Clinical and Regulatory strategies to avoid Pitfalls in Clinical Trials

Summary of session 1

The main purpose of clinical trials is to establish a causal relationship between the developed therapeutic product and the desired clinical effect, conducted objectively. Additionally, as a drug developer you must meet regulatory agencies expectations to obtain a marketing authorization, and the data you generate is supposed to support this. In session one of this two-part webinar, Steffen Thirstrup, Advisory Board Director at NDA presents the fundamentals of designing a successful clinical trial.

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Moving from bench to bedside, deciding whether a drug is ready for clinical trials involves extensive preclinical studies that yield preliminary signs of efficacy, toxicity, pharmacokinetic and safety information. A clinical trial is, nevertheless, a trial, an experiment performed on a sample of patients that should be reasonably representative of the population that the new drug intends to treat and replicate real-life as best as possible. It needs to be objective, preferably completely random, and blinded. A homogenous trial population will more likely give a significant result. However, each patient is an individual, with different disease characteristics, comorbidities and possibly other drug combinations, the trial population will not be representative, and the outcome of the clinical trial may not be equally applicable to patients in real life.

In the last ten to fifteen years, we have seen an increase in approvals of indications with very narrow inclusion criteria, i.e., a product can be approved for a gender or age specific patient population. To avoid having an approval reflecting an overly narrow patient population, this should be as broad as possible, hopefully without too many exceptions in the applicability of the study outcome, to the real-life situation.

As mentioned above, patients are unique, meaning that the outcome may vary among them. Presenting the trial data as the mean effect between the intervention group and the control group when the outcome covers a broad range might not pick up relevant effects in certain individuals. In many cases, regulators would like to see cut-off points to evaluate responders versus non-responders instead of, or as a supplement to the mean effect of the whole study population.

In Europe the average number of patients included in clinical trials to obtain the marketing authorization rarely exceeds 2000 patients. This number is not sufficient to detect rare or serious events. In perspective, the current discussion of side effects of certain COVID-19 vaccines, the risk of thrombotic events occurs in 1:40,000 vaccinated individuals. Such rare events will not be picked up in the clinical trial.

Different trial designs

RCT: randomized controlled trial. This is the golden standard of clinical trials where patients are randomly allocated to a treatment group or a control group and monitored. There may be more than one treatment with different dose levels in this type of trial. Within an RTC, there could be an interest in stratifying the patients, i.e., stratification by males and females before randomization to ensure that the distribution of gender is equal in both groups. An alternative stratification is to plan a stratified breakdown of the different patient data as part of the statistical analysis. A stratified approach requires a higher number of included study participants to reach enough statistical power for the individual strata (e.g., in both males and females).

Rollover RTC: Here, the participants of the control arm of the randomised study are offered the option to rollover into the active arm once the trial period is over. The subsequent open-label study will generate long term safety and efficacy data, even if the latter data are non-randomised and non-blinded. Under some rare circumstances, patients in the control group are allowed to shift over to the active arm of the trial if they don't have the desired effect. This is most often seen in cancer trials. When this happens before the initial trial period has ended, it can reduce the control group and therefor limits the interpretability of the efficacy and safety data.

Crossover RCT: Here, the participants will be randomised into one group and after a pre-planned period switched to the other group (active and control) after a washout period. The advantage of crossover studies is that patients act as their own controls, there is no between subject variability and fewer subjects are needed. There is a risk, however, that the effect of the first treatment period is carried over, introducing a skewness and a bias in the trial. Additionally, there are many chronic conditions that changes over time, which can impact the results in different directions.

Randomized withdrawal: Subjects receive treatment for a specified time and are then randomly assigned either to continue treatment or to a placebo arm (i.e., withdrawal of active therapy). Any differences that emerge between the group receiving continued treatment and the group randomized to placebo will demonstrate the effect of the active treatment. The advantages are that individuals receiving the experimental intervention continue to do so only if they respond, whereas individuals receiving the placebo do so only until their symptoms return. In certain ethical circumstances this can be the preferred trial design.

Single arm trial: A clinical trial without any comparative arm. Single arm trials are difficult to interpret and should be used with caution. Having a strong biological rationale supporting the mode-of-action of the drug could support doing a single arm trial and be accepted. Also, if there is a well-known natural history of the disease to compare to or it may be the only option in a very small patient population where there is no other treatment or alternative treatments are inappropriate.

Basket trial: This is a study of one drug in many different indications in different organs, typically based on a similar mode of action and similar macromolecule or biomarker target in these organs.

Umbrella trial: Here, different drugs used for the same condition are tested, to select the most optimal treatment regimen.

Endpoints

Direct, hard, or clinically relevant endpoints represent or characterize the clinical outcome of interest as opposed to surrogate endpoints. The primary endpoint is the outcome for which the trial is designed. Secondary endpoints can include a wide variety of parameters associated with the trial focus and intervention. A surrogate endpoint could be a laboratory measure or a physical sign that is intended to be used as a substitute for a clinically meaningful endpoint.

Regulators are generally concerned about surrogate endpoints, they need to be sure that these endpoints without reasonable doubt reflects a clinically relevant outcome, something that is beneficial to the patients. Often, validated surrogate endpoints are accepted by regulators, i.e., in diabetes, hypertension or rheumatoid arthritis, where there are lab measures or scoring systems used for evaluating increased risks or the level of active disease. If a surrogate endpoint is not yet validated, validation needs to be incorporated in the clinical trial, or confirmatory data needs to be provided to regulators in some other way.

Guidance and Scientific Advice

There are guidelines developed by regulatory authorities to support drug developers conducting clinical trials. For example, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) have a lot of guidelines, especially in the areas of CMC and non-clinical, whereas ICH guidance is less in the clinical phases. The ICH guidance is less pronounced because treatment of clinical conditions varies across the globe. It is difficult to obtain global harmonization of those guidelines, but in circumstances where ICH guidelines are not sufficient, regulatory authorities such as the European Medicines Agency (EMA) have a list of scientific guidelines, where you can read the regulatory expectations in any field.

When working in small biotech's or in the space of orphan medicinal products, there will often be no scientific guidelines and therefore, there may be a need to consult the regulatory authorities directly by seeking scientific advice. Scientific advice could be very useful before embarking on a clinical trial in any field where existing guidance is limited, outdated or in one way or another not suitable.

The regulators checklist for clinical trials according to Steffen:

The primary and secondary endpoint must be of clinical relevance. Surrogate endpoints should be properly validated

Power and patient number: Minimal Clinical Important Difference (MCID) represents the smallest improvement considered worthwhile by a patient.

Blinding and randomisation: could there be unintentional built-in biases?

Statistical Analysis Plan: stick to the plan. Regulators will question post-hoc analysis.

Comparator(s): Will the new drug be compared to placebo, a comparator drug or standard of care? How should you choose? These methodological issues are relevant to the design of controlled trials of new medicinal products and needs to be carefully considered.

Duration / Follow up: How long is long enough? Decide on the optimal duration of the intervention as well as the follow-up to assess long term efficacy and may in many cases, long term safety.