Clinical Trials

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Contents

1 Introduction **2**
1.1 What is a clinical trial? 2
1.2 Drugs versus Biologics 2
1.3 The Drug Development Process 3

2 Mixed Effects Model **5**
2.1 Motivation 5

Lecture No. 1

Introduction

1.1 What is a clinical trial?

There seem to be a few definitions but they all boil down to the same notion. Clinical trials are investigations where human subjects are used to evaluate the safety, efficacy, and feasibility of a treatment. In even simpler terms: a test on how good a treatment works on humans.

The job of defining how that 'test' should be carried out, what our definition of 'good', and 'treatment' are—those details and considerations are the study of clinical trials.

1.2 Drugs versus Biologics

When we mention the word 'treatment' in the context of clinical trials, most of us have a pretty good idea of what that means. Most things that a doctor would prescribe could perhaps be reasonably considered as a form of treatment. This could encompass things like a pill, an injection, a diet, an ointment, a fungal cream, or even an exercise regime.

From that non-exhaustive list, we can further subdivide or categorise treatments. Some treatments require you to change lifestyle habits like your diet or time you spend exercising. But other treatments require you to go to the pharmacy and obtain medicine for consumption.

These medicines are regularly referred to as drugs. In clinical trials however, there is nuance in how these medicines are categorised. The term 'drug' refers to medicine that is typically manufactured through chemical synthesis. It means that it is made by combining specific chemical ingredients in an ordered process.

A biologic on the other hand is manufactured by a living organism, like a micro-organism, a plant, or animal cells. Most biologics are large, complex molecules, or even mixtures of those molecules. Things like vaccines, insulins, and botox are biologics.

So far, it seems that the only real differences between the two are the way they are made. That is completely true, but that difference is important. Drugs can be analysed to determine their various components, but since biologics are so complex, they are near impossible to analyse in the same way. The consequences of these differences are easier explained by example.

Example 1.2.1. Let's say that a company D has made a drug and through extensive clinical trials, they have found it to have some desired effect in humans. Let's say it improves the quality of sleep. Meanwhile, company B has made a biologic, and after the necessary clinical trials, they found it effective in reducing inflammation for menopausal women. Now, after obtaining regulatory permission to distribute their respective medicines, both companies make tidy profits.

Years go by, and the companies still make the medicines. One day, company D hires a bright young chemist named Jane. Jane is no slouch in the lab, and she knows her subject well, a lethal combination. A few months in, she realises that the process used to produce the drug can be altered to be cheaper, faster, and even safer! After some testing, she presents her findings to the head of research at the company.

Needless to say, they were happy to hear of Jane's breakthrough, and ordered a full battery of chemical tests to ensure the new process produces the same exact drug. The tests all concur with Jane's findings, and so the company sends relevant samples to the regulatory bodies. They have also found that the drugs are indeed the same as before.

Now, over the next few months, the company switches over to Jane's method, and they make more money than before. Jane however, finds a job at company B which happens to be closer to her house. A few months working there, and what do you know, she's gone and done it again! She's managed to find a better way of making their biologic—theoretically.

Again, Jane approaches the head of research and presents her findings. This time, they look at her work and realise that she might be right! Unfortunately, they have no way of chemically analysing whether the two processes yield the same product.

What they instead have to do is order another clinical trial for the new method to determine whether the effect is the same. Only after they establish that fact can they proceed to change their method of production to the newer method. This process takes much longer, as clinical trials take time, as we shall soon see.

1.3 The Drug Development Process

The drug development process costs money and takes a long time. Why? There are a few reasons, the most obvious of them being safety. To ensure safety, the entire process is highly regulated.

Another more sobering reason is that the majority of the easy targets are already gone. The large share of conditions that require good treatments nowadays are generally for chronic and degenerative diseases.

Because the simpler solutions have been discovered, that leaves the harder to find–complex solutions. This means that out of 10,000 molecules, only 1 may be successful—a high rate of failure indeed.

The first step in the process is drug discovery, and it's where all possible drugs which *might* work are identified. This part can take a long time—you can't force discovery after all—anywhere between 2–10 years.

The second step is pre-clinical testing. This consists of laboratory and animal testing, where drugs that cause adverse health issues in the animals for moderate to high doses are removed. This will roughly reduce the number of viable drugs from 10,000 all the way down to around 250, and the process takes about 1–3 years.

The third step is called 'Phase I'. Phase I sets out to answer the question: Is it safe in humans? For this, roughly 10–40 healthy volunteers are recruited, and the process takes up to 12 months, while the number of viable drugs drops to about 100.

Next, we have 'Phase II'—predictable, I know—which tries to find the answer to the question: Does it work? This is where it gets interesting, 100–200 **patients** are recruited to study the effectiveness of the drug and its side effects. Phase II can take up to 2 years, and the number of drugs that pass this stage number about 70.

Then, comes 'Phase III'—who knew?—and here the purpose is to find out all the possible side effects, even in the long term. This is a detailed study where 1000–3000 patients are recruited to learn how the drugs work in the long term, to determine proper dosage, and to identify side effects. As you can readily imagine, a study of this size and depth takes longer, roughly 1–4 years, and as a result, about 30 drugs are left.

Now comes the time to 'show your work'—The regulatory review/approval process. Here, the authorities come to check whether you've done your due diligence in determining whether the drug is both safe and effective. This can take anywhere between 2 months to 7 years, and you're left with a measly 20 drugs left—or thereabouts.

The last step is 'Phase IV', which encompasses real world studies. This involves marketing surveillance, and a large number of patients. The purpose of this step is to validate the clinical work done before, and typically takes 1–2 years..

Because of all these steps and challenges, the process typically spans the duration of 12 years and costs anywhere between US$800M–1200M. As you can imagine, that really puts the issues of example 1.2.1 in perspective.

Each of the 'phases' are what constitute what we call 'clinical trials'. Phases I and II make up the early development 'discovery' portion, and Phases III and IV make up the later development 'confirming' portion.

Lecture No. 2

Mixed Effects Model

2.1 Motivation

As mentioned in chapter 1, clinical trials involve measurements of the effects of a treatment on human subjects. The end goal is to be able to say something specific about the treatment—whether it is safer than another treatment, whether it is faster acting compared to another treatment, or even whether it is more effective than a placebo.

We want to be able to say these things with a certain **level of confidence**. That's a statistical term which comes with a technical definition, but it arises from the intent of those words. For example, let's say that a clinical trial was conducted to test whether a drug is effective in making people fall asleep quickly. The trial recruited a total of 40 healthy individuals, and randomly split them into two groups of 20.