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EDITORIAL

Trials with repeated cross sections: alternatives to parallel group designs in surgery trials

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In this month's journal, Grossi et al. [1] report the results of the CapaCiTY 3 trial, a publically (NIHR) funded, randomized clinical trial that sought to determine the effectiveness of laparoscopic ventral mesh rectopexy for the treatment of patients with high grade internal rectal prolapse presenting with symptoms of constipation and/or obstructed defecation. The results of this study and their clinical importance (or otherwise) are the subject of Andre D'Hoore's contribution to this editorial. My contribution concerns the choice of trial design and its future role in surgical trials.

At the outset, I must make two important remarks. First, I was the Chief Investigator of the CapaCiTY 3 study and so I am in a sense marking my own work; secondly, the profound issues leading to very significant under-recruitment to the CapaCiTY 3 trial undermine what I have to write on the choice of trial design. However, I hope that some latitude can be permitted in both respects.

There is perhaps no field of empirical medicine that is more affected by problems of finding a suitable comparator, masking, equipoise and poor recruitment that that of surgery. Indeed, there are numerous well-rehearsed arguments that underpin the difficulties of delivering high-quality evidence for surgical interventions. Such arguments are not unique to surgery and they are relevant to many 'complex interventions' where the standard explanatory parallel arm design, beloved of drug trials, becomes difficult to implement.

As a consequence, several alternative trial designs have started to find favor in the evaluation of complex interventions, including surgery. These all provide the core 'experimental' step (i.e., they apply randomized allocation to reduce confounding at selection) but have features that may make them easier to apply in practice. Examples include 'Trials within Cohorts' (TWiCS) which are increasingly being chosen for a range of surgical interventions including colorectal surgery [2].

However, another approach in trial design allows for the sequenced introduction of the intervention over time. Historically, these have sometimes been described as 'wait-list controlled trials', but they are better described as trials with repeated cross sections. A very readable description of this subject can be found in the excellent paper by Hooper & Bourke (2015) [3]. The stepped wedge (as used on the CapaCiTY 3 study) is one of a number of designs that fulfill the basic principle of taking multiple cross sections in time as participants cross forward from a state before (B) their intervention to a state after (A) their intervention. Fig. 1 shows three examples of repeated cross section designs, including the design used in the CapaCiTY 3 study and the design used in the ongoing landmark European Society of Coloproctology (ESCP) cluster-randomized EAGLE trial of a quality improvement intervention in anastomosis at right hemicolectomy [4]. The latter differs from the first two examples in having an incomplete cross forward and is described by its appearance as a 'dog leg' design.

There are several theoretical advantages of repeated cross section designs with reference in particular to surgical trials. First, everyone gets the intervention, i.e., there is no control arm that is denied surgery. This differs from standard parallel arm studies where access to the intervention is frequently provided only as 'open label' after the trial. Secondly, having multiple randomized groups allows for an adequate follow up without the cost of a long delay receiving the operation. In CapaCiTY 3, prior PPI work ($n=100$ patients) [5] demonstrated that patients were happy to countenance a mean delay of 2 months with only a 1 in 3 chance of waiting 6 months — this would contrast with a mean wait of 3 months and 1 in 2 chance of waiting 6 months in a standard 2-arm study (assuming 1:1 randomized allocation). The final, and perhaps most important, point is statistical efficiency.

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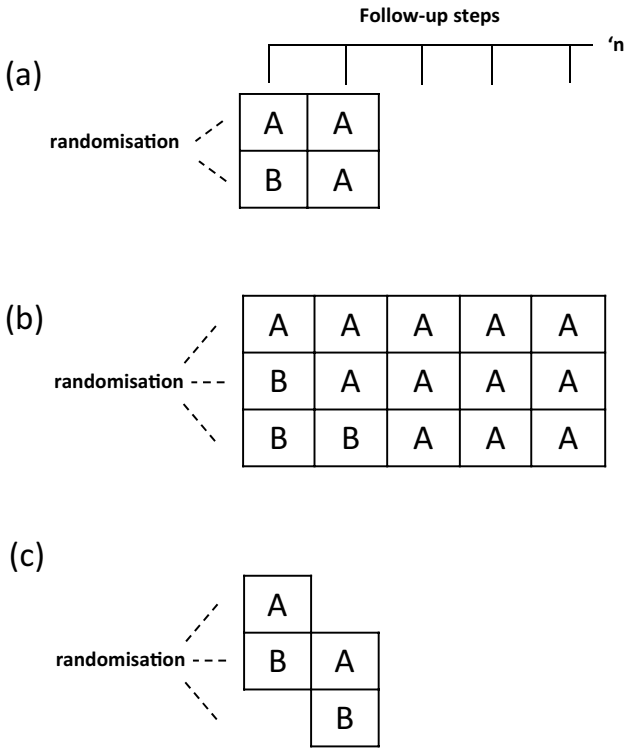

Fig. 1 **a** Stepped wedge design with 2 steps, **b** stepped wedge design used in CapaCiTY 3 study—here there are 3 groups and 5 steps, **c** dog leg incomplete cross forward design. *B* before intervention, *A* after intervention.

Statistical efficiency (in the sense of trial design) can be defined as 'the utility to detect a clinically important effect with given statistical power with the smallest sample size'. Of classic trial designs, the crossover study has great statistical efficiency, but this can only be employed where there is no carryover effect—this is clearly not possible for surgery where the effect does not wash out with time (it is also true for policy changes and quality improvement interventions). The key to statistical efficiency in multiple cross-sectional designs comes from the fact that at any step in any group, this group has both temporal and concurrent controls. Suffice it to write that the maths involved in proving this is complex and the steps involved in calculating required sample sizes for multiple cross sectional designs require simulation rather than direct calculation [6]. Such efficiency savings are now well-established in cluster randomized trial, for example at the level of a general practice or a local community [3, 7] The CapaCiTY 3 trial is an example of randomization to a multiple cross section design at the individual participant level. Statistical efficiency of an individually randomized trial has been less explored in the literature. However, it can be demonstrated that an individually randomized trial with a staggered intervention design needs fewer participants to achieve the same precision or statistical power as a more familiar parallel groups design [8]. Designs with incomplete cross forward as being used for clusters in the EAGLE trial may have similar or greater statistical efficiency [9].

In a way, CapaCiTY 3 reasserts the difficulty of recruitment to surgical trials. Although in this particular instance, the evolving scandal with mesh was the main issue, there is still a need for surgeons to have some familiarity with new trial designs that might improve recruitment and efficiency, even if this familiarity is limited to knowing that there might be another way other than the tried and tested explanatory parallel arm RCT.

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