Making Sense of Biostatistics: Therapeutic Confirmatory Trials

By J. Rick Turner

Following the completion of Phase I trials, an investigational drug can move into Phase II trials, also known as therapeutic exploratory trials. As described in ICH Guidance E8: General Considerations for Clinical Trials, Phase II trials explore the use of a drug for its intended therapeutic indication by employing around 100-300 participants with the medical condition of concern. For example, an investigational antihypertensive drug would be given to participants with high blood pressure. Phase II trials, which are generally relatively short in duration, provide an initial estimate of the drug’s safety and efficacy. Moreover, they provide useful information in preparation for Phase III trials, or therapeutic confirmatory trials. This information includes an estimation of the most appropriate dosage(s), determination of the relevant endpoint(s), and other elements of study design, experimental methodology, and statistical analysis (Turner).

Phase III therapeutic confirmatory trials typically involve around 3,000-5,000 participants with the medical condition of concern. (This number can be much smaller when studying a drug for a rare condition.) Phase III trials are typically longer in duration than Phase II trials. They are comparative in nature, so participants are randomized to a drug treatment group and a control treatment group. In this column, we will consider the case of a superiority trial in which an investigational antihypertensive drug is tested against a placebo. (We will discuss equivalence trials and noninferiority trials in a future column.)

The three primary goals in Phase III therapeutic confirmatory trials are:

- Confirm the investigational drug’s efficacy and clinical usefulness.
- Establish the drug’s clinical safety profile.
- Assess the drug’s benefit:risk balance.

These goals are addressed in this column, and the third will be addressed next month.

An antihypertensive drug is effective if it lowers blood pressure. The endpoint of interest in our trial, therefore, is the degree to which the drug lowers blood pressure. More precisely, it is how much more the drug lowers blood pressure than does the placebo. (It is possible to see a small mean decrease in the placebo group even though the placebo has no antihypertensive action). The first goal of a Phase III trial is to confirm the drug’s efficacy and clinical usefulness. This involves two sequential steps. In this superiority trial, the first step is to demonstrate that the drug is statistically significantly more effective than the placebo. Imagine a trial in which the mean decrease in blood pressure in the drug treatment group is 17 mmHg, and the mean decrease in blood pressure for participants in the placebo treatment group is 2 mmHg. The treatment effect is therefore 15 mmHg. We now test the hypothesis that the drug is superior to the placebo, i.e., that it lowers blood pressure to a statistically significantly greater degree. Imagine that the statistical test employed here yields a p-value of 0.03. Since this p-value is less than 0.05, this result enables us to reject the null hypothesis, which states that the drug does not lower blood pressure statistically significantly more than placebo, in favor of the research hypothesis, which states that the drug does lower blood pressure statistically significantly more than placebo.
The second step, which is only taken following a statistically significant result, is to demonstrate the drug’s clinical significance. A clinically significant treatment effect is one in which the lowest estimate of the drug’s efficacy is still clinically meaningful. This lowest estimate is provided by the lower limit of the confidence interval (CI) that is placed around the treatment effect point estimate. Imagine that 95% CIs were calculated and placed around the point estimate of the treatment effect, resulting in the following values for lower limit, point estimate, and upper limit: 13.5, 15.0, 16.5. This result allows us to declare that we are 95% confident that the true but unknown population treatment effect lies somewhere between 13.5 mmHg and 16.5 mmHg, with a best estimate of 15.0 mmHg. The (minimum) size of a treatment effect that is deemed clinically relevant is best defined by medical, clinical and regulatory specialists (Durham and Turner).

Therapeutic confirmatory trials must provide “substantial evidence” of a drug’s efficacy. The FDA requires this evidence to be provided by two or more identically designed trials, or by studies that are of different design and perhaps evaluate different populations or dosage forms. Consider the case of two identically designed trials. The data collected and results obtained will not be precisely the same (for one reason, different participants take part), but a certain similarity of results is meaningful. Obtaining two statistically significant, (i.e., p-values less than 0.05) and clinically significant results provides very powerful evidence. The hypothesis tested in these trials is usually two-sided. Not only does there have to be a statistically significant result, but the mean drug effect has to be greater than the mean placebo effect. It is theoretically possible that the placebo could lower blood pressure statistically significantly more than the drug, so the statistical tests have to take this unlikely possibility into account. The probability of obtaining a statistically significant result in which the drug is more effective than placebo by chance alone is therefore 0.025 (half of 0.05) in each trial. The probability of this result occurring by chance alone in both trials is 0.025 multiplied by 0.025, i.e., 0.000625, or one in 1,600 (Turner and Durham). Two such results therefore suggest very powerfully that the drug’s treatment effect is real.

The second primary goal of therapeutic confirmatory trials is to further establish the drug’s safety profile by building on safety data collected in previous trials. While human pharmacology trials involve extensive safety measurements on a small number of participants, therapeutic confirmatory trials involve fewer measurements per person but many more participants. Therefore, the overall safety database is expanded considerably. The safety data collected continue to provide pharmacological (toxicological) characterizations of the drug via clinical laboratory tests, vital signs, physical examinations, adverse events, adverse events of special interest, and serious adverse events.

References


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