Group 1: Ethical I - Clinical Trials

First-in-(hu)man (FIH) trials – ethical issues

The phases of a clinical trial include an initial exposure of the compound of interest to the human body. While in other trials prior information on the reaction of the organism on the drug is available, FIH trials fill the gap between preclinical and clinical trial. In most of the cases the human subjects are healthy young men. This practice has several ethical implications and a question one might be inclined to ask is, whether it is ethical to expose healthy volunteers to a potentially harmful substance [1].

Why volunteer in a FIH trial – personal benefits?

It is well known that clinical trials might have severe adverse effects on health, even death as we have seen in the incident in France in 2016 [2]. Despite the risks, people do volunteer to participate in clinical trials. In this section, we will investigate which benefits can arise from FIH clinical trials for healthy young volunteers.

Financial benefit

While clinical trials are not especially well paid (~10$ /h), the amount of time that the subject is usually required to spend in the research facility, makes a relative low per hour remuneration sum up quite quickly [3]. This is an attractive source of income, especially for people having a lot of time at their disposition and low grade of education. Some claim, that the participation in clinical trials could be compared to other risk-prone, unpleasantr, or tedious tasks such as police or military service or jobs that include physical risks, such as electrics. Other than money, participants often are granted access to healthcare, they would otherwise not be able to afford [3][4][5].

Conviction

Volunteers might also be driven by more altruistic motives. The participation in a trial can generate valuable clinical information and thus provide benefit for the society in the form of knowledge [4][5].

Relatives of patients

Clinical justifications of FIH trials

There are several justifications to conduct FIH in healthy subjects rather than patients. First of all, healthy patients are able to tolerate adverse effects induced by a potential drug more easily than patients already suffering from a severe condition. It is even possible that the trial might deteriorate the patients condition which would be ill advised. It is also commonly accepted, that healthy patients provide the cleanest data, such that the measurements are not obscured by effects of other treatments. Furthermore, enrolling a patient in a clinical trial, would mean, that he or she can not continue taking any other treatment, which is ethically challenging, since a patient should always be administered the treatment which is best suited for his/her condition [4][5].

The EMEA Guideline

In March 2006, a first-in-human clinical trial investigating a monoclonal antibody TGN1412 was conducted. The compound had severe toxic and life-threatening effects. This incident made experts aware of the necessity to develop strategies to promote the safety of trials investigating the effects of new pharmaceutical, chemical or biological compounds. Shortly after the incident, the EMEA (European Medicines Agency) issued a guideline document, which in its finalized form has the title "Guideline on Strategies to Identify and Mitigate Risks for First-in-Man Clinical Trials with Investigational Medicinal Products". This guideline is complemented by a variety of documents focussing on more specific aspects of Human Clinical Trials and should not be seen as unique source.
According to the guideline several aspects should be addressed to estimate the risk of a clinical trial. In order to determine the starting dose for trials in humans, most often animal models are used. The relevance of an animal model depends on how similar the model organism is to human concerning the target, structural homology, metabolic pathways as well as pharmacodynamics (effect of a drug on the organism) and pharmacokinetics (effect of the organism on the drug). Since animal models are used to assess PK and PD, as well pharmacological safety and toxicology, the use of an appropriate lab animal is crucial. The aforementioned aspects should also be investigated separately using appropriate in vitro models, such as human cell cultures or in silico approaches. Another key aspect of a FIH clinical trial is the dosage that is administered initially and the steps that are undertaken to estimate NOAEL (no adverse effect level) and/or MABEL (minimal anticipated biological effect level).

With all those aspects synthesized in a guideline, the EMEA focuses on the increase of human safety in clinical trials, but emphasizes that a case-to-case assessment of clinical trials remains crucial [1].

References


Further Reading