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Design and execution of a public randomization ceremony to enhance stakeholder engagement within a cluster randomized trial to improve tuberculosis diagnosis in Uganda

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ABSTRACT

Public randomization ceremonies have been proposed as a strategy to strengthen stakeholder engagement and address concerns and misconceptions associated with trial randomization. However, there are few published examples that describe how to conduct a public randomization ceremony with meaningful stakeholder engagement or how such ceremonies impact stakeholder perceptions about randomization and the randomization process. Cluster randomization for the GeneXpert Performance Evaluation for Linkage to Tuberculosis Care (XPEL-TB) trial was conducted at a public randomization ceremony attended by 70 stakeholders in Kampala, Uganda. Presentations given by the Acting Assistant Commissioner from the Uganda National Tuberculosis and Leprosy Programme and trial investigators emphasized how the trial aimed to further national TB goals, as well as how stakeholders contributed to the intervention design. The purpose and process of randomization were described using simple text and visuals. Randomization was an interactive activity that required participation of stakeholders from each trial site. A survey administered to stakeholders at the end of the ceremony suggested high comprehension of randomization (98%), trust in the randomization process (96%), and satisfaction with randomization outcomes (96%). Public randomization ceremonies should be considered more routinely to engage stakeholders in and address potential concerns about the fairness and impartiality of the randomization process for community-based trials.

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1. Introduction

Randomized trials, which involve the random allocation of individuals or groups to trial arms before the trial starts, are considered the gold standard design for evaluating the effectiveness of clinical interventions. Benefits of randomization include reduced selection bias and balance of potential confounders between trial arms, both of which are important for estimating the true intervention effect [1]. While randomization is important to data integrity, the way in which stakeholders perceive the fairness and transparency of randomization is critical to trial acceptability and implementation. Stakeholders may consider randomization unfair and instead prefer need-based allocation, especially if the context and rationale for randomization are not understood [2]. In addition, stakeholders may not trust the outcome of randomization if not allowed to observe the process or if allocation was not performed by an individual perceived to be impartial or trustworthy [2,3]. Efforts to explain the rationale of the research design in simplified language and to involve stakeholders in trial activities and decision-making have been shown to improve willingness to participate in the trial, as well as adherence and retention during implementation [4,5].

Public randomization ceremonies have been identified as one strategy to increase stakeholder engagement, explain the need for randomization, and increase trust in the randomization process [6–9]. They provide an opportunity to generate awareness about the trial in the community, highlight how the trial is expected to further stakeholder goals, and solicit input on proposed research activities. They also allow researchers to explain how the trial will contribute to the evidence base that is used to develop national policies.

Published examples of public randomization ceremonies are needed to guide their conduct and develop best practices. Our primary objective was to describe the design and execution of the public randomization ceremony for the GeneXpert Performance Evaluation for Linkage to Tuberculosis Care (XPEL-TB) trial (ClinicalTrials.gov identifier: NCT03044158). In addition, we assessed stakeholder understanding of the trial and perceptions about the randomization process following the ceremony. The XPEL-TB trial aimed to evaluate the effectiveness, implementation, and costs of a streamlined TB diagnostic evaluation strategy, which incorporated onsite molecular testing using the GeneXpert Edge platform and was designed to address provider- and patient-level barriers to TB diagnosis and treatment [10,11]. Of the 84 health centers (clusters) that met trial eligibility criteria, 20 were selected with input from the Uganda National Tuberculosis and Leprosy Programme (NTLP)[2] and 10 were randomized to each arm. The trial was approved by institutional review boards at the University of California San Francisco and Makerere University College of Health Sciences, and by the Uganda National Council for Science and Technology.

2. Details of randomization

Prior to the randomization ceremony, the 184,757 possible allocations to divide clusters were reduced using stratification and restriction to achieve balance between trial arms in pre-specified cluster- and patient-level characteristics [10]. Stratification was intended to maintain balance in the primary outcome at baseline between arms and resulted in 63,504 possible random allocation sequences. Restriction to further ensure balance in key cluster- and patient-level characteristics correlated with TB diagnosis and treatment (health center region, health center size, health center distance to GeneXpert testing hub, and HIV prevalence among TB patients) reduced the total number of possible random allocation sequences to 11,382. From this list, 10,000 allocation sequences were randomly selected and labeled 0000–9999. Any of these allocation sequences had equal probability of being chosen during the randomization ceremony.

3. Preparation for randomization ceremony

The director of each participating health center was asked to name 2–3 representatives to attend the randomization ceremony. Individualized invitation letters, drafted by the study team and signed by the Principal Investigators, were then sent to the nominated health center representatives as well as District TB and Leprosy Supervisors and NTLP representatives via e-mail 2–3 weeks prior to the ceremony. Invitations confirmed that travel, lodging and per diem costs would be covered by the study to facilitate attendance.

4. Randomization ceremony

Seventy stakeholders attended the randomization ceremony on August 9, 2018, including 40 health center representatives (18 health center directors, 6 TB focal persons, 2 nurses, and 14 laboratory technicians), 25 District TB and Leprosy Supervisors, and 5 NTLP representatives.

The randomization ceremony began with the Acting Assistant Commissioner for the NTLP introducing the trial in the context of challenges associated with TB diagnosis across Uganda. She endorsed the intervention strategy as a "landmark innovation" that could improve the quality of patient care but reiterated the importance of the control arm to serve as a measure of the routine care against which the intervention could be compared. The Principal Investigator then provided a brief overview of the trial, highlighting stakeholder contributions to the design of the intervention strategy. Participants were reminded that all health centers would receive a GeneXpert device at the end of the trial period. After this session, participants had the opportunity to ask questions, which ranged in topic from logistics (*e.g.,* how to prevent theft of batteries and solar panels at intervention sites) to potential changes in TB caseload as a result of access to onsite GeneXpert testing to expectations of health facility staff.

After a short break, the trial statistician explained the purpose and process of randomization, as well as the concepts of restriction and stratification, using simple text and visuals. A snapshot of the spreadsheet listing all possible random allocation sequences was projected to explain how it should be used and interpreted.

The randomization process was facilitated by the local lead investigator. Ten footballs of the same size and color labeled with a number between 0 and 9 were displayed to the audience before they were placed in an opaque bag (Fig. 1). One by one, randomly selected representatives from four trial health centers picked a numbered football from this bag

Fig. 1. 10 balls used for randomization were placed in an opaque bag.

[2] NTLP refers to the Uganda National Tuberculosis and Leprosy Programme.

Fig. 2. Site representatives after final ball was selected.

and replaced it after selection. This was done to generate a four-digit randomization code used to determine assignment to Group A or Group B. The number on each football corresponded with one number of the four-digit code and the order in which footballs were picked corresponded with the order of the numbers in the four-digit code. The spreadsheet created by the trial statistician was projected for the audience to see and the group assignment for each health center associated with the selected code was read out loud. To make the process more participatory, a representative from each trial health center was asked to retrieve and display large placards printed with their health center's name and number and congregate on either side of the front of the room, depending on group assignment. An NTLP representative was seconded by the audience to pick the last football to determine arm assignment for each group. Photos were taken with health center representatives in each group holding their respective placards and a printed sign to indicate arm assignment (Fig. 2).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.conctc.2021.100707.

5. Participant feedback

A survey was administered to all participants to assess their comprehension of the trial and satisfaction with and acceptability of the randomization process and outcomes. Fifty-four participants responded. The survey comprised seven questions on a 5-point Likert scale and two open-ended questions to collect more detailed information on what participants enjoyed most about the ceremony, as well as suggestions for improvement. Survey results suggested high comprehension of the trial goals and design, as well as satisfaction and acceptability of the randomization process and outcomes (Table 1).

Table 1
Results of the XPEL-TB randomization ceremony evaluation.

Variables	Survey Response (N = 54)	
	n (%) with score ≥ 4	Median (IQR)
I understand the goals and design of the XPEL-TB trial	54 (100%)	5 (4–5)
I believe the XPEL-TB trial is addressing an important topic that is of relevance to improving TB care in Uganda	54 (100%)	5 (5–5)
I understand what randomization is and why it is important	52 (98%)[a]	5 (4–5)
I feel the randomization process was fair	52 (96%)	5 (5–5)
I am satisfied with the outcome of the randomization process	52 (96%)	5 (5–5)
I believe it was important for me to participate in and witness the randomization process	54 (100%)	5 (5–5)
I believe my attendance at the randomization ceremony will help others at my health center to accept the randomization results	53 (98%)	5 (5–5)

[a] N = 53.

Respondents overwhelmingly noted being appreciative of the opportunity to actively participate in the randomization process in free text responses. Half commented that the fairness and transparency of the randomization process was what they enjoyed most about the ceremony, with one participant noting each site had "a 50-50 chance to be [an] intervention or control site". There were no comments indicating that randomization was manipulated to favor a certain health center, region or population.

Approximately one-fifth of respondents (n = 10) indicated that the method of randomization was what they enjoyed most about the ceremony and comments from two participants highlighted the importance of active stakeholder involvement in the randomization process. While the randomization process was clear to respondents, more detailed explanation of complex statistical methods such as stratification and restriction were requested. In addition, respondents expressed that high-volume sites or sites distant from GeneXpert testing hubs should be prioritized for the intervention.

6. Conclusion

The public randomization ceremony raised awareness about the trial among stakeholders and increased trust in the randomization process. High stakeholder engagement during trial implementation may be partly attributed to their attendance of the ceremony and active participation in the randomization process. A more in-depth qualitative study could have better identified how the public randomization ceremony impacted stakeholder perceptions about the trial, and how the ceremony could have been further improved. Researchers planning late-phase trials should consider public randomization ceremonies and provide opportunities for active participation in the randomization process.

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References

[1] K. Suresh, An overview of randomization techniques: an unbiased assessment of outcome in clinical research, J. Hum. Reprod. Sci. 4 (1) (2011) 8–11.
[2] M.M. Kombe, J.M. Zulu, C. Michelo, I.F. Sandoy, Community perspectives on randomisation and fairness in a cluster randomised controlled trial in Zambia, BMC Med. Ethics 20 (1) (2019) 99.
[3] P.A. Newman, C. Rubincam, Advancing community stakeholder engagement in biomedical HIV prevention trials: principles, practices and evidence, Expert Rev. Vaccines 13 (12) (2014) 1553–1562.
[4] D.A. Johnson, Y.A. Joosten, C.H. Wilkins, C.A. Shibao, Case study: community engagement and clinical trial success: outreach to african American women, Clin. Transl. Sci. 8 (4) (2015) 388–390.
[5] M.S. Rayzberg, Fairness in the field: the ethics of resource allocation in randomized controlled field experiments, Sci. Technol. Hum. Val. 44 (3) (2018) 371–398.
[6] E. Ruzagira, K. Baisley, A. Kamali, H. Grosskurth, An open-label cluster randomised trial to evaluate the effectiveness of a counselling intervention on linkage to care among HIV-infected patients in Uganda: study design, Contemp. Clin. Trials Commun. 5 (2017) 56–62.
[7] F.M. Cowan, C. Davey, E. Fearon, P. Mushati, J. Dirawo, S. Chabata, et al., Targeted combination prevention to support female sex workers in Zimbabwe accessing and adhering to antiretrovirals for treatment and prevention of HIV (SAPPH-IRe): a cluster-randomised trial, Lancet HIV 5 (8) (2018) e417–e426.
[8] S. Kapiga, S. Harvey, G. Mshana, C.H. Hansen, G.J. Mtolela, F. Madaha, et al., A social empowerment intervention to prevent intimate partner violence against women in a microfinance scheme in Tanzania: findings from the MAISHA cluster randomised controlled trial, Lancet Glob Health 7 (10) (2019) e1423–e1434.
[9] C.J. Gill, G. Phiri-Mazala, N.G. Guerina, J. Kasimba, C. Mulenga, W.B. MacLeod, et al., Effect of training traditional birth attendants on neonatal mortality

(Lufwanyama Neonatal Survival Project): randomised controlled study, BMJ 342 (2011) d346.

[10] T.F. Reza, T. Nalugwa, K. Farr, M. Nantale, D. Oyuku, A. Nakaweesa, et al., Study protocol: a cluster randomized trial to evaluate the effectiveness and implementation of onsite GeneXpert testing at community health centers in Uganda (XPEL-TB), Implement. Sci. 15 (1) (2020) 24.

[11] A. Cattamanchi, C.R. Miller, A. Tapley, P. Haguma, E. Ochom, S. Ackerman, et al., Health worker perspectives on barriers to delivery of routine tuberculosis diagnostic evaluation services in Uganda: a qualitative study to guide clinic-based interventions, BMC Health Serv. Res. 15 (2015) 10.