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Evidence Notes

Bridge Medical
Evidence that matters

Welcome to the first edition of *Evidence Notes*, a monthly newsletter from Bridge Medical. Our aim with *Evidence Notes* is to write short, informative articles about interesting aspects in the evidence space. We plan to cover areas from study design and methodology through to matters of evidence policy. Unlike other newsletters we will keep ours brief with only one article per month. The content will be jargon free as we aim to stress the applicability of each area to our Clients day to day work. The first piece describes a relatively new study method – the cohort multiple randomised control trial (cmRCT). Although examples of such studies, especially Industry funded examples, are few, we wonder whether the method may have applicability in effectiveness research and where companies have large portfolios in a single therapeutic area. We hope you find this interesting, and please do feel free to suggest topics that you would like us to cover in future articles.

Cohort multiple randomized controlled trials – a useful methodology for effectiveness research?

The cohort multiple randomised controlled trial (cmRCT) has recently gained traction in the literature since its publication as a "new" approach to the design of pragmatic clinical trials (Relton et al 2010). But what is it exactly, how does it differ from established randomised controlled trials (RCTs) and pragmatic designs, and will it allow trialists to have their cake and eat it?

RCTs are the most rigorous approach to establishing the efficacy and safety of medical interventions. However, they are based on "ideal" conditions, recruit unrepresentative patient populations, have limited relevance to clinical practice, are slow to recruit and often lack long-term outcomes. Pragmatic (or effectiveness) trials, on the other hand, attempt to mimic real-world clinical practice and recruit a more representative sample of patients. However, these studies are often open-label (OL), non-randomised and poorly controlled, thus attracting criticism around bias and confounding.

According to its proponents, the cmRCT "hybrid" design addresses these problems and also provides additional benefits. In brief, the design is not a single study but rather an infrastructure to carry out a variety of RCTs in a cohort (registry) of well-characterized patients with the condition of interest and who consent to providing data for this condition. Each patient will generally receive usual therapy and outcome measures will be assessed at fixed time points. For each new RCT, eligible patients from the entire cohort are identified, some of whom will be randomly selected and offered the new intervention(s). Outcomes in these randomly selected eligible patients will then be compared with the other eligible patients (controls) who will simply continue with usual treatment. This can be repeated (either sequentially or in parallel) for other RCTs.

Fig.1 Illustrates the principles of the cmRCT. It starts with the recruitment of a large cohort of interest. As required, RCTs are nested within the cohort, with "treatment as usual" subjects providing control to those randomised to an intervention.

The benefits of the cmRCT design have been described as follows:

- The large observational cohort of all diagnostically eligible subjects overcomes the lack of generalisability & slow recruitment associated with traditional RCTs. It also allows regular measurement of epidemiological data on the natural history of the disease and its response to usual therapy.

Each patient will generally receive usual therapy and outcome measures will be assessed at fixed time points.

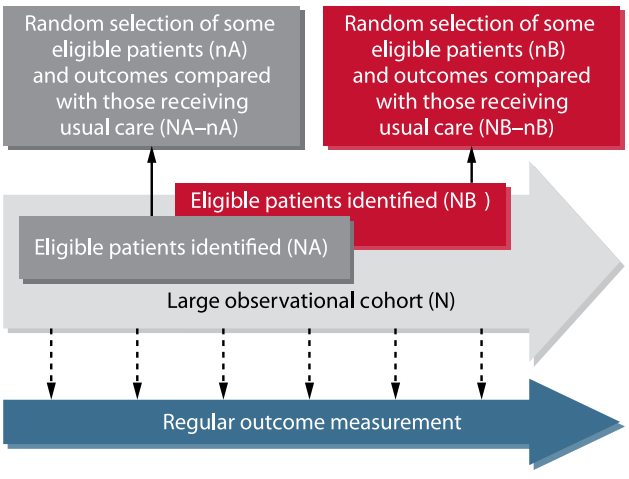

Fig.1
The principles of the cmRCT

- It allows continued recording of data in those who drop-out or decline the new treatment.
- The capacity for multiple RCTs over time in the same cohort improves cross-trial comparisons and thereby reduces heterogeneity, increases trial efficiency and, once the cohort is set-up, reduces cost e.g. reduced numbers of patients could be allocated an expensive treatment vs a larger number of unselected patients.
- Since only eligible and randomly selected subjects are offered the treatment they will not be subject to the negative impact of pragmatic designs in which subjects "denied" the new treatment may withdraw or exert a "disappointment bias" on outcome assessments.
- Consent mimics clinical practice in that there is no need for patients to consent for treatments they won't receive or for them to be told their treatment is chosen at random.

Variations to the OL design have been described, such as the use of double-blind (DB), including placebo-controlled (PC) RCTs, however, not all the "real-world" benefits would accrue (see Sachs et al 2003 – STEP BD – for an example of DB studies "nested" within an observational cohort).

Of course the cmRCT approach is not suitable for all circumstances. A summary of studies for which this design may applicable is shown in the table, *right* (adapted from Relton et al 2010):

Limitations with this approach should also be noted:

- A large sample size is required and the initial setting up of a cohort will be expensive (although, once established this could significantly reduce costs of all subsequent RCTs),
- Statistical techniques may need to be employed if only a few subjects consent to the new treatment (though there is the benefit of being able to continue to collect data on those who decline treatment).
- Outcome measures need to be well characterized, preferably objective, simple and easy to administer to entire cohort.
- The design is most suited to OL and although DB studies can be performed in theory, this limits some of the suggested benefits.
- Although subjects can enter more than one RCT (but not the same RCT), there would be ethical concerns with multiple P/C RCTs as patients may randomly be assigned to repeat placebo.

Further information on cmRCT studies (and similar approaches) can be found in the references provided.

Potential application for the cmRCT design:
Phase IIIB/IV studies: • Where greater generalisability is required (v's Phase III) • Where there may be several key clinical questions to address with a pragmatic design; including several comparator studies • Where long term outcome data on standard of care treatment is needed • When long term information on the diffusion of new treatments and their value is required
Early stages of development (Phase II): • Allows "informal" assessment of new intervention vs control in well characterised patient cohort • Allows continuous evaluation of innovative treatments
Instances where a company has a portfolio of drugs for a given disease state
Instances where patient recruitment is difficult, and establishing a "pre-consented" cohort may result in research efficiencies
Highly desired or expensive treatments

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