Title

Research Methodology Tip - Clinical Trials in Small Patient Populations: Design Considerations & Recommendations

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Research Methodology Tip

Clinical Trials in Small Patient Populations: Design Considerations & Recommendations

In the previous issue, we shared some tips to improve the recruitment and retention rates in clinical research studies. Given Singapore's relatively small population size, a common problem encountered by researchers is the limited number of eligible patients to sample from, especially when it comes to patients with rare diseases, or those with serious or life-threatening outcomes. This problem is compounded by the low availability of multiple participating centres that can screen and recruit additional subjects.

Hence, even with a prolonged recruitment duration, the planned sample size may not be achieved. This results in an underpowered study that may have marked inter-patient heterogeneity in the presentation of clinical symptoms and outcomes. Additionally, it limits the interpretability of the study results. This problem is more evident in large-scale phase III trials (which test novel intervention(s), and compare them with standard care/ placebo/ no treatment), as such trials require good quality data from a few hundred patients in order to draw valid conclusions and substantially inform clinical practice.

In the following page, we present some design considerations that may help to reduce the total sample size of a trial while maintaining the methodological integrity of the trial. Do bear in mind that no study design is without some limitation; thus, due consideration must be given to identify the most suitable and feasible design in order to achieve the maximum benefit from a particular study. As research evolves, grant bodies, regulatory authorities and journals are increasingly supportive of, and open to, innovative trial designs, so long as researchers acknowledge the limitations of the study design they have chosen, and demonstrate that the choice of design was meticulously thought through by presenting their justifications clearly in the research proposal, study protocol, and manuscript submitted for publication.

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Resources

1. EMA/CHMP: Guideline on Clinical Trials in Small Populations. Accessed 9th July 2021. Available from : https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-trials-small-populations_en.pdf.
2. Day S, Jonker AH, Lau LPL, et al. Recommendations for the design of small population clinical trials. *Orphanet J Rare Dis.* **2018**;13(1):195. doi:10.1186/s13023-018-0931-2.
3. Margolis A & Giuliano C. Making the switch: From case studies to N-of-1 trials. *Epilepsy & Behavior reports* **2019**; 12, Article number: 100336. https://doi.org/10.1016/j.ebr.2019.100336.
4. Pallman P, Bedding AW, Choodari-Oskooei B, et al. Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Medicine* **2018**; 16, Article number: 29. doi:https://doi.org/10.1186/212916-018-1017-7.

Suggested study designs which reduce total sample size of a trial without affecting methodological integrity		
Study Design	***Randomization and Choice of Control Group***	***Data Collection and Analysis Plan***
Crossover design For chronic/ stable diseases where there is adequate knowledge available to determine the appropriate washout period.	Use of historical controls, rather than concurrent controls, who share similar demographic and disease profiles with the prospectively treated patients, and where outcome endpoints were evaluated using the same methodology.	• Ensure complete follow-up of recruited patients • Collect longitudinal data (i.e. repeated measurements) • Analyse using appropriate methods (depending on outcomes of interest).
Single patient design (N-of-1) * For progressive diseases where recruitment/ retention may be particularly difficult e.g. palliative care.	Altering the randomization allocation ratio to recruit more patients to the treatment arm than control arm (such as 3:1), and incorporating reliable data from comparable historical controls (using existing databases).	• Maximize the information obtained • Keep multiple specific objectives • Measure multiple outcomes/endpoints (or, composite endpoints combining individual components of similar clinical importance) • Measure early surrogate endpoints.
Adaptive design ** For progressive diseases; it permits scheduled interim analyses and pre-specified changes (planned *a-priori* in the protocol) to the trial's course based on analyses of the accumulated data.	Randomization stratified by important prognostic variables.	• Identify alternate sources of reliable data on safety endpoints e.g. non-clinical animal model data, electronic health records, post-approval safety data, and off-label usage data.

** N-of-1 trials are randomized, double-blind, multiple crossover comparisons of an individual patient receiving a sequence of different treatments. Data from multiple N-of-1 trials can be aggregated to optimize statistical power and overcome clinical/logistical constraints.*

*** Traditional clinical trials follow a fixed, linear sequence of "Design -> Conduct -> Analysis". Adaptive designs add a "Review -> Adapt" (involving pre-specified review(s) and adaptation(s)) loop to the 'Conduct' phase.*