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A Simplified Explanation of the Clinical Trial Process

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Overview of clinical trials

Clinical research is essential in converting basic science discoveries into novel approaches to treat disease. To determine whether investigational therapies are safe and effective in humans, they must undergo rigorous clinical trial testing. Clinical trials remain the cornerstone for evaluating novel disease interventions.[1,2] According to the National Institutes of Health (NIH), a clinical trial is a "research study in which human subjects are assigned to receive a therapy which is then evaluated based on a set expected health outcomes."[3] Clinical trials usually investigate the prevention, screening, diagnosis or treatment of specific health conditions.[1] In this review, we summarize the hallmarks of clinical trial design. We then segue into a brief discussion detailing the clinical trial phases a potential therapy embarks on to receive approval for incorporation into medical practice.

Study question

Clinical trials are developed based on a *specific* study question that is tested in a well-defined patient population. The investigators do not already know the answer to this question and rely on the outcomes of the clinical trial to provide an answer. A hypothetical example of a study question could be "is minoxidil effective in promoting hair growth in adult patients with central centrifugal cicatricial alopecia (CCCA)?"

Study population

Each respective study must *clearly* define a group of patient participants to investigate their question on. It is necessary that the investigators identify an age range of a study cohort, given the physiological differences that exist across the age spectrum. Based off the example used above, adult patients with CCCA (aged 30-50 years) can serve as a hypothetical study patient population.

Inclusion/exclusion criteria

The use of specific, but simple inclusion/exclusion criteria help to create the ideal pool of participants to generate the most useful data for the study.[1] Inclusion criteria are parameters that patients must meet for inclusion into a study, while exclusion criteria are parameters that exclude patients from further consideration. In continuation of the minoxidil clinical trial example, hypothetical inclusion criteria can be patients in the age range of 30-50 years with a diagnosis of CCCA. However, an example of exclusion criteria in this case can be patients currently on cancer chemotherapy treatment, which promotes hair loss. In this case, a 30 to 50-year patient with CCCA could be considered for inclusion into the minoxidil study. However, if that patient is also currently on chemotherapy treatment for a coexisting cancer, this patient can no longer be considered for inclusion into the study.

Treatment groups

Clinical trials have clearly defined treatment groups, usually with a single intervention group along with a single control group. The intervention group receives the treatment that is being investigated. The control group should reflect the best accepted "standard of care" but that is not always the case.[4] In some cases, a "placebo" is administered to the control group. Placebos are chemically inactive agents that permit researchers to evaluate the overall effect of the treatment being investigated.[1,2] In the minoxidil example mentioned

previously, the intervention group will theoretically receive minoxidil while the control group will receive the current standard of care.

Treatment group allocation

Clinical trials should clearly outline how the treatment and control groups are assigned. Many trials utilize randomization, the process by which subjects are randomly assigned to receive either the investigational treatment or the control. This approach prevents any form of selection bias and allows for a more effective and fair comparison of the study outcomes.[1,2] Randomization is currently the "gold standard" of assigning groups and many investigators utilize automated systems that randomly assign patients into their respective groups.

Study outcomes

The primary and secondary outcomes of clinical trials should be clearly stated in a specified time period. Outcomes are usually clinically relevant variables assessing whether the intervention studied results in a benefit that is detectable by the patient. Examples include an improvement in symptoms, functional capacity, or decreased chances of developing a condition or disease complication.[1] In the minoxidil clinical trial example, a primary outcome could be the slowing of disease progression at 48 weeks. Secondary endpoints answer other relevant questions about the same study, for example, whether minoxidil increases the quality of life of CCCA patients.

In 1962, the FDA required proof of both safety and efficacy of new drugs before they can reach the market.[4] A new drug might start with the discovery of a compound with therapeutic potential. This prompts scientists to determine how it works and whether they can harness its positive effects for human health. A new therapy usually emerges from a long course of research that starts with basic science discoveries followed by translational and applied studies, product development research, and clinical testing.[1,2,4] We will now segue into phases of clinical trials that earmark the process of drug development from conception to post-approval studies.

Preclinical research

Preclinical research usually begins in a basic science laboratory at a large pharmaceutical company, or at a startup, or academic research center[4]. There, large numbers of compounds are screened for useful biological activity **(see Figure 1)**. Preclinical investigations include animal studies and evaluations of drug production and purity. From these studies, perhaps ten candidate drugs will make it to the clinical trial stage. As the different phases of clinical trials proceed, most of these drugs will fail due to safety or efficacy concerns, or for business reasons. On average, only one or two will eventually become FDA approved drugs. Depending on the results of the clinical trials, the FDA may require additional monitoring or post approval studies once the drug is on the market. Let us look at each of these different stages.

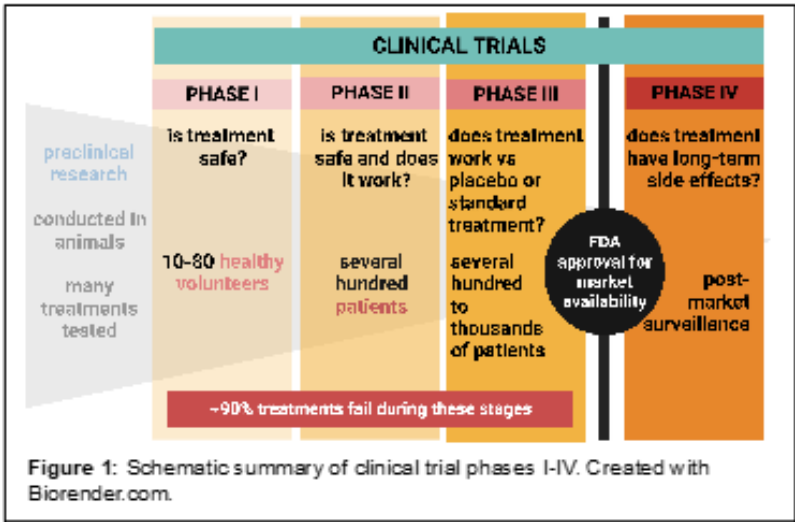

Figure 1: Schematic summary of clinical trial phases I-IV. Created with Biorender.com.

Phase I trial

Following preclinical research, a drug candidate must then be tested in humans (Figure 1). Unlike preclinical research, human testing or clinical trials cannot begin until the drug company receives authorization from the FDA. Phase I trials test a potential therapy, procedure, or drug for the first time in humans.[2] The goal is to **establish a treatment's safety**, determine a safe dosage range, and identify side effects. Another goal is to understand the pharmacokinetics of the drug, that is, how the drug is absorbed, metabolized, and excreted from the body. Phase 1 trials usually consist of about 10 to 80 subjects who are generally *healthy* volunteers

who do not have the disease but can sometimes be patients who do have the disease.[1,4] There is *no control group* in phase I.[1]

Phase II trial

Phase II trials also evaluate a treatment's safety. However, at this stage, investigators begin to determine whether the treatment works (also known as efficacy) (Figure 1). Phase II trials focus on drug safety in patients with the condition to be treated, instead of healthy volunteers.2 These are usually performed with a larger sample size of hundreds of patients. Phase II trials should be well-controlled, meaning that there are two groups: one group that receives the experimental drug and a comparison or control group that receives either placebo or an existing treatment [4].

Phase III trial

Phase III trials confirm a treatment's efficacy against the current standard treatments while monitoring for adverse effects (Figure 1). Phase III trials are usually the **largest trials**, including anywhere from several hundred to several thousands of subjects, often taking many years to complete.[1,4] Ideally, these trials will be randomized, controlled, and blinded, which provide the highest quality of evidence. When phase III trials are complete, there should be enough evidence regarding the **overall risk benefit profile** to make an approval decision about the drug. A drug generally cannot be approved unless the FDA determines that benefits exceed risks.[4] Interestingly, a drug can be approved if benefits exceed risks by any small amount.[4]

Phase IV trial

Phase IV trials (also known as post-approval trials) are conducted once the new treatment has received FDA approval.1 Phase IV trials gather additional information about a drug's overall safety or clinical benefit.[4] This post-market surveillance helps evaluate long-term drug side effects, further establish effectiveness of treatments outside the controlled trial setting and can identify potential new uses for additional patient populations or diseases.[4]

Conclusion

Well-designed and executed clinical trial testing can contribute significantly to the federal push to improve the effectiveness and efficiency of U.S. health care administration. Moreover, progression of an investigational treatment throughout the trial phases is intended to establish therapeutic usefulness in a safe, strategic, and reproducible manner. Through rigorous testing applied to novel drugs coming through the pipeline, clinicians and patients can maintain confidence in the therapies available.

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