CORRESPONDENCE

In reply: When and how should we cluster and cross over: methodological and ethical issues (letters 1 and 2)

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To the Editor,

In their article, Spence *et al.* argue that cluster randomized crossover trials are “the preferred method to evaluate questions of effectiveness” in anesthesia, and that “individual RCTs are not the preferred design.”¹ To illustrate the utility of this design, the authors discuss the B-Free pilot trial and “expect to begin the [full-scale] trial in the summer of 2018.”¹

In our commentary, we argue, “individual (not cluster) randomization is the gold standard study design to evaluate questions of both efficacy and effectiveness.”² Our arguments are not specific to the B-Free trial since, to date, no protocol has been published. Our conclusion is general: “the cluster crossover design... raises methodological and ethical concerns that must be carefully addressed.”²

Lee *et al.* agree that we make “correct statements about methodological concerns for cluster crossover trials in general.”³ They agree that these include increased risks of bias, limited external validity, imbalances in baseline characteristics, and carry-over and period effects, and they

explain how each will be addressed in the full-scale B-Free trial.³ We note that Lee *et al.* make no effort to defend the original thesis that cluster crossover trials are *generally the preferred design* to evaluate questions of effectiveness.

We disagree with several points made by Spence *et al.*⁴ First, they conflate units of randomization and intervention. A cluster level intervention, such as community public health messages, is indivisible at the individual level. But the institutional policy of benzodiazepine administration is an individual-level intervention, as it is divisible individually. Patients in the intervention arm will receive benzodiazepines “unless there are contraindications”¹—and refusal to consent should be a contraindication.

Second, they assert that we take the “extreme position that informed consent is always required for individual-level interventions.”⁴ This is false. Our position is that “[g]enerally . . . [for] individual-level interventions, informed consent is required.”² The qualifier “generally” implies that exceptions may be justifiable. The presumption of consent is shared by other ethical analyses and guidelines specific to cluster randomized trials.^{5–9}

Third, they claim that “established requirements to justify a waiver” and the existence of “many completed and ongoing cluster trials... where a waiver has been accepted” show the permissibility of conducting the B-Free trial without consent.⁴ Yet this ignores the novelty of the cluster crossover design. Canadian and U.S. guidelines were not written with cluster trials in mind.^{10,11} As a result, local research ethics committees that review cluster randomized trials may be unfamiliar with the specific guidelines of this unique design.^{8,9}

Finally, with respect to the flu vaccine trial, contributor roles are outlined in the trial publication¹²: the trial was in progress when Dr. Taljaard joined as an independent collaborator to supervise the statistical analysis.

Conflicts of interest None declared.

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