https://doi.org/10.1038/s41467-024-51486-4

What differentiates clinical trial statistics from preclinical methods and why robust approaches matter

Clinical trial statistics underlie the central decision-making process for whether a therapeutic approach can enter the clinic, but the nuances of this field may not be widely understood. Furthermore, how the statistics used in clinical trials differ from preclinical approaches and why they differ is not always clear. Here, three experts discuss the intricacies of clinical trial statistical planning and analysis as well as common issues that arise and emerging trends. The experts are Dr Tao Chen (Senior lecturer in Biostatistics at the Liverpool School of Tropical medicine), Professor Li Chao (Professor in Biostatistics at Xi'an Jiaotong University) and Professor Yang Wang (Professor in Biostatistics at the Chinese Academy of Medical Sciences and Peking Union Medical College). They have a diverse range of backgrounds across biostatistics and have been involved in numerous clinical trials of varying types.

CREDIT: LEFT TO RIGHT: TAO CHEN, LI CHAO, YANG WANG

1. Statistics for clinical trials is a speciality in and of itself: could you please start by highlighting what differentiates clinical trial statistical approaches and practises from those applied in other areas of life sciences?

While statistics is a fundamental tool across all areas of life sciences, its application in clinical trials is characterized by the specific challenges and requirements associated with testing medical interventions in human populations. Key considerations that distinguish statistics applied to clinical trials include the incorporation of stringent ethical considerations to establish the balance between benefit and risk from the investigational treatment, the need for meticulous regulatory compliance (e.g., The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)), the systematic use of randomization and blinding to eliminate selection bias and confounding effects, the focus on clinically relevant outcomes directly related to the primary objective of the trial, a predetermined sample size calculation to ensure a study is sufficiently powered to assess the desired outcomes (an underpowered study, with limited sample size, may lead to false negative results), and prespecified statistical analysis plans to avoid selective reporting. Collectively, these elements aim to provide robust evidence regarding the safety and efficacy of medical interventions. Meanwhile, they also shape the statistical approaches in clinical trials, setting them apart from methodologies applied in other areas of life sciences research.

2. Clinical trials are separated into different phases and types, how do the statistics differ between phases or types?

Clinical trials are typically organized into different phases (e.g., Phase I to Phase IV) and types (e.g., exploratory trials looking at new effects and confirmatory trials to support previous results), which form a structured framework for evaluating the safety, efficacy, and effectiveness of medical treatments and guide the progression of treatments from initial testing to regulatory approval and post-market surveillance. As such, the emphasis on statistical aspects including sample size, study design, and choice of statistical methods varies to address the unique objectives and challenges of each phase of clinical trials.

For example, a dose escalation design with a small sample size of healthy volunteers is often employed to descriptively characterise the preliminary safety profile in phase I trials before advancing to subsequent phases of clinical trials. Whereas larger-scale trials with complex designs, may be used to confirm efficacy and safety assessments involving rigorous hypothesis testing - such as the establishment of clear and predefined hypotheses (e.g., testing for superiority or non-inferiority), selection of appropriate statistical test and control of type I error rate—These ultimately ensure the reliability and validity of study findings, leading to more informed decisions in clinical practice and healthcare policy.

3. Statistics play an important role in both the analysis and design of clinical trials, could you please define these different roles?

Statistics is integral to both the analysis and design of clinical trials. In the design phase, statistics is employed to plan and structure the trial to prevent bias to ensure validity, efficiency, and ethical conduct and optimize the chances of obtaining meaningful results. Various types of biases could be incurred if deviations from the protocol occurs. These

include attrition bias due to differential loss of participants from different groups (e.g., a higher dropout rate in the control group) leading to biased estimates of treatment effects, ascertainment bias when knowing the treatment allocation prematurely, which inadvertently influence the assessment of outcomes (e.g., giving more attention or ancillary treatments/test for the subjects from intervention group), reporting bias introduced from outcome switching or failure to adjust for the multiplicity which can occur when multiple outcomes are being assessed, and selection bias when there is systematic differences in characteristics between groups being compared in a study(e.g., poor randomisation) as in these situations the probability of obtaining false positive associations increases.

In the analysis phase, the primary goal is to draw valid and reliable conclusions from the collected data, which involves assessing the efficacy and safety of the investigational treatment and making inferences from the trial population to the broader target population but with cautiousness. It remains imperative to consistently consider the pre-specified analysis plan throughout the trial design process and ensure alignment with the overall trial design to maintain scientific integrity, prevent data fishing, facilitate interpretation and reproducibility, as well as comply with regulations and uphold ethical standards.

4. Could you please highlight some of the key issues with statistics in the design of trials that authors, reviewers, and editors should be aware of when assessing manuscripts?

Several critical issues related to statistics in the design of trials should be considered during the manuscript assessment process by authors, reviewers, and editors. These issues may include failure to prospectively register the trial, the absence of the pre-specified statistical analysis plan, ethical lapses, poor randomization, unclear allocation concealment (e.g., Interactive web response system to reduce the chance of guessing the randomisation sequence correctly), unjustified sample sizes calculation, inappropriate selection of endpoints that are not clinically relevant and validated, and imbalanced baseline characteristics or confounding factors between groups. Failure to comply with best practice in clinical trials would result in biased, unreliable, or misleading findings, compromising the validity, integrity, and ethical conduct of the research. For example, absence of a pre-defined analysis plan can lead to publication bias, selective reporting of outcomes, and incomplete dissemination of study results, hindering transparency and misleading conclusions.

5. Specifically, how does trial design influence whether data obtained from a clinical trial is meaningful?

The design exerts influence over various aspects of clinical trials. For instance, meaningful data relies on the careful selection of clinically relevant endpoints that directly measure the outcomes of interest. The use of inappropriate endpoints may lead to results that are inconclusive or even misleading. Similarly, the relevance of the data depends on how well the study population mirrors the target patient population. Excessive restrictions or inappropriate inclusion criteria have the potential to limit the generalizability of the results. Likewise, inadequate sample sizes can result in underpowered studies, diminishing the ability to detect true treatment effects and possibly yielding inconclusive or misleading results. Therefore, a well-thought-out design, aligned with study objectives, ethical standards, and robust statistical methodologies, enhances the validity and relevance of the trial outcomes.

6. It is well known that there are abundant issues with statistical analyses of preclinical studies, could you comment on how these preclinical issues carry over and affect clinical trials?

Issues stemming from preclinical study can significantly influence the planning, execution, and interpretation of subsequent clinical trials. These challenges are multifaceted, including the translatability of preclinical findings, biological variability between animal models and humans, lack of methodological rigors (e.g., randomisation and blinding), potential false positives from multiplicity, hypothesis driven research with small sample size and ethical concerns regarding the applicability of interventions to human subjects. The exploratory nature and challenges inherent in preclinical research findings increase the complexities and uncertainties while designing and analysing in further clinical trials. Therefore, by promoting transparency, judiciously leveraging information from preclinical studies and integrating this prior information into subsequent translational research through rigorous methodologies like Bayesian approaches, and fostering collaborations among researchers to which better align preclinical studies with real-world needs and maximize the translational potential of their findings, we can improve the reliability and translatability of findings throughout the translational process.

7. Could you please highlight some of the key issues with statistics in the analysis of trials that authors, reviewers, and editors should be aware of when assessing manuscripts?

Authors, reviewers, and editors must maintain vigilance to safeguard the credibility, transparency, and reliability of statistical analyses in clinical trial manuscripts. Key concerns over the statistical analysis particularly include the inconsistency between the statistical analysis plan and the reported analyses, departure from the original randomised assignment in the final analysis of a clinical trial, failure to adjust for multiple testing, inadequate handling of missing data, overemphasis on P-values, inappropriate subgroup analyses, outcome switching based on observed result, and change to the hypothesis (e.g., from non-inferiority to superiority) without pre-specification. These issues would introduce the risk of reporting or publication bias and erroneous conclusions. For example, overemphasis on p-values to draw conclusions without considering effect sizes, clinical significance, or context can lead to misinterpretation and undermine the reliability of study results.

Addressing these concerns by collaborating with statisticians at the early stage of the trial and maintaining adherence to methodological standards are essential for establishing robustness and integrity of clinical trial research.

8. Further to their implementation, clear and open reporting is vital for clinical trials: could you please comment on what are some of the major things that should be discussed and reported?

Comprehensive reporting allows researchers, clinicians, and the public to understand the study's methods and results. Also, clear and open reporting ensures that the scientific community can critically evaluate the study, reproduce the research, and consider its findings in the broader context of existing evidence and the limitations of the trial design. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guideline serves as a valuable resource for researchers and research teams to ensure that

clinical trial protocols are comprehensive, transparent, and adhere to best practices with a set of recommendations, such as prospective trial registration, safety monitoring and study design. Correspondingly, researchers are encouraged to refer to the CONSORT (Consolidated Standards of Reporting Trials) and extensions (for specific types of trials, such as non-pharmacological interventions) for the complete checklist and guidance on reporting randomized controlled trials. Some key elements such as the strategies to control Type I error, maintenance of blindness, randomisation procedures, and justification for the non-inferiority margin-a predefined threshold used in non-inferiority clinical trials to determine whether a new treatment is not unacceptably worse than an active comparator treatment, should always be described in detail to strengthen the completeness and transparency of clinical trial reports.

9. In addition to their use in primary reporting of trials, statistical analysis of post-hoc trials is also important; could you please comment on the value of these analyses and describe how these approaches differ from the original analyses?

While post-hoc analyses can provide valuable insights and generate hypotheses for further exploration, it's crucial to acknowledge their distinct characteristics and implications compared to the original analyses, necessitating a cautious approach. Generally, post-hoc analyses involve exploring data without predefined hypotheses, rendering them exploratory in nature and may be considered as supplementary or as validation for the original analysis. Additionally, statistical methods for post-hoc analysis may be less stringent, requiring adjustments for multiple comparisons to mitigate the increased risk of false positives. Overall, there is a risk of data-driven analyses, post hoc changes, or selective reporting of statistically significant results, leading to biased or misleading conclusions for post hoc analysis of trial data without a predefined analysis plan. Therefore, transparency regarding the exploratory nature of these analyses, stating them as such in the manuscripts, timing for conducting the analyses, appropriate statistical adjustments, and validation in independent studies are essential to ensure the reliability and robustness of the findings. Researchers should distinctly delineate between pre-specified analyses and post-hoc exploratory analyses when reporting trial results.

10. Finally, as with all fields of academia, statistics is constantly evolving and changing, could you please mention some of the changes that are happening currently which may influence clinical trial statistical design/analysis in the future?

Statistics, encompassing its application in clinical trial design and analysis, is continually evolving with ongoing technological advancements (e.g., artificial intelligence, digital health and telemedicine) and emerging changes (e.g., precision medicine) that are transforming the future of medicine and improving the quality of life for individuals. Several trends and developments are currently shaping the landscape of statistical approaches in clinical trials. Bayesian methodologies offer flexibility by incorporating prior information, updating analyses as data accumulate, and providing more informative posterior distributions after combining information from the observed data and any prior beliefs. Real-world evidence is gaining importance as it complements traditional clinical trial data, offering insights into long-term outcomes, patient perspectives, and treatment effectiveness in real-world settings. The integration of machine learning and artificial intelligence technologies holds promise for identifying intricate data patterns, optimizing patient recruitment strategies, and enhancing predictive modelling for patient outcomes. Precision medicine approaches, guided by genetic information, are advancing, leading to more targeted and personalized treatments. Clinical trial simulations are gaining recognition as an important component of clinical development programs, offering valuable insights to enhance understanding and inform decision-making at various stages of drug development. These trends collectively underscore the dynamic nature of statistical methodologies in clinical trials, driven by technological advancements, shifts in regulatory landscapes, and a commitment to improving the efficiency and ethical conduct of clinical trials.

Published online: 15 August 2024