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# Getting better value out of smaller sized clinical trials

**Nicholas A. Buckley**[1, 2]

[1]*South Asian Clinical Toxicology Research Collaboration*

[2]*University of Sydney, Sydney, Australia*

There is a need for greater understanding of good clinical research practice, methodology and critical appraisal. There should be a commitment to provide more good quality evidence through RCTs. It is important for such trials to be registered and be reported using CONSORT guidelines. These are all well recognised principles within the pharmaceutical industry. However, investigator led trials are very important, and yet generally small and relatively under-resourced. Deciding how to run these without fundamentally compromising the quality or validity of the trial is a difficult balancing act. The key is to not try to do everything but focus on doing the feasible things well.

Successful development of new treatments involves more than doing one definitive trial. Phase II ("learning") is critical in terms of designing future definitive Phase III ("confirming") trials for:

1) Selecting the preferred dose/duration based on safety and likely efficacy.
2) Selecting an appropriate primary clinical outcome.
3) Selecting secondary clinical outcomes.
4) Selecting biomarker outcomes and timing that provide causal evidence.
5) Determining the sample size and power.
6) Determining the timing and outcomes for interim analyses.

The evidence from small poorly designed RCTs reporting purely clinical outcomes is usually inferior to that provided by careful cohort studies which demonstrate causal evidence: that is scientific evidence of the expected disease modifying action in the population. This can be shown in non-randomised studies from careful evaluation of dose/concentration/time-response data. All small RCTs should include such analysis. This data is particularly critical to determine whether further research is worthwhile following studies with both positive and negative clinical outcomes.