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# **Is the randomized trial design adapted to population health intervention research?**

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## **Abstract**

Randomized trials are frequently used in clinical research and considered the gold standard, but they are less common in population health intervention research (PHIR). We discuss issues that are sometimes shared and sometimes distinct between PHIR and clinical research, notably the randomization unit, design, standardization of the intervention, outcome(s) and ethical issues. In the end, both PHIR and clinical research share the common aim of assessing interventions, and randomized trials should be more widely used in PHIR, provided that how they are planned and conducted is adapted to the PHIR context.

Population health interventions are defined as “*policies, programs and resource distribution approaches that impact a number of people by changing the underlying conditions of risk and reducing health inequities*” (1). Evaluating such interventions is one of the aims of population health intervention research (PHIR) whose final goal is, as stated by the Canadian Institutes of Health Research, “*to produce knowledge about policy and program interventions that operate within or outside of the health sector and have the potential to impact health at the population level*” (2). In the field of clinical research, clinical interventions are often assessed with randomized trials, which are considered the gold standard because they are well suited to limit bias (3). How a randomized clinical trial should be planned, conducted and analyzed is well known, as are the associated legal and ethical issues. Obviously, these general and theoretical well-known rules must be adapted for each specific randomized trial: conducting a trial is indeed far from being as simple as is described in books, and it requires flexibility.

In PHIR, most interventions are complex: they correspond to a series of interrelated events occurring within a broader system that they are in constant interaction with (4). A recent literature review illustrated that randomized trials can be used to assess these interventions, although several other approaches are also common (5). However, conducting a randomized trial in the population health field requires adapting the clinical randomized trial rules to a non-clinical context as follows. First, in most clinical trials, the unit of randomization is the patient whereas individual randomization is rarely well-adapted to PHIR. Because interventions of interest are generally delivered at a group level as opposed to an individual level, randomizing groups such as schools, health centers, geographical areas, etc. is mandatory. Doing so avoids group contamination, which would occur due to interactions between members of a common cluster being allocated to different groups. The trial then becomes a cluster randomized trial. Second, most randomized trials are planned as parallel trials, but other designs may be of interest in PHIR, notably the stepped-wedge cluster

randomized trial (6). In a stepped-wedge cluster design, clusters are randomly allocated to different sequences, each sequence defining the timing of cluster switch from the control to the experimental condition. Thus, all clusters have the opportunity to receive the intervention at some point, which may help reluctant stakeholders participate and may help the logistics of the study because the intervention's roll-out is staggered (7). Third, in clinical trials, standardizing the intervention is generally the rule (besides, we may have weight- or body-surface-area-adapted drug doses), but tailoring the intervention to individual participant needs or the local context is common in complex interventions (4). As an example, rather than using a common information kit, information may be provided differently among centres. This refers to the concept of "standardization by function" as compared with "standardization by form" (4). The core components of the interventions nevertheless need to be well specified and clearly described using for instance the TIDieR checklist (8). They need to be common to all clusters and participants allocated to the intervention group; otherwise, it would hamper the interpretation of the trial results. A consequence of such a tailoring is that in PHIR, beyond assessing the intervention effect in terms of a priori-specified outcomes, process evaluations are welcome to better understand the results obtained and to link implementation variations to effect variations (9). They focus on how the intervention has been implemented to better understand the involved mechanisms (as a pathophysiology study would do in a clinical context) and thus provide information valuable to scale-up the intervention (10). Fourth, in clinical research, it is widely advised to have a unique a priori-specified primary outcome, although some exceptions are accepted (11). Doing so allows for specifying sample size on the basis of a quantitative hypothesis and offers the opportunity for a clear-cut conclusion based on the sole primary outcome result. In PHIR, such an approach is probably reductive. Because interventions are complex and stakeholders numerous, intervention effectiveness may be appraised differently depending on the stakeholder's goal. Results may

also be obtained from both quantitative and qualitative analyses (notably regarding its interaction with the context) for a complete overview of the intervention effect. Obviously, strict rules generally applied in clinical research need to be used, and some guidance on this topic would be welcome. Fifth, while individual randomization ensures group comparability things are more complex with cluster randomization. The number of clusters is often small which favours chance imbalance. Otherwise, in most cluster trials, participants are recruited after cluster randomization without any blinding, due to the real nature of the interventions. This favours group imbalance and bias (12). Statistical analysis then requires some form adjustment and cluster randomized trials are often analysed more as an observational study than as a randomized trial. Sixth, any study involving human beings must be conducted in accordance with international ethical principles and local regulatory guidelines. A lot has been done on this topic since World War II, and the very aim is to ensure participants' protection and also protect their autonomy, which is achieved by informed consent. However, existing regulatory guidelines do not apply well to PHIR, which raise "*distinct ethical challenges relative to clinical medical interventions, primarily because of their focus on prevention (rather than treatment) and their intended impact on the health of a population as a whole (rather than the individual)*" (13). Guidelines have been published on the specific case of the cluster randomized trial, notably defining who is a study participant and under which condition a waiver of individual consent may be accepted (14). However, they have been developed through the prism of the methodological feature of cluster randomization, which surely does not cover the whole specificities of PHIR. More work is undoubtedly needed, as is an accustoming of ethics committees to PHIR, which differs from clinical research. Finally, although admittedly, randomized trials provide the highest level of evidence in clinical research, it is generally agreed that this is not the only way to assess an intervention's impact. The parachute trial is a tremendous parody that illustrates the limitations of randomized trials

(15). Impossibility to randomize is not a prerogative of PHIR: it also exists in clinical research. In 1965, Hill listed 9 criteria allowing to conclude causation rather than association in an observational rather than randomized context (16). Although debatable and debated, these criteria are still used, and surely, there is room to revisit these criteria in the specific context of PHIR.

In the end, both PHIR and clinical research share the same objective of assessing intervention effects. Fundamentals are common: studies need to be comparative and conducted to prevent bias as much as possible. Although “*the most common type of population health research remains the non-interventional observational study*” (17), the randomized design is clearly an option and should be encouraged.

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