Expanding and Scaling Two-way Texting to Reduce Unnecessary Follow-Up and Improve Adverse Event Identification Among Voluntary Medical Male Circumcision Clients in the Republic of South Africa

NCT04327271

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Statistical Analysis Plan (PDF/A) Version Date 8/26/19

Sample size and power:

RCT to determine no inferior AE ascertainment using 2-way texting rather than routine care. Randomization will be 1:1 between routine care and the texting intervention. If routine care AE ascertainment is 0.5% as evidenced from Aurum Institute program records, and 2-way texting increases AE ascertainment to 2.0% similar to our intervention arm AE ascertainment rate for the same intervention in our prior study in Zimbabwe (1.88%), and if we take -0.25% to be our noninferiority margin, and assume 10% LTFU, enrolling 1,104 men will give 80% power to establish noninferiority. In other words, 1,104 men (at least 994 of whom provide analyzable data) will provide at least 80% power to rule out a decrease of more than 0.25% based on the lower bound of the one-sided 95% confidence interval for the difference between arms in the proportion with AEs ascertained.

Sample sizes required to establish noninferior AE ascertainment using 2-way texting.

AE ascertainment		Sample size required for 80% power*		
Routine Care	2wText	N/group	Total N	+ 10% increase for LTFU
0.5%	1.50%	782	1564	1738
0.5%	**2.00%**	**497**	**994**	**1104**

* Calculated using Statistical Solutions Nquery Advisor version 8.4.1.0, two-group test of non-inferiority in proportions.

DATA ANALYSIS:

1. For the 2wT safety outcome of interest is cumulative AE rate (moderate or severe) ≤ Day 14. In RSA, and similar to other countries in the region, moderate AEs are those which include symptoms requiring modification of activity, but not resulting in loss of work or cancellation of social activities while severe AEs are those with incapacitating symptoms, requiring bed rest and loss of work [1]. Incidence of AEs before Day 14 will be extracted from routine VMMC data for both 2wT and control. Incident AEs on Day 14 will be identified, classified, and graded for severity using routine NDOH protocols [2] and recorded on routine VMMC AE forms.

To test our noninferiority hypothesis, we will compare cumulative proportion (rate) of any moderate or severe AE ascertained ≤ Day 14 between groups by comparing the lower limit of the one-sided 95% confidence interval of the difference in proportion between groups, to the noninferioirty margin. The rates will be calculated per arm as: (# moderate + severe AEs)/(total # MC clients who attend 2, 7 or 14 Day follow-up visit). Based on our RCT in Zimbabwe, we may actually observe an increase in AEs; in that case, we will then seek to establish superiority of the two-way texting group by comparing arms with Fisher's exact test. While our study design provides limited power for this comparison (45%), there's no statistical impediment to performing both noninferiority and superiority comparisons in a noninferiority trial. To determine follow-up visit reduction, we will compare the mean number of in-person visits for intervention and control using a t-test. A multivariate linear regression model will further quantify the effect of intervention on visit reduction, adjusting for potential confounders. Secondary outcomes include: AE rates on Day 14, texting response rate, time between 2wT AE text reporting and follow-up, severity of AEs. We will perform appropriate summaries of missing data and LTFU, testing for systematic differences in response by study arm. We will examine individual mediating (e.g., referral follow-up, response rate) and moderating (urban/rural) variables [3]. *We hypothesize that 1) 2wT is non-inferior to routine follow-up for patient safety and that 2) 2wT will reduce unnecessary follow-up over standard care.*

2. For 2wT acceptability, using study recruitment and enrollment logs in addition to the texting database, we will describe levels of acceptance, participation, refusal and drop-out. We will carry out key informant interviews (KIIs) with up to 10 health care workers to gauge acceptability, satisfaction, identify facilitators and barriers to program success, and ascertain suggestions for intervention improvement. KIIs will be audio recorded and transcribed. Atlas.Ti software will be used to create a spreadsheet of key themes, perceived barriers, and suggested facilitators to the program from KIIs. We will also implement questionnaires at the Day 14 visit with a subset of 100 2wT VMMC clients in the main study who were randomized to texting to gauge satisfaction, estimate direct and indirect costs (time away from work, transportation costs), and ascertain suggestions for intervention improvement. Responses from these brief, self-administered, quantitative surveys with VMMC clients will be entered in Excel and frequencies explored in STATA 12.0. For feasibility, costing data will be combined with usability and acceptability information. These comprehensive data will be discussed at a final stakeholder meeting to disseminate study results, validate interpretations and refine recommendations for future scale up and modification of 2wT in RSA and beyond. Additional meetings between local researchers and the NDOH will further determine feasibility for replication and scale-up. *We hypothesize that acceptability, usability, and feasibility will be high, aiding program scalability.*

3. For 2wT costs, we will calculate the relative costs and outcomes (effects) of intervention versus control, including costs for technology, healthcare worker time, and client considerations (travel, text costs, missed work). We will conduct both activity-based costing from the implementation perspective and from the technology perspective to extrapolate our results as costs that would be incurred by the NDOH should they elect widespread scale up of 2wT. **Approach for costing.** First we quantify the total direct and indirect costs of 2wT deployment, a method previously used for technology cost assessment in Malawi [4], which includes comprehensive costs from installation and training, routine maintenance, healthcare worker time associated with 2wT, and staff efficiency gains/losses in addition to the direct cost of technology. Second, we will estimate incremental costs (incremental relative to standard practice) for the intervention. This component entails a micro-costing study using activity-based approaches for costs incurred (trainings, VMMC service provision, follow-up) and costs averted (health costs for providers and patients saved by reducing visits), adapting previous VMMC costing estimates [5] for 2017 dollars when appropriate. Cost data will also be collected from the study budget, public health clinic budgets, published government reports, and the health economics literature. Lastly, to estimate the cost savings associated with 2wT over routine VMMC follow-up, we will conduct a time-motion study [6,7] to quantify time spent for VMMC follow-up, indicating potential time savings for providers and VMMC clients. One trained observer will record VMMC client/provider follow-up interactions for 5-10 days, or approximately 100 reviews, recording times and activities using a pre-established checklist and timing system. During these same 5-10 days, client time from registration through visit completion will be recorded by a second observer. Data will be exported into STATA 12.0 for analysis. The combined, overall costs for the delivery of 2wT in public health clinics will be estimated and compared to standard follow-up. *We hypothesize that 2wT will reduce the costs associated with VMMC patient follow-up over standard care.*

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