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The Power of the Cluster

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The past 50 years have witnessed sea changes in cardiovascular medicine and research.¹ We came to recognize untreated hypertension as a highly malignant disorder and to recognize that medical treatment of hypertension leads to marked reductions in risk of stroke, myocardial infarction, and premature death. We also came to recognize the power of the randomized trial for assessing candidate strategies for prevention and treatment. Indeed, mega-trials conducted by cardiovascular clinician scientists have played a critical role in defining nearly every major evidence-based intervention, from hypertension treatment to cholesterol reduction and use of aspirin.¹

Over the past 10-20 years we have also witnessed marked changes in the delivery of medical care. Instead of individual clinicians caring for individual patients, patients now increasingly find care within integrated systems with teams of providers.² Care ideally goes beyond even integrated health care clinics. In some countries and regions, there is increasing appreciation for expanding the sphere of medical care to communities.^{3,4} As medical care becomes more of a community or systems responsibility – as opposed to merely a single clinical responsibility – we are now coming to recognize the need for powerful methods to assess candidate community interventions, interventions that may come to implement and exploit the benefits of previously proven evidence-based interventions.

By definition, a health care system, or a community within which health care is given, cannot be the same as an individual patient. This may seem obvious, yet has profound consequences for research strategies. It would make little sense to test a community-based intervention, like deployment of community-based health workers, with a traditional randomized trial that treats individual patients as the unit of study. Instead, we can take

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advantage of a long-standing, but increasingly appreciated methodology – the cluster randomized trial.⁵

In a cluster-randomized trial, investigators randomize groups of people instead of individuals. They might randomize hospital units, as was recently done in cluster trials of methicillin-resistant *Staphylococcus aureus* prevention⁶ or of better implementation of internal mammary revascularization in patients undergoing coronary bypass grafting.⁷ Or they might randomize whole communities, as in a recently reported trial on community health workers and enhanced physician education for treatment of hypertension in Pakistan.⁸

In this issue of *Circulation*, Yan and colleagues report on an intriguing randomized cluster trial of a “simplified cardiovascular management program (SimCard)” for management of patients at high-risk for cardiovascular disease.⁹ The investigators randomized 27 rural Chinese villages and 20 rural Indian villages to either control or to the SimCard intervention, in which community health workers were deployed to manage patients with an Android “app” that promoted anti-hypertensive medications, aspirin, and two lifestyle modifications. There were 2086 high-risk patients enrolled. The investigators found that the SimCard intervention led to increased use of anti-hypertensive medications and aspirin and led to a small decrease in systolic blood pressure; however, the intervention led to no material lifestyle changes.

A close look at the methods and data showed two important differences between the Chinese and Indian villages and patients. First, the investigators randomized the Chinese villages with stratification for township and county; they did not perform any stratification in the Indian villages. This difference may have been important, as there were a number of marked baseline differences among the Indian patients, but not among the Chinese patients. Second, the Chinese community health workers were “village doctors” who had the right to prescribe medications, whereas the Indian community health workers were not authorized to prescribe medications. They instead had to work “in partnership” with local licensed physicians. This difference may explain why the difference for the primary end-point of anti-hypertensive medication use was much more clear cut in the Chinese villages – the intervention villages saw a 10-fold increase in use while the control villages had absolutely no change (Figure 3b of the paper). In the Indian villages, anti-hypertensive medication use increased substantially in both the intervention and control groups – perhaps because of cross-contamination as the licensed physicians who prescribed medications may have interacted with patients in both intervention and control villages. The differences in the prescribing powers of the community health workers may in a similar way explain why the Chinese villages saw a fairly marked decline in systolic blood pressure (-4.1 mm Hg) while the Indian villages saw no significant change (-0.8 mm Hg).

How can we analyze the robustness of this cluster-randomized trial? Meurer and Lewis just published a framework that includes 4 key questions⁵: 1) Was the use of clustering well-justified?; 2) Was there potential bias?; 3) Was intra-cluster correlation properly considered?; and 4) Was the sample size appropriately justified and were any clusters lost follow-up? Let’s consider each of these issues in turn.

Was clustering well justified? The question considered here, whether community health workers armed with a smart-phone app could improve cardiovascular care, is arguably perfectly suited for a cluster trial. The investigators, pioneers in global health implementation research, were interested in assessing a community intervention, just the kind of intervention that occurs within a cluster and therefore should be tested within a cluster. Indeed, one could argue that not only was clustering well justified, an individual-patient randomized trial might have been the lesser design.

Was there potential bias? By the very nature of the intervention, it was impossible to blind caregivers and patients. In the Chinese villages there may have been some degree of quasi-blinding in that the intervention villages were unlikely to “contaminate” the control villages. Presumably, the community health workers in the intervention villages did not provide care “on the side” in the control villages. Furthermore, since they had full prescription rights, they would have had less need to communicate with physicians who were also caring for control patients.

Was intra-cluster correlation properly considered? Intra-cluster correlation refers to similarities that patients within clusters have that are greater than similarities among patients in different clusters.⁵ We might expect patients from Village A to be more similar to each other than to patients from Village B. Intra-cluster correlation represents a threat to the power of cluster trial – the greater the intra-cluster correlations, the lower the effective sample size. The investigators did account for intra-cluster correlation in their power calculations and found that the intra-cluster correlation coefficient was low, only 0.02.

Finally, was the sample size appropriately justified and were clusters lost to follow-up? The authors did conduct careful prospective sample size calculations, though the structural differences between the Chinese and Indian components – no stratification and no prescription-writing author in the Indian villages – may have diminished the study’s effective power. It is reassuring that no villages were lost to follow-up, but it is a bit concerning that 12% of the patients was lost to follow-up.

The SimCard Trial exemplifies the power of the cluster-randomized trial, a trial design that is especially useful for assessments of systems- or community-based interventions. We look forward to further community-based cluster trials that consider who has prescribing rights, that incorporate practicing physicians when appropriate⁸, and that focus on hard clinical endpoints.¹⁰ Given our increasing appreciation that cardiovascular disease is emerging as the number one threat to global health¹¹ and given our increasing appreciation of the value of systems- or community-based interventions for effective management, we also look forward to seeing investigators conduct many more similar cluster-randomized trials to enhance the scientific evidence-base underlying cardiovascular medicine.

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