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Importance of proper conduct of clinical trials

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Clinical trials provide the evidence that forms one of the cornerstones of modern evidence-based medicine, together with clinical judgement and patient values and preferences.[1] The US National Institutes of Health defines a clinical trial as, 'a research study in which human subjects are prospectively assigned to one or more interventions (including placebo or control) to evaluate the effects of those interventions on health-related biomedical or behavioural outcomes'.[2] Clinical trials have a long history. Arguably, the first description of one can be found in the 'Book of Daniel' in The Bible.[3] In approximately 600 Before the Common Era, the Babylonian King Nebuchadnezzar ordered his people to eat meat and drink wine, which was a diet that he believed would keep them in good physical condition. Daniel of Judah and his friends (Shadrach, Meshach, and Abednego, who were convinced vegetarians) refused the royal diet and proposed to the royal steward the first recorded clinical trial protocol: 'Test your servants for 10 days; let us be given vegetables to eat and water to drink. Then let our appearance and the appearance of the youths who eat the king's rich food be observed by you, and according to what you see deal with your servants'. Daniel and his youthful friends who ate a vegetarian diet and drank water were found in better physical condition than the 'meat and wine group', and so the king issued a new edict allowing his subjects to also eat legumes and drink water. This first open-label unblinded trial presented methodological issues that remain important in contemporary research: equipoise, selection bias, inadequate controlling for confounders and sample size, unclear outcomes definitions and assessment, but it did lead to an important change in routine practice (i.e. the diet as a form of preventive measure). Interestingly, the trial report was short and effective, even though it was only published 400 yr after study completion.[4]

Clinical trials are usually conducted to evaluate the efficacy, safety, or cost-effectiveness of an intervention with an acceptable margin of uncertainty. The ultimate goal is still the same: improving patient care. RCTs, the randomised evaluation of an intervention against a control, are currently considered the most reliable source of data in medical practice and are widely considered 'the gold standard' of hypothesis testing. However, RCTs are time and effort consuming for patients, investigators, and the healthcare system in general. Moreover, clinical application of their results is not straightforward, as they derive from an experiment on an intervention that is conducted under well-defined circumstances and rigorous criteria in a specific cohort of patients. All of these aspects can be different from those present in clinical practice when physicians decide whether or not to apply an intervention to an individual patient. Indeed, interpretation of results can be difficult for clinicians, and many study questions cannot be tested in clinical trials, in most cases for ethical reasons. Clinicians are not only faced with questions about generalisability; there are also problems with differences in quality of study methodology and evidence. Some of these barriers can be overcome with standardised assessment of the quality and strength of the body of evidence for a clinical question. This is the aim of the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach used in clinical practice guidelines, where evidence from clinical trials and expertise from content experts are merged to provide recommendations.[5] It is interesting to note that, although the importance of clinical trials for improving medical care is largely recognised, the body of literature evaluating their impact in comparison with other sources of evidence is still small. Since the initial growth of the use of clinical trials in the late 1960s and 1970s, researchers have developed more

precise and stringent rules and criteria to be applied to protect enrolled participants, reduce biases and uncertainty, and improve the strength of the evidence produced by trials. The study, refinement, and application of these aspects have developed into a new scientific discipline named 'clinical trial methodology'.[6]

We recently assembled a new collection of articles published in the *British Journal of Anaesthesia* (BJA) on the conduct of clinical trials (https://bjanaesthesia.org/the-conduct-of-clinical-trials) to highlight work being done in this discipline important points of methodology in clinical trials. The selection of the specific outcomes is pivotal for tests of the superiority, non-inferiority, or equivalence of interventions. Selection of outcomes should be done in the very earliest stage of planning of a study, and the selected outcome should inform the study design. Since 2009, the BJA has made it a requirement that clinical trials should have been registered in an open clinical trial database, with the full methods, including study outcomes and statistical analysis plan, specified in advance of study initiation. Use of core outcome sets (COS) enhances reproducibility of the results from clinical trials focusing on relevant endpoints, even those relevant to the patient point of view, with standard definitions and time points. This collection therefore includes reports of rigorously produced expert consensus statements that followed the Core Outcome Set-STAndards for Development to define COS in many clinical and research fields relevant to anaesthesia and perioperative medicine.[7–9] Examples of other important issues discussed in the articles included in the collection are the appropriate use of GRADE approach for evidence grading,[5] gender disparity in trial inclusion,[10] and barriers to high-quality clinical research in both high-[11] and low- and middle-income countries.[12]

Inference in statistics is a process of drawing conclusions about a population (i.e. parameters) based on data calculated from a sample drawn from that population (i.e. statistics). This is a core process in clinical trials when an intervention is tested on a patient sample drawn from the whole population with the characteristics of interest. To be valid, this process must be strictly regulated, from the selection of adequate samples to the estimation of the data to be inferred for the whole population under a certain margin of uncertainty (probability). There are two major approaches in inferential statistics: frequentist inference and Bayesian inference. Sir Ronald A. Fisher (1890–962) is considered the founder of the frequentist method that makes predictions of the underlying 'truth' (parameters in the population) using only data from the current experiment. He was a lifelong critic of the 'inverse probability' concept that shares the assumptions of the Bayesian theory that incorporates prior knowledge of similar experiments to be combined with current experimental data to make conclusions.[13] Fisher's opinions influenced the common approach to statistical inference for decades, making the frequentist method the standard one for clinical hypothesis testing.[13] The difficulty in translating trial conclusions into clinical practice, the risk of inconclusive results of trials designed with classic frequentist methods, and the advent of artificial intelligence (that can enable integration of large amounts of prior data with new data) in both clinical practice and research have led to increasing use of Bayesian inference in clinical trials. The collection includes articles aimed to help clinicians interpret the results of clinical trials designed with Bayesian methods.[14,15]

A pivotal type of inference in the healthcare setting is causal inference through which an association between an intervention and an outcome can be considered to be linked by a true causal relationship (factor X is the *cause* of factor Y). The randomisation process in an RCT is fundamental (but not enough) to ensure that an eventual association is not attributable to known or unknown confounding factors (i.e. a spurious association). In observational studies, patients are not allocated to different interventions randomly. This poses additional difficulties concerning demonstration of casualty between variables, as observational studies are prone to many types of systematic error, or *bias*, in experimental design (e.g. selection, information, or confounding bias). The collection therefore includes articles that can help clinicians understand the concepts of association, casualty, bias, and confounding. They include guidance on the interpretation of causal inference in observational studies in perioperative medicine,[14,16,17] where it is increasingly frequent to analyse data from large patient cohorts with high external validity to evaluate associations.

This latest BJA collection on the conduct of clinical trials should be a useful resource, where clinicians and researchers can find recent articles on some of the most important current issues regarding clinical trial methodology. After almost 2500 yr since the first clinical trial, knowledge on how to conduct and interpret clinical trials is more important than ever!

Authors' contributions

Both authors contributed substantially to the conception of the content, drafting the paper or revising it critically for important intellectual content, and read and approved the final version of the paper.

Declarations of interest

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Revisiting postoperative complications after abdominal robot-assisted surgery: applying the Core Outcome Measures in Perioperative and Anaesthetic Care

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In considering the Assessment of Ventilation during general AnesThesia for Robotic surgery (AVATaR) study published in the *British Journal of Anaesthesia*,[1] we would like to reflect on the definition and clinical relevance of postoperative complications after abdominal robot-assisted surgery. Queiroz and colleagues[1] performed this substantial multicentre prospective clinical trial assessing postoperative pulmonary complications (PPCs) in 905 abdominal robot-assisted surgical patients from 34 hospitals in nine countries. They concluded that PPCs occur frequently (20%) in the first 5 days after abdominal robot-assisted surgery, are not associated with perioperative ventilator parameters, but are associated with a longer hospital stay. An important concern with regard to these findings is the clinical relevance of the surrogate outcome 'unplanned need for oxygen', defined in the trial as a Pa_{O_2} <60 mm Hg or Sp_{O_2} <92% in room air, or Sp_{O_2} <88% when