SMALL CLINICAL TRIALS:  
ISSUES AND CHALLENGES

Clinical trials have a long history of well established, documented, and validated methods for design, conduct, and analysis. Appropriate study design includes sufficient sample size \((n)\) and statistical power, and control of bias to allow for a meaningful interpretation of the results. The number of participants in a clinical trial should always be large enough to provide a sufficiently precise answer to the research question posed, but should also be the minimum necessary to achieve this aim. Adequately powered randomized clinical trials and double-blinded, randomized clinical trials are generally regarded as the most authoritative research methods for establishing the efficacy of new therapeutic interventions. By allocating sufficient numbers of individuals to groups, for example, experimental or control, investigators can estimate or determine with some degree of certainty the effect of a given intervention.

However, when the clinical context does not provide a sufficient number of research subjects for an adequately powered and controlled trial—for example, because treatments are unavailable for a rare disorder or a unique patient population such as astronauts, or because studies require the participation of patients with terminal or severely debilitating or incapacitating disorders—researchers are often faced with insufficient design and analysis tools that would allow them to move forward.

In response to the need for such tools, an Institute of Medicine committee was asked to assess the current methodologies and appropriate situations for conducting clinical trials with small sample sizes. The committee’s report, *Small Clinical Trials: Issues and Challenges*, contains recommendations that describe approaches that can be taken in the design and analysis of trials involving a small sample of individuals to obtain reliable and valid results.

**When the Standard Approach to Clinical Trials is Not Feasible**

Situations that might warrant a small trial include rare diseases, unique study populations (e.g., astronauts), individually tailored therapies, isolated
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Some distinctive research populations—such as astronauts or members of a small, isolated community—may consist of less than five individuals. This research situation, in which large numbers of study participants cannot be obtained, is defined as the small n clinical trial, where n refers to the sample size. The sample size in small clinical trials might be very small, for example, a group of astronauts during space flight, or could range upward to more than 100. This contrasts with the typical sample size of some large clinical trials where the n is in the thousands.

In general, a small trial is conducted because of external constraints, not necessarily by choice. Nonetheless, the general requirements for small trials are no different than for adequately powered trials, that is, they must be sufficiently designed and appropriately analyzed so as to provide a reasonable measure of the effect of an intervention. They should be designed to have an outcome measure for determining success, a baseline for measuring change, and a means to follow up to assess change. Because of the design and analysis constraints of small trials and because of inherent uncertainties, it is likely that they will require at least as much thought—and probably more—than traditional, large-scale clinical trials.

In some cases, however, properly designed small trials can contribute to substantial evidence of efficacy; however, those conclusions may require assumptions and inferences given the paucity of data. Conditions in which small trials may successfully be used include: diseases or conditions with a well described natural history with little variation; when sensitive pharmacodynamic effects are directly related to pathophysiology; when there are good non-human models available; and when the intervention has a large effect on efficacy, produces a predictable relationship between measurable drug levels and effects, and has been applied to a related condition. Small n studies are least likely to be useful for complex disease syndromes with highly variable outcomes (for example, some chronic diseases such as arteriosclerotic cardiovascular disease); for drugs with less than dramatic effects in vitro; for illnesses where correlates of success are unclear; in situations where the risk of short-term death is high; and for surgical procedures where there are many complex and confounding factors.

Because of the constraints of conducting research with small sample sizes, the committee makes several recommendations regarding: defining the research
question; tailoring the study design giving careful consideration to alternative
methods; clarifying sample characteristics and methods in reporting small clinical
trial results; performing corroborative analyses to evaluate consistency and ro-
bustness of small clinical trial results; and exercising caution in interpreting the
results before attempting to extrapolate or generalize the findings of small clinical
trials. The committee also recommends that more research be conducted on the
development and evaluation of alternative experimental designs and analysis
methods for studies with small sample sizes.

Because of the limitations of small clinical trials it is especially important that
results are reported with accompanying details about the sample size, characteris-
tics, and study design. The details necessary to combine evidence from several
related studies should be published, for example, measurement methods, main
outcomes, and predictors for individual subjects. There are two reasons for this:
first, it allows the clinician to appropriately interpret the data within the clinical
context; and second, it paves the way for future analyses of the study, for exam-
ple, as part of a meta-analysis. In the clinical setting, the consequences might be
greater if one misinterprets results. In the research setting, insufficiently described
design strategies and methods diminishes the study’s value for future analyses.

**Design of Small $n$ Clinical Trials**

Bearing in mind the statistical power, precision, and validity limitations of
small sample sizes, there are innovative design and analysis approaches that can
improve the quality of such trials. A number of
trial designs especially lend themselves to
small sample size studies, including $n$-of-1 de-
signs, sequential designs, “within subject” de-
signs, decision analysis-based designs, ranking
and selection designs, adaptive designs, and
risk-based allocation designs. Data analysis for
small $n$ trials, in particular, has to be focused.

Despite the value of these design ap-
proaches, new approaches are needed for small
sample sizes that can assess the potential
therapeutic efficacy of drugs, biologics, de-
vices, and other medical interventions. For ex-
ample, a possible alternative is to assess ther-
apeutic results in a single treated population by
sequentially measuring whether the interven-
tion is falling above or below a pre-established
probability range of efficacious outcome. Such
a clinical trial could be considered to have
demonstrated efficacy when the cumulative
observed results fall within or above the pre-
scribed confidence range, or the trial could be
stopped when the cumulative observed effect falls below the pre-established level
of confidence. A major question, however, for this and other approaches is

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**Design Methods for Clinical Trials**

*Traditional Design Issues for Clinical Trials*
- Parallel Group Design
- Cross-over Design
- Factorial Design
- Add-on Design
- Randomized Withdrawal Design
- Early Escape Design

*Special Design Issues for Small Clinical Trials*
- $n$-of-1 Design
- Sequential Design
- Decision Analysis-based Design
- Ranking and Selection Design
- Adaptive Design
- Risk-based Allocation Design
...in some cases, it might be more practical than in large trials to involve the subjects in the design of the trial. By doing so, the investigator can increase the likelihood of compliance, adherence to regimen, and willingness to participate in monitoring and follow up activities.

Whether the science base of alternative methods alone or in combination is sufficiently developed for these non-randomized clinical trials to be effective in demonstrating efficacy in studies with small sample size.

Because of the constraints of small trials, that is, unique, rare, or inaccessible research subjects, it is particularly important to define the research questions and select outcome measures that are going to make the best possible use of available research subjects while minimizing their risks. In small n trials, it is more likely that the sample population will share several unique characteristics, for example, disease, exposures, or environment. Thus, in some cases, it might be more practical than in large trials to involve the subjects in the design of the trial. By doing so, the investigator can increase the likelihood of compliance, adherence to regimen, and willingness to participate in monitoring and follow up activities.

The committee concluded that the research base in this area requires further development. Alternative designs have been proposed in a variety of contexts; however, they have not been adequately examined in the context of small clinical trials. Studies of the use and effectiveness of various designs should be conducted and new methods developed.

**Statistical Approaches to Analysis of Small Clinical Trials**

A necessary companion to a well-designed clinical trial is its appropriate statistical analysis. Assuming that a clinical trial will produce data that could reveal differences in effect between two or more interventions, statistical analyses are employed to determine whether such differences are real or due to chance. Data analysis for small sample size trials, in particular, has to be focused. In general, certain types of analyses are more amenable to small sample size studies, including: sequential analysis; hierarchical analysis; Bayesian analysis, decision analysis; statistical prediction; meta-analysis; and risk-based allocation. Analysis should include confidence intervals when appropriate although in small n trials they will often be uninformative because they will be too wide.

Since the data analysis for small clinical trials will inevitably involve a number of assumptions, the use of several different statistical analyses is likely to enhance the acceptance (or rejection) of various assumptions. For example, if several different analyses give consistent results, under differing assumptions, one can be more confident that the results are not due to unwarranted assumptions. Conversely, if the analyses produce different results, depending on which sets of assumptions are used, one might be less certain about the original assumptions than might have been the case before the trial was conducted. In sum, the use of alternative statistical analyses might help identify the more sensitive variables and the key interactions in applying heterogeneous results across trials, or in trying to generalize across trials.
Appropriate federal agencies should increase support for expanded theoretical and empirical research on the performance of alternative designs and analysis methods that can be applied to small studies. Areas worthy of more study may include theory development, simulated and actual testing, including comparison of existing and newly developed or modified alternative designs and methods of analysis, study of limitations for differing sample sizes, and modification of a trial midstream.

The importance of only conducting small \( n \) trials when there are no alternatives cannot be overemphasized. The does not encourage the use of small \( n \) trials, but rather provides advice on strategies that should be considered in the design and analysis when the opportunity to perform an adequately powered, randomized, clinical trial is not possible. In doing so, it recognizes that small \( n \) studies frequently need to be viewed as part of a continuing process of data collection. Thus, for some trials, it might be impossible to definitively answer the research question with high confidence. In those cases, perhaps the best one can do is assess the next set of questions to be asked.

**SUMMARY OF THE COMMITTEE’S RECOMMENDATIONS**

**RECOMMENDATION 1:** Define the research question. Before undertaking a small clinical trial it is particularly important that the research question be well defined and that the outcomes and conditions to be evaluated be selected in a manner that will most likely help clinicians make therapeutic decisions.

**RECOMMENDATION 2:** Tailor the design. Careful consideration of alternative statistical design and analysis methods should occur at all stages in the multi-step process of planning a clinical trial. When designing a small clinical trial, it is particularly important that the statistical design and analysis methods be customized to address the clinical research question and study population.

**RECOMMENDATION 3:** Clarify methods of reporting of results of clinical trials. In reporting the results of a small clinical trial, with its inherent limitations, it is particularly important to carefully describe all sample characteristics and methods of data collection and analysis for synthesis of the data from the research.

**RECOMMENDATION 4:** Perform corroborative statistical analyses. Given the greater uncertainties inherent in small clinical trials, several alternative statistical analyses should be performed to evaluate the consistency and robustness of the results of a small clinical trial.

**RECOMMENDATION 5:** Exercise caution in interpretation. One should exercise caution in the interpretation of the results of small clinical trials before attempting to extrapolate or generalize those results.

**RECOMMENDATION 6:** More research on alternative designs is needed. Appropriate federal agencies should increase support for expanded theoretical and empirical research on the performances of alternative study designs and analysis methods that can be applied to small studies. Areas worthy of more study may include theory development, simulated and actual testing including comparison of existing and newly developed or modified alternative designs and methods of analysis, simulation models, study of limitations of trials with different sample sizes, and modification of a trial during its conduct.
For More Information…

Copies of Small Clinical Trials: Issues and Challenges are available for sale from the National Academy Press; call (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area), or visit the NAP home page at www.nap.edu. The full text of the report is available online at http://books.nap.edu/catalog/10078.html.

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