size

Sample size refers to the number of participants included in a study. The sample size influences the power of the study, which is the ability to measure the clinically relevant effect of the intervention. Therefore, calculations of sample size are an essential part of study design and should preferably be done by a statistician. A larger sample size increases the statistical power, but also the costs. The main components that are needed to determine potential sample sizes are: hypotheses, control arm data, effect size of interest, and type I and II error rates.

2.8 Recruitment of participants

Obtaining sufficient study participants within a reasonable time is difficult. Therefore, a clinical trial design should include a detailed plan of recruitment strategies. Strategies that increased recruitment rates are increasing awareness of the health problem, health questionnaires and direct contacting of potential participants. The most common and effective recruitment strategies included direct participant appeal, by television or internet advertisements, or an indirect appeal, via patient organizations or physician referral. Financial compensation for time, effort and expense of visiting the clinic are used to motivate participants to join the study. In phase I studies with healthy volunteers, this payment is generally higher, because they are put at more risk and they will not personally benefit from the intervention. Ethics review committees should decide whether the height of the reimbursement is ethical, since participants should not be paid more for taking more risk.

Recruitment of participants often gradually accelerates, but plans should be made to start from the beginning to prevent recruitment lags. Performing a pilot or feasibility study could be helpful when there is lack of data about specific participant sources. In case of recruitment lags, the identified sources should be expanded. When the investigator recognizes the lagging recruitment, there are few things he can do. Firstly, a smaller number of participants could be accepted, but this will reduce the power of the study. Secondly, the inclusion criteria could be relaxed, but only if the study design is not impaired. The most common option is to extend the time for recruitment or add other recruiting centres. However, this is also very costly and it delays the period where a new drug is under development. Lastly, broadening or changing the pre-specified primary response variable could increase the event rate and reduce the needed sample size. In chapter *4 Recruitment of diverse populations* recruitment strategies, barriers and recommendations for special minorities will be explained.

2.9 Multicentre study

In line with the previous paragraph, conducting a multicentre trial is extremely helpful to enrol enough participants. In addition, it improves the generalisation of the results, since it includes a wide geographical representation, especially in an international multicentre trial. Geography, race, socioeconomic status, and lifestyle of participants may be more representative for the general populations if participants are enrolled by many centres. However, there are limitations and concerns with globalization of trials. For example, it is unethical to enroll participants from underdeveloped countries to save money or to avoid regulatory oversight, when the population will not benefit from the intervention or does not have access to the intervention after the trial. In addition, it is debatable if findings from a clinical study performed in low- and middle-income countries can be extrapolated to high-income countries and vice versa. Therefore, investigators have to consider whether results from geographically and culturally different places is appropriate.

2.10 Conflict of interest

Conflicts of interest on the part of the investigators is a great concern in clinical trials. Conflicts of interest can lead to bias in design, conduct, data analysis, interpretation and reporting of findings. Given that investigators receive research funding to conduct a clinical trial, the idea that investigators only have interests in the well-being of the study participants and public health is unrealistic. Possible financial support may come from parties that are interested in the outcome of the study, for example the government, industry, research foundations or private investors. Therefore, many investigators do not avoid them, but manage conflicts of interests. Ethical committees have to decide beforehand if the financial relationships are acceptable. In late phase clinical trials, data analysis should be conducted by groups that do not have economic interests in the outcome and are thus independent of the sponsor. In addition, investigators should disclose financial partners to participants and in journals.

3 REGULATION

Clinical trials should be safe for participants, but outcomes of the clinical trial should also be reliable. To ensure this, clinical trials should comply with national regulations, which are most often based on international guidelines. The International Conference on Harmonisation (ICH) guidance documents were created to make clinical trials more comparable internationally[4]. The ICH Good Clinical Practice (ICH-GCP) guideline is an important ethical and scientific quality standard for designing, conducting and reporting clinical trials[5]. These guidelines are based on some key documents about ethical principles in research with human subjects like the Nuremberg Code (1947), the Declaration of Helsinki (1964) and the Belmont Report (1979)[6–8].

Individual regulatory agencies among countries decide about the implementation of these guidelines. The Food and Drug Administration (FDA), the agency that reviews medical products for marketing in the United States, recommends applying the ICH-GCP guidelines and in the European Union they are now a legal obligation for all trials involving the investigation of medicinal products. In the Netherlands, regulatory authorities will enforce rules according to the Wet medisch-wetenschappelijk onderzoek met mensen (WMO), which has implemented the European Union recommendations about using the ICH-GCP guidelines[9].

3.1 GOOD CLINICAL PRACTICE

Clinical trials conducted in accordance with the ICH-GCP guidelines should comply with ethical principles and have detailed protocols approved by ethics committees[5]. It is particularly important that the benefits should outweigh the risks. The rights, safety and well-being of participants should be preserved by obtaining voluntary informed consent. Qualified personnel and access to data are essential. For further details, consult ich.org. The remainder of this chapter will focus on some of the most important regulations that are consistent with the ICH document about Good Clinical Practice, including information about the ethics committee, informed consent, termination of a clinical trial and publication of data.

3.1.1 Ethics committee

Before start of a clinical trial that involve drugs, devices and biologics, investigators have to gain regulatory approval by an ethics committee. In the US such a committee is called an Institutional Review Board (IRB). These committees make sure all clinical trials are performed in accordance with regulations and guidelines. An important part of the application is the research protocol. It has to contain all relevant information for conducting the clinical trial, from recruitment strategies to data publishing.

3.1.2 Informed consent

One crucial requirement of a clinical trial is the voluntary informed consent. These are designed to inform the patient about the nature and duration of the clinical trial, to show the participants their rights and to protect the privacy of the participants' data. In addition, the informed consent should state what the participant can expect after the trial is over, for example if the participants have access to the intervention. The ICH-GCP contains recommendations for the exact details that should be implemented in an informed consent. For example, informed consent can be withdrawn at any time with no reason by the participant. However, it is less clear to what extent participants have the right to refuse any type of follow-up. For researcher and participant, this can be crucial information. In addition, under special conditions, when informed consent is not possible, clinical trials can be approved, but under very strict conditions. Also, special guidelines exist for research on minors or other vulnerable populations.

3.1.3 Termination of a trial

During a trial investigators and sponsors are obliged to report to the ethics committees any serious adverse events seen during the trial. In addition, they have to ask for approval to modify the protocol. For example, trials may only be stopped earlier than expected if it the reason is one of the following: (1) there are serious side effects, (2) there are greater than expected beneficial effects for the intervention group, (3) if it becomes clear that reaching a statistically difference at the end of the trial is improbable, (4) the number of required participants is not reached because of lagging recruitment, (5) the scientific question is already answered by others or the question is not relevant anymore. These reasons require regular monitoring of benefits and side effects. Frequently, this is done by an independent monitoring committee. Importantly, a trial may not be stopped because the sponsor decides to quit providing the required resources.

3.1.4 Publication

All investigators are obliged to report trial findings. To minimize publication bias it is now also required to register the trial at initiation in one of several accepted registration sites. Additional documents and presentations are required if the investigators want to get market approval for the new intervention.

4 RECRUITMENT OF DIVERSE POPULATIONS

4.1 BARRIERS AND SOLUTIONS

A lack of inclusion of diverse groups in research can be explained by several barriers acting at multiple levels. The most well-known obstacle is the inability of individuals to speak, read or fully understand English, the main language of communication in trials in the USA and Europe. A related barrier includes the inability to understand the basics of the clinical trials. These individuals do not only include migrant ethnic groups, but also other populations experiencing lack of education or disabilities. Another reason people are resistant to participate, is a lack of trust in research, doctors and medical industry. Furthermore, a lack of access to clinical trials, from a lack of information about relevant clinical trials to the inability to reach the research centre, further impairs the inclusion of diverse research participants. Some practical barriers, like indirect costs associated with participating, time or childcare were other reasons not to participate. Sometimes eligibility criteria disproportionately exclude people in under-represented groups, including pregnant women, obese individuals and people withs severe mental illness.

Investigators have several evidence-based strategies to overcome these barriers. For example, literature suggests that inclusion in trials improves when staff had received specific training on that topic. For example, knowledge about culturally important practices is beneficial to improve the recruitment of diverse populations. Furthermore, establishment of a diverse community advisory panel to improve the relationship between researchers and underrepresented groups is an effective strategy. Lastly, increasing the recruitment of staff from under-served groups ensures closing the gap between researchers and under-represented groups.[10]

4.2 FDA RECOMMENDATIONS

In 2020, the FDA released a document with nonbinding recommendations for enhancing the diversity of clinical trial populations[11]. The FDA encourages sponsors to consider the approaches outlined in the guidance. Firstly, the FDA recommends broadening eligibility criteria and avoiding unnecessary exclusions. For example, increasing data about drug-drug interactions from early studies could decrease exclusions related to concomitant medications. In addition, each exclusion criteria should be justified for reasons to assure safety, not because it was a criterion from phase 2 studies. Exclusion criteria can sometimes also be narrowed down. For example, do not exclude all patients with organ

dysfunction, but only those with severe organ dysfunction. Furthermore, several other approaches are highlighted. Sponsors should enrol participants who reflect the characteristics of clinically relevant populations. It is recommended to include children, adolescents, women and racial or ethnic minorities in clinical trials and perform separate analysis for the subgroups. In addition, sponsors should consider various methodological approaches that will facilitate enrolment of a broader population. For instance, they should consider characterizing drug metabolism and clearance across populations in early clinical development to make appropriate dose adjustments. Furthermore, they should think about relaxing the enrichment criteria by enrolling participants across the full spectrum of disease severity. Making trials less burdensome for patients and adopt enrolment practices that enhance inclusiveness, like providing resources in multiple languages and including personnel with different backgrounds, are additional recommendations.

In December 2022, President Biden signed the Consolidated Appropriations Act 2023 which includes the Food and Drug Omnibus Reform Act of 2022 ("FDORA")[12]. This act consists of several provisions to promote diversity in clinical trial enrolment, encourage of decentralized clinical trials and streamline clinical trials. The act is based on three federal agency efforts to enhance diversity in clinical research, including the FDA's 2020 guidance on enhancing the diversity of clinical trial populations as discussed above. Sponsors now have to submit a 'diversity action plan' to the U.S. Department of Health and Human Services for certain late-stage drug trials. Part of this plan is the sponsor's goals for enrolment, the rationale for those goals and a plan how the sponsor wants to meet them. This is the first time that there is a statutory requirement for diversity in clinical trials.

5 CLOSING WORDS

In summary, a clinical trial is a study in which human subjects are prospectively assigned to an intervention to evaluate the effect of this intervention on health-related biomedical or behavioural outcomes. Clinical trial design requires careful considerations about scientific, ethical and safety aspects. A good clinical trial design is essential to interpret and determine the generalisability of the results. International guidelines, especially the Good Clinical Practice guidelines, ensure high quality standard for designing, conducting and reporting clinical trials. Various barriers contribute to the lack of diversity in clinical trial populations. Broadening eligibility criteria and improving recruitment strategies are recommended approaches to enhance diversity.

This handout represents a selection of available information about clinical trials. The handout is established with the goal to give students and teachers a short overview of several aspects of clinical trials, based on *Fundamentals of Clinical Trials* (2014) by Lawrence M. Friedman and others[1]. Furthermore, emphasize was placed on study population and recruitment, because these are important factors for diversity and inclusion in clinical trials. To engage students and increase learning effectiveness[13], a concomitant e-learning course module about clinical trials is available, based on the contents of this handout. Furthermore, students are asked to dive into a specified topic, prepare a short 'conference'-talk about the advantages and disadvantages of the approach and answer critical questions from peers[14]. The assignment is explained at the end of the e-learning course.

6 LITERATURE

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