**Ethical challenges in using Stepped Wedge Cluster Randomized Controlled Trials- *Atmiyata* Case Study**

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**Abstract:**

Background: Stepped Wedge Cluster Randomized Controlled Trials (SWCRCT) are a novel type of cluster randomized trials (CRT), and pragmatic in nature. The design is useful in evaluating large-scale and ‘real-life’ interventions particularly when en-bloc roll-out of intervention is not possible. The design involves random and sequential cross-over of clusters from control to intervention till each cluster is exposed to the intervention. The phased roll-out of an intervention not only has logistical and political advantages and an opportunity to learn as the intervention is delivered but is also ethically appropriate as all clusters finally get the intervention. The *Ottawa Statement* and the Council for International Organizations of Medical Sciences (CIOMS) guidelines which are universal standardized ethical guidelines for the conduct of randomized control trials, provide relevant ethical guidance to the design and conduct of CRTs; however, there is no specific mention of SW-CRCTs in these guidelines. The two major ethical challenges with SWCRCTs are whether they can be classified as research and whether the research design follows the principle of ‘clinical equipoise’.

Method: The paper focuses on ethical challenges with the SWCRCT design using *Atmiyata* as a case study. *Atmiyata* is a rural community-led intervention using a tiered model of community volunteers, called Champions, to identify and provide evidence-based counselling for persons with common mental disorders (CMD).

Discussion: It is important to justify the use of SWCRCTs considering delay in roll-out of an effective intervention, and to consider SWCRCTs as research which needs to adhere to ethical principles of biomedical research including oversight by an independent ethics review committee and informed consent of participants. There is a need to develop specific ethical guidance for SWCRCTs considering their complex design, potential to produce a robust evidence for public health and increasing use in implementation research.

**Keywords:** Stepped-wedge cluster randomized controlled trials, Ethics of SWCRCT, Atmiyata, Community mental health, research ethics committee

**Background:**

Stepped wedge cluster randomised trials (SWCRCT), a novel and pragmatic research trial design are a sub-type of cluster randomised trials (CRT). Since their inception 40 years ago, SWCRCTs have largely been used to evaluate health policy, service delivery interventions and to study effectiveness of an already proven intervention (1). SWCRCT was first employed in the Gambia hepatitis intervention study in 1980 to test the long-term effectiveness of hepatitis B vaccine in the prevention of liver cancer and chronic liver disease before including the vaccine in Gambia’s national immunization schedule (2). SWCRT is a useful design to test the effectiveness of large-scale intervention. The hallmark of the design is all clusters ( E.g.- hospitals, primary care services, entire communities or schools), gradually cross over from control to intervention conditions according to a randomised schedule which is ethically more acceptable than conventional CRTs where the control clusters do not get the intervention (1).

There are two types of SWCRCT designs- cohort and cross-sectional (1). In cohort design the same participants within clusters are followed over time and crossover between interventions happens at both the subject and cohort level. In cross-sectional design, new participants are included after each step and crossover of the intervention only takes place at the cluster level (3). The main difference between two types is that all participants in a cluster do not get the intervention in a cross-sectional SWCRCT.

Brown et al (4) state that SWCRCT designs do offer a comprehensive option from a research perspective, but they come with their own implementation and ethical challenges. SWCRCTs are used both in explanatory as well as pragmatic research. In explanatory research, the intervention is implemented to study its effect and then rolled out to larger population. Phased roll-out is a practical method for rolling out an implementation to a population when conducting explanatory research (5). However phased implementation has its own implementation challenges, such as need for repeated training activities, multiple time recruitments and continuous engagement with clusters in control arm to avoid drop-outs. This increases the workload for implementation team as more clusters get added to the intervention over time and high cost for conducting the study. Furthermore, it may be difficult to ensure that randomization is complied with which can pose an ethical issue (6). In contrast, in pragmatic research, the intervention is offered to prove its expected benefits to the population; research effect is secondary (5).

The main reasons for adopting a stepped wedge design are ethical, logistical and political or social (7). Stepped wedge randomised trial designs involve roll-out of an intervention to participants (individuals or clusters) in a fixed sequence and over a fixed time period. The study design must have a minimum of 2 sequences and 3 time-periods to classify as SWCRCT. By the end of the study, all clusters and participants will have received the intervention, although the order in which cluster or participants receive the intervention is determined at random. The design is particularly relevant where it is predicted that the intervention will do more good than harm. In such situations, a parallel cluster randomized design in which certain clusters and participants do not receive the intervention will be regarded as unethical. SW-CRCT design is also useful where, for logistical or financial reasons, it is difficult to deliver the intervention to all participants at the same time. However, with their complex design SWCRCTs have their own ethical challenges which are different from those associated with CRTs.

**Existing Ethical Guidance on Cluster Randomized Trials**

Since SWCRCTs are a type of cluster randomized trials, similar ethical guidelines apply as for CRTs. There are two guidelines which need to be followed when designing CRTs- Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials,2012 (8) and the Council for International Organizations of Medical Sciences’ (CIOMS) International Ethical Guidelines for Health-related Research Involving Humans,2016 (9). The *Ottawa Statement* provides comprehensive guidance on the ethical design and conduct of cluster randomized trials and lays down 7 ethical principles which include: 1. Justifying the cluster randomized design; 2. Ensuring appropriate ethics review; 3. Identifying research participants; 4. Obtaining informed consent; 5. Role and authority of gatekeepers; 6. Assessing benefits and harms; and 7. Protecting vulnerable participants (8).

Guideline no 21 in CIOMS relates to the ethical acceptability of a ‘no intervention’ (placebo/no treatment) group (9). Frequently, CRTs investigate interventions that have been proven to be effective in different context or geography. E.g.- an intervention proven to be effective in high-resource settings now tested in low-resource settings. In such cases, the placebo controls will not receive an existing effective treatment. This creates an ethical issue whether it is acceptable to withhold an effective intervention from the control population (9). In SWCRCT, this issue transforms into justifying a delay in roll-out of an effective intervention. CIOMS states that a study is not ethically justifiable if withholding a proven intervention from control group will increase the amount of risk which is more than minimal. Researchers are ethically responsible to provide appropriate care for research participants from control area to reduce the likelihood of harm due to denial of an effective intervention, till they receive this intervention. Research ethics committees (REC) also have a responsibility to decide if the proposed study design is ethically acceptable and if not, which alternative designs may be ethical acceptable. (9). The CRTs include multiple clusters or organizations; so, gatekeeper permission must be obtained. The gatekeeper can be a community leader, local health council or headmaster of a school who holds the legitimate authority. The gatekeeper must ensure that risks of participation in the study are less than potential benefits to the participants and their community. Researchers must obtain gatekeeper permission, but it is not an alternative to obtaining individual informed consent (9). Commonly, gatekeepers are approached to give cluster permission before taking informed consent from individual research participants (10).

While the Ottawa Statement and CIOMS guidelines, both address ethical issues for CRTs, neither provides specific ethical guidance for SW-CRCTs.

**Ethical challenges with SWCRCT**

Our current knowledge and understanding of research ethics are from individually randomized trials which are based on moral principles of- respect for persons, beneficence, justice and respect for communities (11). In classical randomized clinical trials: - randomization, observation and intervention happens at an individual (research participant) level. However, in SWCRCT randomization takes place at cluster level and the intervention at an individual level (1). Furthermore, we lack complete knowledge of moral status of groups (clusters). This can complicate applying the standard research ethical principles to SWCRCT and pose challenges for researchers and research ethics committee to fulfil their respective roles (11). We will like to discuss two important ethical challenge in conduct of SWCRCT.

The first and most important ethical consideration is whether SWCRCTs should be classified as research studies or should they be considered as routine service evaluation. And who are the research subjects. If SW-CRCTs are research, they should follow all ethical processes associated with research studies such as obtaining an ethical approval for conduct of the trial, prospective registration with a trial registry and informed consent of research participants. A systematic review (12), found that most SWCRCTs do not have ethics approval and are not registered with an appropriate trial registry.

If SWCRCTs are considered as research studies, it raises ethical issues regarding equipoise, a fundamental ethical principle for randomized controlled trials. Equipoise means that researchers truly do not know whether the intervention being studied is effective before they do the trial. Clinical equipoise exists when there is a state of a clear disagreement amongst experts or professionals about preferred treatment (13). When the researchers plan a SWCRCT they need to be clear about where the equipoise lies (4,13,14). It may lie in uncertainty about the effectiveness of an intervention whose efficacy has been established, or in uncertainty about potential efficacy in a setting that is substantially different from those of previous studies. However, the equipoise has to lie somewhere because without it there is no ethical justification for delaying implementation in some clusters (7). SWCRCTs can be ethically justified if the objective of the research is to know more about a particular intervention in a real world setting or in a new context or if there are new outcomes which are not previously reported (5).

**Case study: *Atmiyata***

*Background:* Mental illness is a substantial public health burden in India and 10.6% of the population experience some form of mental illness (15,16). Majority of them are affected by common mental health disorders (CMD), such as anxiety and depression. People with mental health problems often face stigma and discrimination in their communities (17,18) which hinders their seeking support from mental health professionals. At the same time, a smaller number of trained mental health professionals in rural parts of India (19), means that there are insufficient human resources to address the burden of CMD in the community (20).

At the village level, though community health workers like ASHAs are available and provide health services, but they are not trained to detect or identify mental health problems. There are existing approaches to addressing mental health issues in India, largely through intervening in formal health care services in the public sector (i.e. training community health workers).

*Study design*: The Atmiyata study is based in rural Mehsana district in the state of Gujarat, India. Mehsana has a rural population of approximately 1 million adults. “*Atmiyata*” (meaning empathy or shared compassion) is a community led intervention to improve access to mental health and social care which utilizes social capital and build capacity of community-based volunteers. The trained volunteers identify and provide basic, low intensity counselling to people with CMDs (21). A SW-CRCT was conducted to determine the effectiveness the *Atmiyata* intervention in reducing symptoms associated with CMD when implemented across a large scale.

There are 56 primary health centres (PHCs) in Mehsana district, and each PHC covers villages within a geographical area. Each village in the geographical area which comes under a PHC is a cluster in this study. We created 4 groups of clusters (A, B, C, D), each made up of villages covered by 14 PHCs. The groups or clusters are created in a way that the probability of contamination is minimized between groups. Thus, villages in Group A are farther from Group B villages and villages in Group C are farther from Group D and so on. All groups (A, B, C, D) are allocated to intervention condition at different steps. A ’Step’ is the order in which a group of clusters switches from control to intervention condition. On the other hand, ’Period’ is defined as group of observations by time of measurement. The duration of each period is 5 months to accommodate for baseline and 3 months follow-up data collection [Figure 1]. While the research participants under intervention condition received low-intensity counselling, we provided enhanced usual care (EUC) for participants under control condition. EUC provides information on about the impact of distress, available public mental health care services, and help lines for mental health support and for domestic violence in and around Mehsana district. Under EUC, the data collectors also provided active support to participants in crisis like self-harm or suicidal thoughts or recent suicidal attempt.

This study uses a repeated cross-sectional design with outcome data derived from different participants in each period. All four clusters start at baseline in the control condition and are exposed to the intervention at regular time period of five months [Figure 1].

**Figure 1**- **SW-CRCT design**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Clusters | Period 1 | Period 2 | Period 3 | Period 4 | Period 5 |
| Cluster A  (14 PHCs) | Control | Intervention | Intervention | Intervention | Intervention |
| Cluster B  (14 PHCs) | Control | Control | Intervention | Intervention | Intervention |
| Cluster C  (14 PHCs) | Control | Control | Control | Intervention | Intervention |
| Cluster D  (14 PHCs) | Control | Control | Control | Control | Intervention |

*Geographical areas/villages 56 PHCs are allocated to four clusters (A,B,C,D) of 14 clusters each. Each time period (1, 2, 3, 4 and 5) represents data collection points. Each unit (control and intervention) represents one time period for each group of clusters.*

Intervention

Control

*Consent and ethical approvals:* Permission was obtained from the Department of Health for the State of Gujarat for project implementation and data collection. TheIndian Law Society’s Ethics Committee approved the study (ILS/14/2017) and additional ethical approval was obtained from the local ethics committee from the Hospital for Mental health, Ahmedabad. The trial is registered prospectively with clinical trial registry, India and the Clinical Trial registry number- CTRI/2017/03/008139. Before approaching individual participants, village heads (Sarpanch) were informed about the study and the purpose of the data collection. Here, village heads acted as gatekeepers giving a permission to enrol the cluster. Written informed consent was obtained from each participant enrolled in the trial during the control and intervention phase. The information provided to each of these participants included the purpose of the study, benefits and risks for the participant and information about withdrawal from the study.

**Ethical evaluation**

*Classification of the design: is it research**?*

In *Atmiyata* case study, the objective is to conduct a robust evaluation of the effectiveness at a large scale in real world settings. Also, the purpose of *Atmiyata* SWCRCTistoobtain evidence for wider dissemination to policy makers for further scale-up. In our opinion, *Atmiyata* study should be classified as research and not service evaluation because it is designed to provide generalizable evidence for wider contexts. We believe that such SW-CRCTs should be registered in an appropriate clinical trials registry; obtain ethical permissions and monitoring from local ethics body and have an appropriate process of informed consent to protect against any harm to research participants.

*Delayed roll-out of the intervention that had promising effect*:

The core of *Atmiyata* programme is delivering low intensity counselling to people with CMD via trained community volunteers. Evidence based counselling techniques are used, namely active listening, activity scheduling and problem solving. Several research studies have demonstrated the efficacy of approaches using community health workers or primary care level health workers to deliver community based mental health care for common mental disorders in India and elsewhere (22,23,24). A Cochrane review on non-specialist lay mental health workers concluded that while evidence exists on the impact of lay workers on mental health, more research is needed on the type of lay worker, the intervention and their effectiveness (25). Patel et al conducted randomized controlled trial (RCT) in Goa, India to demonstrate an effectiveness of a brief psychological treatment delivered by the lay health counsellors in a primary care setting for people with moderate to severe depression (26). The *Atmiyata* intervention underwent a pilot evaluation across 40 villages (21). Thus, there is considerable evidence, but not at scale and in different context, of efficacy of *Atmiyata* like interventions. Given this evidence, it can be argued that it is unethical to delay the intervention from clusters and participants. However, we believe there is a reasonable justification to conduct a randomized evaluation to examine effectiveness in local context, for wider dissemination and when the intervention is likely to result in no greater than minimal harm. The care gap for mental health is so wide that we need low cost, effective, scalable and sustainable interventions which are tested in local context and at scale. *Atmiyata* SWCRCT therefore attempts to obtain evidence for generalizability to other parts in rural India and in different contexts which will assist policy makers make evidence-based decisions to allocate financial and human resources to effective interventions to improve access to mental healthcare. *Atmiyata* SWCRCT aims reduce this research gap and hence in our opinion is not unethical to delay implementation of the intervention in some geographical area (clusters). In addition, research participants in the control arm of *Atmiyata* SWCRCT are provided with enhanced usual care to reduce the likelihood of harm.

**Recommendations**

We recommend SWCRCTs should be classified as a research methodology and therefore, researchers should get an approval from REC and register their trial in an appropriate trial registry. The researchers justify the design based on a clinical equipoise, identify research participants and seek informed consent. REC and sponsors should be equipped with the knowledge about SWCRCT design.

**Conclusion**

SWCRCTs are a robust evaluation method to study effectiveness of large-scale interventions but they are complex, time consuming and expensive and researchers need to have adequate reasons to use these designs. Though SWCRTs are ethically more justifiable than CRT, they pose different set of ethical challenges which need to be addressed carefully. There is an urgent need for specific ethical guidelines for the use of SW-CRTs to contribute to responsible functioning of these trials and adequate protection of its participants.

**List of abbreviations**

SWCRCT: Stepped Wedge Cluster Randomized Controlled Trial

CRT: Cluster Randomized Trial

CIOMS: Council for International Organisation of Medical Sciences

REC: Research Ethics Committee

CMD: Common Mental Disorders

PHC: Primary Health centre

EUC: Enhanced Usual Care

**Declarations**

**Ethics approval and consent to participate**

Not applicable

**Availability of data and material**

Not applicable

**Competing interests**

The authors declare that they have no completing interests

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**Authors’ Contributions**

All authors read and approved the final manuscript. DP and KJ wrote the first draft, SP, LSZ and JK have provided feedback and edited the draft. KJ finalised the draft.

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