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Financial Incentives to Increase Uptake of Pediatric HIV Testing (FIT): Study Protocol for a Randomized Controlled Trial in Kenya

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Running head: Financial incentives for child HIV testing

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ABSTRACT (297/300)

Introduction: Index case testing (ICT) to identify HIV-infected children is efficient but has suboptimal uptake. Financial incentives (FI) have overcome financial barriers in other populations by offsetting direct and indirect costs. A pilot study found FI to be feasible for motivating pediatric ICT among HIV-infected female caregivers. This randomized trial will determine the effectiveness of FI to increase uptake of pediatric ICT.

Methods and analysis: The FIT trial is a 5-arm, unblinded, randomized controlled trial to determine whether FI increase timely uptake of pediatric ICT. The trial will be conducted in multiple public health facilities in western Kenya. Each HIV-infected adult enrolled in HIV care will be screened for eligibility: primary caregiver to one or more children of unknown HIV status ages 0-12 years. Eligible caregivers will be individually randomized at the time of recruitment in equal 1:1:1:1:1 allocation to one of five arms ($0 [control], $1.25, $2.50, $5.00, and $10.00 USD). The trial aims to randomize 800 caregivers. Incentives will be disbursed at the time of child HIV testing using mobile money transfer or cash. Arms will be compared in terms of the proportion of adults who complete testing for at least one child within 2 months of randomization and time to testing. A cost-effectiveness analysis of FI for pediatric ICT will also be conducted.

Ethics and dissemination: This study was reviewed and approved by the University of Washington Institutional Review Board (UW IRB) and the Kenyatta National Hospital Ethics and Research Committee (KNH ERC). Trial results will be disseminated to health care workers at study sites, regional and national policymakers, and with patient populations at study sites (regardless of enrollment in the trial). Randomized trials of caregiver-child FI interventions pose unique study design, ethical, and operational challenges, detailed here as a resource for future investigations.

Registration details: ClinicalTrials.gov NCT03049917 (Registered February 3, 2017)

Version: Protocol version 4.0, February 18, 2018

Keywords: pediatric HIV testing, index case testing, financial incentive, conditional cash transfer, protocol

ARTICLE SUMMARY

Strengths and limitations of this study

- The 5-arm individual-level randomized design with a concurrent control arm will enable a rigorous comparison of pediatric HIV testing uptake between incentivized and un-incentivized groups, controlling for background temporal trends.
- The inclusion of four levels of financial incentives (FI) will allow for the direct comparison of uptake between different levels of FI and identify any asymptotic relationships in the dose-response curve.
- Study staff will aim to randomize all eligible clients very early at the time of first contact to minimize selection bias that is common in randomized trials.
- Randomization will utilize a scratch card approach to allow for conceptual transparency in the randomization process; FI are disbursed using mobile money transfer technology to reflect the dominant banking practices in a Kenyan setting.
- Trial sites are in western Kenya where pediatric index case testing campaigns have already had high penetration; incentives may have a different effect in settings where such campaigns have been less common.

INTRODUCTION

Perinatally-acquired HIV infection is associated with high morbidity and mortality[1]. While prompt initiation of antiretroviral therapy (ART) reduces mortality and morbidity and promotes growth and development[2-6], delayed diagnosis and treatment until a child is severely ill limits the benefits of ART[7-9]. Global scale up of prevention of mother-to-child-transmission of HIV (PMTCT) systems have markedly reduced the number of new infant HIV infections[10]. However, many older HIV-infected children remain undiagnosed, either through PMTCT drop out or due to infant infections attributable to incident maternal infection during pregnancy or postpartum[11] when HIV incidence is high[12] and repeat maternal HIV testing is low[13 14]. Infant infections due to incident maternal infection are often missed by traditional prevention and early infant diagnosis systems [15].

Index case testing (ICT), whereby the children of an HIV-infected adult (the "index case") receiving HIV care are tested for HIV, is an efficient approach to case detection with high prevalence among children tested, but uptake remains sub-optimal[16 17]. In a previous study in Nairobi, only 14% of adults offered systematic pediatric ICT had their child tested for HIV[18]; in this study, barriers to pediatric HIV testing included structural, interpersonal, emotional, logistical, and financial issues[19]. Previous studies have addressed interpersonal and emotional barriers through assisted disclosure and support group interventions[20], systems-level barriers through medical record flags[21], and logistical barriers through offering a choice of home- or clinic-based testing[17 18]. However, these approaches may be expensive and rely on additional health care workers. In the context of limited health resources, approaches that minimize costs and maximize uptake are needed. A recent randomized trial showed that small financial incentives (FI) ($2USD) were successful in increasing uptake of HIV testing among children and adolescents ages 8-17 years, using a community-based recruitment approach[22]. Our team recently completed a feasibility pilot study of small FI to motivate uptake of pediatric ICT[23], but there have been no studies to date that have evaluated the effectiveness of FI to increase the uptake of pediatric ICT.

There are several unique ethical, logistical, and analytic challenges in designing a study to assess the effectiveness of incentivizing caregivers to complete HIV testing for their children. Ethical concerns, including randomizing a person of authority to act on another's behalf, assessing child-caregiver relationships to avoid inadvertent disclosure of maternal HIV status, ensuring child's well-being is not compromised, and reducing risks of social harms have been addressed elsewhere[24]. Logistically and analytically, there are unique challenges in managing FI randomization and disbursement, minimizing the drop-off between recruitment and randomization, minimizing contamination effects leading to presentation of ineligible individuals, and accounting for competing interventions in the region.

This study–Financial Incentives to Increase Uptake of Pediatric HIV Testing (FIT)–is a randomized controlled trial to determine whether FI increases uptake of pediatric ICT, and determine the cost-effectiveness of various levels of FI. This paper details the study protocol and describes design considerations specific to trials incentivizing pediatric testing.

METHODS AND ANALYSIS

Conceptual framework

FI may motivate parents who are willing to test, but face logistical or financial barriers, to take action to test. Unwilling parents, who face extreme fear or real dangers from revealing their HIV status may not be motivated by FI to take action to test. Social services (SS)—including enhanced counseling and peer support groups—may help parents move from unwilling to willing. We hypothesize that the proposed FI intervention will primarily move willing parents from "Willing to test" to "Taking action" (Figure 1).

Pilot study

A pilot study (NCT02931422) was conducted between October 2016 and January 2017. In the pilot study (N=60), values of $5, $10, and $15 USD were tested; these were based on cost data from a previous pediatric ICT study conducted by the same team in Nairobi[18]. The lowest incentive value reflected the 75th percentile of direct non-medical costs (transportation, childcare, and food/drink outside the home), the middle value reflected the 75th percentile of direct non-medical and indirect costs (lost wages from paid and unpaid work), and the highest value reflected the direct costs, indirect costs, and a second day of lost wages[23].

Study design

The FIT trial is a 5-arm, unblinded, individual-level randomized controlled trial (RCT) of FI. Eligible individuals will be randomized using a 1:1:1:1:1 allocation to no incentive, $1.25, $2.50, $5.00, or $10.00 2016 USD (Figure 2). Randomized individuals can redeem the value of their incentive upon completing testing with study staff within 2 months of randomization. The study will employ a roving, multi-site model in which multiple clinic sites run concurrently, but each site will only be active for recruitment for 2 months. This model was selected to limit the extent to which clients at the facilities became aware of the FI opportunity through word of mouth, to limit the number of clients screened more than once (as most clients visit the clinic every 3 months), and to allow for sampling approximately proportional to facility size.

Design Considerations: Alternative study designs that included historic and lead-in control periods, as well as cluster randomization were considered, but ultimately not selected. Historic and lead-in control periods from within the same study sites could have suffered from depletion of susceptibles, in which the virtually fixed target population of index cases decreases over time as the most susceptible individuals experience the outcome of interest (e.g. complete ICT for their children). While new individuals are diagnosed with HIV each day, the rate at which those individuals are added to the population in care is slow relative to the number of individuals active in care at the beginning of a study. Additionally, there are many events—rapid HIV testing campaigns, school holidays, guideline changes—that could have occurred during either the control or intervention periods and led to temporal trends that could not be robustly controlled for. A concurrent control arm was considered to limit the extent to which these temporal and epidemiologic trends would impact the estimation of the effect of FI on testing.

A cluster RCT (cRCT) was also considered, which would have limited contamination; in the context of this study, contamination would have been the extent to which individuals within a clinic became aware of the other values of FI being offered and discouraged by receiving less than the maximum FI value. However, a cRCT design for a 5-arm trial would have required a prohibitively large number of clinics to detect meaningful differences in uptake, which was not feasible.

Determination of incentive values

Trial incentive values: Incentive values were determined using results from the FIT pilot study described above[23]. Uptake of testing in the pilot study was high and comparable between the 3 arms (75%, 70%, 75% across arms, respectively)[23]. Because it was unclear whether uptake was similar across the pilot study FI values because we had reached the top of the demand curve (e.g. where even higher FI would yield no increase in testing) or whether we were clustered in the middle of a demand curve (whereby higher or lower values would provide further differences in testing uptake), we decided to widen the range of FI values to remove the highest value and include lower values.

The trial incentive values will be $1.25, $2.50, $5.00, and $10.00, and a control with no FI ($0). Participants will be compensated and additional $3.00 for transportation costs regardless of arm; this reimbursement will be included to ensure more equitable benefit for those in the control arm for research participation, and will not be described to participants prior to the testing visit in order to not act as an additional incentive.

Incentive Considerations: Alternative formats of incentives were considered, including lottery-based incentives and non-financial incentives such as household items or agricultural items. Lottery-based incentives were considered less acceptable by some co-investigators due to a perception that this was similar to gambling, which has a negative connotation for some religious groups in Kenya. Agricultural and household items (and non-financial commodities in general) were felt to be more attractive for those living in rural settings, but had additional costs involved in procurement, distribution, and tracking of commodities, which would increase program costs. Cash or mobile money transfer was thus adopted as the most fungible, widely-acceptable, accountable, and low-cost FI format to deliver in the context of an intervention.

Study sites

The trial will be conducted at several government health facilities in western Kenya, including facilities in Kisumu, Siaya, and Homa Bay counties. Study team members will simultaneously operate up to 3 sites, and then relocate to new sites following 2 months of recruitment. Facilities will be selected one to two months in advance and approved by the county health director's office and facility heads. Sites will be selected based on high volume of adults in HIV care and relatively low penetration of recent pediatric ICT campaigns or programs. A full list of study sites will be provided in the trial results manuscript.

Recruitment processes & eligibility criteria

Index adult clients attending the HIV care clinics will be screened by study staff to determine eligibility: being HIV-infected and having one or more children of unknown HIV status ages 0-12 years. Children will be considered of unknown status if they have never been tested for HIV or tested negative during infancy but did not complete confirmatory negative testing after 18 months or following cessation of breastfeeding. Index client caregivers will be allowed to test any child formally in their care, both biological children and children to whom they serve as guardian. This decision was made to address the high burden of undiagnosed HIV infection among orphans and vulnerable children, and the ethical obligation to include them in potentially beneficial interventions. There are no restrictions regarding concomitant care or interventions for caregiver participation.

For male index cases, an additional eligibility criterion is that the child's mother is HIV-infected. For male clients that do not know the status of the child's mother, the index will not be randomized until maternal testing has been offered. Male clients with children whose biological mother has died are eligible.

Design considerations: Recruitment staff will aim to screen every client who passes through the clinic to accurately measure the true absolute and relative denominator of eligible adults. All approached clients will be invited to provide oral informed consent for eligibility determination and randomization. Eligibility (number of children and child HIV test history) will be assessed at recruitment, before potential participants are informed about the incentives, in order to reduce the likelihood of caregivers bringing in children of known HIV status or children who are not their own. No instances of inappropriate testing or deception were uncovered in the pilot study.

Randomization

Caregivers will be randomized immediately following determination of eligibility in order to minimize bias associated with the attrition between referred and enrolled participants, which is common in RCTs. Caregivers will be invited to select a scratch card from an opaque bag and to scratch the metallic strip to reveal their randomization arm (Figure 3). This randomization allocation technique has been used previously in this setting [25]. Minimal optional data will be collected at the time of randomization, which link scratch cards from origin to testing, including caregiver age and sex, number of children, and telephone contact number. Caregivers will be invited, but not required, to provide these data at the time of randomization; data will be collected to link caregivers to their randomization values in case the scratch card is lost. Caregivers will be called up to 3 times after randomization to schedule/reschedule enrollment and testing visits.

Randomization sequence was generated by a statistician not involved in the study using STATA 14 using the "*ralloc*" command. Scratch cards were manufactured by Scratch Off Systems (www.scratchoff.com); 800 cards were created in batches of 15 (3 cards with each of the 5 randomization arms per batch). Fixed size batches were selected instead of variable size batches to allow for batches to be fully used at each facility site to ensure relative balance of the 5 study arms within a site, and therefore balance of the sites between the 5 arms.

Blinding: Caregivers and study clinic staff will not be blinded to participant allocation post-randomization, given the nature of the incentive allocation. Study staff who are not directly involved in participant management (including study coordinators, data managers and analysts, and other co-investigators) will be blinded to participant study arm. Unblinding will be permissible in the event of adverse event reporting; participant allocation arm will be requested from the statistician who conducted the randomization.

Enrollment and Testing

Index participant enrollment: Enrollment and child testing will occur during the same visit, usually after randomization, although same-day enrollment and testing will be allowed. Caregivers will provide written consent for child testing, and given the option of having their older children (≥7 years) provide assent for study participation. Enrollment and testing visits must occur within 2 months of randomization in order to receive the FI; individual exceptions will be made to accommodate school and national holidays. Testing during weekdays and weekends is allowed. At the time of enrollment, detailed information about caregiver demographics; testing and treatment history; income and costs; and child PMTCT, health, and testing history will be collected. Participants will be also screened to determine whether they are at risk of intimate partner violence (IPV) and referred to existing clinical services as appropriate.

Child testing services: Children will be tested according to the Kenyan National HIV Testing Guidelines[26]. At the time of protocol development, children >18 months are tested by rapid HIV test kit; those who test positive during the first test kit are tested by a second rapid test kit; discrepant results are referred to an HIV care clinic for repeat of the rapid test algorithm. HIV-exposed children 0-18 months are tested using DNA PCR on a filter paper. Children diagnosed as HIV positive will be referred to the HIV care clinic of the caregiver's choice. Children who are identified as having ongoing HIV exposure (e.g. breastfeeding or lacking final confirmatory test 6 weeks post cessation of breastfeeding) will be referred to the PMTCT clinic of the caregiver's choice for continued prophylaxis and infant testing (Table 1).

Cash disbursement and accounting: FI values and travel reimbursement will be disbursed to caregivers at the end of the testing visit. Caregivers will be given the choice of receiving the incentive using mobile money transfer (transfer fees paid by the study) or in cash. Each financial transfer (cash or mobile money) will be recorded in an accounting log, and the randomization card will be collected.

Participant follow-up: Caregivers and their children who test HIV negative will not be followed beyond the testing visit. Caregivers with one or more children who test HIV positive will be contacted by phone or clinic visit at 1, 3, 6, 9, and 12 months post-diagnosis, or until linkage to care has been determined, to assess linkage to care, child treatment status, emotional coping, risk of violence, and child welfare. Any social harms noted during this follow up will be referred or reported, as appropriate, using existing systems within the Kenyan public health and legal systems.

Discontinuation, withdrawal, or allocation modification: Participants may withdraw consent for participation at any point after randomization; principal investigators may withdraw a participant from the study on a case-by-case basis if the study intervention poses a risk to the participant. Participants who withdraw consent for participation will not be contacted further by the study team. Participants who are randomized but do not complete testing within the 2-month window will be considered as non-testers and included in the final analysis.

Data collection and management

Study staff will use mobile phones and tablets to collect data. Electronic data collection improves data accuracy by eliminating the extra step of entering data from paper forms into an electronic database[27]. The program used to collect and store the data is entitled Open Data Kit (ODK) and is available as an open-source platform[28]. Data will be stored on the password-protected phone/tablet until they are uploaded through an encrypted connection to the study's secure electronic database, at which point they will be automatically deleted from the phones and no longer accessible. Weekly enrollment and testing reports will be generated to track study progress and ensure quality data collection. Study investigators will have access to the de-identified, unblinded dataset after follow-up is completed.

Outcome measures

The primary study outcomes are: 1) proportion of index cases who complete pediatric HIV testing for one or more children within 2 months of randomization and 2) time to HIV testing completion. *A priori* stratified analyses will be conducted, stratified by caregiver sex, caregiver age, and whether the caregiver has one or more than one eligible child for testing.

Sample size and power analysis

Eight hundred index cases will be randomized; given 160 adults in each of 5 randomization arms, we will have >80% power to detect a minimum of 10-20% difference in uptake between each of the arms (Table 2). Assumptions about uptake for the un-incentivized group were based on data from the previously conducted un-incentivized testing study in the same population[18]. We will have sufficient power to detect differences over a range of uptake scenarios (Table 2). All power calculations are shown using pairwise comparisons between randomization arms (e.g. $0 vs $1.25); we will have additional power for comparisons between arms with larger separation of FI values (e.g. $1.25 vs $10.00).

Statistical methods and analysis

Primary outcome analyses: We will compare the proportion of index cases bringing at least one child for testing within 2 months between groups randomized to control versus each of the 4 FI levels, using a generalized linear model (GLM) with log link and binomial or Poisson distribution, adjusting for facility. If randomization fails to balance potential confounders, we will perform the aforementioned analysis, adjusting for unbalanced confounders. We will additionally compare the time to testing between each of the 5 arms, using a stratified Cox proportional hazards regression model, which adjusts for facility in estimating a pooled hazard ratio, and adjusting for unbalanced confounders as necessary. We will conduct intent-to-treat analyses as the primary analyses. We will conduct a modified intent-to-treat analysis (removing any individuals randomized but found to be ineligible following randomization) as a sensitivity analysis. Multiple imputation will be conducted to address any data missingness in outcomes or confounders. Complete case analysis will be conducted as a sensitivity analysis.

Stratified analysis: Both primary outcome analyses will additionally be performed stratified by caregiver sex, caregiver age (above and below median age), number of eligible children (dichotomized as one child or more than one child).

Secondary analyses:

Characteristics of testers between arms: We will compare index-level and child-level characteristics between testers in each arm. We will compare the following index-case characteristics between index cases who completed testing in each arm: income, sex, partnership status, history of HIV testing and treatment, and number of eligible children in the house. We will use GLM and control for facility. We will compare the following characteristics between children who were tested in each arm: sex, history of HIV testing, number of eligible children in the house, and sibling HIV status. We will use generalized linear mixed models (GLMM), clustering on index case and controlling for facility.

Differences in uptake based on proportion of clients eligible: We will test the association between the proportion of clients eligible for randomization in a facility and uptake of testing across incentive values. We

hypothesize that sites with fewer eligible clients will have lower levels of uptake across incentive values than sites with a greater proportion of eligible clients. This is hypothesized because sites with a lower proportion of eligible index cases have likely already benefitted from interventions to motivate those individuals who are "willing to test" to "take action" (Figure 1), leaving a disproportionate number of index cases who are "unwilling to test," a population that is less susceptible to an FI intervention.

ETHICS AND DISSEMINATION

Ethical considerations

FI, while commonly used to motivate various health behaviors, also commonly raise ethical concerns related coercion, undue inducement, and lack of voluntariness. The study team engaged in discussions with Kenyan pediatricians and other health care workers, Kenyan program implementers, and with Treuman Katz Center for Pediatric Bioethics (Seattle Children's Hospital) in the US. The bioethics consultation offered several clarifying points, which are described elsewhere[24].

This study was reviewed and approved by University of Washington Institutional Review Board (UW IRB) and Kenyatta National Hospital Ethics and Research Committee (KNH ERC). It is registered on ClinicalTrials.gov (NCT03049917). A data monitoring committee will not be convened due to no planned interim analyses and minimal risk potential of the intervention.

Trial status

This trial began recruitment and enrollment on January 31, 2017. It is anticipated to close recruitment in July 2018 and enrollment in September 2018.

Dissemination plans

We will plan to share trial results with health care workers at study sites, regional and national policymakers, and with patient populations at study sites (regardless of enrollment in the trial). We have deposited the full protocol on a publically available website through the National Clinical Trials registry. We will utilize the International Committee of Medical Journal Editors (ICMJE) criteria for authorship and will not hire professional writers.

DISCUSSION

FI have been effective to promote a variety of desired health behaviors, including adult and adolescent HIV testing. It is important to assess whether this intervention is effective to promote timely uptake of pediatric ICT in sub-Saharan African settings where HIV-related morbidity and mortality remain high for undiagnosed children. This study is the first that we are aware of to test FI to improve uptake of ICT for children.

The pilot study conducted by this team evaluated 3 levels of FI and saw high, but flat, uptake of testing across the study arms[23]. Therefore, the larger trial will evaluate a wider and lower range of FI, including a non-incentivized control arm. This 5-arm RCT with a concurrent control arm will enable inference about the effect of FIs generally, and at various levels, to promote timely uptake of pediatric ICT.

This study has faced several operational challenges to date. The Kenyan public health system has faced two large nationwide healthcare worker strikes (doctors' strike from December 2016 through February 2017; nurses' strike from May through November 2017), which limited the number of patients presenting for services. Additionally, there was a contested presidential election in August 2017 and a contested repeat election in October 2017, which produced widespread disruption of service provision. To overcome these challenges, the study increased the number of sites enrolling concurrently to achieve the desired sample size.

Study limitations

The study sites represent one geographical region in Kenya, which may not be generalizable to other settings with lower HIV prevalence or different social dynamics, including HIV-related stigma. Clinics will be chosen to maximize the number of clients enrolled, and therefore will represent mostly high-volume sites; volume of clinic is not expected to influence uptake of testing, but any bias that might occur as a result of clinic selection would likely apply equally to all 5 randomization arms, influencing absolute but not relative estimates of uptake. Kenya has had widespread ICT campaigns nationwide in the past 4 years, leaving relatively few individuals in care with undiagnosed children in their care; the impact of FI might be expected to differ in a population of HIV-infected caregivers who were ICT naïve. This trial does not include qualitative work to investigate the mechanism of FI. Finally, this intervention targets children ages 0-12 years for testing; however, many HIV-

infected adults report having adolescent children (age ≥13) of unknown HIV status at home[23], who were not eligible for the current trial. Alternative strategies to target and provide acceptable and accessible HIV testing services to adolescents are critically needed.

CONCLUSION

In summary, this large multi-site RCT will produce robust data on the effect and cost-effectiveness of varying levels of FI on uptake of pediatric ICT. Additionally, this paper describes design considerations and lessons learned that can be broadly informative in the design of pediatric HIV trials as well as the design of FI trials.

Author contributions

INN and JAS are the principal investigators and supervised the trial protocol development and implementation. ADW, INN, JN, RB, JBB, CL, EMO, DCW, GJS, and JAS participated in designing the trial and data collection tools. VOO and VAO coordinated the study and collected study data. ADW, INN, GJS, and JAS are responsible for the statistical design of the trial and data analysis. ADW, INN, and JAS wrote the first draft of the manuscript. All authors critically revised, read, and approved the final manuscript.

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TABLES & FIGURE LEGENDS

Figure 1: Conceptual framework: Financial incentives (FI) may motivate caregivers who are willing to test to move to take action to test. However, they are unlikely to motivate caregivers who are unwilling to test to take action. Social services (SS) interventions may be needed to move those parents who are unwilling to test to take action.

Figure 2: CONSORT diagram

Figure 3: Randomization scratch card before randomization arm reveal

Table 1: *Adapted Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Diagram*

	STUDY PERIOD	
	Enrolment & Allocation	Close-out
TIMEPOINT**	*0*	t_1
ENROLMENT:		
Informed consent	X	
Eligibility screen	X	
Randomization	X	
INTERVENTIONS:		
$0 (control arm)		
$1.25		
$2.50		
$5.00		
$10.00		
ASSESSMENTS:		
Caregiver sex and number of children	X	
Testing for 1+ children		X
Sociodemographics, HIV testing and treatment history, costs		X

Table 2: *Power calculations*

No incentive	Power	$1.25 USD	Power	$2.50 USD	Power	$5.00 USD	Power	$10.00 USD
13%	>99%	40%	95%	60%	98%	80%	71%	90%
13%	96%	30%	96%	50%	96%	70%	90%	85%
13%	84%	26%	82%	40%	95%	60%	82%	75%
13%	39%	20%	54%	30%	96%	50%	78%	65%

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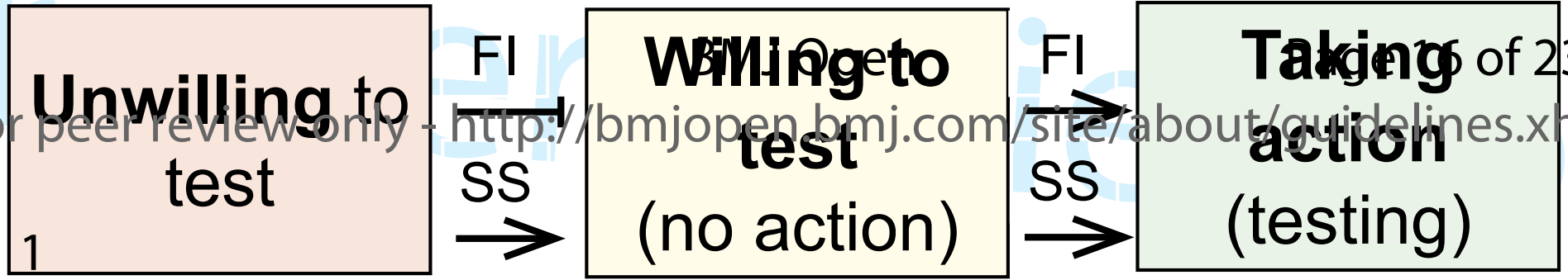

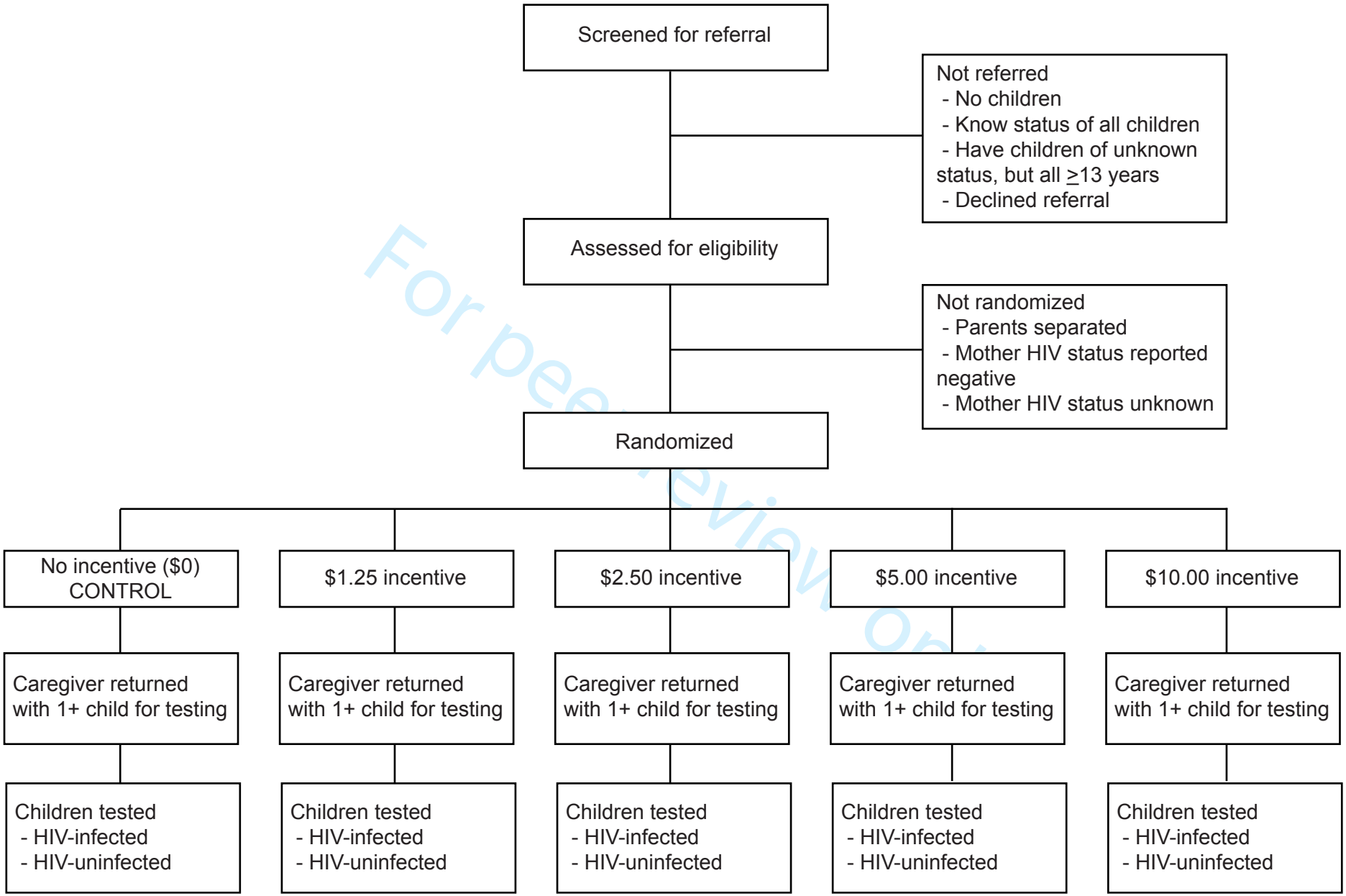


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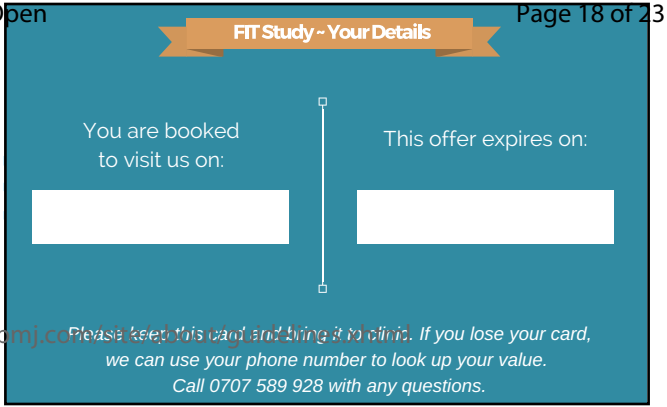
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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	confirmed
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1&11
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	5-6
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4&5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5, 6, 7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8&9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7&8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8&9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8&9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6&7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	10
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Financial Incentives to Increase Uptake of Pediatric HIV Testing (FIT): Study Protocol for a Randomized Controlled Trial in Kenya

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Keywords:	pediatric HIV testing, index case testing, financial incentive, conditional cash transfer, protocol

Financial Incentives to Increase Uptake of Pediatric HIV Testing (FIT): Study Protocol for a Randomized Controlled Trial in Kenya

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Running head: Financial incentives for child HIV testing

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Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the sponsors. The sponsors gave feedback to the study investigators during the trial design phase, but did not make the ultimate decision about study design. The sponsors do not have any role in the study data collection, management, analysis and interpretation, writing of reports, nor decisions to submit reports for publication.

Competing interests: The authors have no conflicts of interests to declare.

WORD COUNT: Abstract 297/300, Manuscript 3,999/4,000

ABSTRACT (297/300)

Introduction: Index case testing (ICT) to identify HIV-infected children is efficient but has suboptimal uptake. Financial incentives (FI) have overcome financial barriers in other populations by offsetting direct and indirect costs. A pilot study found FI to be feasible for motivating pediatric ICT among HIV-infected female caregivers. This randomized trial will determine the effectiveness of FI to increase uptake of pediatric ICT.

Methods and analysis: The FIT trial is a 5-arm, unblinded, randomized controlled trial to determine whether FI increase timely uptake of pediatric ICT. The trial will be conducted in multiple public health facilities in western Kenya. Each HIV-infected adult enrolled in HIV care will be screened for eligibility: primary caregiver to one or more children of unknown HIV status ages 0-12 years. Eligible caregivers will be individually randomized at the time of recruitment in equal 1:1:1:1:1 allocation to one of five arms ($0 [control], $1.25, $2.50, $5.00, and $10.00 USD). The trial aims to randomize 800 caregivers. Incentives will be disbursed at the time of child HIV testing using mobile money transfer or cash. Arms will be compared in terms of the proportion of adults who complete testing for at least one child within 2 months of randomization and time to testing. A cost-effectiveness analysis of FI for pediatric ICT will also be conducted.

Ethics and dissemination: This study was reviewed and approved by the University of Washington Institutional Review Board (UW IRB) and the Kenyatta National Hospital Ethics and Research Committee (KNH ERC). Trial results will be disseminated to health care workers at study sites, regional and national policymakers, and with patient populations at study sites (regardless of enrollment in the trial). Randomized trials of caregiver-child FI interventions pose unique study design, ethical, and operational challenges, detailed here as a resource for future investigations.

Registration details: ClinicalTrials.gov NCT03049917 (First posted February 10, 2017)

Version: Protocol version 4.0, February 18, 2018

Keywords: pediatric HIV testing, index case testing, financial incentive, conditional cash transfer, protocol

ARTICLE SUMMARY

Strengths and limitations of this study

- The 5-arm individual-level randomized design with a concurrent control arm will enable a rigorous comparison of pediatric HIV testing uptake between incentivized and un-incentivized groups, controlling for background temporal trends.
- The inclusion of four levels of financial incentives (FI) will allow for the direct comparison of uptake between different levels of FI and identify any asymptotic relationships in the dose-response curve.
- Study staff will aim to randomize all eligible clients very early at the time of first contact to minimize selection bias that is common in randomized trials.
- Randomization will utilize a scratch card approach to allow for conceptual transparency in the randomization process; FI are disbursed using mobile money transfer technology to reflect the dominant banking practices in a Kenyan setting.
- Trial sites are in western Kenya where pediatric index case testing campaigns have already had high penetration; incentives may have a different effect in settings where such campaigns have been less common.

INTRODUCTION

Perinatally-acquired HIV infection is associated with high morbidity and mortality[1]. While prompt initiation of antiretroviral therapy (ART) reduces mortality and morbidity and promotes growth and development[2-6], delayed diagnosis and treatment until a child is severely ill limits the benefits of ART[7-9]. Global scale up of prevention of mother-to-child-transmission of HIV (PMTCT) systems have markedly reduced the number of new infant HIV infections[10]. However, many older HIV-infected children remain undiagnosed, either through PMTCT drop out or due to infant infections attributable to incident maternal infection during pregnancy or postpartum[11] when HIV incidence is high[12] and repeat maternal HIV testing is low[13 14]. Infant infections due to incident maternal infection are often missed by traditional prevention and early infant diagnosis systems [15].

Index case testing (ICT), whereby the children of an HIV-infected adult (the "index case") receiving HIV care are tested for HIV, is an efficient approach to case detection with high prevalence among children tested, but uptake remains sub-optimal[16 17]. In a previous study in Nairobi, only 14% of adults offered systematic pediatric ICT had their child tested for HIV[18]; in this study, barriers to pediatric HIV testing included structural, interpersonal, emotional, logistical, and financial issues[19]. Previous studies have addressed interpersonal and emotional barriers through assisted disclosure and support group interventions[20], systems-level barriers through medical record flags[21], and logistical barriers through offering a choice of home- or clinic-based testing[17 18]. However, these approaches may be expensive and rely on additional health care workers. In the context of limited health resources, approaches that minimize costs and maximize uptake are needed. A recent randomized trial showed that small financial incentives (FI) ($2USD) were successful in increasing uptake of HIV testing among children and adolescents ages 8-17 years, using a community-based recruitment approach[22]. Our team recently completed a feasibility pilot study of small FI to motivate uptake of pediatric ICT[23], but there have been no studies to date that have evaluated the effectiveness of FI to increase the uptake of pediatric ICT.

There are several unique ethical, logistical, and analytic challenges in designing a study to assess the effectiveness of incentivizing caregivers to complete HIV testing for their children. Ethical concerns, including randomizing a person of authority to act on another's behalf, assessing child-caregiver relationships to avoid inadvertent disclosure of maternal HIV status, ensuring child's well-being is not compromised, and reducing risks of social harms have been addressed elsewhere[24]. Logistically and analytically, there are unique challenges in managing FI randomization and disbursement, minimizing the drop-off between recruitment and randomization, minimizing contamination effects leading to presentation of ineligible individuals, and accounting for competing interventions in the region.

This study–Financial Incentives to Increase Uptake of Pediatric HIV Testing (FIT)–is a randomized controlled trial to determine whether FI increases uptake of pediatric ICT, and determine the cost-effectiveness of various levels of FI. This paper details the study protocol and describes design considerations specific to trials incentivizing pediatric testing.

METHODS AND ANALYSIS

Conceptual framework

FI may motivate parents who are willing to test to take action to test by either offsetting costs or by motivating more prompt action. Unwilling parents, who face extreme fear or real dangers from revealing their HIV status may not be motivated by FI to take action to test. Social services (SS)—including enhanced counseling and peer support groups—may help parents move from unwilling to willing. Hypothesis: We hypothesize that the proposed FI intervention will primarily move willing parents from "Willing to test" to "Taking action" (Figure 1).

Pilot study

A pilot study (NCT02931422) was conducted between October 2016 and January 2017. In the pilot study (N=60), values of $5, $10, and $15 USD were tested; these were based on cost data from a previous pediatric ICT study conducted by the same team in Nairobi[18]. The lowest incentive value reflected the 75th percentile of direct non-medical costs (transportation, childcare, and food/drink outside the home), the middle value reflected the 75th percentile of direct non-medical and indirect costs (lost wages from paid and unpaid work), and the highest value reflected the direct costs, indirect costs, and a second day of lost wages[23].

Study design

The FIT trial is a 5-arm, unblinded, individual-level, superiority randomized controlled trial (RCT) of FI. Eligible individuals will be randomized using a 1:1:1:1:1 allocation to no incentive, $1.25, $2.50, $5.00, or $10.00 2016 USD (Figure 2). Randomized individuals can redeem the value of their incentive upon completing testing with study staff within 2 months of randomization. The study will employ a roving, multi-site model in which multiple clinic sites run concurrently, but each site will only be active for recruitment for 2 months. This model was selected to limit the extent to which clients at the facilities became aware of the FI opportunity through word of mouth, to limit the number of clients screened more than once (as most clients visit the clinic every 3 months), and to allow for sampling approximately proportional to facility size.

Design Considerations: Alternative study designs that included historic and lead-in control periods, as well as cluster randomization were considered, but ultimately not selected. Historic and lead-in control periods from within the same study sites could have suffered from depletion of susceptibles, in which the virtually fixed target population of index cases decreases over time as the most susceptible individuals experience the outcome of interest (e.g. complete ICT for their children). While new individuals are diagnosed with HIV each day, the rate at which those individuals are added to the population in care is slow relative to the number of individuals active in care at the beginning of a study. Additionally, there are many events—rapid HIV testing campaigns, school holidays, guideline changes—that could have occurred during either the control or intervention periods and led to temporal trends that could not be robustly controlled for. A concurrent control arm was considered to limit the extent to which these temporal and epidemiologic trends would impact the estimation of the effect of FI on testing.

A cluster RCT (cRCT) was also considered, which would have limited contamination; in the context of this study, contamination would have been the extent to which individuals within a clinic became aware of the other values of FI being offered and discouraged by receiving less than the maximum FI value. However, a cRCT design for a 5-arm trial would have required a prohibitively large number of clinics to detect meaningful differences in uptake, which was not feasible.

Determination of incentive values

Trial incentive values: Incentive values were determined using results from the FIT pilot study described above[23]. Uptake of testing in the pilot study was high and comparable between the 3 arms (75%, 70%, 75% across arms, respectively)[23]. Because it was unclear whether uptake was similar across the pilot study FI values because we had reached the top of the demand curve (e.g. where even higher FI would yield no increase in testing) or whether we were clustered in the middle of a demand curve (whereby higher or lower values would provide further differences in testing uptake), we decided to widen the range of FI values to remove the highest value and include lower values.

The trial incentive values will be $1.25, $2.50, $5.00, and $10.00, and a control with no FI ($0). Participants will be compensated and additional $3.00 for transportation costs regardless of arm; this reimbursement will be included to ensure more equitable benefit for those in the control arm for research participation, and will not be described to participants prior to the testing visit in order to not act as an additional incentive.

Incentive Considerations: Alternative formats of incentives were considered, including lottery-based incentives and non-financial incentives such as household items or agricultural items. Lottery-based incentives were considered less acceptable by some co-investigators due to a perception that this was similar to gambling, which has a negative connotation for some religious groups in Kenya. Agricultural and household items (and non-financial commodities in general) were felt to be more attractive for those living in rural settings, but had additional costs involved in procurement, distribution, and tracking of commodities, which would increase program costs. Cash or mobile money transfer was thus adopted as the most fungible, widely-acceptable, accountable, and low-cost FI format to deliver in the context of an intervention.

Patient and Public Involvement:

The research intervention and outcome were informed by formative research with the patient population: the concept of FI emerged from qualitative and quantitative work with patients [19]; the value and format of the FI were reviewed by patients during the pilot [23]. Site specific, and overall, study results will be shared with the research facilities in closeout meetings; we do not have ethical permission to re-contact individual study participants to share study results.

Study sites

The trial will be conducted at several government health facilities in western Kenya, including facilities in Kisumu, Siaya, and Homa Bay counties. Study team members will simultaneously operate up to 3 sites, and then relocate to new sites following 2 months of recruitment. Facilities will be selected one to two months in advance and approved by the county health director's office and facility heads. Sites will be selected based on high volume of adults in HIV care and relatively low penetration of recent pediatric ICT campaigns or programs. A full list of study sites will be provided in the trial results manuscript.

Recruitment processes & eligibility criteria

Index adult clients attending the HIV care clinics will be screened by study staff to determine eligibility: being HIV-infected and having one or more children of unknown HIV status ages 0-12 years. Children will be considered of unknown status if they have never been tested for HIV or tested negative during infancy but did not complete confirmatory negative testing after 18 months or following cessation of breastfeeding. Index client caregivers will be allowed to test any child formally in their care, both biological children and children to whom they serve as guardian. This decision was made to address the high burden of undiagnosed HIV infection among orphans and vulnerable children, and the ethical obligation to include them in potentially beneficial interventions. There are no restrictions regarding concomitant care or interventions for caregiver participation.

For male index cases, an additional eligibility criterion is that the child's mother is HIV-infected. For male clients that do not know the status of the child's mother, the index will not be randomized until maternal testing has been offered. Male clients with children whose biological mother has died are eligible.

Design considerations: Recruitment staff will aim to screen every client who passes through the clinic to accurately measure the true absolute and relative denominator of eligible adults. All approached clients will be invited to provide oral informed consent for eligibility determination and randomization. Eligibility (number of children and child HIV test history) will be assessed at recruitment, before potential participants are informed about the incentives, in order to reduce the likelihood of caregivers bringing in children of known HIV status or children who are not their own. No instances of inappropriate testing or deception were uncovered in the pilot study.

Randomization

Caregivers will be randomized immediately following determination of eligibility in order to minimize bias associated with the attrition between referred and enrolled participants, which is common in RCTs. Caregivers will be invited to select a scratch card from an opaque bag and to scratch the metallic strip to reveal their randomization arm (Figure 3). This randomization allocation technique has been used previously in this setting [25]. Minimal optional data will be collected at the time of randomization, which link scratch cards from origin to testing, including caregiver age and sex, number of children, and telephone contact number. Caregivers will be invited, but not required, to provide these data at the time of randomization; data will be collected to link caregivers to their randomization values in case the scratch card is lost. Caregivers will be called up to 3 times after randomization to schedule/reschedule enrollment and testing visits.

Randomization sequence was generated by a statistician not involved in the study using STATA 14 using the "*ralloc*" command. Scratch cards were manufactured by Scratch Off Systems (www.scratchoff.com); 800 cards were created in batches of 15 (3 cards with each of the 5 randomization arms per batch). Fixed size batches were selected instead of variable size batches to allow for batches to be fully used at each facility site to ensure relative balance of the 5 study arms within a site, and therefore balance of the sites between the 5 arms.

Blinding: Caregivers and study clinic staff will not be blinded to participant allocation post-randomization, given the nature of the incentive allocation. Study staff who are not directly involved in participant management (including study coordinators, data managers and analysts, and other co-investigators) will be blinded to participant study arm. Unblinding will be permissible in the event of adverse event reporting; participant allocation arm will be requested from the statistician who conducted the randomization.

Enrollment and Testing

Index participant enrollment: Enrollment and child testing will occur during the same visit, usually after randomization, although same-day enrollment and testing will be allowed. Caregivers will provide written consent for child testing, and given the option of having their older children (≥7 years) provide assent for study participation. Enrollment and testing visits must occur within 2 months of randomization in order to receive the FI; individual exceptions will be made to accommodate school and national holidays. Testing during weekdays and weekends is allowed. At the time of enrollment, detailed information about caregiver demographics; testing and treatment history; income and costs; and child PMTCT, health, and testing history will be collected. Participants will be also screened to determine whether they are at risk of intimate partner violence (IPV) and referred to existing clinical services as appropriate.

Child testing services: Children will be tested according to the Kenyan National HIV Testing Guidelines[26]. At the time of protocol development, children >18 months are tested by rapid HIV test kit; those who test positive during the first test kit are tested by a second rapid test kit; discrepant results are referred to an HIV care clinic for repeat of the rapid test algorithm. HIV-exposed children 0-18 months are tested using DNA PCR on a filter paper. Children diagnosed as HIV positive will be referred to the HIV care clinic of the caregiver's choice. Children who are identified as having ongoing HIV exposure (e.g. breastfeeding or lacking final confirmatory test 6 weeks post cessation of breastfeeding) will be referred to the PMTCT clinic of the caregiver's choice for continued prophylaxis and infant testing (Table 1).

Cash disbursement and accounting: FI values and travel reimbursement will be disbursed to caregivers at the end of the testing visit. Caregivers will be given the choice of receiving the incentive using mobile money transfer (transfer fees paid by the study) or in cash. Each financial transfer (cash or mobile money) will be recorded in an accounting log, and the randomization card will be collected.

Participant follow-up: Caregivers and their children who test HIV negative will not be followed beyond the testing visit. Caregivers with one or more children who test HIV positive will be contacted by phone or clinic visit at 1, 3, 6, 9, and 12 months post-diagnosis, or until linkage to care has been determined, to assess linkage to care, child treatment status, emotional coping, risk of violence, and child welfare. Any social harms noted during this follow up will be referred or reported, as appropriate, using existing systems within the Kenyan public health and legal systems.

Discontinuation, withdrawal, or allocation modification: Participants may withdraw consent for participation at any point after randomization; principal investigators may withdraw a participant from the study on a case-by-case basis if the study intervention poses a risk to the participant. Participants who withdraw consent for participation will not be contacted further by the study team. Participants who are randomized but do not complete testing within the 2-month window will be considered as non-testers and included in the final analysis.

Data collection and management

Study staff will use mobile phones and tablets to collect data. Electronic data collection improves data accuracy by eliminating the extra step of entering data from paper forms into an electronic database[27]. The program used to collect and store the data is entitled Open Data Kit (ODK) and is available as an open-source platform[28]. Data will be stored on the password-protected phone/tablet until they are uploaded through an encrypted connection to the study's secure electronic database, at which point they will be automatically deleted from the phones and no longer accessible. Weekly enrollment and testing reports will be generated to track study progress and ensure quality data collection. Study investigators will have access to the de-identified, unblinded dataset after follow-up is completed.

Outcome measures

The primary study outcomes are: 1) proportion of index cases who complete pediatric HIV testing for one or more children within 2 months of randomization and 2) time to HIV testing completion. *A priori* stratified analyses will be conducted, stratified by caregiver sex, caregiver age, and whether the caregiver has one or more than one eligible child for testing.

Sample size and power analysis

Eight hundred index cases will be randomized; given 160 adults in each of 5 randomization arms, we will have >80% power to detect a minimum of 10-20% difference in uptake between each of the arms (Table 2). Assumptions about uptake for the un-incentivized group were based on data from the previously conducted un-incentivized testing study in the same population[18]. We will have sufficient power to detect differences over a range of uptake scenarios (Table 2). All power calculations are shown using pairwise comparisons between randomization arms (e.g. $0 vs $1.25); we will have additional power for comparisons between arms with larger separation of FI values (e.g. $1.25 vs $10.00).

Statistical methods and analysis

<u>*Primary outcome analyses:*</u> We will compare the proportion of index cases bringing at least one child for testing within 2 months between groups randomized to control versus each of the 4 FI levels, using a generalized linear model (GLM) with log link and binomial or Poisson distribution, adjusting for facility. If randomization fails to balance potential confounders, we will perform the aforementioned analysis, adjusting for unbalanced confounders. We will additionally compare the time to testing between each of the 5 arms, using a stratified Cox proportional hazards regression model, which adjusts for facility in estimating a pooled hazard ratio, and adjusting for unbalanced confounders as necessary. Primary outcome analyses will include a Hochberg's adjustment to p-values to address multiplicity. We will conduct intent-to-treat analyses as the primary analyses. We will conduct a modified intent-to-treat analysis (removing any individuals randomized but found to be ineligible following randomization) as a sensitivity analysis. Multiple imputation will be conducted to address any data missingness in outcomes or confounders. Complete case analysis will be conducted as a sensitivity analysis.

<u>*Stratified analysis:*</u> Both primary outcome analyses will additionally be performed stratified by caregiver sex, caregiver age (above and below median age), number of eligible children (dichotomized as one child or more than one child). These analyses will include a Hochberg's adjustment to p-values to address multiplicity.

Secondary analyses:

Characteristics of testers between arms: We will compare index-level and child-level characteristics between testers in each arm. We will compare the following index-case characteristics between index cases who completed testing in each arm: income, sex, partnership status, history of HIV testing and treatment, and number of eligible children in the house. We will use GLM and control for facility. We will compare the following characteristics between children who were tested in each arm: sex, history of HIV testing, number of eligible children in the house, and sibling HIV status. We will use generalized linear mixed models (GLMM), clustering on index case and controlling for facility.

Differences in uptake based on proportion of clients eligible: We will test the association between the proportion of clients eligible for randomization in a facility and uptake of testing across incentive values. We hypothesize that sites with fewer eligible clients will have lower levels of uptake across incentive values than sites with a greater proportion of eligible clients. This is hypothesized because sites with a lower proportion of eligible index cases have likely already benefitted from interventions to motivate those individuals who are "willing to test" to "take action" (Figure 1), leaving a disproportionate number of index cases who are "unwilling to test," a population that is less susceptible to an FI intervention.

ETHICS AND DISSEMINATION

Ethical considerations

FI, while commonly used to motivate various health behaviors, also commonly raise ethical concerns related coercion, undue inducement, and lack of voluntariness. The study team engaged in discussions with Kenyan pediatricians and other health care workers, Kenyan program implementers, and with Treuman Katz Center for Pediatric Bioethics (Seattle Children's Hospital) in the US. The bioethics consultation offered several clarifying points, which are described elsewhere[24].

This study was reviewed and approved by University of Washington Institutional Review Board (UW IRB) and Kenyatta National Hospital Ethics and Research Committee (KNH ERC). It was first posted on ClinicalTrials.gov (NCT03049917) on February 10, 2017, This slight delay occurred as we initially attempted to register both the pilot and trial phases of the study as two protocols under one record, but this was ultimately deemed infeasible and confusing, so the trial phase was registered as a separate record. A data monitoring committee will not be convened due to no planned interim analyses and minimal risk potential of the intervention. A steering/management committee was not deemed applicable in this trial.

Trial status

This trial began recruitment and enrollment on January 31, 2017. It is anticipated to close recruitment in July 2018 and enrollment in September 2018.

Dissemination plans

We will plan to share trial results with health care workers at study sites, regional and national policymakers, and with patient populations at study sites (regardless of enrollment in the trial). We have deposited the full protocol on a publically available website through the National Clinical Trials registry. We will utilize the International Committee of Medical Journal Editors (ICMJE) criteria for authorship and will not hire professional writers.

DISCUSSION

FI have been effective to promote a variety of desired health behaviors, including adult and adolescent HIV testing. It is important to assess whether this intervention is effective to promote timely uptake of pediatric ICT in sub-Saharan African settings where HIV-related morbidity and mortality remain high for undiagnosed children. This study is the first that we are aware of to test FI to improve uptake of ICT for children.

The pilot study conducted by this team evaluated 3 levels of FI and saw high, but flat, uptake of testing across the study arms[23]. Therefore, the larger trial will evaluate a wider and lower range of FI, including a non-incentivized control arm. This 5-arm RCT with a concurrent control arm will enable inference about the effect of FIs generally, and at various levels, to promote timely uptake of pediatric ICT.

This study has faced several operational challenges to date. The Kenyan public health system has faced two large nationwide healthcare worker strikes (doctors' strike from December 2016 through February 2017; nurses' strike from May through November 2017), which limited the number of patients presenting for services. Additionally, there was a contested presidential election in August 2017 and a contested repeat election in October 2017, which produced widespread disruption of service provision. To overcome these challenges, the study increased the number of sites enrolling concurrently to achieve the desired sample size.

Study limitations

The study sites represent one geographical region in Kenya, which may not be generalizable to other settings with lower HIV prevalence or different social dynamics, including HIV-related stigma. Clinics will be chosen to maximize the number of clients enrolled, and therefore will represent mostly high-volume sites; volume of clinic is not expected to influence uptake of testing, but any bias that might occur as a result of clinic selection would likely apply equally to all 5 randomization arms, influencing absolute but not relative estimates of uptake. Kenya has had widespread ICT campaigns nationwide in the past 4 years, leaving relatively few individuals in

care with undiagnosed children in their care; the impact of FI might be expected to differ in a population of HIV-infected caregivers who were ICT naïve. This trial does not include qualitative work to investigate the mechanism of FI. Finally, this intervention targets children ages 0-12 years for testing; however, many HIV-infected adults report having adolescent children (age ≥13) of unknown HIV status at home[23], who were not eligible for the current trial. Alternative strategies to target and provide acceptable and accessible HIV testing services to adolescents are critically needed.

CONCLUSION

In summary, this large multi-site RCT will produce robust data on the effect and cost-effectiveness of varying levels of FI on uptake of pediatric ICT. Additionally, this paper describes design considerations and lessons learned that can be broadly informative in the design of pediatric HIV trials as well as the design of FI trials.

Author contributions

INN and JAS are the principal investigators and supervised the trial protocol development and implementation. ADW, INN, JN, JBB, EMO, DCW, GJS, and JAS participated in designing the trial and data collection tools. VOO and VAO coordinated the study and collected study data. ADW, INN, GJS, and JAS are responsible for the statistical design of the trial and data analysis. ADW, INN, and JAS wrote the first draft of the manuscript. All authors critically revised, read, and approved the final manuscript.

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TABLES & FIGURE LEGENDS

Figure 1: Conceptual framework: Financial incentives (FI) may motivate caregivers who are willing to test to move to take action to test. However, they are unlikely to motivate caregivers who are unwilling to test to take action. Social services (SS) interventions may be needed to move those parents who are unwilling to test to take action.

Figure 2: CONSORT diagram

Figure 3: Randomization scratch card before randomization arm reveal

Table 1: *Adapted Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Diagram*

	STUDY PERIOD	
	Enrolment & Allocation	Close-out
TIMEPOINT**	*0*	t_1
ENROLMENT:		
Informed consent	X	
Eligibility screen	X	
Randomization	X	
INTERVENTIONS:		
$0 (control arm)		
$1.25		
$2.50		
$5.00		
$10.00		
ASSESSMENTS:		
Caregiver sex and number of children	X	
Testing for 1+ children		X
Sociodemographics, HIV testing and treatment history, costs		X

Table 2: *Power calculations*

No incentive	Power	$1.25 USD	Power	$2.50 USD	Power	$5.00 USD	Power	$10.00 USD
13%	>99%	40%	95%	60%	98%	80%	71%	90%
13%	96%	30%	96%	50%	96%	70%	90%	85%
13%	84%	26%	82%	40%	95%	60%	82%	75%
13%	39%	20%	54%	30%	96%	50%	78%	65%

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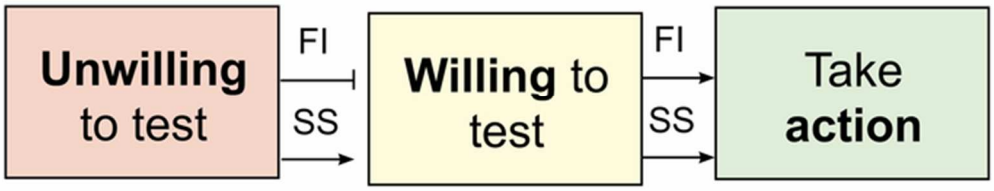

Figure 1: Conceptual framework: Financial incentives (FI) may motivate caregivers who are willing to test to move to take action to test. However, they are unlikely to motivate caregivers who are unwilling to test to take action. Social services (SS) interventions may be needed to move those parents who are unwilling to test to take action.

29x5mm (600 x 600 DPI)

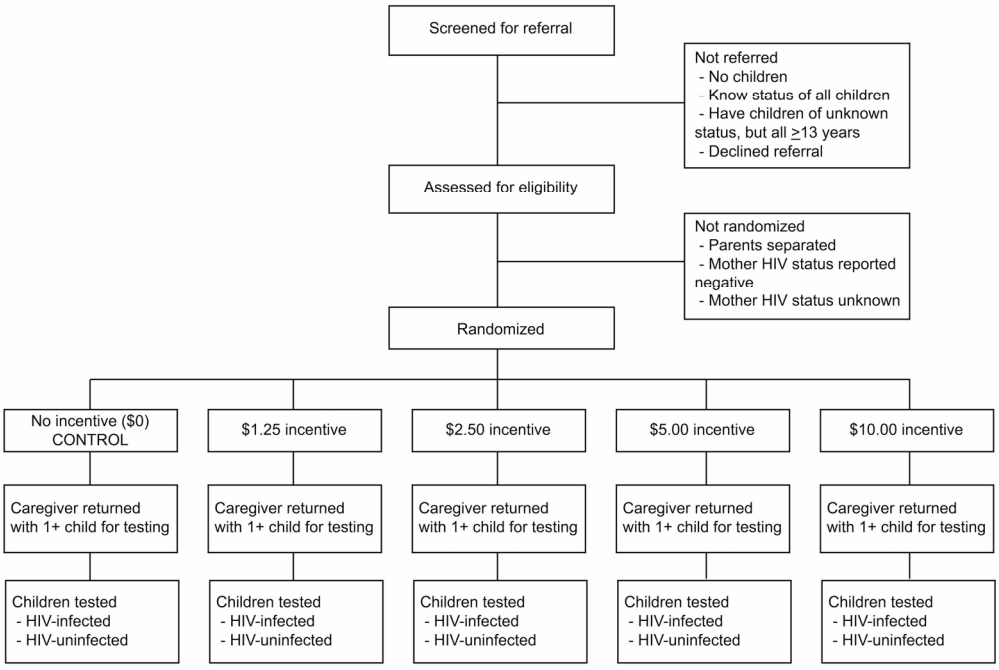

Figure 2: CONSORT diagram

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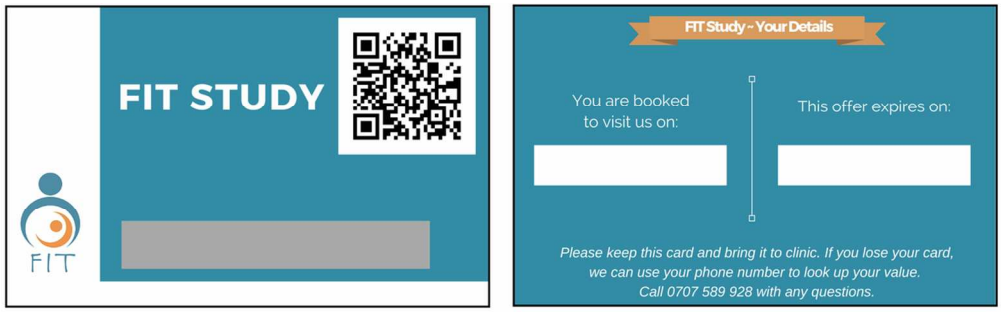

Figure 3: Randomization scratch card before randomization arm reveal

54x16mm (600 x 600 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	confirmed
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1&11
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	5-6
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4&5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5, 6, 7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8&9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7&8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8&9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8&9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6&7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	10
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.