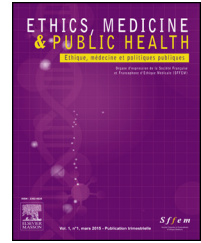




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## SHORT REPORT

# Ethical concerns of including too few or too many participants in clinical studies

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### KEYWORDS

Participants;  
 Research ethics;  
 Research waste;  
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### Summary

**Background.** – Ensuring an appropriate sample size is crucial for ethical reasons when conducting a clinical study.

**Discussion.** – Insufficient participants may lead to underpowered studies, jeopardizing the detection of true effects and exposing individuals to suboptimal treatment. On the other hand, an excessive number of participants raise ethical concerns, subjecting individuals to unnecessary risks and burdens, and contributing to research waste, such as the misuse of resources.

**Conclusion.** – Overall, there is a significant emphasis on striking a balance in participant inclusion to attain accurate, generalizable, and ethical outcomes in clinical trials.

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## Introduction

Clinical research is an essential aspect of medical science that aims to improve the well-being of humans. However, clinical research studies can raise ethical concerns, particularly regarding the number of human participants involved. The ethical issues in clinical research primarily involve

the protection of the rights, safety, and well-being of the research participants<sup>1</sup> One of the ethical concerns raised by clinical research is whether and when it can be acceptable to expose some individuals to risks and burdens for the benefit of others [1].

There are numerous guidelines and statements available about research integrity and ethical concerns in clinical research [2–5]. However, these statements do not mention the issue of either including too few or too many participants in clinical studies. In this brief communication, we will discuss why including both too many and too few participants in a clinical trial may be equally unethical.

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## Why it may be unethical to include too few participants in a clinical trial?

Clinical trials require a sufficient number of participants to ensure that the hypothesized benefit can be shown, i.e. obtain statistical significance, and that the results can be generalized to the population of interest [6]. For this purpose, we perform sample size calculations. These calculations must be performed before study initiation; thus, they are a crucial step in the design of a clinical trial, and they serve several important purposes.

A sample size calculation is important to ensure adequate statistical power to detect a clinically meaningful effect of an intervention on an outcome if it exists [6]. Statistical power is the probability that the study will correctly reject a false null hypothesis (i.e. correctly identify a real effect). Insufficient sample sizes can lead to underpowered studies and thereby increase the risk of not detecting a true effect even if it exists. Consequently, participants in the control group of the study receive suboptimal treatment. Furthermore, this leads to an increased allocation of participants to the less effective control arm in future studies, ultimately depriving them of optimal treatment. If the intervention is harmful, this will instead affect participants allocated to the intervention arm. In either case, participants are potentially treated unethically.

Performing a sample size calculation is part of the ethical responsibility of researchers. It helps to ensure that an adequate number of participants are enrolled to answer the research question, thereby minimizing the exposure of individuals to potential risks associated with participation in a trial arising from interventions as well as control arms [7]. Regulatory bodies often require a well-justified sample size calculation as part of the study protocol, and the demonstration that the trial is appropriately powered is important for obtaining ethical and regulatory approvals. The researcher must always ensure to take the potential number of participants that drop out or are lost to follow-up into account when calculating the sample size, and adequate and realistic final sample sizes contribute to the scientific validity of the study. Thus, performing sample size calculations before a clinical trial is essential to ensure that the study is designed with sufficient statistical power, precision, cost-efficiency, and ethical considerations to generate meaningful and reliable results. To ensure this, the choice of primary outcome for the sample size calculation is of course important. In general, the sample size for a continuous outcome, e.g. outcomes related to time, will be lower than the sample size of a categorical outcome, e.g. event occurring yes/no, though dependent on the estimated effect of the intervention. Rather than letting the required sample size guide the choice of outcome, this should be guided by what is relevant for participants, clinicians, and stakeholders. Core outcome sets have been developed to gather this information and guide researchers, thus, a relevant core outcome set should be consulted in the design phase.

Including too few participants in a clinical trial can lead to inaccurate results, which can have severe consequences for participants and the healthcare system. For example, if a clinical trial includes too few participants, detecting the rare harms of a new treatment may not be possible. This

can lead to approval of a harmful or ineffective treatment, putting future patients at risk. Even though small trials can be combined in a meta-analysis to evaluate statistical differences, it takes substantially more trial participants to gather small trials in a meta-analysis than conducting a large trial in the first place [8]. Therefore, small trials can expose more participants to potential harm.

Results from underpowered studies may be less reliable and not generalizable to the broader population [6]. If the aim of the study is to generalize results to different populations, sample size planning should consider this. Including too few participants in a clinical trial can lead to a lack of diversity in the study population. This can limit the generalizability of the results to the broader population, particularly for underrepresented groups. For example, if a clinical trial includes too few women or minorities, the results may not be applicable to these groups, leading to disparities in healthcare [6].

## Why it may be unethical to include too many participants in a clinical trial?

Including too many participants in a clinical trial can also raise ethical concerns. One of the primary ethical concerns is exposing some participants to risks and burdens for the benefit of others [1]. An extensive number of participants in a clinical trial pose ethical concerns by subjecting more individuals to risks and burdens than required. If a trial enrolls an excessive number of participants, it may unnecessarily expose them to risks such as frequent blood draws, invasive procedures, and the potential for harm from the intervention. Furthermore, those allocated to the control group may miss the benefits of the intervention if it proves superior.

Adequate sample sizes contribute to the precision of estimates. The larger the sample size, the narrower the confidence intervals around the estimated effects, and narrower confidence intervals provide more precise estimates of the true population parameters. It is possible for a study to have a large sample size that produces statistically significant results, but those results may not necessarily be clinically relevant. Moreover, in the search for more confidence in the estimate, more participants could be allocated to ineffective treatment or control arms [9]. It is, therefore, not advisable to choose a larger sample size than strictly needed. When selecting the sample size, it is important to consider the study's objective. If the study only aims to explore and does not seek statistical support for generalizations, a small sample size may be justified.

Including too many participants in a clinical trial can lead to a waste of resources, i.e. research waste, including poor methodological quality or invisible or underreported research [10]. Inefficient utilization of resources can lead to a considerable loss of time, money, and valuable personnel. Such wastage can ultimately lead to delays in the approval of new treatments, thereby increasing healthcare costs. Additionally, including too many patients in a clinical trial can lead to a lack of feasibility, making it difficult to recruit and retain participants, which can compromise the validity of the results [7].

Including an excessive number of patients in a clinical trial can extend its duration, potentially exposing participants to outdated protocol interventions and control treatments. Additionally, an unnecessarily large sample size, coupled with an extended accrual period, increases the risk that standard treatments may evolve during the trial. This evolution could render participants included at the beginning of the trial incomparable to those included at the end.

## Conclusion

Determining an appropriate sample size is crucial for optimizing resource allocation, and ensuring the study is neither excessively large nor too small. An overly large trial can be wasteful, while a too-small trial may yield unreliable results and cause unethical treatment of participants. Ethical concerns arise when including both too few and too many participants in a clinical trial. Insufficient inclusion can lead to inaccurate results, a lack of diversity in the study population, and limited generalizability. Conversely, including too many patients exposes individuals to unnecessary risks and burdens, squanders resources, and jeopardizes the validity of results. Hence, to guarantee accurate, generalizable, and ethical results it is imperative to include an appropriate number of patients in a clinical trial—not too few and not too many.

## Human and animal rights

The authors declare that the work described has not involved experimentation on humans or animals.

## Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s) and/or volunteers.

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## Disclosure of interest

The authors have not supplied their declaration of competing interest.

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