Investigating interventions to increase uptake of HIV testing and linkage to care or prevention for male partners of pregnant women in antenatal clinics in Blantyre, Malawi

Augustine Talumba Choko

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Department of Infectious Disease Epidemiology

Faculty of Epidemiology and Population Health

London School of Hygiene & Tropical Medicine

Funder: Wellcome Trust, UK

Supervisor: Professor Katherine Fielding
Professor of Medical Statistics
Department of Infectious Disease Epidemiology
Faculty of Epidemiology and Population Health
London School of Hygiene & Tropical Medicine

Co-supervisor: Professor Liz Corbett
Professor of Tropical Epidemiology
Department of Clinical Research
Faculty of Infectious and Tropical Diseases
London School of Hygiene & Tropical Medicine

Other advisory committee members:

Professor Nigel Stallard
Professor of Medical Statistics
Statistics and Epidemiology Group
Warwick Medical School
University of Warwick

Dr Nicola Desmond
Medical Anthropologist
Department of Clinical Sciences
Liverpool School of Tropical Medicine

Dr Aurelia Lepine
Lecturer in Health Economics
Department of Global Health and Development
Faculty of Public Health and Policy
London School of Hygiene & Tropical Medicine

Collaborating institutions:

1. Malawi Liverpool Wellcome Trust Clinical Research Programme (MLW), Malawi
2. London School of Hygiene and Tropical Medicine (LSHTM), UK
3. Liverpool School of Tropical Medicine (LSTM), UK
4. Warwick Medical School (WMS), UK
5. Blantyre District Health Office, Malawi
6. World Health Organisation

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Full name: **AUGUSTINE TALUMBA CHOKO** Student ID: **REPH246459**

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Thesis Abstract

Improved availability of HIV tests has led to increases in numbers testing and starting treatment in sub-Saharan Africa. Despite such remarkable progress, men continue to lag behind in HIV testing in the region including men in well-established heterosexual relationships, in which context HIV transmission is surprisingly high. We previously found HIV self-testing (HIVST) to be very effective at increasing the uptake of HIV testing in the general population in urban Blantyre, Malawi. This PhD investigated the effect of partner-delivered HIVST, providing HIVST kits to pregnant women in antenatal clinics (ANC) with or without additional interventions, including financial incentives, on uptake of testing and linkage to care or prevention. The PhD is made up of three main pieces of work:

First, a systematic review was conducted to investigate the existing evidence regarding the effectiveness of *demand-side* (given to users) financial incentives on linkage to HIV treatment or voluntary medical male circumcision (VMMC) in low and middle income (LMIC) countries. Relevant electronic databases and conference proceedings were searched for randomised controlled trials. Seven trials were identified out of 1099 citations, with all showing significant improvement in linkage: four investigated VMMC and three investigated ART. Manuscript currently under review.

Secondly, a formative study was carried out to identify additional potential interventions and to refine interventions identified as promising through the systematic review, before being tested in a subsequent trial. Undertaking this formative study ensured that interventions being considered for inclusion in the trial design were adapted to the local environment and prevailing social norms, by seeking input and feedback from would-be users of the service. Paper published in J Int AIDS Soc, 2017.

Thirdly, a multi-arm two-stage cluster-randomised trial was conducted in Blantyre, Malawi. The paper describing the trial design is published in Trials, 2017; trial results manuscript is under review. Antenatal care clinic days were randomized to standard of care (SOC: personalised invitation to male friendly clinic for standard HIV testing and fast-track referral for HIV treatment or VMMC services) or one of five intervention arms: SOC plus two partner-delivered self-test kits with a) no addition, or financial incentives of b) US$3, c) US$10, d) lottery (10% chance of winning $30), or e) phone call. All incentives were conditional on attending the male friendly clinic. The primary outcome at 28 days, measured through attendance at the male friendly clinic, was: referral for antiretroviral therapy (ART) for HIV-positive men; or voluntary male medical circumcision (VMMC) scheduled if HIV-negative/uncircumcised; or counselling if HIV-negative/circumcised. At the end of stage 1, a planned interim analysis was performed and the HIVST-lottery arm was dropped for futility.

Male partner HIV-testing was substantially increased in all HIVST arms (range 87.0% to 95.4% in the 5 arms, compared to 17.4% in the SOC arm), according to self-report by the woman at 28 days. Reaching the primary linkage outcome at 28 days was most likely for the partners of participants in clinic days randomised to the HIVST-$3 and the HIVST-$10 arms, with geometric means of 40.9% (adjusted risk ratio [aRR] 3.01, 95%CI:1.63-5.57) and 51.7% (aRR 3.72, 95%CI:1.85-7.48), respectively. Successful male linkage was also more likely in the HIVST-phone reminder (geometric mean 22.3%, aRR 1.58, 95%CI:1.07-2.33) and HIVST-alone (geometric mean 17.5%: aRR 1.45 (95%CI:0.99-2.13) compared to SOC (13.0%). Linkage in the HIVST-lottery arm (geometric mean 18.6%, aRR 1.43, 95%CI:0.96-2.13) was less pronounced than with the $3 or $10 fixed conditional-incentives, and clients disliked the uncertainty.

Overall, 42/46 (91.3%) newly diagnosed HIV-positive men initiated ART and 135/222 (60.8%) HIV-negative and previously uncircumcised men had VMMC. No serious adverse events were reported. Cost per male partner attended clinic with confirmed HIV test result was $23.73 and $28.08 for $10 and $3 arms, respectively.

Secondary distribution of HIVST kits from ANC clinics greatly increased partner-testing, and timely linkage within 28 days increased 3-fold with the combination of fixed financial incentives plus partner-delivered HIV self-test kits in this hard to reach group. This PhD project has demonstrated that novel trial designs such as adaptive MAMS can be applied to address pressing public health problems in Africa. The approach followed here, combining systematic review, qualitative pilot study, and multi-arm randomised trial is ideal for rapidly generating high quality evidence for interventions, such as financial incentives, where the effectiveness of different amounts may vary from one setting to the next.

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1.4 Abbreviations and acronyms

ACASI	Audio Computer Assisted Self Interview
ANC	Antenatal Clinic
ART	Antiretroviral Treatment
CI	Confidence Interval
COM	College of Medicine
COMREC	College of Medicine Research and Ethics Committee
CROI	Conference on Retroviruses and Opportunistic Infections
CRT	Cluster Randomised Trial
CSV	Comma Separated Values
DHO	District Health Office
DU	Drug Users
DSFI	Demand side financial incentive
DSMB	Data Safety and Monitoring Board
EMBASE	Excerpta Medica dataBASE
FGD	Focus Group Discussion
FI	Financial Incentive
FTE	Full Time Equivalent
FWER	Family-wise Error Rate
HIV	Human Immunodeficiency Virus
HIVST	Human Immunodeficiency Virus Self-Testing
HTC	Human Immunodeficiency Virus Testing and Counselling
IAS	International AIDS Society
IDI	In-depth Interview
IQR	Interquartile Range
LMIC	Low and Middle Income Countries
LSHTM	London School of Hygiene & Tropical Medicine
MAMS	Multi-Arm Multi-Stage
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical Subject Headings
MLW	Malawi Liverpool Wellcome Trust Clinical Research Programme
NAC	National AIDS Commission
OR	Odds Ratio

ODK	Open Data Kit
PHC	Primary Health Centre
PI	Principal Investigator
PITC	Provider-initiated Testing and Counselling
PLWH	People living with HIV
PMTCT	Prevention of Mother to Child Transmission
RCT	Randomised Controlled Trial
SD	Standard Deviation
SOC	Standard of Care
STAR	Self-Testing Africa
SMS	Short Messaging Service
SSA	Sub-Saharan Africa
VMMC	Voluntary Male Medical Circumcision
WIN	Weighted Inverse Normal

1. Introduction

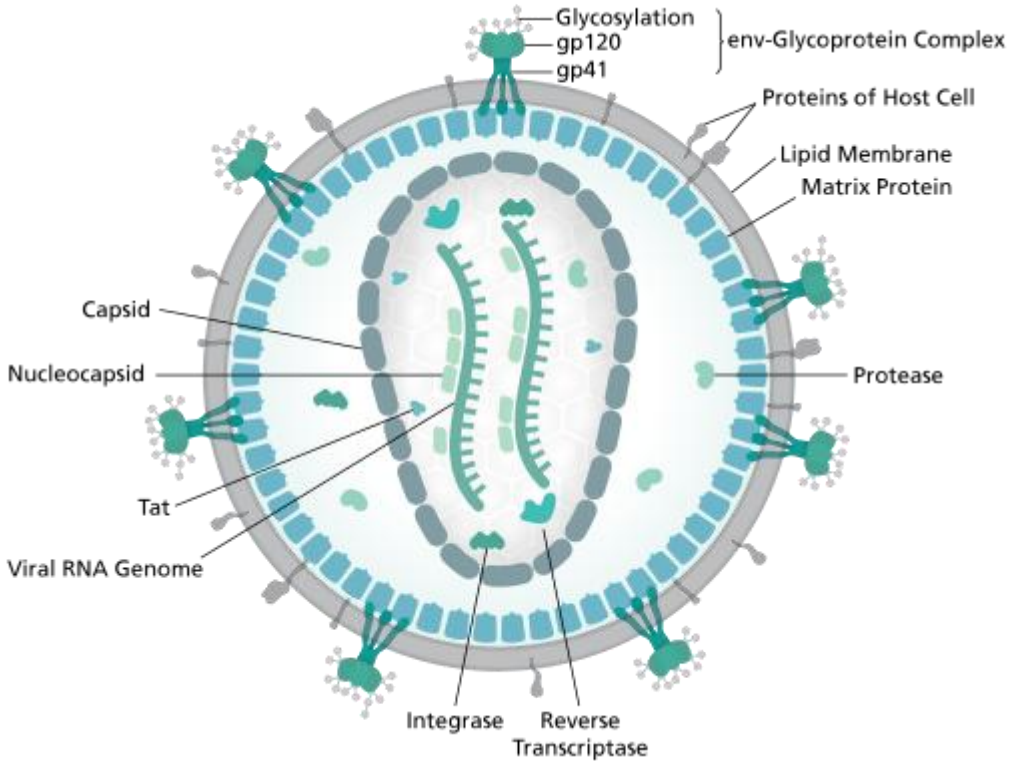
1.1 Background

1.1.1 The Global HIV Epidemic

Acquired Immunodeficiency syndrome (AIDS) was first recognised in 1981 [1] (and named in 1982 [2]), following a cluster of unusual infections and malignancies in gay men [1,3,4,5]. Human immunodeficiency virus (HIV) was identified as the causative agent in 1984 [6,7,8], with the first diagnostic tests developed within 12 months of the virus first being isolated and identified [9].

HIV is a retrovirus, defined by the presence of the viral enzyme (retrotranscriptase) that enables "back-translation" of the viral single-stranded genetic material (ribonucleic acid: RNA) into deoxyribonucleic acid (DNA) once the viral particle has penetrated a suitable host cell [6,10]. Retroviral DNA is then integrated into the host cell genome, where it is translated back to RNA to make proteins and new viral genomes by the standard host enzymes and cell machinery [11] (Figure 1.1.1-1).

Figure 1.1.1-1: Diagram of the HIV virus



Source: Watts et al., Nature [12]

HIV was the first recognised “exogenous” infectious retrovirus to infect humans, although retroviruses are widespread in nature, typically causing life-long infections characterised by cancers and immunodeficiency syndromes in many different animal species. Retroviruses are even present in degenerate “endogenous” forms in the germ-line DNA of species as diverse as insects, fish, reptiles, and mammals: about 8% of human DNA is of retroviral origin [13].

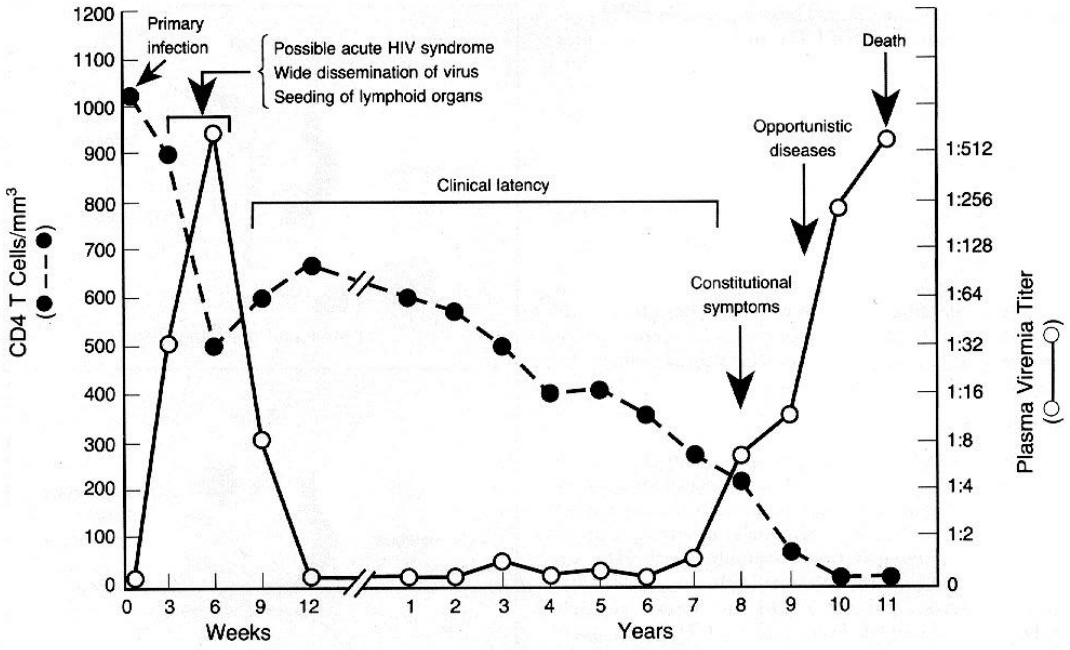
The link to Africa was soon recognised, with the magnitude of the Africa AIDS epidemic far exceeding that elsewhere, and establishing Africa as the likely continent of origin of HIV [5,14,15].

Modes of transmission of HIV include sexual transmission [16], mother to child [17,18], and percutaneous routes [5], with heterosexual transmission being the predominant mode in Africa [16].

1.1.2 HIV infection and diagnosis

HIV infection has a number of immunological and virological features, including very high viral production and turnover with constant viraemia from time of infection to time of death in most people that makes serological diagnosis of HIV extremely reliable [19,20,21,22] (Figure 1.1.2-1).

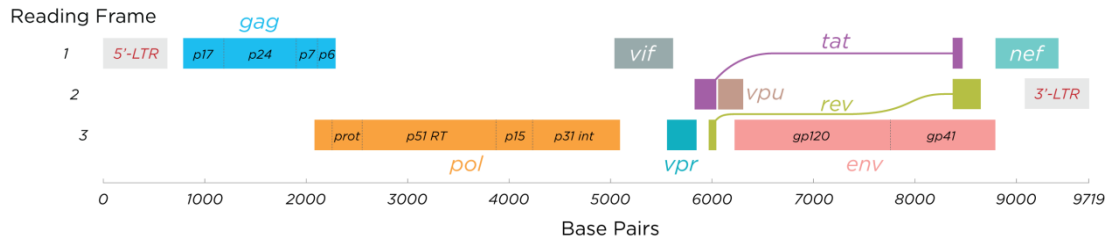
Figure 1.1.2-1: Typical time course of untreated HIV infection in adults, showing the time-course of two diagnostic indicators: CD4 count and HIV viraemia



Source: Fauci AS et al, Ann Intern Med [22]

Broad but ineffectively neutralising anti-HIV antibodies are produced to very high titre in almost all infected individuals within a few weeks of primary HIV infection [9,12,21,22]. These antibodies are directed against multiple HIV proteins that have no human equivalents, allowing tests of exceptionally high specificity and sensitivity to be developed using combinations of HIV-1 antigens, for instance a typical serological test may detect targets on the p24, gp41, and gp120 HIV proteins and glycoproteins [8,12] (Figure 1.1.2-2).

Figure 1.1.2-2: Structure of the RNA genome of HIV-1



Antibody-based tests can also be produced at low cost ("lateral flow assays" with unit costs below US$1) for rapid diagnosis and point-of-care use: these types of kits are by far the most commonly used globally, and can be performed by briefly trained lay health workers [23,24,25].

1.1.3 Global response to the HIV epidemic

Early efforts to mitigate the HIV epidemic initially focused on drug and diagnostic developments for use in high-income countries, and were extremely successful although there is still no cure for HIV[26,27] and no effective vaccine [5,28]. By 2003, however, the overwhelming scale of deaths and hospitalisations in the high HIV prevalence countries of Southern and East Africa forced a major global investment into LMIC treatment programmes [29]. First taking shape as the "3-by-5" initiative of WHO [30], scale-up of treatment programmes has been highly successful and is still being supported by custom-made global funding initiatives notably The U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFTATM) [31].

Although the HIV epidemic is still growing and there are more people living with HIV (PLHIV) than ever before , life-expectancy has returned to near-normal in highly affected countries [32,33] and numbers of both deaths and new HIV infections have fallen substantially [34] (Table 1.1.3-1).

Table 1.1.3-1: Overview of the global HIV/AIDS epidemic

Description	2016/17 Estimates [34]	Peak Numbers and Year [34]	Key Policy Initiatives [30,35]	Role of HIV testing
People living with HIV	36.7 million	36.7 million in 2017 (cumulative global total 76.1 million) [36]	HIV prevention aiming for fewer new infections than annual deaths	"Gateway" to HIV treatment and prevention General HIV epidemics: annual testing of adults, more frequent in high risk groups
Annual Deaths from HIV	1.0 million	1.9 million in 2005 (cumulative global total 35.0 million in 2017)	Global Health Finance Initiatives to fund the scale-up of ART in LMIC	Survival improved by early HIV diagnosis and ART, also cotrimoxazole
Annual new HIV infections: adults	1.8 million	3.5 million in 1997	Initially "ABC" behaviour change campaigns had modest success [37]. Now combined with biomedical interventions: Treatment- as-prevention; VMMC, Discordant couples management; Pre-exposure prophylaxis for highest risk groups [38,39].	Linkage to post-test services based on HIV sero-status. Regular testing, use of PrEP and in discordant couples
People alive on ART	20.9 million	<0.5 million in 2003	2003: "3-by-5" Initiative 2013: "90-90-90" Targets of "Fast-Track Strategy"	Scale up to reduce "testing gap" (% PLHIV unaware of HIV status), which was 55% in 2013 [40]
Annual new HIV infections: children	160,000	490,000 in 2000	Prevention of mother to child transmission initiative	Routine provider-initiated HIV testing of all pregnant women a key component
Annual HIV test volumes	200 to 350 million: not routinely reported to WHO	<20 million in 2002	MTCT initiatives from 2003: "3-by-5" Initiative 2013: "90-90-90" Targets of "Fast-Track Strategy"	Market dominated by low cost finger-prick rapid diagnostic tests (RDTs) since development in 2002
Annual HIV self-testing volumes	2017 orders for 2018 ~ 4 million oral test kits (OraQuick)	Negligible volumes in 2015	WHO Guidelines in 2016 (HIVST gives complementary coverage and increased testing frequency) [41]. OraQuick approved for routine LMIC use in 2017.	Aiming for a 10% to 20% share of the global market post-2020

HIV: Human immunodeficiency virus; ART: antiretroviral therapy; LMIC: low and middle income countries; ABC strategy: Abstinence, be faithful, use a condom; PrEP: pre exposure prophylaxis; VMMC: voluntary medical male circumcision; PLHIV: people living with HIV; WHO: World Health Organization; MTCT: Mother to child transmission; RDT: Rapid diagnostic test; HIVST: HIV self-testing

1.1.4 Approaches to HIV prevention

HIV prevention involves applying interventions to stop the transmission of HIV. Thus these interventions can offer individual-level, community-level, and population-level protection from transmission. Prevention efforts were initially hampered by profound stigma against PLWIH in the early days of the epidemic as HIV was labelled a "gay disease". This view quickly changed and soon HIV/AIDS was accepted as a disease that affected all people [5] although stigma was still common. Early prevention efforts focused on protecting health workers including laboratory personnel and persons caring for AIDS patients [42,43]. Counselling was offered to HIV negative women to avoid becoming infected with HIV to prevent perinatal infection [18].

The ABC strategy (Abstinence, Being faithful, using Condoms) was extensively promoted in Africa to fight HIV/AIDS and other sexually transmitted infections (STIs) [44]. In general, this approach focused on delaying sex debut among youngsters until marriage, being faithful to one's long term sexual partner and using effective barrier contraceptives such as condoms. This strategy was credited for reducing the percentage of PLWH in Uganda from 15% to around 5% between 1990 and 2001 [37].

Among the shortcomings of the ABC approach were that it was too individualistic, did not fully address tenets that contribute to risky behaviour [45], nor address the need for children in discordant couples. And that for women who may have limited control of their sexual relationships, ABC was not a relevant intervention. Therefore, the new approaches to HIV prevention include components from *behavioural, biomedical and structural* interventions [46,47]. Behavioural interventions are aimed at reducing the risk of HIV transmission by addressing risky behaviours, and these include counselling, sex education, stigma and discrimination programmes, and conditional cash transfers. Biomedical interventions reduce HIV transmission through medical and clinical interventions such as antiretroviral therapy, HIV testing, condoms, needle exchanges and prevention of mother to child transmission. Structural interventions address social, cultural, political and economic situations that put individuals at risk of HIV transmission. For instance, these interventions may address discrimination against vulnerable groups such as female sex workers, or homosexuality.

Treatment as prevention (TasP) [48,49], voluntary medical male circumcision (VMMC) [50], pre-exposure prophylaxis (PrEP) [51] are among key notable single interventions that are highly effective at preventing HIV transmission and are strongly recommended by WHO [35]. Reductions in HIV transmission were first observed in a trial that offered treatment for STIs in Mwanza district in Tanzania, reporting a 42% reduction in HIV incidence [52]. In Taiwan, transmission was reduced by 53% following the introduction of a policy to offer free ART [53]. Despite being highly effective at reducing transmission [54] and improving patient health, ART was not available to all who needed it

in resource-poor settings and was provided based on CD4 count due to costs [55]. However, in 2016 WHO recommended a test-and-treat approach [38,56] following effective advocacy from a mathematical modelling exercise projecting the likely impact of extremely effective ART scale up and retention effects. This showed that the gains outweighed the costs if ART was immediately offered to all newly diagnosed patients [57].

1.1.5 HIV testing services and post-test linkage to HIV care and prevention services

The focus of my thesis is on HIV testing strategies, specifically HIV self-testing, and the uptake of services post-test ("linkage"). HIV testing services (HTS) have played an integral part in supporting HIV care and prevention, and will continue to be needed for many decades to come [58]. Expansion of HIV services to meet the UNAIDS Fast Track Strategy "90-90-90" testing and treatment targets requires an estimated 400 million HIV tests annually by 2020 [35].

HIV testing can be offered through a number of approaches (Table 1.1.5-1) in order to maximise the percentage of people who are aware of their HIV status. Early models of HIV testing included provider-initiated testing and counselling (PITC) or facility-based testing. PITC involves the direct offer of an HIV test to people who are attending a hospital or clinic for other investigations [58]. A key example where PITC has worked very well is among pregnant women attending antenatal care clinic, where HIV testing increased from 65.0% to 99.9% following the introduction of PITC in Zimbabwe [59]. Facility-based testing is cheap, easy to integrate into existing services but does not serve certain population groups well (female sex workers, men who have sex with men, adolescents, and men generally).

HTS is also offered through stand alone sites at hospitals, clinics or private providers to increase coverage. Other HTS approaches include community-based testing, home-based testing, mobile testing and workplace testing which involves offering testing to targeted groups. The targeted groups are often vulnerable e.g. female sex workers or are less likely to access testing in conventional sites of testing e.g. truck drivers. The key barriers for many standard HTS approaches include lack of privacy, convenience, confidentiality, fear of stigma, and costs of access and opportunity cost [60]. Community-based testing approaches are expensive, need dedicated outreach services, but provide complementary coverage of difficult to reach groups, and can be targeted.

HIV self-testing (HIVST) is a process whereby a person who wants to know his or her HIV status collects a specimen, performs a test and interprets the test result in private [61]. As with all HTS, positive results are considered preliminary and have to be confirmed before starting ART but in most settings, negative results have high enough negative predictive value to be considered as such.

HIVST was strongly recommended by WHO in 2016 [62] because of increased coverage and frequency. The key characteristic of HIVST leading to its success at increasing HIV testing uptake is that it offers true privacy and convenience [63]. Very few people want to be tested by someone they personally know. However, people are willing to collect self-test kits from someone they know, including their neighbour [64]. This fact allows HIVST to be decentralised in a way that no other testing strategy can.

Table 1.1.5-1: Description of type of HIV testing services

Type of HIV testing service	**Main aim**	**Key observations on the approach**
Provider initiated testing and counselling (PITC) • Preventative (PMTCT) • Diagnostic (in patients, people with TB symptoms, etc)	To increase HIV testing coverage by offering testing to people attending clinic or hospital. Can be targeted for prevention (PMTCT) or as diagnostic e.g. in patients or TB investigations	• Low cost with high coverage of specific sub populations, but programmes have not successfully implemented routinely to all OPD attendees due to logistical difficulties • Tends to identify advanced HIV, but has the lowest cost per new positive of all strategies • Unclear if would give sufficient population coverage to meet 90-90-90 targets
Community-based testing • Free standing testing centres (e.g. New Start centres) • Campaigns • Mobile outreach • Home-based testing and counselling • Work place • Testing week (s) in community	To increase HIV testing coverage by making it available in the community aiming to address access barriers for people who otherwise would not self-present at the facility for HIV testing.	• Expensive due to delivery costs and logistics • Needs effective advertising to maintain high throughput • High access costs, with low overall coverage of populations due to insufficient number of outlets nationally • Low HIV prevalence compared to facility-based services • Identifies early HIV • Increases couples testing, testing of key populations and men

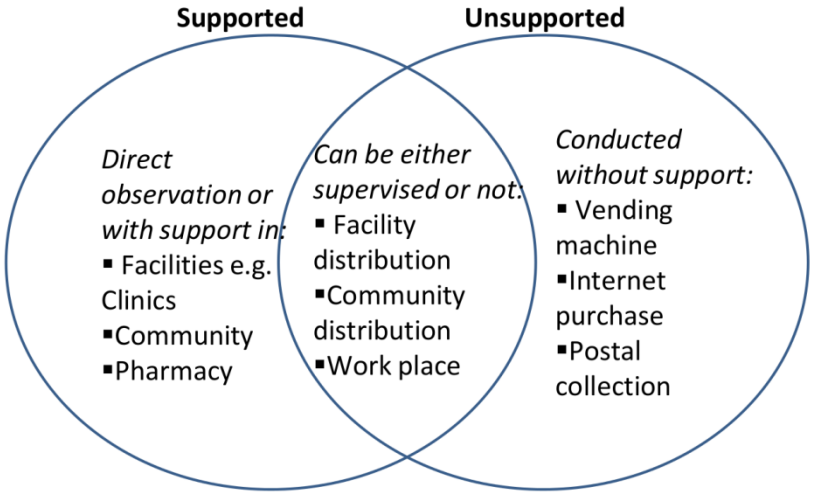
PMTCT: prevention of mother to child transmission; OPD: out-patient department
TB: Tuberculosis

Table 1.1.5-2 (ct'd): Description of type of HIV testing services

Type of HIV testing service	Main aim	Key observations on the approach
HIV self-testing, either supported or unsupported (see figure 1.5.1-1)	To increase HIV testing by providing test kits to untrained individuals to conduct their own testing either in private without support or with direct in-person support.	• Positive self-test results need to be confirmed at a facility • Addresses nearly all key barriers to testing, and thus may increase coverage and frequency of testing in many populations including key populations and men • Was strongly recommended to complement existing HIV testing approaches by WHO in 2016
Mandatory HIV testing and counselling	To screen blood for infections before donation of blood or other bodily fluids.	• Not recommended other than for special circumstances, particularly for donation of blood or other bodily fluids or organs

The two forms of HIVST are *supported* and *unsupported* (Figure 1.1.5-1) [61]. Supported HIVST involves either direct supervision or support from a trained person while conducting the test. With unsupported HIVST, the individual conducts the test without support or observation from a trained person.

Figure 1.1.5-1: Overview of HIV self-testing delivery pathways

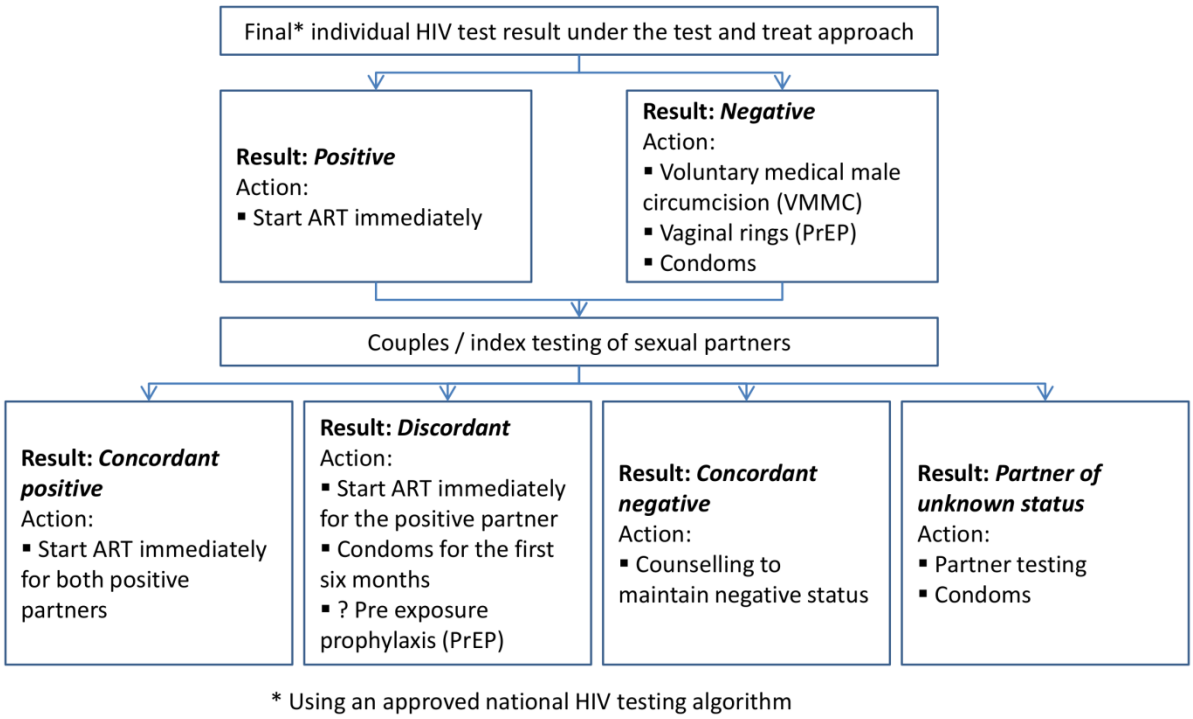


Linkage to care or prevention steps (Figure 1.1.5-2) are crucial if the HIV epidemic is to be under full control (the point at which new HIV infections have decreased and fall below the number of AIDS-related deaths) by 2030, as targeted by UNAIDS in the Fast Track Strategy [35]. For people with a confirmed HIV positive result, immediate initiation of ART regardless of CD4 count is now recommended under the test-and-treat approach [65]. Linkage estimates are high (range: 55% - 61%) for people testing HIV positive in health facilities or facilities offering both HIV testing and ART [66] especially when measured over a 12 month period. The main facilitator is likely to be the convenience of completing subsequent steps such as confirmation of the initial HIV positive result and immediate offer to start ART on the same day.

Linkage to care is suboptimal for all HIV testing strategies implemented outside of health facilities such as home, community campaigns and mobile testing (range 26% - 37%) [66] over a period of one month to twelve months. Key barriers to linkage for such strategies include costs, opportunity cost associated with the need to confirm HIV results at a health facility, and fear of stigma [67]. HIVST studies have reported linkage to care, defined as attending a clinic for confirmatory testing, ranging from 18% to 53%. For HIVST strategies, measuring linkage to care remains a challenge [64]. Here, true privacy and being in control of one's own testing, which are the key advantages of HIVST, have the disadvantages that people may choose not to disclose a positive self-test result to the distributor. The test provider is no longer aware of the numbers of new HIV positives identified during their testing intervention (i.e. numerators and denominators become less certain). Additionally, people may link to care in other facilities that are not measuring linkage from the HIVST strategy thereby being missed in the count although this is not unique to HIVST only [64].

While linkage to care has always been an integral part of HIV testing programmes, only recently has there been emphasis on linkage to prevention for people who test HIV negative [38]. For men who test HIV negative and are uncircumcised, VMMC is recommended (Figure 1.1.5-2). For high risk groups, PrEP (if available) is recommended, while condoms are encouraged generally for everyone who tests HIV negative [38].

Figure 1.1.5-2: Overview of linkage options following HIV testing



* Using an approved national HIV testing algorithm

1.1.6 HIV testing and men

In 2017, Sub-Saharan Africa (SSA) accounted for 70% of the global HIV burden and still has 44% of new HIV infections and 72% of HIV deaths, despite rapid scale up of HIV services including testing [68]. Analysis of the HIV care cascade indicates a striking fall-off in numbers between testing and linkage into care or HIV prevention [69,70,71]. Men regularly feature among populations with lower uptake of HIV testing across SSA [72], and have lower rates of linkage into care or prevention [73] in the current era of extremely ambitious targets for HIV service delivery [74].

1.1.7 Antenatal clinic testing services

As discussed in section 1.1.5, male partners of antenatal care (ANC) attendees are not well served under conventional HTS: less than 35% accept an offer to undergo HIV testing when invited through their partner [75,76,77]. African women face substantial risk of new infection (3.6% per pregnancy in research cohorts) that carries unusually high risk to the infant [78]. Due to biological and behavioural changes, pregnancy *per se* doubles the risk of transmitting HIV to an uninfected partner [79] but also presents an opportunity to reach both partners with HIV testing and counselling (HTC) services [80].

A number of different strategies for improving the uptake of HIV testing among male partners of ANC attendees have shown effect: these include home-based testing [81,82], provider-initiated

testing and counselling (PITC) [83], couples testing during antenatal visits [84] and home-based couple or partner testing [76,85]. Key limitations of these strategies include: - logistical difficulties of wide scale implementation where home visits are required; lack of convenience; user costs (including indirect and opportunity costs); lack of confidentiality; and failure to prioritise men's own health [60,86,87]. My thesis investigates HIV self-testing (HIVST) as a novel approach to achieving high coverage of testing and linkage to care or prevention among male partners of ANC attendees. Since starting my PhD, success has been reported for coverage of HIVST in male partners of ANC attendees in Kenya [88], but with no clear measurement and reporting of linkage. HIVST is a novel approach that has potential to increase couple or partner testing [89] and was found to be highly acceptable to men living in the general community in Malawi. [64,89,90].

I define *HIVST-plus* as offering HIV self-testing along with an additional intervention aimed at improving linkage into care or prevention. Such additional interventions include facilitated linkage [91], financial incentives (FI) [92,93,94], and short messaging services (SMS) [95,96,97]. The wider increase in male engagement may then lead to increased utilisation of prevention-of-mother-to-child transmission (PMTCT) programmes in Africa [75,76] and potentially improve maternal outcomes [98,99].

A myriad of candidate HIVST-*plus* interventions exist that could maximise both uptake and linkage into HIV care or prevention. For example, different monetary levels (low, medium and high) and forms (fixed or lottery) of financial incentives [92,93]. This wide range of potential interventions presents technical challenges related to appropriate study design and analysis methods in order to identify optimal strategies [100]. Such complexity can be handled by applying adaptive trial designs, which are more flexible (allow pre-specified adaptations at interim analyses) as well as more efficient (time and cost) than standard parallel designs [101,102]. In multi-arm multi-stage (MAMS) phase II designs, several interventions are compared to a control arm using interim analyses [101], providing an unbiased approach to investigating and selection of multiple phase II candidates under consideration for a future phase III trial [102]. Although predominantly used in the pharmaceutical industry to date, adaptive trial designs could have value in public health evaluations.

The aim of my fellowship was to conduct a phase II adaptive MAMS cluster randomised trial (CRT) randomising clinic days (not individual women) to identify leading HIVST-plus candidate interventions for male partners of ANC attendees in Blantyre, Malawi. To my knowledge, this was the first study to focus on linkage into care or prevention as the main outcome related to HIVST, although a number of other studies were planned (Kahn K; South Africa) or underway [103] investigating the uptake of HIVST for male partners of pregnant women.

1.1.8 Interventions with potential to increase timely service uptake (linkage)

The implication of the test and treat approach is to start HIV care (ART) immediately following confirmation of positive HIV status. However, without deliberate interventions, linkage to care or prevention is usually suboptimal especially for HIV testing strategies outside of health facilities [66,104], and this may undermine efforts and the gains that have been made on the cascade of HIV services [105]. Interventions with evidence or potential to increase linkage to care or prevention include: reminders, facilitation by a health worker, providing information, counselling, offering financial or non-financial incentives, rapid service provision, point of care CD4 testing, and combinations of these interventions.

Short messaging service (SMS), phone call, internet and smart phone application-based reminders have showed mixed effects on linkage to care or prevention [106]. However, facilitating linkage to care by giving information on where to get services for people who are newly tested HIV positive is effective at increasing linkage [91,107,108]. Offering health information including referral letters has minimal effect (<35% overall within 6 months) on linkage to care [104], and so does counselling only [109]. Conditional financial incentives offered as fixed as opposed to lottery have showed effect on increasing linkage to VMMC in Africa [110] but not linkage to care in the USA [111]. Linkage to care increases with immediate or on-the- spot offer of follow-on services such as confirmatory testing, CD4 testing and ART [112]. Finally, complex interventions (e.g. SEARCH: Sustainable East Africa Research of Community Health – Uganda and Kenya [113]) comprising a battery of proven interventions have been shown to increase linkage to care or prevention [114,115]. However, these types of interventions are complex too scale up, potentially costly and it is hard to isolate which components of the intervention were effective.

1.1.9 Design approaches to multi-arm comparisons

There are different choices of study designs available for evaluating many interventions that can potentially improve the uptake of HIV testing and subsequent linkage to care or prevention. The randomized controlled trial (RCT) design is the gold standard due to random allocation of the participant or community to the intervention or control treatment, thereby minimising selection bias and confounding [116]. A standard RCT involves randomization, either individually or cluster (group) level and comparison of two arms [117]. A multi-arm RCT design is preferred in situations where two or more interventions are to be compared to a control arm [101,118]. More importantly, investigators may wish to perform well –defined interim analyses of the accumulating data in the early stages of the multi-arm trial to inform the conduct of the remaining part of the trial [100,101].

In this case, the trial becomes multi-arm and multi-stage (MAMS) and is adaptive due to the changes made at each interim analysis [100].

The majority of MAMS trials are individually randomized and have so far been in drug development trials where several potential regimens have been compared with a control treatment and for dose-finding [118,119]. Other choices of RCTs include multi-factorial designs [120]. For example, in a 2x2 factorial there are three comparisons to the control arm: two involving each of the two interventions separately and one with both interventions applied together versus the control [120]. The key problem with MAMS and factorial designs is that the statistical considerations are more complex.

1.2 Structure of thesis

This is a ”research paper” style thesis generally presenting manuscripts and scholarly articles such as conference abstracts and policy briefs in their published form or as prepared for submission. Four articles were written, two of which were already published at the time of writing the thesis while two were under review by peer-reviewed journals. These four articles form the main chapters of this thesis and are accompanied by a cover letter and a short introduction.

Where necessary, additional analysis and text follow each article and is clearly marked as these may have been removed due to journal space constraints. Tables and figures are given in text where they are first referenced but for published papers or manuscripts prepared for publication tables and figures are given placed after the reference list. References are given at the end of each chapter of the thesis, with the exception of chapter 6 where additional references are given for the additional analysis section.

The rest of this chapter presents description of what led to the research question being addressed in this thesis and the methodological approaches that were followed to address the question. Furthermore, this chapter describes: my role in each piece of work presented in this thesis; the collaborations that I formed during my PhD work; the institutional review boards that approved the studies undertaken and other ethical components; and funders.

The second chapter presents the thesis aims followed by chapter three which describes a systematic literature review I conducted of randomised trials (individual or cluster-randomised) of financial incentive(s) as an intervention for improving linkage to HIV treatment or voluntary medical male circumcision in low and middle income countries. This work was done in order to identify interventions that use behavioural economics such as fixed and lottery type of incentives for potential inclusion in a trial. This work is under journal review.

The fourth chapter describes formative work, in particular a qualitative study that was undertaken in order to understand whether or not the population of interest would take up the proposed interventions. Additionally, this work explored other interventions that the population of interest suggested for inclusion in the trial. The paper reporting this work was published in J International AIDS Society, in 2017.

The fifth chapter summarises the trial design, an adaptive multi-arm multi-stage (MAMS) cluster randomised trial, and sample size methodology I developed. The paper describing the trial design was published in Trials, in 2017.

Chapter six presents a manuscript under journal review describing the findings of the adaptive multi-arm multi-stage Phase II cluster randomised trial I conducted for my PhD. Additional analyses of trial data are also reported, after the manuscript.

An overall discussion of the thesis is given in chapter seven followed by key limitations, and strengths of the approaches followed to address the research questions. This chapter ends with recommendations and conclusions from the thesis.

Given the public health relevance of the research question, a number of research dissemination activities were undertaken either invited speaker or abstract driven and these are presented in Appendix 8.9 of the thesis. The local Ministry of Health is keen to widely implement the concepts of this project and I have had meetings with the officials.

1.3 Problem conception and scientific approach

The topics for this thesis arose from my involvement in an Implementation Research Workshop held in London in November 2013, which was primarily aimed at defining the scope of work and research questions to be addressed in a multi-country proposal to Unitaid for support to scale up the implementation and evidence-base for HIV self-testing. I had by then been working with Professor Liz Corbett on HIV self-testing in Malawi since 2009, and had globally unique experience of the practicalities of self-testing, with no other research groups investigating large scale HIV self-testing at that time. We had shown very high uptake of the offer of HIV self-testing in all of our target subpopulations in Blantyre slums [90], and the importance of proactive interventions to encourage linkage to services following HIV self testing [91]. The relevance of HIV self-testing to the UNAIDS 90-90-90 targets was clear from these data.

At the proposal-writing workshop, the difficulty of how to choose between multiple potential linkage interventions became apparent, with no cluster-equivalent of a MAMS trial already developed, as

did the lack of data at that time on facility-based HIV self-testing strategies, including secondary distribution. This precluded consideration of facility-based strategies or financial incentives in our ultimately successful application to Unitaid, and highlighted these areas as important knowledge gaps to me: had we had the evidence in this Thesis in 2013, the Unitaid application would have been very different.

I wanted to continue in the field of HIV self-testing, which had very exciting potential for scale-up, and to be able to use my statistical background to investigate a number of approaches in one study in a short time (<2 years), aiming to increase the uptake of both testing and linkage to post-test prevention and care services. During literature review, I found that such a trial design had not previously been developed, with no means to perform sample size calculation, or hypothesis testing.

My study design was then a cluster randomised MAMS trial, with the first year to be spent developing the methodology to support the need raised by the self-testing Africa (STAR – HIV self-testing consortium funded by Unitaid) proposal workshop for a system that would allow randomising of multiple interventions to clustered units, with ability to discard ineffective arms early as in MAMS individually-randomised trials.

In summary, my two broad research questions were: -

1) How can the effects of a clustered unit of randomisation be included in the sample size calculations and analysis stages of a multi-arm multi-stage study design, retaining the option to test and drop interventions that are not better than the standard of care?
2) Which are the most promising candidate interventions for increasing HIV testing and linkage to HIV treatment and prevention for hard to reach groups such as male partners of pregnant women?

I spent the first year of my PhD studying statistical designs that could be adapted to address the first problem. This work included conducting simulation studies to understand statistical properties of the chosen trial design with Professor Nigel Stallard at Warwick University.

Once the study design was clarified, I spent the remaining time conducting a systematic literature review of existing evidence of financial incentives as potential interventions to include in the trial. A number of potential interventions were identified from the systematic review and from past similar trials. The next step was to conduct a formative qualitative study. This was to assess the perceived acceptability of the chosen model of distributing self-test kits (via pregnant women) and the chosen interventions. Additionally, this allowed participants to suggest any other interventions for inclusion in the trial. The subsequent adaptive multi-arm multi-stage cluster randomised trial then tested

candidate interventions that were identified through the systematic review and the qualitative study.

I was able to combine qualitative and quantitative because of my previous experience working with Professor Liz Corbett as well as theoretical skills through my MSc in Epidemiology obtained from the London School of Hygiene & Tropical Medicine.

1.4 My role

I led on all of the work that is included in this thesis although the implementation of the qualitative study was led by a social scientist (Mr Moses Kumwenda). I conceived the overall approach to addressing the research questions before seeking input from my supervisors. The supervisors were then able to advise me on the appropriate collaborators to include for specific components of the project. For example, Professor Nigel Stallard was contacted to collaborate on the statistical design. I wrote and revised the study protocols for the two studies and obtained ethics approvals locally from the College of Medicine Research Ethics Committee (COMREC) and the London School of Hygiene & Tropical Medicine Ethics Committee. Once ethics approvals were obtained, I was responsible for finalising data collection tools and standard operating procedures. I trained my data collection team as well as primary health clinic staff responsible for trial procedures.

I was involved in piloting of data collection tools and recording of the audio computer assisted self-interview audios. The data were managed at the Data Department of Malawi Liverpool Wellcome Trust Clinical Research Programme with my close input. For the qualitative study, I organised data analysis sessions where the translated and transcribed data were coded and analysed.

For the trial described in chapter 5 and 6, I was the chief investigator and managed all aspects of the trial. I managed staff, set-up the data safety and monitoring board, cleaned and analysed the data, disseminated the findings nationally and internationally, and wrote the manuscript.

I wrote Stata do-files to clean the quantitative data before analysis in Stata or R as appropriate. I wrote the first drafts of all the manuscripts and was responsible for revisions and final submission to a chosen journal. Dr Hendramoothy Maheswaran assisted me with detailed costing work that is included in the adaptive trial (Chapter 6).

1.5 Collaborations

Existing collaborations that were utilised in the course of this project were with:

a) Professor Liz Corbett and Professor Katherine Fielding (London School of Hygiene & Tropical Medicine)

b) Dr Hendramoothy Maheswaran (University of Warwick)
c) Ms Cheryl Johnson (World Health Organization)
d) Dr Jeremiah Chikovore (Human Sciences Research Council, Cape Town, South Africa)
e) Dr Nicola Desmond (Liverpool School of Tropical Medicine & Malawi Liverpool Wellcome Trust Clinical Research Programme)
f) Mr Moses Kumwenda (Liverpool School of Tropical Medicine & Malawi Liverpool Wellcome Trust Clinical Research Programme)

New collaborations formed during the project were with:

a) Professor Nigel Stallard (University of Warwick)

1.6 Ethical considerations

Ethical approvals were obtained for each study locally from the College of Medicine Research Ethics Committee (COMREC) and the London School of Hygiene & Tropical Medicine Ethics Committee. No participants were enrolled until approval was given in writing by the committees and all participants gave written or thumb print-witnessed consent.

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2. Research aims

This thesis had three research aims:

a. To assess the effectiveness of *demand-side* (given to users) financial and other incentives in increasing linkage into voluntary male medical circumcision (VMMC) and antiretroviral treatment (ART). This is as reported in the literature.

b. To conduct a formative qualitative study to refine candidate interventions to include in a proposed trial.

c. To design and conduct a Phase II adaptive multi-arm multi-stage (MAMS) cluster randomised trial (CRT) to investigate interventions for increasing the uptake of HIV testing and linkage into care or prevention for male partners of pregnant women attending antenatal clinic (ANC).

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	AUGUSTINE TALUMBA CHOKO
Principal Supervisor	KATHERINE FIELDING
Thesis Title	Investigating interventions to increase uptake of HIV testing and linkage to care or prevention for male partners of pregnant women in antenatal clinics in Blantyre, Malawi

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	PLoS ONE
Please list the paper's authors in the intended authorship order:	Augustine Talumba Choko, Sophie Candfield, Hendramoothy Maheswaran, Aurelia Lepine, Elizabeth Lucy Corbett, Katherine Fielding
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the idea,developed the search strategy, conducted the searches, and I wrote the manuscript

Student Signature: [redacted] **Date:** 12 June 2018

Supervisor Signature: [redacted] Date: 13/6/2018

3. Systematic literature review

3.1 Introduction

A systematic literature review was undertaken to examine the existing evidence regarding the effectiveness of *demand-side* financial incentives (FI) on outcomes related to the proposed trial (linkage into care or prevention). Demand-side FIs are provided to users as opposed to suppliers of a good or service. Despite HIV testing being part of the primary outcome in this work, it was not included in this review because it was investigated in one of two recent systematic reviews. [1,2] Although only one trial was included [3] use of FIs increased the uptake of HIV testing.

This review was submitted to PLoS ONE Journal in February 2018 and is described verbatim as published below.

3.2 Systematic review paper

Title: The effect of demand-side financial incentives for increasing linkage into HIV treatment and prevention: a systematic review and meta-analysis of randomised controlled trials in low- and middle-income countries

Authors: Augustine Talumba Choko[§1, 2], Sophie Candfield[2], Hendramoothy Maheswaran[3], Aurelia Lepine[2], Elizabeth Lucy Corbett[1, 2], Katherine Fielding[2]

Affiliation:

1. TB/HIV Theme, Malawi-Liverpool-Wellcome Clinical Research Programme (MLW), Blantyre, Malawi
2. London School of Hygiene & Tropical Medicine (LSHTM), London, UK
3. Department of Public Health and Policy, University of Liverpool, UK

[§]Corresponding author

Malawi Liverpool Wellcome Trust Clinical Research Programme

P.O Box 30096

Chichiri

Blantyre 3

E-mail: augutc@gmail.com

Cell: +265999577452

Running head: Demand-side financial incentives for improving uptake of ART and VMMC

Abstract

Introduction

Linkage to HIV treatment is a vital step in the cascade of HIV services and is critical to slowing down HIV transmission in countries with high HIV prevalence. Equally, voluntary medical male circumcision (VMMC) has been shown to reduce HIV transmission by 60% and increasing numbers of men receiving VMMC has a substantial impact on HIV incidence. However, only 48% of newly diagnosed HIV positive people link to HIV treatment let alone access HIV prevention methods such as VMMC globally.

Methods

A systematic review investigating the effect of demand-side financial incentives (DSFIs) on linkage into HIV treatment or VMMC for studies conducted in low- and middle-income countries. We searched the title, abstract and keywords in eight bibliographic databases: MEDLINE, EMBASE, Web of Science, Econlit, Cochrane, SCOPUS, IAS Conference database of abstracts, and CROI Conference database of abstracts. Searches were done in December 2016 with no time restriction. We fitted random effects (RE) models and used forest plots to display estimates and 95% CIs separately for each of the two review outcomes.

Results

Of the 1099 citations identified from searches, 43 full text articles were reviewed culminating in seven articles in the final analysis. Three trials investigated the effect of DSFIs on linkage to HIV treatment while four trials investigated linkage to VMMC. From our RE model, we estimate that fixed financial incentives increase linkage to care on average by 22% pooled risk ratio (RR) 1.22 (95% CI: 1.05; 1.42). However, there was considerable heterogeneity with I-squared = 71.4%, p = 0.030. We estimate an average 4-fold increase in the uptake of circumcision among HIV negative uncircumcised men from our fitted RE model with overall RR 3.75 (95% CI: 2.52; 5.59). There was negligible heterogeneity in the estimates from the different studies with I-squared = 0.0%; p = 0.537.

Conclusions

Overall, DSFIs significantly improved the uptake of VMMC by over 3-fold but only marginally improved linkage to HIV treatment. Demand-side financial incentives could improve linkage to HIV treatment or VMMC in low- and middle-income countries although uptake by policy makers remains a challenge.

Key words: financial incentives, HIV, circumcision, ART

Introduction

There are approximately 1.1 million deaths every year due to HIV infection worldwide with an estimated 1.9 million annual incident infections, the majority in low- and middle-income countries (LMIC). [4] Nearly 40% of people living with HIV (PLWH) remain unaware of their HIV status, and only 46% of those aware of their HIV positive status have started antiretroviral therapy (ART). [4] The benefits of timely initiation of ART [5] and effective HIV prevention including voluntary medical male circumcision (VMMC) [6,7,8,9] have changed the emphasis of HIV testing and services (HTS) from learning one's status to appropriate linkage and retention. [4] However, uptake of HTS and linkage into care or prevention remains below current targets [10] in most LMIC. [11]

Recent UNAIDS targets aim to ensure that 90% of all PLWH are aware of their HIV status, with 90% of those found HIV positive started onto ART. [12] Efforts to increase access to HTS also provide an opportunity to ensure those men found HIV negative are offered VMMC. But, at best currently only 48% of newly diagnosed HIV positive people start ART globally [13] and VMMC was way below 30% in priority countries in Africa among 15-49y old men. [14] Of more concern has been the finding that whilst HIV incidence decreased before 2010, it has remained static since, [15] highlighting the need to increase uptake of effective HIV treatment and prevention strategies. One approach to increasing demand for HIV treatment and prevention is through the use of financial incentives.

Financial incentives (FI) are a potential strategy for increasing demand for health services by compensating users' direct (e.g. transport) and indirect costs (e.g. opportunity cost of time). [16] Conditional FIs require a pre-specified action before receipt of the incentive, [16] and thus psychologically nudge individuals to prioritize health service utilization. [17] Recently there has been significant interest in LMICs on using demand-side financial incentives (DSFIs) to encourage desirable public health outcomes including for HIV. [1] DSFIs are incentives offered to a specified target population (as opposed to providers of goods or services) with the aim of increasing demand for goods or services of merit to that population. [18] Evidence in the literature suggests DSFIs can lead to increased use of preventive and treatment services. [19] The use of DSFIs may be contributory to meet HIV treatment and prevention goals in LMICs. We therefore conducted a systematic review and meta-analysis to investigate the effect of DSFIs as an intervention in LMICs for increasing linkage into HIV treatment or VMMC. We have not identified a meta-analysis specifically summarizing the effect of incentives on linkage to care or VMMC thus far.

Methods

A systematic literature review and meta-analysis of published and unpublished trials (PROSPERO 2015: CRD42015029248) was conducted. [20] For a trial to be eligible it had to be an individually randomised controlled trial (RCT) or a cluster randomised trial (CRT) undertaken in a low- and middle-income country (LMIC). There was no time or language restriction. The review was restricted to LMICs because the epidemiology and management of HIV, as well as the economic conditions in the region, differ substantially to other settings. Trials were separated into two broad categories namely; studies investigating linkage into HIV treatment (ART) and linkage into VMMC as two primary outcomes and a trial was included if it reported either of these two outcomes. These outcomes were not necessarily primary outcomes in the original studies. We defined linkage to care as newly diagnosed HIV positive patients attending a clinic to be assessed for ART eligibility (e.g. CD4 measurement, ART initiation). Linkage to VMMC was defined as undergoing the procedure within a specified period of time as indicated by the study investigators.

Types of Interventions

This review included both conditional and unconditional DSFIs. Incentives included cash, goods, vouchers or microfinance such as a loan (Table 3.1-1). Trials that offered supply-side financial incentives to health workers, for example to improve their performance, were excluded.

Information sources and search strategy

Initial searches were done in MEDLINE and Cochrane library to determine if the review question had already been addressed. We searched the title, abstract and keywords in eight bibliographic databases in December 2016, namely: MEDLINE, EMBASE, Web of Science, Econlit, Cochrane library, SCOPUS, international AIDS Society (IAS) and conference on retroviruses and opportunistic infections (CROI) conference databases of abstracts. We also searched the reference lists of all selected papers to see if any studies were missed. Review of abstracts from two main HIV conferences and slides was done for conferences held between 2004 and 2016 to identify unpublished trials. This time restriction was for ease of searching purposes particularly for online published abstract books for conferences. Record identification data were then extracted and entered into an Excel database for initial screening.

Our search keywords comprised three main categories linked by 'AND', with keywords within each category linked by 'OR' (Figure 3.1-1): keywords to restrict to LMIC using a search filter based on World Bank 2014 definition of LMIC; keywords related to ART and VMMC; keywords related to FIs

(Table 3.1-1). Appropriate combination of key words and characters were used for each database searched. The search strategy was initially piloted in Medline by AC to determine the best approach.

Study selection

AC was responsible for running all the searches and removing duplicates from records. Two reviewers (AC and SC) first reviewed titles and abstracts, and removed records that were not relevant before doing full text review. If the abstract was judged by either reviewer to be potentially relevant, a full text review was conducted. For conference abstracts, the presentation slides were accessed from the conference website if available. For inclusion in the final review, both reviewers reviewed all full articles/conference presentations, if both agreed, data were independently extracted and compared by both AC and SC and any discrepancies resolved. A third reviewer (KF) resolved any lack of consensus regarding inclusion of an article.

Data analysis and quality assessment

A PRSIMA flow diagram was used to provide detailed description of the review process including the number of titles returned to trials that were finally included (Figure 3.1-2). Trials are described with respect to setting, study population, outcomes and risk ratios (RRs) and 95% confidence intervals (CI), as presented by the original authors of the trial. For trials that reported odds ratios (OR) we converted these effect estimates into RRs in order to standardize reporting across trials. [21] Meta-analysis was used to combine results from studies to obtain a summary RR, comparing interventions with FIs versus no FIs (control). We used a random effects (RE) regression to estimate the summary RR and 95% confidence interval (CI) and used forest plots to display estimates and 95% CIs, separately for each of the two primary outcomes. Heterogeneity across the studies was assessed using the I^2 statistic. We added 0.5 in the numerator for trials with zero outcomes. [22] For trials with more than one intervention arm, we included each independent comparison as if from a different study. [22]

The quality of studies included was assessed by AC and SC using the Downs and Black checklist for randomised studies. [23] This is a score-based assessment tool with five different domains: reporting, external validity, bias, confounding, and power with a maximum score of 32 across the domains.

Results

Search results

Of 1099 citations identified from searches in databases, conference abstracts and snowballing titles and abstracts, 903 (82.2%) remained after removal of duplicates (Figure 3.1-2). A total of 860 citations were excluded after title and abstract screening because they reported other outcomes (661) or they were in another disease area than HIV (199). A total of 43 articles had a full text review of which seven were finally included in this systematic review (Figure 3.1-2). The majority (15/36) of the full text articles excluded were non-randomised studies. Of the seven studies included one was based on a conference abstract.

Description of included studies

Three trials investigated the effect of DSFIs on linkage to HIV treatment and four trials investigated linkage to VMMC (Table 3.1-2). All studies included adult participants (age range: 18-70 years). Five of the seven studies were individually randomised, and all but one trial was undertaken in sub-Saharan Africa. Trial sizes ranged from 120 to 2201 participants. Within a trial the number of comparisons to the control arm ranged from one to five. The majority of trial arms evaluated fixed (n=10) incentives while some evaluated lottery based incentives (n =2). Only one trial provided cash incentives [24] while the rest implemented non-cash incentives including mobile airtime as described in the protocol, [25] food vouchers, [26,27] smart phones through raffle draw, [28] and subsidy for the VMMC procedure fee. [29]

In two studies (2 arms), investigators provided a larger fixed amount incentive (e.g US$ 5) initially, followed by a smaller (e.g. US$ 1) incremental incentive conditional on clinic attendance or attainment of pre-specified goals. [24,30] In one trial, [31] investigators compared the control arm to a complex intervention consisting of five components: point of care CD4; accelerated ART initiation; telephone reminder; health information; and non-cash incentives (mobile airtime). [25] One trial, conducted among people who inject drugs (PWID), compared two incentives: the control arm offered a lottery prize equivalent to $4 with eligibility for the lottery not conditional on meeting treatment targets, whilst the intervention arm offered non-cash vouchers (US$4-8) conditional on meeting HIV treatment targets. [30]

Quality assessment

Quality of the trials included were assessed as generally good, with Downs and Black scores ranging from 19-29 out of a maximum of 32 (Table 3.1-3). For the unpublished study only the abstract and

conference presentation slides were assessed and we were unable to assess for blinding, adverse events, loss to follow-up and adjustment for potential confounding factors which resulted in a lower score. [31] Solomon *et al.* 2014 [30] had a slightly lower score (28) due to potential selection bias because participants were drawn from individuals (drug users) available to outreach providers. Such sampling frame may not represent the source population as the majority of HIV patients who inject drugs in LMICs may not be in this patient category. Chinkhumba *et al.* 2014 [29] had the lowest quality score of 16 because only p-values were reported with no numerators and denominators and intervention effect estimates. Furthermore, there was no sample size section reported.

Linkage into HIV treatment

All three trials [24,30,31] found that fixed FIs significantly improved linkage to care as reported by the original authors (Table 3.1-4). The percentage of participants who linked for HIV treatment ranged from 67.3% to 92.0%) in intervention arms, and from 53.7% to 83.0% in control arms. The RRs for this outcome ranged from 1.10 (95% CI: 1.07; 1.14) among new HIV positive adults in Swaziland to 1.44 (95% CI: 1.10; 1.87) among HIV PWID in India. Meta-analysis of these three studies estimated that fixed FIs significantly increased linkage to care on average by 22% (pooled RR: 1.22, 95% CI: 1.05; 1.42). However, there was considerable heterogeneity between the studies (I-squared = 71.4%, p = 0.030) (Figure 3.1-3).

Linkage into voluntary male medical circumcision (VMMC)

Among HIV negative men, fixed FIs appeared to improve the proportion of men undergoing circumcision as reported by the original authors (Table 3.1-4). The proportion of HIV negative men who had circumcision was generally low in the studies with uptake ranging from 0.7% to 8.4% in intervention arms and 0-1.6% in control arms, over a follow-up period ranging from 2 to 6 months. However, the effect appeared stronger with higher compared with smaller values of incentives. [26] For example, while USD15.0 improved uptake of circumcision within 2 months in Kenya, USD2.5 did not RR: 5.72 (95% CI: 2.54; 12.25) vs. 1.10 (95% CI: 0.40; 3.18), [26] respectively. One study had a lottery FI arm (mean value of $12.5), as well as a fixed FI intervention arm, but in contrast to the fixed FI, the lottery FI did not significantly improve the uptake of VMMC within 3 months aRR 2.45 (95% CI: 0.80; 7.42). [27] A trial offering five varying subsidies for the circumcision procedure to uncircumcised men found that offering full subsidy (free circumcision) increased uptake from 0.0% without subsidy to 3.0% (Table 3.1.4). One study was not included in meta-analysis because there were no denominators and the outcome was VMMC increases analysed as a difference in differences that did not fit with the overall analytical approach. [28]

We estimate an average 4-fold increase in the uptake of circumcision among HIV negative uncircumcised men from our fitted RE model (Figure 3.1-4) with overall RR 3.75 (95% CI: 2.52; 5.59). There was negligible heterogeneity in the estimates from the different studies with I-squared = 0.0%; p = 0.537.

Discussion

This systematic review and meta-analysis found that DSFIs significantly improved linkage into HIV treatment for those testing HIV positive and the uptake of VMMC among men testing HIV negative, in low and middle-income countries. Most studies provided fixed FIs (cash, food vouchers, mobile airtime) of varying levels and only one study had a lottery arm. We identified very few studies that investigated the use of FIs to improve linkage to HIV treatment or prevention in LMICs, and the type and amount of the incentive was found to determine effectiveness. FIs given as a fixed amount, where participants would definitely receive the incentive, appeared to be more effective than those given as a lottery, where participants may not necessarily win the amount. Only one study had a lottery arm. The findings highlight the value of using FIs for increasing demand for HIV treatment and prevention services in the region, especially where healthcare providers may be exploring approaches to rapidly scale up coverage of these services.

The WHO recently emphasized the need for closer integration of HIV prevention services to HIV testing services, particularly VMMC and pre-exposure prophylaxis (PrEP). [4] VMMC has been shown to be potentially cost saving at scale [32] and ensuring high levels of coverage in countries facing a generalized HIV epidemic has the potential to avert millions of new HIV infections. [32] However, recent estimates suggest over 20 million young adults are still to be reached by VMMC services in high priority countries. [15] The evidence from this systematic review suggests there is a potential role of DSFIs to meet these goals in LMICs hardest hit by the HIV pandemic. [4] VMMC does not require adults to attend health facilities multiple times over long-time periods, which may explain why DSFIs were found to increase demand.

Previous studies have found FIs may be more effective for simpler than complex behavioural change. [33,34] The value of incentives given in the studies reviewed ($2.50 to $15.0) was considerably lower than previously estimated costs for performing VMMC ($ 75-95 in 2010 prices). [32] Although providing FIs may increase VMMC intervention costs, the resulting increase in uptake of VMMC may still result in the intervention being cost-effective. It is important to note that even with FIs, VMMC uptake only increased by 9%, implying other strategies than FIs may be needed to address residual barriers. [29] Thirumurthy *et. al* [26] and Chinkhumba *et. al* [29] provide important insight into the

dosing effect of FIs. The authors found that unless the incentive exceeded a certain threshold value, it was not found to be effective. This suggests that careful assessment of the size of the incentive on offer is warranted if incentives are to be effective.

We were intrigued by the apparent lack of effect by lottery-type of incentives as these have been shown to work in other settings albeit in different disease areas. [35] Lottery-based FIs have also been shown to reduce HIV incidence within the African region by influencing sexual behaviour patterns. [36] One study – and only one arm investigated this intervention, hence more studies may be required to understand the impact of lottery interventions. The theory behind lottery is that individuals tend to overestimate the probability to win and thus are more likely to take the risk. [37]

Although linkage to care had an overall modest improvement with the use of DSFIs, we note that the actual linkage proportions were high in the intervention arms of three trials: 66.7-92.0%, [24,30,31] and in control arms with range: 53.7-83.0%. It was interesting to note that among PWID, a fixed incentive was more effective than the control at increasing linkage. Furthermore, 50% of participants receiving the fixed incentive linked to clinic within 5 days of randomisation. [30] This is an important finding as it suggests that DSFIs can be used to improve rapid linkage [14] which may lead to earlier viral suppression and therefore long term good health, especially in patients with low CD4 count (<500 cells/μ). [38]

There are a number of limitations with this systematic review. First, we treated each arm as a separate study hence for the three trials with more than one intervention arm we made more than one comparison with the control arm. This may have led to spurious findings due to multiplicity whereby the CIs of the estimates would have been incorrect due to more than one comparison being made against the same control arm. However, this approach is commonly used and is recommended for such meta-analyses. [22] Second, we broadly categorized incentives as fixed or lottery which may lack directness on what specific type of incentive (cash, voucher, gift, or subsidy) may be more effective. However, a recent comparison of cash vs. voucher incentives concluded that cash incentives were more preferred by both the program and recipients in a humanitarian aid context in DRC. [39] Third, for linkage to VMMC, outcomes were measured over different follow-up periods, an element not accounted for in the analysis. Fourth, we included one trial whose linkage to HIV treatment outcome only included attendance for CD4 count which may not necessarily mean initiation of HIV treatment. Finally, some trials may have missed because the search key words did not include ART, or because the primary outcome of the review was not the primary outcome of the original trials.

HIV testing is seen as key to ensuring universal access to HIV treatment and prevention services, however, linkage into these services after HIV testing remains sub-optimal. In this systematic review we found the use of DSFIs significantly improved linkage into HIV treatment and the uptake of VMMC in LMICs. As HIV testing services are being scaled-up across LMICs to meet UNAIDS targets, healthcare providers in countries where ART and VMMC coverage remains low may need to consider offering FIs to increase demand. Further work is needed to explore the use of FIs along the HIV cascade of services from testing, linkage to viral suppression.

Acknowledgments

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Grant holder: ATC

Conceived of the study: ATC, ELC, AL, SC, KF

Conducted the searches: ATC

Screened titles: ATC and SC with KF breaking the tie

Drafted the manuscript: ATC and SC

All authors contributed to refinement of the study protocol and approved the final manuscript.

3.3 Tables and figures

Figure 3.3-1: Search Strategy consisting 3 main categories (Low and middle income countries; HIV; and financial incentives)

1-294 World Bank filter for LMIC
295. limit 294 to clinical trial, all
296. exp "HIV infection"/
297. hiv.mp.
298. 296 or 297
299. "conditional economic incentive*".mp.
300. "contingency management*".mp.
301. "financial incentive*".mp.
302. exp "reward"/
303. micro-financ*.mp.
304. microfinanc*.mp.
305. "cash transfer".mp.
306. "microloan*".mp.
307. "cash reward*".mp.
308. "cash incentive*".mp.
309. "material incentive*".mp.
310. "economic asset*".mp.
311. "school fee*".mp.
312. "school uniform*".mp.
313. "coupon*".mp.
314. "financial benefit*".mp.
315. "reward*".mp.
316. "demand side".mp.
317. 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316
318. 294 and 295 and 298 and 317

Figure 3.3-2: Flow diagram of search results

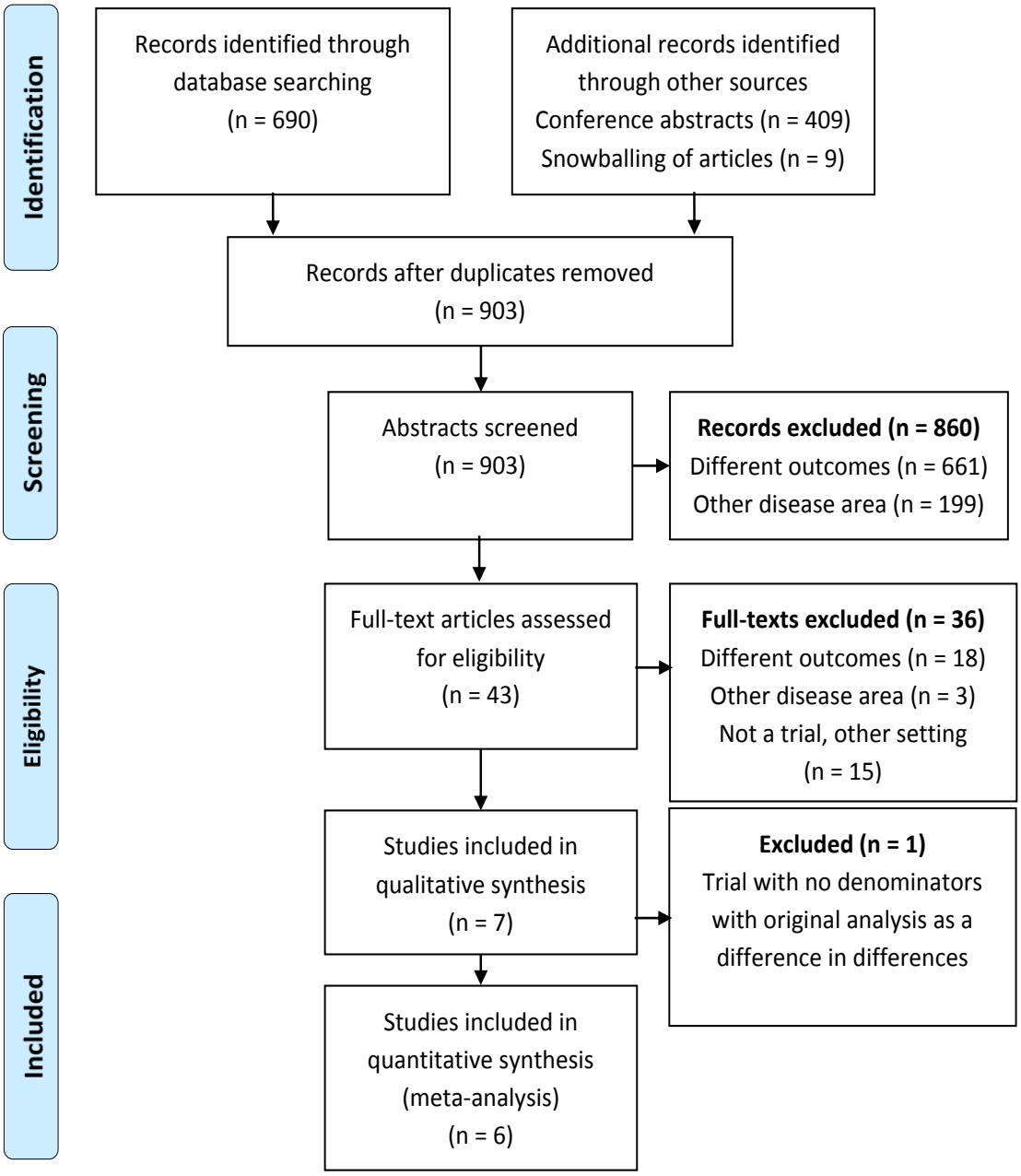


Table 3.3-1: Some financial incentives and their definitions

Form of financial incentive	Definition
Cash	Hard cash given to the participant directly or indirectly
Voucher	Coupon given to participant or their representative to redeem e.g. at a shop, or to buy airtime, or to cover part of the cost of a health good or service
Goods	Anything tangible given to the participant e.g. soap, sweets, school uniform
Microfinance	Any financial assistance given directly or indirectly to the participants or their representative e.g. loan and school fees

Table 3.3-2: Characteristics of included studies

Author, year	Country	Type	Sample size	Arms	Study population	Outcomes	Intervention (s)
Outcome: linkage to ART							
Yotebieng, 2016	DR Congo	RCT	433	2	Newly diagnosed pregnant women Age 29 (IQR 25-34)	**PO**: Retention at 6 weeks postpartum Uptake of PMTCT services *Acceptance of proposed services postpartum* †	US$5, plus US$1 increment at every subsequent clinic visit
McNairy, 2016	Swaziland	CRT	2201	2	Newly diagnosed HIV positive Age 32 (IQR 26-40)	*Linkage to care in 1 month* **PO:** Retention in care at 12m	Combination of: point of care CD4; accelerated ART initiation; phone reminder; health information; and airtime incentive
Solomon, 2014	India	RCT	120	2	HIV positive Injecting drug users Age 38 (IQR 32.5-44)	**PO:** *Linkage to care in 1m* Clinic visit in 12m eg refill HIV RNA suppression at 12m	Control: Voucher incentives through lottery Intervention: Target-based voucher incentives ($4 for linkage, max $48 over 12m)
Outcome: linkage to voluntary medical male circumcision (VMMC)							
Thirumurthy, 2016	Kenya	RCT	909	3	Uncircumcised men Age 29.0 (SD: 6.0)	**PO:** *VMMC uptake in 3m*	Intervention 1: Food voucher ($12.5) Intervention 2: Lottery equivalent of $12.50
Bazant, 2016 *	Tanzania	CRT	*	2	Uncircumcised men Age 27.6 (SD: 9.7)	**PO:** *Number of VMMCs in 3m*	Lottery: weekly smartphone raffle
Thirumurthy, 2014	Kenya	RCT	1502	4	Uncircumcised men Age range: 25-49	**PO:** *VMMC uptake in 2m*	Fixed incentives: $2.5, $8.75, $15.0
Chinkhumba, 2014	Malawi	RCT	1634	7	Uncircumcised men Age 26.7 (SD: 5.8)	**PO:** *VMMC uptake in 6m*	Fixed subsidy for VMMC procedure: (Full subsidy $6, $5.67, $5.3, $4.67, $2.67, $0)

RCT: randomized controlled trial; CRT: cluster randomized trial; PMTCT: prevention of mother to child transmission; PO: primary outcome used by the original authors (Italic: outcome used in this review); SD: standard deviation

† including giving blood sample for CD4 count testing at 6 weeks

* Trial not included in meta-analysis (Table 3) due to lack of denominator data. Original analysis as difference in differences

Table 3.3-3: Quality assessment of the included studies

Author, year	Assessment domains					Maximum score = 32 Score
	Reporting	External validity	Bias	Confounding	Power	
Yotebieng 2016	9	3	6	6	5	29
McNairy, 2016	8	3	5	5	5	26
Solomon 2014	9	3	6	6	4	28
Thirumurthy, 2016	9	3	5	6	5	28
Bazant, 2016*	8	3	4	4	4	23
Thirumurthy, 2014	10	3	5	6	5	29
Chinkhumba, 2014	5	3	7	4	0	19

Possible total score: Reporting (11); external validity (3); bias (7); confounding (6); power (5)

Rated using the Downs and Black checklist

* Trial not included in meta-analysis (Table 3-3-4) due to lack of denominator data. Original analysis as difference in differences

Table 3.3-4: Trial outcomes: linkage to ART and voluntary male medical circumcision

Author, year	Outcome from trial used	Trial arm†	N	n	%	RR (95% CI)‡
Outcome: linkage to ART						
Yotebieng 2016	Acceptance of proposed services postpartum*	Control	216	116	53.7%	1
		Fixed incentive	217	146	67.3%	1.26 (1.08; 1.48)
McNairy, 2016	Linkage to care in 1m	Control	1101	914	83.0%	1
		Combined strategy	1100	1012	92.0%	1.10 (1.07; 1.14)
Solomon 2014	ART initiation in 1m	Control	60	33	55.0%	1
		Fixed incentive	60	47	78.3%	1.42 (1.09; 1.96)
Outcome: linkage to voluntary medical male circumcision (VMMC)						
Thirumurthy, 2016	VMMC uptake in 3m	Control	299	4	1.3%	1
		Fixed incentive	308	26	8.4%	6.58 (2.34; 16.54)
		Lottery incentive	302	10	3.3%	2.45 (0.80; 7.42)
Thirumurthy, 2014	VMMC uptake in 2m	Control	370	6	1.6%	1
		Fixed $2.50	374	7	1.9%	1.10 (0.40; 3.18)
		Fixed $8.75	381	25	6.6%	4.08 (1.68; 9.26)
		Fixed $15.0	377	34	9.0%	5.72 (2.54; 12.25)
Chinkhumba, 2014	VMMC uptake in 6m	No subsidy	175	0	0.0%	1
		$6 Full subsidy	395	12	3.0%	5.32 (0.70; 40.57)
		$5.67 subsidy	416	17	4.1%	7.15 (0.96; 53.32)
		$5.3 subsidy	221	7	3.2%	5.54 (0.69; 44.63)
		$4.67 subsidy	215	5	2.3%	4.07 (0.48; 34.51)
		$2.67 subsidy	211	2	0.9%	1.66 (0.15; 18.14)

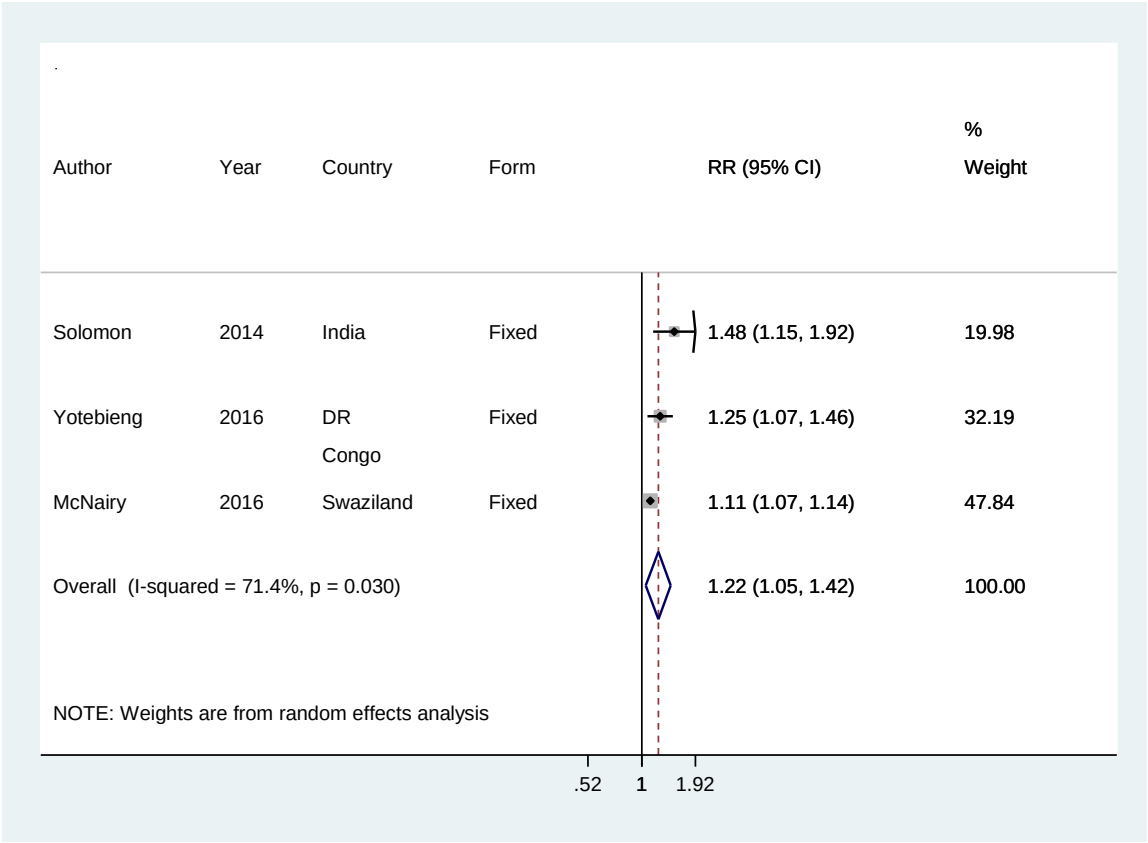
RR: risk ratio; CI: confidence interval; VMMC: voluntary medical male circumcision

† See Table 2 for full description of interventions

‡ Estimates as reported by the original authors or recalculated using the original data if not reported

* Includes CD4 count testing

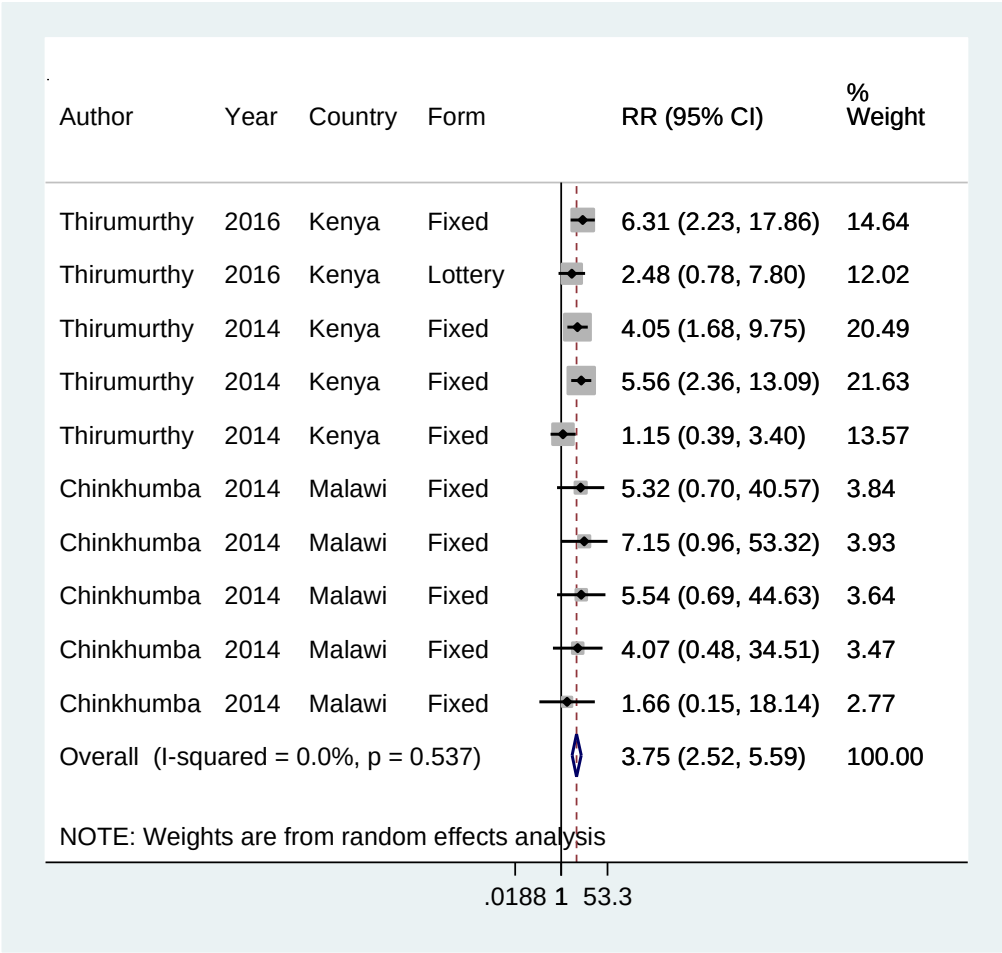
Figure 3.3-3: Forest plot of linkage to HIV treatment estimates



From meta-analysis of the data reported by the original authors (Table 3-3-4)

Form: mode of giving financial incentive

Figure 3.3-4: Forest plot of linkage to voluntary medical male circumcision estimates



From meta-analysis of the data reported by the original authors (Table 3-3-4)

Form: mode of giving financial incentive

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London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	AUGUSTINE TALUMBA CHOKO
Principal Supervisor	KATHERINE FIELDING
Thesis Title	Investigating interventions to increase uptake of HIV testing and linkage to care or prevention for male partners of pregnant women in antenatal clinics in Blantyre, Malawi

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Journal of the Internal AIDS Society (JIAS)		
When was the work published?	26 June 2017		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	No	Was the work subject to academic peer review?	Yes

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the idea for this work, developed the research protocol and wrote the manuscript. Dr Moses Kumwenda led and conducted data collection.

Student Signature: [redacted] **Date:** 12 June 2018

Supervisor Signature: [redacted] Date: 13/6/2018

4. A formative qualitative study

4.1 Introduction

Following the systematic review, a formative qualitative study was conducted in order to identify new interventions that may have been missed during the systematic review. Crucially, the aspects of the interventions that were identified through the systematic review needed to be refined to the local context hence the formative study was conducted. This chapter describes the methods and the results from this qualitative study and shows some key modifications that were made to the original design of the candidate interventions. The paper from this study was published in JIAS, 2017.

At the beginning of data collection for this qualitative study I was based in London but a graduate Social Scientist (Mr Moses Kumwenda) was employed on the project to lead fieldwork. I maintained regular discussions on a weekly, sometimes daily basis with Moses as the data tools were revised after feedback from each focus group discussion. I developed the protocol and the question guides for the qualitative study with input from the Social Scientist and other key collaborators such as Dr Nicola Desmond.

4.2 Formative study paper

Title: Acceptability of woman-delivered HIV self-testing to the male partner, and additional interventions: a qualitative study of antenatal care participants in Malawi

Authors: Augustine Talumba Choko[§1, 3], Moses Kelly Kumwenda[1, 2], Cheryl Case Johnson[8], Doreen Wongera Sakala[1], Maria Chifuniro Chikalipo[2, 7], Katherine Fielding[3], Jeremiah Chikovore[5], Nicola Desmond[1,6], Elizabeth Lucy Corbett[1, 4]

Affiliation:

TB/HIV Theme, Malawi Liverpool Wellcome Trust Clinical Research Programme
University of Malawi, College of Medicine
Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine
Department of Clinical Research, London School of Hygiene & Tropical Medicine
Human Sciences Research Council
Department of Clinical Research, Liverpool School of Tropical Medicine,
University of Malawi, Kamuzu College of Nursing
World Health Organization, Geneva, Switzerland

[§]**Corresponding author**

Malawi Liverpool Wellcome Trust Clinical Research Programme

P.O Box 30096

Chichiri

Blantyre 3

E-mail: augutc@gmail.com

Cell: +265999577452

Running head: Woman-delivered HIV self-testing in Malawi

Abstract

Introduction

In the era of ambitious HIV targets, novel HIV testing models are required for hard-to-reach groups such as men, who remain underserved by existing services. Pregnancy presents a unique opportunity for partners to test for HIV, as many pregnant women will attend antenatal care. We describe the views of pregnant women and their male partners on HIV self-test kits that are woman-delivered, alone or with an additional intervention.

Methods

A formative qualitative study to inform the design of a multi-arm multi-stage cluster randomised trial, comprised of six focus group discussions and 20 in-depth interviews, was conducted. Antenatal care attendees were purposively sampled on the day of initial clinic visit, while men were recruited after obtaining their contact information from their female partners. Data were analyzed using content analysis, and our interpretation is hypothetical as participants were not offered self-test kits.

Results

Providing HIV self-test kits to pregnant women to deliver to their male partners was highly acceptable to both women and men. Men preferred this approach compared with standard facility-based testing, as self-testing fits into their lifestyles which were characterised by extreme day-to-day economic pressures, including the need to raise money for food for their household daily. Men and women emphasised the need for careful communication before and after collection of the self-test kits in order to minimise the potential for intimate partner violence although physical violence was perceived as less likely to occur. Most men stated a preference to first self-test alone, followed by testing as a couple.

Regarding interventions for optimising linkage following self-testing, both men and women felt that a fixed financial incentive of ~ USD$2 would increase linkage. However, there were concerns that financial incentives of greater value may lead to multiple pregnancies and lack of child spacing. In this low-income setting, a lottery incentive was considered overly disappointing for those who receive nothing. Phone call reminders were preferred to short messaging service.

Conclusions

Woman-delivered HIV self-testing through antenatal care was acceptable to pregnant women and their male partners. Feedback on additional linkage enablers will be used to alter pre-planned trial arms.

Keywords: HIV, rapid HIV test, HIV self-testing, financial incentives, ANC, Malawi, sub-Saharan Africa

Introduction

About 54% of people with HIV in sub-Saharan Africa (SSA), the region hardest hit by the HIV epidemic, do not know their status. [1] The mortality rate in men is nearly twice that of women within the first three months of starting antiretroviral therapy (ART), [2] predominantly due to late diagnosis. [3] Although HIV prevalence is higher in women than in men in most parts of Africa, [4] men account for a disproportionately high number of undiagnosed HIV infections. [5] Indeed despite rapid scale up of HIV testing services (HTS) in sub-Saharan Africa high levels of discrimination and stigmatization associated with HIV testing and positive diagnosis impede impactful progress. [6] A number of strategies have shown effect on increasing the uptake of HIV testing for both men and women including home-based testing, provider initiated testing and counselling (PITC), and the promotion of couples-testing during antenatal visits. [7,8] A novel alternative strategy, HIV self-testing (HIVST), is now the subject of wider-scale implementation, with ongoing research aiming to define best practice for various populations. [9]

Antenatal care services provide a unique opportunity for reaching partners using couple-centred interventions including couples HIV testing services (cHTS). [10] Male involvement may improve maternal outcomes, in addition to contributing to more effective implementation of prevention of mother to child transmission (PMTCT) of HIV. [11] Male partner tracing in Malawi, [12] and distribution of woman-delivered HIVST during antenatal care (ANC) attendance in Kenya [13,14] were shown to be effective ways to increase uptake of HTS among men in three recent studies.

HIVST which involves an individual collecting their own sample, conducting the test and interpreting their result [15] overcomes most traditional barriers which hinder people's access to HTS. In particular, men commonly cite lack of transport, opportunity cost, being busy, fear of testing positive while with partner, and stigma among chief barriers to male partner testing and cHTS. [16,17,18] HIVST is usually offered and performed closer to people's homes making it convenient and less costly to individuals. [19,20] A self-test guarantees privacy and confidentiality which may allay fears of testing positive with a sexual partner, remove the stigma of being in the vicinity of an HIV testing point, [21] and caters for individuals whose busy schedule otherwise make testing less convenient. [15] Therefore, it seems little surprise that HIVST has achieved high uptake in different populations across the world. [22,23] As part of preliminary work to inform interventions for a proposed multi-arm multi-stage cluster-randomised trial we sought views regarding the acceptability of offering HIV self-test kits alone or in combination with a linkage intervention to ANC attendees aimed primarily at their male partners.

Methods

Design, setting and participants

We carried out a formative qualitative study using focus group discussions (FGDs) and in-depth interviews (IDIs) for data collection between October 2015 and February 2016. The study recruited ANC attendees at three primary health clinics (PHC) of Ndirande, Bangwe and Zingwangwa, in urban Blantyre, Malawi. These three PHCs were chosen because they serve a low-income urban population that is likely to benefit from future scale up of the interventions under investigation. Male partners of pregnant women, not necessarily as couples, who were attending these PHCs were also invited to participate in the study. Our conceptual framework (Figure 4.1-1) is based on the fact that there are many barriers which hinder or delay male partners from testing for HIV and linking to care or prevention. We expected that pregnant women-delivered HIVST alone or in combination with another intervention would address some of these barriers thereby increasing male partner testing and linkage into care or prevention.

Sampling, sample size and eligibility

Participants in the FGDs were purposively sampled with the aim of having between 8-12 participants per FGD. Two FGDs each with women only, men only and mixed gender were conducted (six in total), followed by twenty IDIs (10 men and 10 women) with some of the FGD participants. A group information session was held with women in the ANC waiting area; those who were interested were then screened for eligibility after completing their ANC attendance processes. Inclusion criteria were age (≥18 years, residence in urban Blantyre, and current ANC attendance (for women) or having a pregnant partner currently attending ANC (for men), and willingness to provide consent.

Female FGD participants were randomly selected from the list of eligible ANC attendees. For male FGD participants, we asked for partner contact information from the eligible ANC attendees, contacted the male partners to ascertain their eligibility and willingness to participate, and randomly selected (22-25) for men only FGD and seven for the mixed gender FGD. At the end of each FGD, participants were asked to participate in a follow-up IDI. Fifteen men and fifteen women were randomly selected from among those willing to participate in the IDIs (Table 4.1-1). All interviews were conducted at a convenient location and time in consultation with participants. A demonstration of HIVST was made during FGDs but participants were not offered the test, hence all results are based on a hypothetical framework.

Open-ended questions in the local language seeking to capture different key issues such as barriers to male partner testing, HIVST, adverse events due to HIVST and additional interventions) were used

to guide the FGDs (Figure 4.1-1). Similar themes were covered in IDIs although with a greater focus on soliciting individual perspectives. Doing the IDIs after participating in FGD likely allowed participants to reflect more on their individual experiences. Furthermore, IDIs may have helped participants feel more at ease to express their views than was the case in the FGD. [24]

Ethical considerations

The study was approved by University of Malawi, College of Medicine Research and Ethics Committee (COMREC), approval number: P.08/15/1784 and London School of Hygiene & Tropical Medicine (LSHTM) Ethics committee, approval number: 10332. All participants either gave written informed consent in the local language, or witnessed consent plus thumb-print if illiterate before participation. An impartial witness, usually a nurse at ANC read and helped the participants to understand the study information before consent was given. Participants were given MWK1000 (USD1.33) compensation for their time which is the minimum recommended by COMREC. Participants were given a number with which they were identified during FGDs, IDIs and during data analysis in order to uphold anonymity.

Data analysis

FGDs and IDIs lasted an average of two hours and 40 minutes, respectively. Data were captured using digital audio recorders and field summaries; the latter provided quick impressions about emerging issues and helped researchers to determine whether or not saturation of information was reached. Recorded data were translated and transcribed verbatim before being cleaned and stripped of any details that might make it possible to identify participants. Each transcript was manually coded by AC, MK, DS and MC using a predefined codebook and then compared across the four coders to assess inter-coder reliability. Simple descriptive content analysis was used to analyse the data in a process that involved the four researchers independently extracting data and later discussing each emerging category. The primary data coding was deductively done under two major themes namely: acceptability of woman delivered HIVST and potential linkage enablers that could be added to woman-delivered HIVST.

Results

Participation and characteristics of participants

Acceptance to participate was higher for women (78.9 to 87.5%) compared to men (32 to 40%) for separate gender FGDs (Table 4.1-1). However, men were more likely to actually participate in FGDs or IDIs once they accepted the invitation (Table 4.1-1). Of the 42 FGD participants, 18 (42.9%) were

men and 24 (57.1%) were women with each FGD varying in size from 6-8 participants (Table 4.1-2). Men were older [median age: 28.5, inter quartile range [IQR]: (25.0-31.0) vs. 23.5; IQR: 19.0-29.0)], had higher educational attainment, and were more likely to be employed compared to women. About two-thirds said they had ever tested together for HIV. Ten women and ten men participated in IDIs as planned. We present the data under three key themes that emerged: barriers to couple testing at ANC; acceptability of woman delivered HIVST; and additional interventions to HIVST to encourage partner linkage following HIVST. These themes echoed our conceptual framework (Figure 4.1-1).

Barriers to couple testing at ANC

Participants in both FGDs and IDIs cited well known and documented barriers operating at different levels (structural, community, couple, individual and economic) as hindrances to couple testing at ANC. Of note: stigma, discrimination and costs, both direct and indirect as well as time constraints in light of competing needs featured highly in discussions and interviews:

"Considering what happens here at ANC clinic, I don't see my husband escorting me anymore because you find he is alone among many women and he has to listen to some things concerning birth. …it's better if couples are given a private room to discuss" Female, FGD, Ndirande.

Fear of stigma and perceived lack of confidentiality was of concern to men:

"Before I escorted my wife to antenatal clinic I thought, if I go I will be the only man in a group of women and if I am tested all these women will know my status" Male, Zingwangwa, FGD.

Sociocultural norms often shaped men's decision-making around ANC and couple testing:

"My friends were just laughing at me, for example the day before yesterday when my wife told me to come to ANC clinic, when I told my friends they all said 'I was stupid because ANC clinic is not for men'" Male, Ndirande, FGD.

Couple-related aspects such as fear of blame, divorce and partner's reaction were gendered and were raised mostly by men especially in the context of potential discordant results:

"The problem is that you are afraid and worried about couple testing because you think if one tests negative and another positive it means the marriage will break up. Because of this fear and worry you prefer not to test" Male, Ndirande, FGD.

Men often said they could not balance economic needs and ANC attendance particularly as they had to get income on a daily basis:

"A person leaves his economic activities for the whole day to go to the clinic. Here in town, very few people have food for tomorrow. Most of us only have food for today. Now you go to the clinic, when you return, people (at home) *have no food, so it's better to go look for food f than to the ANC clinic"* Male, FGD, Zingwangwa.

Acceptability of pregnant woman-delivered HIVST

Most participants felt that this model of delivering HIVST would address most of the barriers that deter men from testing together with their partners at ANC. Convenience was among the top factors men highlighted.

"I feel like it's acceptable because maybe the day that the woman wants to go to ANC clinic you might not be able to escort her, so she can just bring you the test kits when she is coming back from ANC and the next time she is going for ANC then you can go together." Male, FGD, Ndirande.

Men and women felt that this model offers privacy and would remove stigma associated with men attending ANC and testing:

"Actually it will be very simple because it will be like 'ohh they have helped me here, I don't have to go to antenatal care and meet a lot of women.' It is better I just do it on my own because you cannot be shy with your wife especially if you know that your ways are faithful, you can just do it right there with your wife." Male, Mixed FGD, Ndirande.

For men, being the first to know meant HIVST offered control over their testing environment including disclosure, unlike the standard testing procedure:

"Men would definitely accept … they would say, 'aaah, why should the doctor test me? Aaah, it's better to be the first to know my HIV status.' *You would feel shy when meeting the doctor who knows that you are HIV positive."* Male, IDI, Ndirande.

Men emphasised the need to be the first to know your results:

"It [being tested at ANC] *did not really have privacy, but with how you have set it up to say one can test themselves using the test kits and know the results by themselves first then the privacy is there."* Male, FGD, Ndirande.

Concerns around woman-delivered HIVST

Some participants also highlighted *lack of immediate counselling* as potentially problematic as well as concerns around *trust*. Some men and women indicated that physical or psychological IPV or

verbal abuse may occur depending on how the woman has presented the issue or if prior consultation was not done with the man:

"There are some women with poor approach. They just begin by saying here are the test kits you have been dodging the subject and today I have brought them and we will test here at home [..laughs]. *So you can just slap her* […laughs] *and say go tell your Doctor to self-test with you not me* […laughs]." Male, FGD, Zingwangwa.

"They [taking self-test kits for him] *can cause misunderstandings if the man doesn't like it. He can ridicule you in everything you do or say. He will say you are stupid because you make decisions on your own and this can cause arguments and you can have no peace of mind."* Female, FGD, Zingwangwa.

Having said this, there was a general perception that a pregnant woman may not suffer physical IPV as a consequence of delivering HIVST to the partner:

"Even if the man can get angry, it's difficult for a man to beat his pregnant wife no matter how short tempered he is -- even if he has a history of beating her or abusing her in other ways." Male, FGD, Ndirande.

Women also agreed that physical IPV may be less likely to occur solely by dislike of test kits:

"…because in marriages there are things that make one to fear. Other men are difficult, yes others would manage but some cannot manage ... The only problem would perhaps be that he would just refuse and that is it, but not reaching the extent of beating [the woman]*, no.* Woman, FGD, Zingwangwa.

There were concerns from participants regarding the potential lack of counselling for the male partner with the woman-delivered HIVST model considering that HIV remains greatly feared by the society:

''AIDS is something scary, so if the person self-tests without a doctor maybe he can have suicidal thoughts or try to hurt himself. … When you are tested at the hospital, afterwards they counsel you. So if you just test yourself and find that you are positive, you can hurt yourself because there is no one to advise you about what to do next." Male, FGD, Bangwe.

Some participants expressed concern that when a woman brings HIVST kits into the relationship, it might be construed as a sign of mistrust towards the male partner:

"… you have brought me these? It just shows that you don't trust me'. So there really can be some problems, more especially if the approach was also not good." Male, Mixed FGD, Ndirande.

Conversely, men were said to prefer using the test kits secretly first particularly if they knew they had engaged in infidelity:

"…you just go out secretly and follow the method and right there it's as easy as drinking a glass of water. You quickly place it in the bottle and hide it since you want to check yourself first (participants laugh). *When the results are out you will check them and you will know the outcome yourself right?"* Male, FGD, Ndirande.

Communication

How a woman communicated to the male partner before and after collecting the test kits was considered vital to the success of the model:

''*The self-testing approach can be accepted by men provided they are told first before the woman collects the test kits. They should discuss it first as a family, that there is an approach being provided at ANC. Only after reaching an agreement can the woman collect the test kits.''* Male, IDI, Ndirande.

Men suggested that bedtime is the best for introducing such an issue to the relationship:

"... if the woman is smart, when people have just had supper, she goes 'aah let's retire now'. The time you go to your bedroom that's the time you can now start telling him to say 'my husband, I went to the hospital and I have come back with these [test kits]*…. this is how we use these materials."* Male, FGD, Zingwangwa.

The suggestion of using bedtime to introduce HIVST also featured highly in FGDs with women:

"When he is coming, show that he is welcome home. Greet him and ask how work was then you can discuss the other things in the bedroom when going to bed. When he gets home, don't just start talking to say I was at the hospital and this is what they have said and they have given me test kits so that we test ourselves. Is the man going to listen? But when we go to the bedroom where things between a man and a woman end." Female, FGD, Ndirande.

Some participants suggested the use of an official letter addressed to the male partner from the clinic as a means of easing the burden on women to introduce such a sensitive issue:

"We were given these forms [the invitation letters]*, so I feel like it would be a good way to also give them* [men] *something to read. After reading, they would be able to understand and when you get the kits, it will be an issue that they already know about."* Female, FGD, Zingwangwa.

Views regarding additional interventions to HIVST to encourage partner linkage following HIVST

Participants were asked about different pre-defined types of strategies that could be added to HIVST provided through ANC in order to increase HIV testing and linkage into care (such as antiretroviral treatment (ART) or prevention (condom use, counselling uptake and voluntary medical male circumcision). These strategies included: fixed financial incentives (low amount-transport equivalent ($3); higher amount-to cover transport and opportunity cost ($15); lottery incentive ($3 equivalent) with a 10% chance of winning; and short messaging service (SMS) or phone reminders). The choice of $3 was guided by a recent study conducted in the same setting which found that people spent an average USD3.91 to access HIV testing [20]. In short, virtually all participants preferred cash as opposed to voucher incentives.

Transport-equivalent incentive

Participants said that providing a low amount financial incentive would increase the number of male partners who would test and link into care or prevention. Such a strategy would remove a crucial economic barrier linked to transport costs as shown in the quote:

"Because when he self-tests, if you tell him to go to the clinic to receive counselling, he would say he has no transport to go there. But if transport money is there, he won't have any excuse." Female, FGD, Ndirande.

High amount financial incentive

Participants agreed that high financial incentives of about $10 would definitely improve linkage into care or prevention as this would compensate for opportunity cost as illustrated by the quote below:

"When you come to the clinic, you spend the whole day with no food for today. Providing a high financial incentive would encourage other male partners, upon hearing that their friend just got food for the day by simply going to the clinic" Male, FGD, Zingwangwa.

However, any amount considered excessive such as more than $10 was considered potentially problematic as it may lead to unintended negative consequences.

Some saw such an incentive as potentially promoting multiple sexual partnerships: or discouraging child spacing in marriages:

"You can wish you had brought with you three pregnant wives [for maximum financial incentive]*"* Male, FGD, Zingwangwa.

"It will be difficult for people to have adequate child spacing [with high financial incentive]*"* Male, FGD, Ndirande.

Lottery-type of incentives

Views regarding lottery-based incentives were predominantly negative among both men and women as most participants perceived lotteries as being highly inequitable and unfair:

"You may find that after the lottery, people that are better off -- who came by car -- are the ones who win the lottery. What would other people think?" Male, FGD, Ndirande.

Other participants felt that a lottery might even, as a result have an unintended negative group effect:

"And its only one person who has won while the ones who have lost are many, so the message that will be spread will be from the ones that have lost because they are many." Male, Mixed FGD, Ndirande.

However, some participants still felt that lotteries were acceptable to men and could help draw them into care, as described in the quote below:-

"It can also be good to the men because it will be like an encouragement for them to come and test; they will know that after testing 'I may win a prize'." Female, IDI, Ndirande.

Short messaging service (SMS) versus phone call reminder

Although participants agreed that SMS reminders would encourage male partners to test and link into care or prevention, they felt that a phone call reminder would offer greater room for dialogue and conversational engagement compared to an SMS reminder.

"Not many people read the SMS when they receive it. …many just ignore it, mistaking it for Airtel [Network provider] *promotional SMSs, even deleting before even reading. Better if it is phone calls..."* Male, FGD, Zingwangwa.

Problems that were highlighted with respect to phone call reminders mainly revolved around trust and lack of face-to-face dialogue when discussing sensitive issues. Women, for instance, expressed concern that their male partners may not like their phone numbers to be shared with the healthcare providers:

"I feel like the approach of calling someone can cause marriage breakups… The man can wonder what sort of conversation culminated into his partner to give his phone number." Female, Mixed FGD, Ndirande.

Being unable to read the mood of the call recipient and the mere absence of face-to-face interaction were flagged as potentially problematic with phone call reminders:

"Other people maybe you call them when they are in a bad mood or they just quarrelled with the wife, that's the problem of using phones." Female, Mixed FGD, Ndirande.

Discussion

Our investigation and data interpretation is based on a hypothetical framework in which women accessing ANC for their first visit would be offered HIV self-test kits alone or in combination with an additional intervention aiming to deliver to their male partner. This study has shown that providing HIVST kits to pregnant women who are accessing ANC with the aim of reaching out to their male partner would be acceptable to both men and women primarily because it was perceived to address key barriers associated with existing clinic-based HTS models. However, the results suggest that financial incentives may be useful in improving linkage into HIV care and prevention particularly in settings with extreme poverty. The use of lottery incentives was not preferred by participants, contrary to what is expected from economic theory which posits that given a high expected gain people are willing to take a risk. [25] The period of pregnancy is of high economic pressure and therefore may make partners risk averse. A number of modifications were made to the initial design of the cluster randomised trial following results observed here (Table 4.1-3).

High acceptability rates of HIVST have been documented globally in the general population, [26] healthcare workers, [27] key populations particularly among men who have sex with men (MSM), [28] and people coming to out-patient departments. [29] The findings observed here indicate very high perceived acceptability and these results are consistent with results from quantitative studies within the African region. [23] Two recent studies in Kenya showed that the uptake of HIV testing among male partners was 2-3 times higher in the arm that provided two self-test kits to pregnant women attending ANC compared to a standard male partner invitation letter. [13,14] However, the uptake of HIV testing was measured through surrogate reporting by the women or through self-reporting by men in both studies, which may in either case have led to overestimation. The ANC set-up was clearly not conducive for couple testing as many of our participants expressed concerns around stigma, discrimination and lack of privacy; barriers which are directly addressed by home use

of HIVST kits. These and other well-known barriers imply that currently strategies may not achieve high uptake among men and couples. [16,18,30]

Our data show that physical IPV was perceived to be less likely to occur for pregnant women delivering self-test kits to the partner especially if the kit were introduced at the right moment such as bedtime. This finding contrasts sharply with literature which suggests high prevalence of IPV among pregnant women within the African region (around 15%) [31] and in Malawi (21%). [32] However, in relationships with pre-existing IPV, participants suggested a more careful approach when introducing the topic of HIVST with bedtime suggested as the best time. It is important to also note that this perception that physical IPV may not occur may not generalise to other settings, and may not apply to all forms of IPV such as controlling behaviours or psychological, verbal and economic abuse. Two cases of IPV were reported among postpartum women in a woman-delivered model in Kenya. [13] In both cases, partners reconciled and in one case a man who was HIV-positive started HIV care. This study from Kenya used woman's reporting of male partner testing as the primary outcome whereas our design is around the proportion of men who test and link to the clinic.

Our findings that deliberate additional interventions to encourage male partners who self-test to link into care or prevention services are needed are consistent with an earlier controlled randomized trial conducted in Malawi that reported that the offer of optional home initiation of two weeks' worth of ART increased demand for ART compared to providing self-test kits only. [33] Furthermore, participants in the study cited well documented barriers that may pose additional challenges for people to link into ART or HIV prevention following HIVST. [34,35] A notable intrinsic barrier with HIVST is that individuals are diagnosed early in their disease progression implying that they may be less likely to prioritise the linkage step, and this may be particularly difficult for men. [30]

The data presented here suggest that the enduring economic pressure including finding food for the day that male partners face especially during the time their partner is pregnant may exacerbate their reluctance to seek HIV care or let alone prevention services. [36] Therefore, offering a cash financial incentive conditional on clinic attendance and receiving HIV care or prevention services may enable men to compensate for opportunity cost associated with clinic attendance. Views expressed here suggest that there is need to carefully design the type of financial incentive-based interventions as lottery-type of incentives were considered as likely to be less effective than fixed incentives. Two recent randomised controlled trials, one in Kenya [37] and another in Tanzania [38] showed no significant difference in the uptake of voluntary medical male circumcision between a lottery-based intervention and a control arm. These quantitative studies render more weight to our findings which suggest that in settings with extreme poverty, lotteries are perceived as potentially counter-

effective. Whilst we are uncertain as to why this may be the case, a possible explanation is that lotteries may take one's only hope of winning a big prize away. Furthermore, these findings may be explained by contextual differences or indeed the way lottery was presented to study participants.

Providing reminders is a low cost intervention that was thought of as an important strategy to ensure that male partners remember to prioritise a clinic appointment over other daily pressing activities. However, our results showed that a SMS reminder is not perceived as a good strategy for improving linkage. Based on other studies, the SMS intervention has shown effect in increasing HIV testing [39] and improving ART adherence[40] although other studies have reported no discernible difference for viral suppression [41] and adherence to TB treatment. [42] We found two aspects of the proposed SMS intervention to be potentially problematic and hence likely to lead to no effect: First, participants may not be able to actually read the contents of the SMS with the influx of "junk" SMSs due to unsolicited adverts leading to participants ignoring or deleting the SMS when it is just received. Second, due to the monologue nature of the SMS, participants may have unanswered questions relating to how to find the clinic or aspects of study procedures. Therefore, a phone call was suggested by the participants as the best form of reminder over an SMS.

Following this formative study a number of modifications were made to the initial design of the trial (Table 4.1-3) including giving cash as opposed to voucher incentives; reducing the high incentive amount from $15 to $10, making a phone call as opposed to sending an SMS as a reminder. Due to infidelity some men expressed preference to self-test alone first before repeat couple self-testing. This implied that three self-test kits should be provided to the woman during her ANC visit. The project budget does not allow us to provide three self-test kits as preferred by the participants. Similarly, a decision was made to maintain the lottery arm in the trial in order to formerly test the effect of a lottery incentive on linkage into ART or HIV prevention in this population.

We acknowledge a number of potential limitations. Firstly, being a qualitative study means that we were unable to actually offer participants the choices or the interventions in order to measure uptake of testing and linkage into care or prevention. Secondly, participants were purposively sampled such that the views may not necessarily represent all pregnant women and their male partners. The final set of interventions would have been best critiqued through a stakeholder workshop before formal testing in the trial but we were unable to conduct the workshop due to lack of time. However, high participation was observed in the FGDs even for mixed gender FGDs. The additional IDIs with previous FGD participants strengthens our study findings further as participants in the IDIs were now better placed to give their individual account having understood the questions from the FGD. Finally, we did not know the HIV status of the study participants as clearly this would

shape one's views differently. However, as we recruited women after receipt of ANC service, we believe they knew their HIV status at the time of the FGD or IDI.

Conclusions

Woman-delivered HIVST was perceived as highly acceptable to both male partners and their pregnant women attending antenatal care in urban Blantyre, Malawi. The introduction of this model was not considered to lead to adverse events including IPV. However, additional interventions will likely be required to encourage male partners who self-test to link into HIV care and HIV prevention including the use of conditional financial incentives. Feedback from the study was used to alter the design of a multi-arm multi-stage cluster randomised trial.

Competing interests: All authors have no competing interests to declare

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Authors' contributions

Grant holder: ATC
Conceived of the study: ATC and ELC
Provided input in the design of the study: ATC, MKK, ND, JC, KF, ND and ELC
Recruited participants and managed study data: MKK, DWS and ATC

Conducting data analysis: ATC, MKK, DWS, MCC
All authors contributed to refinement of the study protocol and approved the final manuscript.

4.3 Tables and figures

Table 4.3-1: Summary of participation

	Approached	Accepted		Participated	
Data source	n	n	%	n	%
FGD 1, women only	16	14	87.5	8	57.1
FGD 2, women only	19	15	78.9	6	40.0
FGD 3, men only	25	10	40.0	8	80.0
FGD 4, men only	22	7	32.0	6	85.7
FGD 5, mixed gender	14	6	42.9	6	100
FGD 6, mixed gender	12	8	66.7	8	100
Total, FGDs	108	60	55.6	42	70.0
IDI, men	15	13	86.7	10	76.9
IDI, women	15	15	100	10	66.7
Total, IDIs	30	28	93.3	20	71.0

FGD: focus group discussion; IDI: in-depth interview

Table 4.3-2: Characteristics of focus group discussion participants by gender (N = 42)

		Men		Women		Overall	
Characteristic		n	%	n	%	n	%
Total	Number	18	42.9	24	57.1	42	100
Age	Median (IQR)	28.5	25-31	23.5	19-29	27.5	22-30
PHC	Ndirande	8	44.4	10	55.6	18	42.9
	Zingwangwa	8	50.0	8	50.0	16	38.1
	Bangwe	2	25.0	6	75.0	8	19.0
Education	Primary	6	30.0	14	70.0	20	47.6
	Secondary	7	50.0	7	50.0	14	33.3
	Higher	5	62.5	3	37.5	8	19.1
Occupation	Paid employee	6	100	0	0.0	6	14.3
	Paid domestic worker	3	100	0	0.0	3	7.1
	Self-employed	6	66.7	3	33.3	9	21.4
	Unemployed	1	4.8	20	95.2	21	50.0
	Student	1	100	0	0.0	1	2.4
	Other	1	50.0	1	50.0	2	4.8
Marital Status	Married	17	44.7	21	55.3	38	90.5
	Never married	1	33.3	2	66.7	3	7.1
	Separated	0	0.0	1	100	1	2.4
Tested with partner before?	Yes	13	48.2	14	51.8	27	64.3
	No	5	33.3	10	66.7	15	35.7

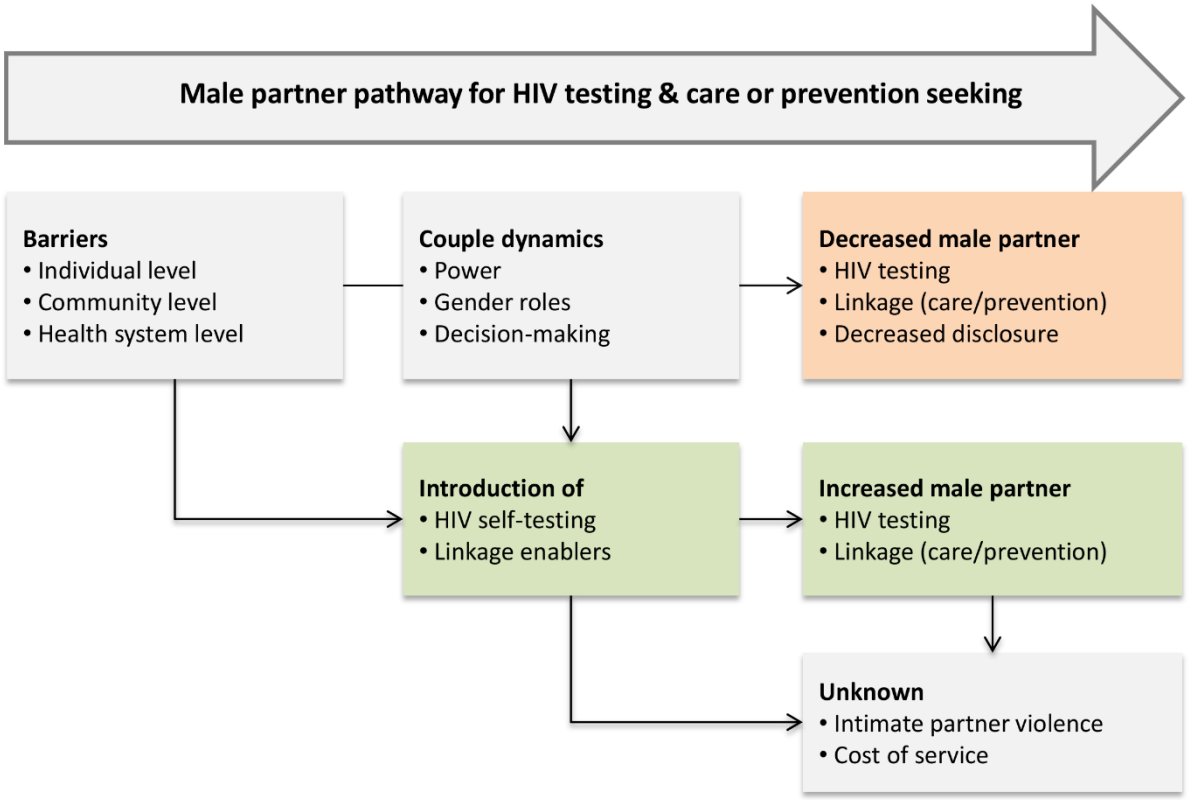
IQR: inter quartile range; PHC: primary health clinic

Table 4.3-3: Trial design tentative modifications post formative work

Prior plan	Post formative study plan
Give women 2 HIV self-test kits to take home	Give women 3 HIV self-test kits to take home*
Give voucher incentives	Give cash incentives
Have a medium incentive intervention arm	No longer have medium incentive arm
Give US$15 in the high incentive arm	Give US$10 in the high incentive arm
Only one winner in the lottery incentive arm	No modification to allow quantitative comparison
Send SMS to participants in the reminder arm	Make phone call in the reminder arm

* No change in the final design due to budgetary constraints

Figure 4.3-1: Conceptual framework



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London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	AUGUSTINE TALUMBA CHOKO
Principal Supervisor	KATHERINE FIELDING
Thesis Title	Investigating interventions to increase uptake of HIV testing and linkage to care or prevention for male partners of pregnant women in antenatal clinics in Blantyre, Malawi

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Trials		
When was the work published?	24 July 2017		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I wrote the protocol desecribed in this manuscript and wrote the manuscript

Student Signature: [redacted] **Date:** 12 June 2018

Supervisor Signature: [redacted] Date: 13/6/2018

5. Design of the adaptive multi-arm multi-stage cluster randomised trial

5.1 Introduction

This chapter describes the details of the protocol for the adaptive multi-arm multi-stage cluster randomised trial. The methodology as well as the candidate interventions that were finally taken forward after the systematic review and the formative work are discussed. This work was published in Trials Journal in 2017 and is given below as published.

5.2 Trial design and protocol paper

Investigating interventions to increase uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in antenatal clinics in Blantyre, Malawi: study protocol for a cluster randomized trial

Augustine T. Choko*[1,4], Katherine Fielding[4], Nigel Stallard[5], Hendramoorthy Maheswaran[5], Aurelia Lepine[4], Nicola Desmond[1,2], Moses K. Kumwenda[1,3], Elizabeth L. Corbett[1,3,4]

Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, Malawi

Liverpool School of Tropical Medicine, Liverpool, United Kingdom

College of Medicine, Blantyre, Malawi

London School of Hygiene & Tropical Medicine, London, United Kingdom

School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Warwick Medical School, Coventry, United Kingdom

ATC: augutc@gmail.com

KF: Katherine.Fielding@lshtm.ac.uk

NS: N.Stallard@warwick.ac.uk

HM: H.Maheswaran@warwick.ac.uk

AL: aurelia.lepine@lshtm.ac.uk

ND: Nicola.Desmond@lstmed.ac.uk

MKK: kumwenda@gmail.com

ELC: lizcorbett04@gmail.com

Corresponding author*

Malawi Liverpool Wellcome Trust Clinical Research Programme

P.O Box 30096

Chichiri

Blantyre 3

E-mail address: augutc@gmail.com

Mobile number: +265999577452

Abstract

Background

Despite large scale efforts to diagnose people living with HIV, 54% remain undiagnosed in sub-Saharan Africa. The gap in knowledge of HIV status and uptake of follow-on services remains wide with much lower rates of HIV testing among men compared to women. Here we design a study to investigate the effect on uptake of HIV testing and linkage into care or prevention of partner-delivered HIV self-testing alone or with an additional intervention among male partners of pregnant women.

Methods

A Phase II adaptive multi-arm multi-stage cluster randomised trial randomising antenatal clinic (ANC) days to six different trial arms. Pregnant women accessing ANC in urban Malawi for the first time will be recruited into either the standard of care (SOC) arm (invitation letter to the male partner offering HIV testing) or one of five intervention arms offering oral HIV self-test kits. Three of the five intervention arms will additionally offer the male partner a financial incentive (fixed or lottery amount) conditional on linkage after self-testing with one arm testing phone call reminders.

Assuming 25% of male partners link to care or prevention in the SOC arm, 6 clinic days, with a harmonic mean of 21 eligible participants, per arm will provide 80% power of detecting a 0.15 absolute difference in the primary outcome. Cluster proportions will be analysed by a cluster summaries approach with adjustment for clustering and multiplicity.

Discussion

This trial applies adaptive methods which are novel and efficient designs. The methodology and lessons learned here will be important as proof of concept of how to design and conduct similar studies in the future. Although small, this trial will potentially present good evidence on the type of effective interventions for improving linkage into ART or prevention. The trial results will also have important policy implications on how to implement HIVST targeting male partners of pregnant women who are accessing ANC for the first time while paying particular attention to safety concerns. Contamination may occur if women in the intervention arms share their self-test kits with women in SOC arm.

Trial registry name: ISRCTN. Number: ISRCTN18421340. Date registered: 31 Mar 2016

Key words: adaptive trials; HIV self-testing; cluster randomized trials; HIV, multi-arm multi-stage

Introduction

Sub-Saharan Africa (SSA) accounts for 70% of the global HIV burden despite rapid scale up of HIV services including testing. [1] Analysis of the HIV care cascade indicates a striking fall-off in numbers between testing and linkage into HIV care or prevention. [2] Men regularly feature among populations with lower uptake of HIV testing across SSA [3] and lower rates of linkage into care or prevention [4] in the era of extremely ambitious targets for HIV. [5] The 90-90-90 targets aim to diagnose 90% of all HIV cases, start 90% of diagnosed HIV cases on treatment, and achieve viral suppression in 90% of those started on HIV treatment. [5] Awareness of HIV status amongst male partners of antenatal clinic (ANC) women attendees is low with less than 35% undergoing HIV testing when invited through their partner. [6] African women face substantial risk of acquiring HIV infection estimated at 3.6% per pregnancy in study cohorts. [7] Over 90% of pregnant women access ANC services, providing an ideal opportunity to reach both partners with HIV testing and counselling services (HTS). [8]

A number of strategies have been found to increase uptake of HIV testing among male partners of ANC attendees, including home-based testing, [9,10] provider initiated testing and counselling (PITC), [11] couples testing during antenatal visits [12] and home-based couple or partner testing. [13,14] Key limitations of these strategies include: logistical difficulties of wide scale implementation where home visits are required, lack of convenience, costs, lack of confidentiality and failure to prioritise men's own health. [15,16,17] HIV self-testing (HIVST) is an alternative approach with potential to increase couple or partner testing [18] and has been found to be highly acceptable to men in Malawi. [19,20] Here we define *HIVST-plus* as offering HIV self-testing along with an additional intervention aimed at improving linkage into HIV care or prevention. Such additional interventions include facilitated linkage, [21] financial incentives (FI), [22] and short messaging services (SMS). [23]

This wide range of interventions presents technical challenges related to appropriate study design and analysis methods in order to identify optimal strategies. [24] Such complexity can be handled by applying multi-arm multi-stage (MAMS) designs, which are more flexible by allowing pre-specified adaptations at interim analysis, as well as more efficient with respect to time and cost than standard parallel designs. [25,26] In MAMS designs, several interventions are included in the first stage of the trial with pre-specified adaptations at interim analysis. Such a trial may either be a multi-stage Phase II or III, or can be done as a seamlessly trial combining all the three trial phases separated by interim analyses. [27] In general, MAMS designs involve comparing each of several interventions to a control arm using interim analysis, [25] providing an unbiased approach to investigating and selecting

multiple Phase II candidates under consideration for a future Phase III trial. [26] Although predominantly used in the pharmaceutical industry to date, MAMS trial designs could have value in public health evaluations where randomising at the cluster level is often preferred. Furthermore, public health interventions are often complex involving multiple components and understanding the effect of each component may help inform the optimal choice. [28]

Here we describe the design of a Phase II adaptive MAMS cluster randomised trial (CRT) with clinic day (not individual women) as the unit of randomisation. Our primary objective is to identify leading candidate interventions based on HIVST for improving HIV testing and linkage into care or prevention for male partners of ANC attendees in Blantyre, Malawi.

Methods

Design

This is a Phase II adaptive MAMS cluster randomised trial using ANC day as the unit of randomisation. As a Phase II trial the study is intended to investigate *efficacy* relating to uptake of testing and subsequent HIV services by the male partner, *safety outcomes, and* to provide an estimate of *acceptability* to the pregnant woman. The trial will have one interim analysis during which pre-planned adaptations will be made as described below, followed by final analysis at the end of the second stage (2-stage MAMS design). The first stage will have six arms with one SOC and five intervention arms (Figure 5.1-1). At the end of the first stage, a 3-point criteria will be considered by an independent data safety and monitoring board in order to drop intervention arms. Each intervention versus the SOC yielding $p > 0.2$ will be considered to be dropped; safety concerns; and costs will guide recommendations to drop or retain an intervention arm at the end of the first stage. The trial will not stop for efficacy at the interim analysis.

Analysis of second stage (end of trial) data will potentially lead to a definitive study (Phase III) involving arms that show promise at the end of the second stage. Sample size of 36 ANC days (6 per arm) will be required for the first stage (see Sample size section below for justification). In order to control the family-wise error rate (FWER) at the specified significance level ($\alpha=0.2$) for the five comparisons with the SOC arm, the Dunnett's test [29] will be applied.

Trial simulation

A simulation study was set up to compute the overall probability of the trial to find at least one intervention whose efficacy is different compared to the SOC arm at the end of stage two (minimal power). The simulation was conducted under the alternative hypothesis with an assumed effect of

29-40% vs. 25% in the SOC arm (Table 5.1-1). Additional key assumptions included that each ANC day (cluster) would have 20 participants with power set at 80% for each stage (Table 5.1-1). The simulation showed that at least two interventions would significantly improve the trial primary outcome (Table 5.1-2). These interventions would then be further tested in a potential Phase III trial.

Study setting and population

The study will recruit participants from Ndirande, Zingwangwa and Bangwe primary health clinics (PHC) in urban Blantyre, Malawi. All women attending antenatal care for the first time at these PHCs and their male partners will be eligible for participation. Women and their male partners will be excluded if they received couple or partner HIV testing in the current pregnancy; either are aged <18 years old; if male partner is reported to be HIV positive by the pregnant woman; already recruited in this trial; and not urban Blantyre resident. Malawi has recently (September 2016) implemented the test and treat approach where everyone diagnosed with HIV starts antiretroviral treatment immediately.

Randomisation and recruitment flow

Each ANC day was randomised to any one of the six trial arms using a randomised permuted block design in a ratio of 1:1:1:1:1:1 (Figure 5.1-2). All three PHC clinics are of comparable size and serving comparable catchment populations, and therefore stratification was not deemed necessary. The allocation sequence was generated by an independent statistician using computer-generated random numbers. [30] The file containing the complete randomisation sequence will only be accessible to the independent statistician.

Field workers will enrol women into one of the six study arms on the morning of each ANC day after receiving the randomisation allocation for that ANC day. Women will receive study information in a group while in the ANC waiting area followed by one-on-one eligibility assessment and subsequent recruitment. Study information given during group sessions will not reveal details of arm-specific procedures to avoid potential non-participation associated with knowledge of procedures for each arm. All women who show interest at this stage will provide unwritten consent to participate by show of hands followed by written or witnessed thumb print consent.

Standard of care arm (SOC)

In the SOC arm women will receive a personalised letter only addressed to their male partner inviting him to go to the male friendly clinic (MFC) to have an HIV test, receive HIV care or prevention and pregnancy related education. The MFC is being implemented by the trial, and will

offer men attending confirmatory HIV testing, facilitate linkage to HIV care or voluntary male medical circumcision (VMMC), and pregnancy-related health education.

Intervention arms

In all five intervention arms, the woman will receive self-test instructions and two self-test kits to take home. The test kits, test instructions and a personalised letter will be delivered to the male partner by the woman in order to initiate dialogue for him to test and link to the MFC for HIV care or prevention as appropriate.

The five intervention arms differ with respect to financial incentives, participation in a lottery, and phone call reminders received by the male partner. Women in the first intervention arm will only receive the letter and the two self-test kits. In the two fixed financial incentive (FI) arms, male partners who self-test (test) and link into the MFC will receive an equivalent of $3 or $10 in the low and high FI arms, respectively. In the lottery FI arm, male partners who test and link into the MFC will have a 10% chance of winning $30. In the final intervention arm, male partners will get a phone call, through a number given to the study team by the woman at enrolment, to remind him to test and link into the MFC. All FIs will be disbursed as cash through mobile money in the trial in order to safeguard the safety of staff and are conditional on the male partner linking into the MFC.

Primary and secondary outcomes

The primary outcome is the proportion of male partners of ANC attendees who test for HIV and link into HIV care or prevention within 28 days of enrolling the woman (Figure 5.1-3). Thus, the primary outcome is defined as presentation of the male partner at the MFC with a used self-test kit (if in the intervention arm) or undergoing on spot HIV testing with a study HIV counsellor within 28 days AND being referred for HIV care if HIV positive or VMMC if HIV negative and uncircumcised. There are four secondary outcomes: the proportion of male partners who test for HIV within 28 days (as reported by the woman); the proportion of women who accept to participate in their allocated trial arm; risk of serious adverse events (SAEs) by males and females in the study; and the total cost of implementing each trial arm. All outcomes will be analysed at cluster level (see statistical analysis section).

Outcome measurement

All male partners who present at the male friendly clinic in the SOC arm will be offered a single finger prick HIV test with Determine 1/2™ as per Malawi national testing algorithm. An HTS counsellor will re-read a used self-test kit if the participant returns one as evidence of self-testing in

the intervention arms. Participants who return with unused self-test kits or without self-test kits will be requested to self-test in the presence of the counsellor. All HIV results will be recorded on a data form followed by confirmation of HIV positive results in parallel using Determine 1/2™ and Uni-Gold, with facilitated linkage to HIV care. All men who test HIV negative and report to be uncircumcised will be offered VMMC to be conducted by Population Services Internal (PSI). Thus, measurement of primary outcome includes evidence of an HIV test, confirmatory testing, and referral to HIV care or VMMC as appropriate within 28 days of the woman being recruited.

The secondary outcome of HIV testing among male partners will also be measured though proxy reporting by the woman using audio computer-assisted self-interview (ACASI) during her next ANC visit four weeks later. Participation in the allocated trial arm will be measured by computing the proportion of women who accept to participate after receiving trial-arm specific information using the denominator of the total number of women who are eligible. All women will be asked to report any adverse events through ACASI at their next ANC visit while men who present to the MFC will be asked to report any adverse events. A costing tool validated in urban Blantyre [31] will be used to capture the costs associated with providing the service in each trial arm. The cost and outcome data will be used to estimate the cost per male partner tested for HIV, and cost per male HIV-positive identified through all SOC and intervention arms.

Sample size considerations

A modification of the formula for sample size calculation for a MAMS design for binary outcomes [32] was made based on the methodology for cluster randomised trials (CRTs) [33] to identify each stage of the trial. We assume that each ANC day will have at least 40 women attending for the first time, 90% will satisfy the eligibility criteria and at least 60% will consent to participate, so having a cluster-size of at least 21. We also assume that in the SOC arm 25% of males will satisfy the definition of the primary outcome. [34] For the first stage six ANC days per arm (36 days in total) would be needed to detect an absolute difference of 15% in linkage compared to 25% in the SOC arm using a FWER of 0.2 with 80% pair-wise power and a coefficient of variation (k) of 0.10. [21] In general, under the stated assumptions the trial has 80% chance of detecting a 1.6-fold increase in testing and linkage within 28 days compared to SOC at 5% significance level. Sample size for the second stage will be re-calculated based on empirical estimates at interim analysis with FWER of 0.1 and 80% power.

Very little clustering within ANC days is expected hence we have assumed that k=0.10 (intraclass correlation coefficient = 0.003). The simulation study assumed k=0.2 and differs with the final design

in this respect resulting in six and seven clusters per arm in the final design and the simulation, respectively. A larger than conventional (0.05) FWER of 0.2 and 0.1 for stage 1 and stage 2, respectively may lead to erroneously taking forward an ineffective intervention. However given that this is a Phase II trial this is not a major concern as it guards against dropping interventions that may otherwise prove to be effective in a larger, Phase III trial. A more conventional pair-wise power of 0.8 was chosen to ensure that there is a high chance of taking forward most of the efficacious interventions from stage 1.

Statistical analysis

Analyses will be done in R [35] and Stata 14.0 (Stata Corp, Texas, USA). Baseline characteristics will be computed as proportions or median (interquartile range [IQR]), as appropriate, by arm in each of the two stages of the trial. Any variables that show imbalances will be adjusted [33] for when analysing the trial outcomes at the end of the second stage. We will assume that the two stages of the trial are independent [26] and will proceed to carry out a test of the null hypothesis of no difference in effectiveness of each intervention compared to the SOC. We will do this by analysing data from the first stage first followed by interim decisions to drop arms; then we will conduct and analyse data from the second stage (no overlap of participants from the first stage). Analysis of the whole trial will then be based on combined p-values from both the first stage and the second stage using the weighted inverse normal (WIN) method [36] for arms that are not dropped at interim. A weighted average of the log (risk ratio [RR]) will be computed for the whole trial using estimates from each trial stage. All analyses will be by intention-to-treat taking as the denominator the number of women who were eligible and take into account the clustered design.

Given the small number (six) of clusters per arm in the first stage, analysis will be by cluster-level summaries using mean of proportion of male partners per clinic day who link to care or prevention in each arm. [33] The proportion of male partners who link into care or prevention will be computed per clinic day for each arm with number of men achieving the primary outcome and the number of women eligible and recruited in ANC on enrolment day as denominator. A log transformation of the clinic day proportions will be applied if a positive skew is observed. [33] The geometric mean of clinic day proportions in each of the five intervention arms will be compared to the SOC arm using unpaired t-test. [33] An estimate of the RR and a 95% CI will also be computed for each comparison by dividing the geometric mean of proportions in each intervention arm and the geometric mean of proportions in the SOC arm. [33]

This analysis involves more than two comparisons with a single control arm which can lead to higher than the specified family wise error rate (FWER) or significance level. Therefore, a Dunnett's test [29] will be applied to the t-statistics generated from the unpaired t-test to control the stage-wise FWER. Final decision-making at interim analysis will compare the Dunnett's-corrected p-values to stage 1 FWER of 0.2. The first of the 3-part criteria for dropping trial arms will then be considered after examining final p-values at the end of the first stage (interim analysis). Although sample size will be re-calculated at the end of stage 1, the total number of clinic days per arm is still presumed to be small for stage 2. Since the two stages are assumed to be independent, cluster level summaries approach analogous to stage 1 analysis will also be followed in stage 2 comparing intervention arms that proceed to stage 2 with the SOC arm. A detailed analysis plan will be developed to guide analysis of the trial.

Adaptations at interim analysis (end of stage 1)

Interim analysis at the end of stage 1 will assess whether any of the five intervention arms should be dropped as recommended by an independent data monitoring and safety board (DSMB) based on a 3-part criteria. First, an arm whose statistical comparison to the SOC arm yields a p-value>0.2 will be considered for dropping for futility. Second, any intervention arm with *high* incidence of SAEs i.e. grade 3, 4 or 5 (Table 5.1-3) compared to SOC will be considered for dropping. It is the discretion of the DSMB to decide based on absolute number of SAEs in each intervention trial arm whether they are high or not. Such an observation and recommendation will then be shared with the investigators who will make the final decision. Thirdly, an arm may be maintained after taking into account the costs associated with providing the service in light of the p-value from statistical analysis. For this cost analysis, we will provide the DSMB estimates of the incremental cost per male partner tested, and incremental cost per male HIV positive identified through the intervention arms in comparison to the SOC arm. The investigators will access the first stage data only after the last follow-up visit for participants has occurred in order to perform interim analysis. The CRT extension to the CONSORT [37] will be followed when reporting the data.

Discussion

This is the first study that we are aware of that will use adaptive trial methodology in the context of randomising clusters rather than individuals. In this paper, we describe the methodological approaches to developing an adaptive CRT, to provide timely and cost-efficient understanding of optimal strategies to improve uptake of HIV testing and linkage into HIV care and prevention amongst male partners of pregnant women in a high HIV prevalent setting. The methodology and

lessons learned here will be important as proof of concept of how to design and conduct similar studies in the future. Being a Phase II trial means that fewer resources can be allocated to a "learning" phase of a major Phase III trial to narrow down to interventions that hold true rather than assumed potential effectiveness. As a multi-arm trial it allows the investigation of interventions that can act on their own, such as providing self-test kits only, or in combination, where an incentive or a reminder is given. This approach, which is one of the key strengths of adaptive trials allows generation of clear evidence relating to specific intervention components that are effective when compared to the standard of care.

The 2020 UNAIDS targets set in 2014 aims to get 90% of people living with HIV diagnosed and to start on ART 90% of those diagnosed leading to virus suppression in 90% of those on ART. [5] While HIVST has been shown to increase uptake of HIV testing to within the first 90, very limited evidence exists on effective interventions for improving linkage into care, the second 90. In a recent trial in rural South Africa and Uganda, having a lay counsellor visit newly diagnosed individuals had minimal impact on linkage (risk ratio of 1.04). [38] A combination strategy of conducting point-of-care CD4 at the time; accelerated ART initiation for adults with CD4< 350cells/uL; mobile phone appointment reminders; health educational packages; and non-cash financial incentives improved from 83% in the SOC arm to 92% in cluster randomised trial in Swaziland. [39] However, the authors acknowledged that the multiplicity of interventions offered in the trial obscure the isolation of successful intervention components. Therefore, though small this trial will potentially present good evidence on the type of effective interventions for improving linkage to HIV care or prevention, and also the right dose for financial incentives that may be effective.

The trial results will also have important policy implications on how to implement HIVST targeting male partners of pregnant women who are accessing ANC for the first time while paying particular attention to safety concerns. In a recent cohort study where HIV negative pregnant women collected three oral self-test kits in Kenya 51% reported that their male partners had self-tested with none of the women reporting any serious adverse events. [40] Unlike in the Kenya study where only HIV negative pregnant women were eligible this trial will recruit pregnant women regardless of HIV status who are attending their first ANC. The group of women recruited here receives the offer of an HIV test routinely making this trial design readily scalable. Measuring actual HIV testing is extremely difficult with HIVST as by definition disclosure depends on the individual. Our HIV testing outcome will be measured objectively through observed returned used/unused self-test kits by the man and also proxy reporting by the woman which minimises information bias.

A major anticipated constraint is potential for serious adverse events resulting mainly from intimate partner violence (IPV) to women, although evidence from studies using other populations and other HTS models suggests this approach is unlikely to increase this problem. [6] A recent large HIV self-testing study in Malawi found no increase in IPV, despite an active community liaison system among 27,000 self-testing participants. [20] We will carefully monitor IPV, and have deliberately listed this as a secondary (safety) outcome. Although it will not be possible for participants and recruiting staff to predict the next-day recruiting arm, the knowledge of FI arms may result in altered decision-making about health care seeking. For example, a woman may choose to postpone her ANC attendance in the hope of being recruited in a FI arm, or indeed want to switch between arms.

There is potential for contamination if women in the intervention arms share their self-test kits with women in standard of care arm. In order to minimise this problem, we will ask women and their male partners in the intervention arms to bring used or unused self-test kits at follow-up and when they link into the male friendly clinic, respectively. We will also attempt to measure the magnitude of this problem by asking all women and male partners who link into the male friendly clinic in the standard of care arm if they received self-test kits. There is potential bias in the estimation of the treatment effect and confidence intervals due to interim selection process of potential effective interventions which we will not explore.

Trial status

At the time of submission on 9 November 2016 32 of 36 clusters (total of 800 participants recruited) were covered for the first of the two trial stages. Interim analysis is planned for 20th January 2017. Second stage is planned to run for four months, we will compute the required sample size for the second stage at interim analysis to achieve the specified 80% power.

Abbreviations and acronyms

ACASI	audio computer assisted self-interview
ANC	antenatal clinic
ART	antiretroviral treatment
CI	confidence interval
COMREC	College of Medicine Research and Ethics Committee
CRT	cluster randomised trial
DSMB	data safety and monitoring board
FI	financial incentive
FWER	family-wise error rate
HIV	human immunodeficiency virus
HIVST	HIV self-testing
HTS	HIV testing services
IQR	interquartile range
LSHTM	London School of Hygiene & Tropical Medicine
MAMS	multi-arm multi-stage
MFC	male friendly clinic
MLW	Malawi Liverpool Wellcome Trust Clinical Research Programme
PHC	primary health centre
PI	principal investigator
PITC	provider-initiated testing and counselling
RR	risk ratio
SAE	serious adverse events
SD	standard deviation
SOC	standard of care
SMS	short messaging service
SSA	sub-Saharan Africa
VMMC	voluntary male medical circumcision
WIN	weighted inverse normal

Declarations

Ethical Approval and Consent to participate

Ethics approval was obtained locally from the College of Medicine Research Ethics Committee (COMREC) in Malawi (approval number P.04/16/1932) and from the London School of Hygiene & Tropical Medicine Ethics Committee (approval number 11308). A letter of permission was obtained from the Blantyre district health office under which the three primary health centres of recruitment fall. This letter was used to introduce the trial to the in-charges of each clinic and no specific approval was required for this introductory process All trial participants will give written or witnessed (with thumb print for illiterate participants) consent before undergoing any trial procedures. Written consent for male partners was waived by the two ethics committees because the first contact is with the woman. Only authorised personnel will handle the study data with password protection of both the computer and the study database. Final data will be fully anonymised to remove any participant identifying information to uphold confidentiality.

Consent for publication

Not applicable

Availability of supporting data

Not applicable

Competing interests

The authors declare that they have no competing interests.

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QA844), WC1E 7HT, Keppel Street, +44 20 7636 8636, London, United Kingdom. Contact person: patricia.henley@lshtm.ac.uk.

Authors' contributions

Grant holder: ATC

Conceived of the study: ATC and ELC

Provided statistical expertise in trial design: KF and NS

Provided expertise in interventional design: ATC, HM, AL, ND, MKK, and ELC

Implemented the trial: ATC and MKK

Conducting primary statistical analysis: ATC and KF

All authors contributed to refinement of the study protocol and approved the final manuscript.

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Dr. Medson Matchaya, District Health Officer for Blantyre for giving permission to recruit from the primary health clinics.

Authors' information

Not applicable

Additional files

Additional file 1: SPIRIT checklist

5.3 Tables and figures

Table 5.3-1: Simulation inputs

Description	Input
Number of ANC days (clusters) per arm for both stages	6-20
Number of participants per ANC day	20
Linkage to care or prevention for the SOC arm in stages 1 and 2	25%
Linkage to care or prevention for the 5 intervention arms in stages 1 and 2	29-40%
SD of the mean of cluster-level proportions per arm (7 clusters, stage 1)†	0.05-0.08

ANC: antenatal care; SOC: standard of care

SD: standard deviation

†Computed using $\sigma = k \times \mu$ where σ is the standard deviation of the true cluster-level proportions; k is the coefficient of variation (assumed to be 0.2) and μ is the mean of the proportions per arm

Operating characteristics: stage 1 α=0.2; stage 2 α=0.1; 1-β=0.8

Table 5.3-2: Simulation results

Study arm	First stage *Proportion	SD**	Simulations in which arm was dropped at interim‡ Proportion	Assumed Proportion†
1 Standard of care	0.250	0.048	NA	0.250
2 Intervention	0.291	0.055	0.441	0.290
3 Intervention	0.299	0.058	0.336	0.300
4 Intervention	0.310	0.059	0.215	0.310
5 Intervention	0.321	0.061	0.114	0.320
6 Intervention	0.400	0.078	0.000	0.400

Note: Exact intervention not specified here as there is no evidence about a particular one of the 5 interventions being investigated

SD: standard deviation

* Proportion of male partners linked to care or prevention

** Assumed (0.050, 0.058, 0.060, 0.062, 0.064, 0.080) in arms 1-6, respectively

† Scenarios assumed for the six trial arms at the start

‡ If p-value was > 0.2 at interim analysis, discontinued from recruitment

Table 5.3-3: Adverse events grading

GRADE 1 (Mild)	GRADE 2 (Moderate)	GRADE 3 (Severe) (Within 30 days)	GRADE 4 (Potentially life-threatening) (Within 30 days)
Verbal, emotional or psychological Intimate-partner violence (IPV) Denying access to household resources Being ignored Being controlled (e.g. not allowed to leave house)	Coercion to self-test. Coercion to disclose a self-test result IPV that includes pushing, or slapping with an open hand that does not result in pain, or visible marks >24hrs Severe or prolonged psychological or emotional IPV leading to disruption of daily activities Psychologically coercive sex	IPV that leads to pain, bruising or marks >24hrs. Threat of life-threatening violence (e.g. statement of intent to kill, mock strangulation, threatened with a knife or gun Physically coercive sex Reports fearing for her life Marriage break-up	IPV leading to hospitalisation or death Suicide or attempted suicide Attack using potentially lethal force (e.g. knife, gun, hammer, kicks to the head)

Grade 1 indicates a mild event

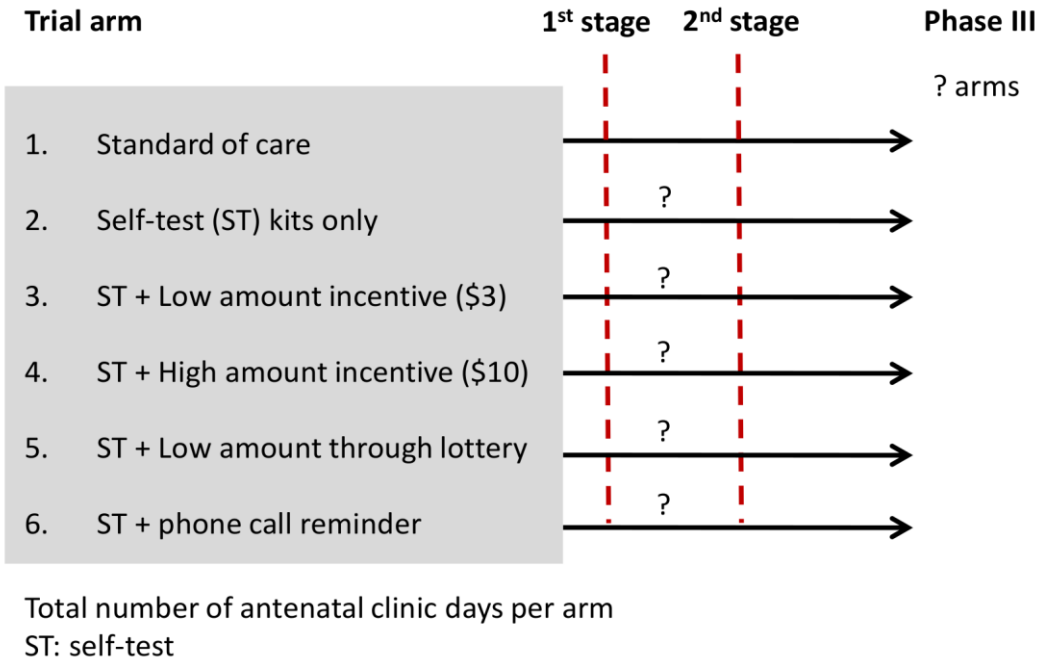
Grade 2 indicates a moderate event

Grade 3 indicates a severe event

Grade 4 indicates a potentially life-threatening event

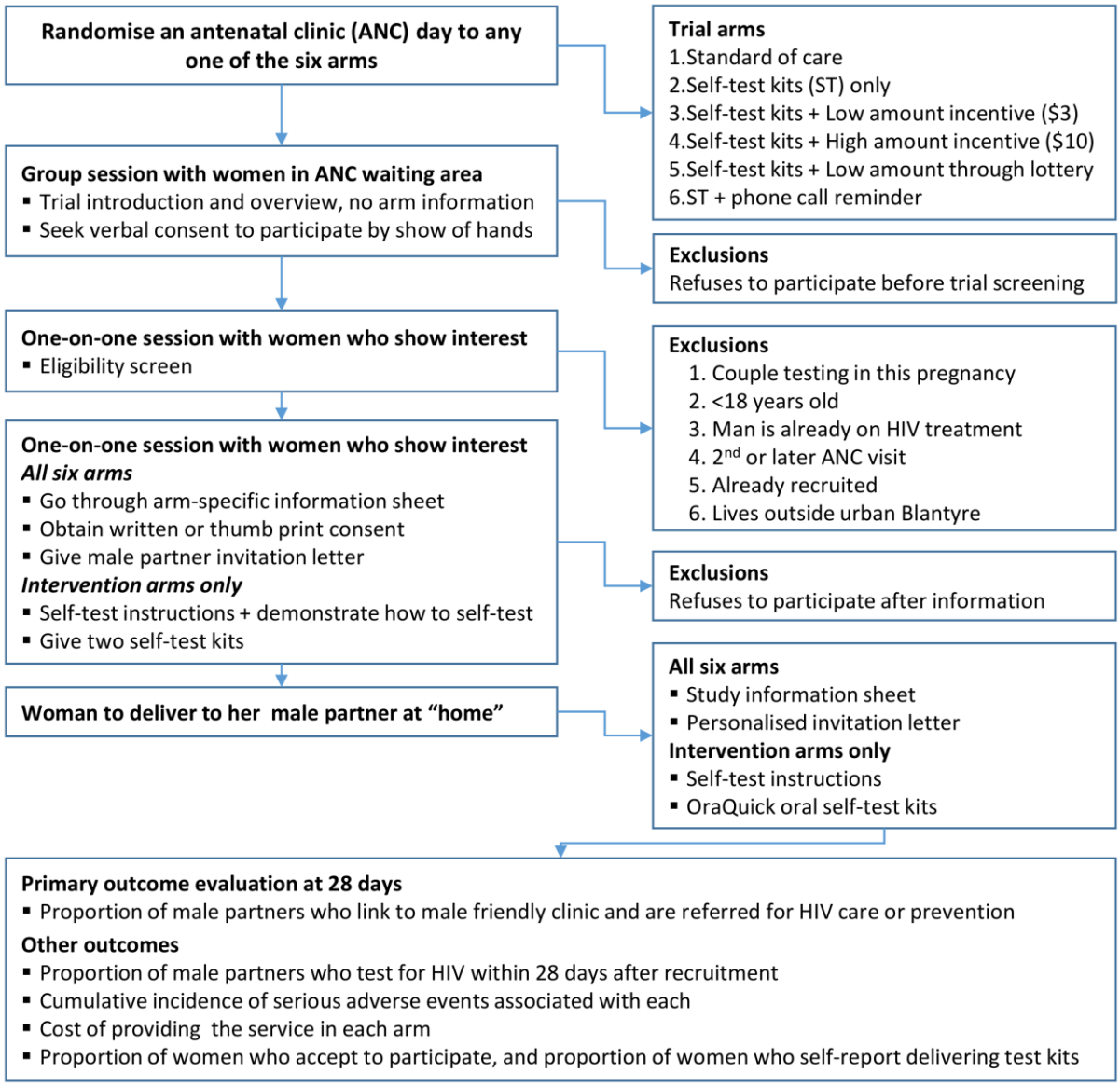
Grade 5 indicates death. Not indicated on the table

Figure 5.3-1: Schema of the Phase II adaptive multi-arm multi-stage cluster randomised trial



A 2-stage multi-arm multi-stage (MAMS) trial design starting with six arms in the first stage. At interim analysis (end of first stage) some trial arms may be dropped, with recruitment to the remaining arms aiming to narrow down to a few arms that may be carried forward to a definitive (Phase III) trial.

Figure 5.3-2: Randomisation, recruitment, and outcome evaluation



Each cluster (antenatal clinic day) is randomised to any of the six trial arms. All women attending their first antenatal clinic are briefed about the general purpose of the trial without getting trial arm-specific information. Women then undergo one-on-one eligibility screen and arm-specific information. Women who are eligible and accept to participate are then given a male partner invitation letter alone or with two self-test kits to take home.

Figure 5.3-3: Schedule of enrolment, interventions and assessments (SPIRIT)

		STUDY PERIOD						
	Pre Enrolment	Enrolment	Allocation	Post-allocation				Close-out
TIMEPOINT	*-t_1*	*Week 0*	Week 0	*W_1*	*W_2*	*W_3*	*W_4*	*W32*
RANDOMISATION AND ALLOCATION	X							
ENROLMENT:								
Group education		X						
Eligibility screen		X						
Informed consent			X					
Allocation			X					
INTERVENTIONS:								
Invitation letter only				♦—	—	—	—♦	
Invitation letter + 2 ST kits				♦—	—	—	—♦	
Invitation letter + 2 ST + $3				♦—	—	—	—♦	
Invitation letter + 2 ST + $10				♦—	—	—	—♦	
Invitation letter + 2 ST + lottery				♦—	—	—	—♦	
Invitation letter + 2 ST + reminder				♦—	—	—	—♦	
ASSESSMENTS:								
Demographics, HIV testing history		X	X					
Had an HIV test; linked to clinic					X		X	X
Had adverse event; cost per person tested and linked				X	X	X	X	X

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London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
www.lshtm.ac.uk

Registry
T: +44(0)20 7299 4646
F: +44(0)20 7299 4656
E: registry@lshtm.ac.uk

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SECTION A – Student Details

Student	AUGUSTINE TALUMBA CHOKO
Principal Supervisor	KATHERINE FIELDING
Thesis Title	Investigating interventions to increase uptake of HIV testing and linkage to care or prevention for male partners of pregnant women in antenatal clinics in Blantyre, Malawi

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
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If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	PLoS Medicine
Please list the paper's authors in the intended authorship order:	Augustine T. Choko, MSc, for the TB/HIV Group; Elizabeth L. Corbett, PhD; Nigel Stallard3, PhD; Hendramoorthy Maheswaran, PhD; Aurelia Lepine, PhD; Cheryl C. Johnson, MA; Doreen Sakala, BA; Thokozani Kalua, MSc; Moses Kumwenda, MSc; Richard Hayes, MSc; Katherine Fielding, PhD
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I conceived the idea of the trial and was the chief investigator, wrote the protocol, managed all aspects of the trial including staff and field work. I analysed the data and wrote the manuscript

Student Signature: [redacted] **Date:** 12 June 2018

Supervisor Signature: [redacted] **Date:** 13/6/2018

6. Trial results and other trial components

6.1 Introduction

This chapter gives the main and posthoc results from the adaptive cluster randomised trial. The methodology for the trial is briefly described with the assumption that this is fully described in chapter 5. These results were submitted to PLoS Medicine and the submitted manuscript is given below verbatim. Some additional analyses are presented at the end of the manuscript. These results were not included in the main trial results paper because they do not compare the trial arms.

6.2 Trial results paper

Title: A multi-arm trial of HIV self-testing and linkage incentives for partners of pregnant women (PASTAL)

Authors:

Augustine T. Choko[1, 2], MSc, for the TB/HIV Group; Elizabeth L. Corbett[1, 8], PhD; Nigel Stallard[3], PhD; Hendramoorthy Maheswaran[4], PhD; Aurelia Lepine[5], PhD; Cheryl C. Johnson[6, 8], MA; Doreen Sakala[1], BA; Thokozani Kalua[7], MSc; Moses Kumwenda[1], MSc; Richard Hayes[2], MSc; Katherine Fielding[2], PhD

Affiliations:

1. TB/HIV Group, Malawi-Liverpool-Wellcome Clinical Research Programme (MLW), Blantyre, Malawi
2. Dept. of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine (LSHTM), London, UK
3. Warwick Medical School, University of Warwick, Coventry, UK
4. Institute of Psychology, Health and Society. University of Liverpool, Liverpool, UK
5. Dept. of Global Health and Development, London School of Hygiene & Tropical Medicine (LSHTM), London, UK
6. World Health Organization, Geneva, Switzerland
7. Ministry of Health, HIV Unit, Malawi.
8. Dept. of Clinical Research, London School of Hygiene & Tropical Medicine (LSHTM), London, UK

Corresponding author

Augustine T. Choko

Malawi Liverpool Wellcome Trust Clinical Research Programme

P.O Box 30096

Chichiri

Blantyre 3

augutc@gmail.com

+265999577452

RUNNING HEAD: Impact of HIVST and incentive interventions on linkage

QUESTION: What are the most promising candidate interventions for increasing uptake of HIV testing and linkage into care or prevention for partners of pregnant women attending antenatal clinics in Blantyre, Malawi?

FINDINGS: In this adaptive multi-arm multi-stage cluster randomized trial with 2349 eligible pregnant women, self-test kits greatly increased the proportion of male partners who had an HIV test. Subsequent linkage for HIV treatment or prevention within 28d was: 13.0% in standard of care; 17.5% with self-test kits (ST) only; 40.9% and 51.7% with ST+$3 and ST+$10 financial incentive, respectively; ST+lottery 18.6%; and 22.2% with ST+phone reminder.

MEANING: Additional interventions such as financial incentives may encourage men to link to HIV treatment or prevention following partner-delivered self-test kits.

Abstract

BACKGROUND

Men remain underserved by HIV services. We investigated HIV self-testing (HIVST) delivered through antenatal care (ANC).

METHODS

In a multi-arm two-stage cluster-randomised trial in Malawi, ANC days (clusters) were randomised to standard-of-care (SOC: personalised invitation letter) or five intervention arms: SOC plus two partner-delivered HIVST kits with a) no addition, or conditional incentives of b) US$3, c) US$10, d) lottery (mean US$3) to attend clinic, or e) phone call. The primary outcome was: clinic attendance regardless of test results within 28 days, with referral for antiretroviral therapy (ART) if HIV positive or circumcision if HIV negative and uncircumcised. Women were interviewed at 28 days about partner testing and adverse events. Cluster-level summaries compared each intervention vs. SOC using eligible women as denominators (intention-to-treat).

RESULTS

Between August 2016 and June 2017 2349/3137 (74.9%) women participated (71 ANC days). HIVST increased male testing (range 87.0%-95.4% per arm) over SOC (71/408, 17.4%), p<0.001 in each arm. Reaching primary outcome was more likely in the $3 with geometric mean of 40.9%, $10, 51.7% and phone reminder 22.3% arms; adjusted risk ratios (aRR) 3.01 (95%CI:1.63-5.57), 3.72 (95%CI:1.85-7.48), and 1.58, 95%CI:1.07-2.33), respectively, than SOC, 13.0%. HIVST alone had 17.5%: aRR 1.45 (95%CI:0.99-2.13), and lottery 18.6%: aRR 1.43 (95%CI:0.96-2.13).

Overall, 42/46 (91.3%) men initiated ART and 135/222 (60.8%) were circumcised. No serious adverse events were reported. Cost per male partner attended clinic with confirmed HIV test result was $23.73 and $28.08 for $3 and $10 arms, respectively.

CONCLUSIONS

Men's linkage increased three-fold using conditional fixed financial incentives plus partner-delivered HIVST; combinations were potentially affordable.

KEYWORDS: Adaptive; HIV self-testing; cluster randomized trial; HIV; multi-arm multi-stage; financial incentives; ANC;, Malawi; sub-Saharan Africa.

TRIAL REGISTRATION: ISRCTN. Identifier**:** ISRCTN18421340

Introduction

In 2016, 1.0 million people died from HIV, and 1.8 million were newly infected.[1] Eastern and Southern Africa have been disproportionately affected by the epidemic, and face challenges in reaching men: regionally, only 52% of men living with HIV are aware of their infection[2] whilst deaths from AIDS-related illnesses are 27% higher amongst men than women.[1] Achieving the 2020 United Nation's targets of 90% of all people living with HIV (PLWH) diagnosed, 90% of those diagnosed on antiretroviral treatment (ART) and 90% of those on treatment virally suppressed[1] should bring major reductions in HIV incidence and mortality, but may also require novel service delivery approaches.[1]

HIV self-testing (HIVST), whereby an individual collects their own sample (oral or blood), conducts the test and interprets their result,[3] is highly acceptable and has been shown to increase coverage and frequency of testing in high-risk men .[4] In Malawi, community-based distribution of HIVST kits, plus home-based ART initiation, in an urban slum setting increased demand for ART, and was shown to be cost-effective.[5,6] In Kenya, secondary distribution of HIVST kits by antenatal care (ANC) attendees to their male partners increased uptake of HIV testing, though subsequent uptake of post-test HIV care and prevention services ("linkage") was not optimally measured.[7] Linkage after HIVST has been previously evaluated from the perspective of antiretroviral therapy (ART),[6,8,9] but not HIV prevention.

Antenatal services in east and southern Africa have achieved near-universal HIV testing amongst pregnant women, [10] providing an ideal opportunity for engaging male partners and extending benefits to the unborn child. [11] We used a novel multi-arm multi-stage (MAMS) cluster-randomised trial (CRT) design [12] to evaluate the efficacy, safety and costs of a number of candidate interventions including HIVST alone, or in combination with conditional fixed financial incentives, lotteries or phone reminders.

Methods

Design, setting and participants

This was a two stage Phase II multi-MAMS adaptive CRT conducted at three primary health clinics in Blantyre, Malawi, between August 2016 and June 2017.[12] We randomised ANC days (clusters) to one of six trial arms (standard of care [SOC] and 5 intervention arms; ratio 1:1:1:1:1:1) in stage one. Women were screened for eligibility at their routine ANC care visit. Those eligible (first ANC visit for current pregnancy, residence in Blantyre, with a male partner not known to be on ART) and who

provided informed consent, received the study arm allocated to that day. At the end of stage 1, intervention arms could be dropped if p>0.2 compared to SOC, or for safety concerns including intimate partner violence (IPV), guided by an independent data safety monitoring board (DSMB). Further ANC days, as determined by sample size re-calculation, were then equally randomised to the remaining trial arms for stage 2.

Interventions

In the SOC arm, women were given an invitation letter addressed to their male partner informing them of the importance of having an HIV test, and the availability of HIV testing and fast track referral for HIV treatment or voluntary male medical circumcision (VMMC) services through a male-friendly clinic (MFC) set-up within the recruiting facility. [13]

All five intervention arms included SOC letter and clinic access together with two prequalified oral HIVST kits (OraQuick HIV Self Test, OraSure Technologies, Bethlehem, PA, USA) for the woman to take home for their male partner: one arm offered this combination of letter with only ("ST"). Two arms offered a fixed cash financial incentive of ($3 or $10, referred to as "ST+$3" and "ST+$10", respectively), and a fourth arm offered a 10% chance of winning $30 ("ST+lottery"). Incentives were given to men and were conditional on clinic attendance within 28 days for confirmation of HIV testing and referral for HIV treatment or prevention services. The choice of $3, $10 and phone reminder used formative study results. [13] The $3 amount reflected out-of-pocket costs of accessing facility HIV testing services in this setting. [14] The fifth arm used a phone call to the male partner on the day the woman enrolled, which was repeated five days later if partner had not come to clinic ("ST+reminder").

Outcomes and measurement

The primary outcome was the proportion of male partners who attended the clinic with confirmed HIV test results within 28 days of enrolling the woman, assuming one man per enrolled woman. All men had to present a used HIVST kit or underwent on spot HIV testing with a study HIV counsellor at the MFC. In the SOC arm, HIV testing used finger-prick rapid diagnostic test kits following Malawi national HIV testing guidelines, provided to male partners who attended the MFC.

Confirmatory testing followed national guidelines and was conducted in all arms. There was referral for ART if HIV positive, or for VMMC if HIV negative and uncircumcised, or counselling if HIV negative and already circumcised. In two post-hoc analyses we first restricted the numerator to confirmed

HIV positive men referred for ART and HIV negative men referred for VMMC, thus excluding men who were HIV-negative and already circumcised. Secondly the numerator was restricted to men who started ART or got circumcised.

The secondary outcomes were: proportion of male partners who had an HIV test within 28 days, as reported by women through audio computer assisted self-interviews (ACASI) at follow-up; risk of serious adverse events (SAEs) [12] within 28 days of enrolling the woman associated with each trial arm as reported through ACASI.

Analysis and sample size

Assuming 25% of male partners achieved the primary outcome in the SOC arm and coefficient of variation (k) of 0.10,[12] six clusters per arm in stage 1 and seven clusters per arm in stage 2 gave 80% power to detect a 15% absolute difference in proportions at 20% and 5% significance level for stage 1 and stage 2, respectively. The intention-to-treat principle was followed using the number of consented women as the denominator in each cluster.

Baseline male characteristics, as reported by women, were compared across trial arms. A planned interim analysis at the end of stage 1 was conducted in order to make pre-planned trial adaptations. We analysed combined stage 1 and 2 data by comparing each intervention arm to the SOC arm and computing a risk ratio (RR)[15] and 95% confidence interval (CI), using a cluster-level summaries approach[15] due to the small number of clusters per arm. Any baseline imbalance was adjusted for using a two-step approach [15]: firstly, using a logistic regression model with baseline covariates to obtain an expected outcome; secondly, the cluster-level ratio of observed:expected outcomes were compared by arm. A t-test was used to compute a p-value for each comparison, followed by a Dunnett's test to correct for multiple comparisons. [16] The statistical analysis approach is described in Appendix 6.2-1.

Cost analysis

For each trial arm we estimated: cost per male partner tested for HIV and attended MFC; and cost per male partner tested for HIV and either started ART or referred to VMMC (Appendix 6.2-2). Costs were estimated from the health provider perspective and presented in 2016 US Dollars.

Ethical considerations

The trial was approved in Malawi by the College of Medicine Research Ethics Committee and by the London School of Hygiene & Tropical Medicine Ethics Committee. Women gave written or witnessed (with thumb print for those illiterate) consent before undergoing any trial procedures. Written consent for male partners was waived by the two ethics committees.

Results

In total, 3137 pregnant women (71 clusters (ANC days): 36 in stage 1 and 35 in stage 2) were screened, of whom 2349 (74.9%) were eligible and consented (Figure 6.2-1). Baseline characteristics of men, as reported by their partners, were reasonably balanced across trial arms except for male partner HIV testing history. Recruitment clinic was also imbalanced by trial arm (Table 6.1-1). All analyses were adjusted for these two covariates.

At interim analysis the ST+lottery arm was dropped (p=0.211; see Table 6.2-6). Four intervention arms and the SOC arm continued to stage 2. The HIVST only arm was maintained on advice of a DSMB being the *a priori* preferred option for policy makers in Malawi (p=0.211; Table 6.2-6).

Primary outcome

Overall, 676/2349 (28.8%) men had an HIV test and attended the MFC within 28 days of enrolling the woman (Table 6.2-2). Geometric mean clinic attendance was: ST only arm 17.5%, risk ratio (RR) 1.35 (95% CI: 0.90; 2.01); ST+$3 40.9%, RR 3.15 (95% CI: 2.11; 4.70); ST+$10 51.7%, RR 3.98 (95% CI: 2.66; 5.95); ST+lottery 18.6%, RR 1.43 (95% CI: 0.96; 2.13); and ST+reminder 22.3%, RR 1.71 (95% CI: 1.15; 2.55) compared to 13.0% in SOC (Table 6.2-2, Figure 6.2-2). In adjusted analysis controlling for male testing history and recruitment clinic (n=2233), the estimates were: adjusted risk ratio (aRR) 1.45 (95% CI: 0.99; 2.13) in ST only arm; 3.01 (95% CI: 1.63; 5.57) in ST+$3; aRR 3.72 (95% CI: 1.85; 7.48) in ST+$10; aRR 1.53 (95% CI: 0.93; 2.52) in ST+lottery and aRR 1.58 (95% CI: 1.07; 2.33) in ST+reminder (Table 6.2-2). Fidelity for phone call intervention was good; nearly three-quarters of men received at least one call.

Of the 676 men who attended the clinic 46 (6.8%) had a newly confirmed HIV positive result, all were referred for ART and 42 (91.3%) started ART the same day of their HIV diagnosis. Of the 630 (93.2%) HIV negative men, 408 (64.8%) were already circumcised. The remaining 222 (35.2%) uncircumcised men all agreed to referral for VMMC with 135/222 (60.8%) undergoing the procedure within 28 days and a further 30 a month later.

Post-hoc outcomes

A total of 268 men were either referred for ART as tested HIV positive or referred for VMMC as tested HIV negative and not already circumcised (Table 6.2-2). Compared to SOC, the ST+$3 and the ST+$10 interventions improved referral for ART or VMMC with aRR 3.06 (95% CI: 1.43; 6.57) and 3.76 (95% CI: 1.76; 8.03), respectively. There was weak evidence that the ST kits only and the ST+reminder interventions improved this outcome with aRR 1.41 (0.79; 2.50) and aRR 1.68 (0.90; 3.15), respectively. Estimates were similar although larger for the outcome of starting ART or undergoing circumcision.

Secondary outcomes

In the SOC arm 71/408 (17.4%) women reported through ACASI that their male partner had had an HIV test following trial participation (Table 6.2-3). In all intervention arms, partner HIV testing as reported by women was much higher, ranging from 87.0%- 95.4% ($p<0.001$ for comparison to SOC for all intervention arms).

No SAEs were reported. Three women each reported a grade 2 AE in stage 1, with no adverse events reported in stage 2 (Table 6.2-3 and Appendix 6.2-4). Two women were in the ST kits only arm and one in ST+$10 incentive arm. In each case, the AE occurred from women pressurising their partner to use a self-test kit, leading to disagreements culminating in temporary (2-3 days) separation. No physical or sexual violence was reported, and all three events resolved in less than three days.

Cost analysis

In the SOC arm the average cost per male partner tested for HIV within 28 days was US$9.85, and the average cost per male partner started ART or underwent VMMC was US$39.81 (Table 6.2-9). The average cost per male partner tested for HIV within 28 days for the five intervention arms ranged from US$23.73 (ST+US$3) to US$41.24 (ST+reminder). The average cost per male partner started ART or referred for VMMC for the five intervention arms ranged from US$94.32 (ST+US$3) to US$167.95 (ST+lottery).

Discussion

HIVST was recently recommended.[3] With several low cost products emerging in the market, including one WHO prequalified and four others approved for procurement through major donors HIVST is becoming more feasible. Self-testing provides complementary coverage and enables novel out-of-clinic strategies, such as the secondary distribution model detailed here, aimed at reaching

target populations such as men, adolescents and key populations who are not well served by clinic-based testing services.[17]

Pregnancy and postpartum are periods of unusually high HIV risk for both partners as well as the child, so that reaching the male partners of pregnant women with HIV services has high societal and public health value. [11] In our study, women reported high uptake of HIVST by their male partner at 28 days (range 87.0% to 95.4% in the 5 HIVST intervention arms). Previous ANC-based studies in Kenya [7,18] and Uganda [19], also reliant on proxy-reporting, estimate testing by 90.8% to 91.1% of men using secondary distribution of self-test kits. This is in stark contrast with previously disappointing results from interventions in the same population e.g. provider-initiated testing and counselling, [20] establishing HIVST as a leading candidate for routine ANC policy and practice in high HIV prevalence settings.

Although merely testing as a couple can reduce sexual risk taking,[21] timely uptake of ART if HIV positive, and effective prevention if HIV negative, are key to maximising and maintaining health benefits of all testing modalities.[1] Improving previously poor linkage into HIV care following standard HIV testing has been a major recent focus of HIV programs, globally.[22] For HIVST, reconstructing the standard HIV care cascade[1] is generally not possible,[5] but demand for post-test services at population level (without knowledge of underlying HIV prevalence) provides an alternative measure of effect.[6]

Here, using a composite HIV care and prevention outcome, we show significant benefits from two fixed conditional financial incentive arms. Financial incentives, including one-off rewards of desired behaviour, have shown a consistently positive effect on uptake and completion of standard HIV testing.[23,24,25] Interestingly, our results differ in that men's uptake of HIVST was not influenced by incentives, based on self-report by women. Instead, uniformly high kit usage rates in all self-testing arms suggests high intrinsic motivation for self-testing to which incentives add relatively little. HIVST has high user-acceptability[17], is strongly preferred over alternative approaches[17], and incurs negligible inconvenience or user-costs when delivered at home.[14] Combining HIVST with conditional fixed financial incentives did, however, increase the proportion of men attending clinic-based HIV care and prevention services within 28 days from 13.7% in the SOC arm to 52.0% in the ST+$10 arm. This includes a significant increase in the hard prevention outcomes of ART initiation and VMMC, and adds to the body of mixed evidence concerning incentives and linkage,

[26,27] as well as establishing the principle that linkage interventions can increase health benefits from secondary HIV self-testing strategies.

Our costing suggests that of the five interventions evaluated, the US$3 and US$10 incentive arms offered the best value for money. Malawians incur approximately US$3 to access free facility-based HIV testing, [14] and this cost often deters men. [28] The ST+$10 incentive arm was considered by potential participants as the likely maximally efficacious amount to cover all their opportunity costs.[13] Although providing financial incentives and HIV self-test kits is costly, it may be necessary to reach the UN 2020 targets. The potential to rapidly test and optimise locally relevant financial incentives is strength of multi-arm adaptive trial designs, modified here to support clustered units of randomisation. For instance, we anticipated but did not find high acceptability/effectiveness of lottery-based incentives following a behavioural intervention trial that significantly reduced HIV incidence in Lesotho. [29]

Limitations of the study are the relatively small number of ANC days randomised to each arm, and proxy-reporting to estimate usage of HIVST by male partners. Computer-based interview (ACASI), however, was used to minimise misreporting due to social desirability bias.[30] Risk behaviour, condom use, and retention in care were not evaluated,[31] and due to service availability restrictions, not all men were followed through from booking to VMMC.

Here, we show pronounced effects on testing and high safety from secondary distribution of HIVST kits, in keeping with previous estimates from ANC, with no additional benefit from accompanying financial incentives. Incentives of $3 and $10, conditional on attending clinic-based services within 28 days, did, however significantly increase timely uptake of HIV treatment and prevention to an extent likely to be cost-saving. Compared to SOC, we saw only marginal evidence of increased uptake of follow-on prevention and care services from provision of HIVST kits only, with or without phone call reminders. Secondary distribution of HIVST kits, ideally accompanied by interventions promoting timely linkage into HIV care and prevention cascades, is a promising new approach for routine ANC services to reach male partners, intensify prevention of mother-to-child transmission, and contribute more broadly to country-level HIV prevention targets.

ARTICLE INFORMATION

Authors' Contributions: Grant holder: ATC

Conceived of the study: ATC and ELC
Provided statistical expertise in trial design: KF and NS
Provided expertise in interventional design: ATC, HM, AL, ND, MKK, and ELC
Implemented the trial: ATC and MKK
Conducting primary statistical analysis: ATC and KF
Conducted economic analysis: HM
All authors contributed to refinement of the study protocol, commented on earlier drafts of manuscript and approved the final manuscript.

Conflict of Interest Disclosures: All authors declare no conflict of interest.

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The Role of the Sponsor: The trial sponsor was London School of Hygiene & Tropical Medicine (Ref, No.: QA844), WC1E 7HT, Keppel Street, +44 20 7636 8636, London, United Kingdom. Contact person: patricia.henley@lshtm.ac.uk. Neither the sponsor nor the funder played a role in the design and conduct of the study: collection, management, analysis, and interpretation of the data; review or approval of the manuscript; and decision to submit the manuscript for publication.

Previous Presentation: The data reported here were presented at a STAR Satellite during the International AIDS Society Conference 2017 in Paris, France.

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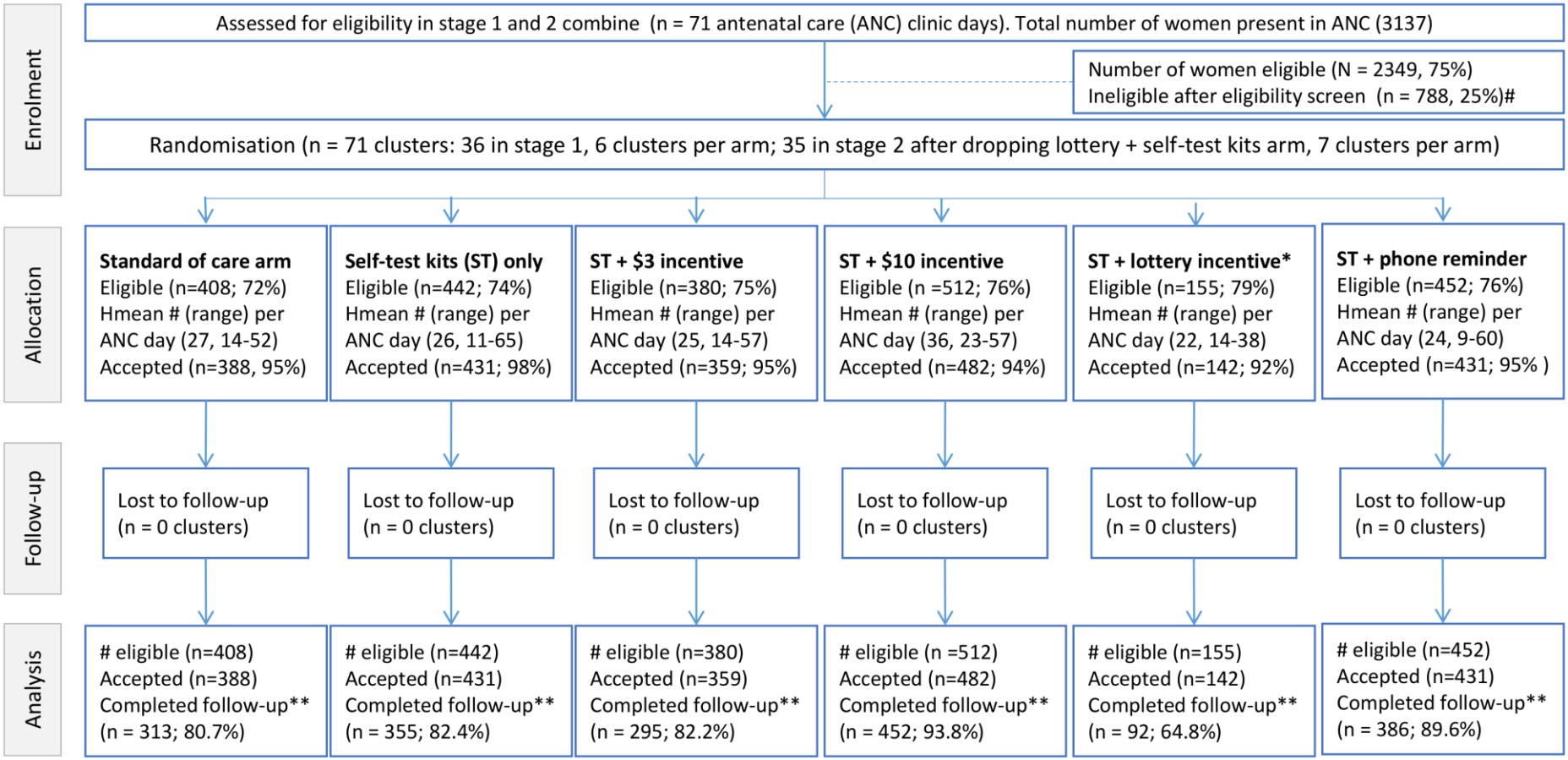
Figure 6.2-1: Trial profile (stage 1 and 2 combined)



ANC: antenatal clinic; Hmean: harmonic mean.
Reasons for ineligibility in order of frequency: under age (<18y); absent partner; male partner already on ART; not 1st ANC visit
* ST + lottery arm was dropped at interim analysis (end of stage 1)
Accepted: eligible, consented and continued with the allocated arm
** Completed follow-up: based on the women being interviewed 4 weeks after enrolment with data used to measure some secondary outcomes

Table 6.2-1: Baseline characteristics of men as reported by women at enrolment (N = 2349; stage 1 and 2 combined)

		Trial arm					
Variable	**Characteristic**	**SOC**	**ST**	**ST + $3**	**ST + $10**	**ST + Lottery***	**ST + reminder**
Eligible	n	408	442	380	512	155	452
Age (years)	Mean (sd)	29.95 (8.51)	29.58 (6.05)	28.89 (6.37)	29.31 (6.54)	30.30 (10.94)	29.31 (6.38)
Able to read and write	Yes	377 (97.2)	425 (98.6)	354 (98.6)	476 (98.8)	140 (98.6)	420 (97.4)
Level of education attained	Primary / no school	100 (25.8)	82 (19.1)	85 (23.6)	98 (20.3)	38 (26.8)	90 (20.9)
	Secondary, no MSCE	135 (34.8)	152 (35.3)	125 (34.8)	157 (32.6)	58 (40.8)	166 (38.5)
	Secondary, MSCE	127 (32.7)	157 (36.4)	121 (33.7)	169 (35.1)	36 (25.4)	142 (32.9)
	Any tertiary	26 (6.7)	40 (9.3)	28 (7.8)	58 (12.0)	10 (7.0)	33 (7.7)
Occupation	Paid employee	216 (55.7)	275 (63.8)	193 (53.8)	282 (58.5)	68 (47.9)	233 (54.1)
	Paid domestic worker	20 (5.2)	21 (4.9)	36 (10.0)	31 (6.4)	18 (12.7)	36 (8.4)
	Self-employed	130 (33.5)	111 (25.8)	108 (30.1)	123 (25.5)	43 (30.3)	135 (31.3)
	Unemployed	14 (3.6)	12 (2.8)	10 (2.8)	30 (6.2)	7 (4.9)	15 (3.5)
	Student	7 (1.8)	6 (1.4)	4 (1.1)	9 (1.9)	2 (1.4)	6 (1.4)
	Other	1 (0.3)	6 (1.4)	8 (2.2)	7 (1.5)	4 (2.8)	6 (1.4)
Ever tested for HIV	Never tested before	193 (49.7)	169 (39.2)	167 (46.5)	213 (44.2)	65 (45.8)	159 (36.9)
	Tested > 12m ago	98 (25.3)	140 (32.5)	101 (28.1)	153 (31.7)	49 (34.5)	170 (39.4)
	Tested ≤ 12m	97 (25.0)	122 (28.3)	91 (25.3)	116 (24.1)	28 (19.7)	102 (23.7)
Recruitment PHC	Ndirande	73 (17.9)	67 (15.2)	98 (25.8)	99 (19.3)	42 (27.1)	66 (14.6)
	Bangwe	150 (36.8)	76 (17.2)	162 (42.6)	142 (27.7)	85 (54.8)	307 (67.9)
	Zingwangwa	185 (45.3)	299 (67.6)	120 (31.6)	271 (52.9)	28 (18.1)	79 (17.5)

SOC: standard of care; ST: self-test kits; sd: standard deviation; MSCE: Malawi school certificate of education (4 years); PHC: primary health clinic

* ST + lottery arm was dropped at interim analysis (end of stage 1)

Note: Data are for all the male partners of eligible women, including those who discontinued participation after giving consent and learning trial arm

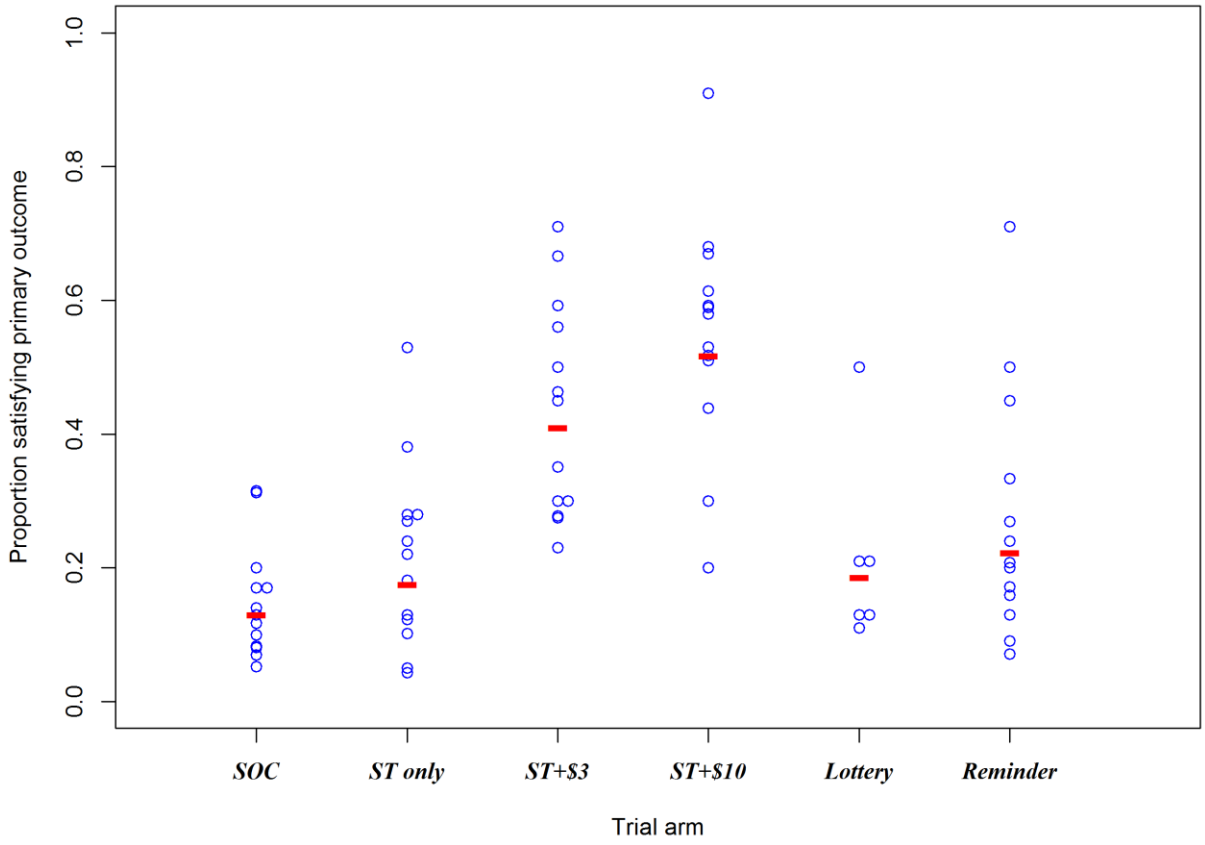
Table 6.2-2: Unadjusted and adjusted intervention effects by trial arm and trial stage for the primary outcome* and post-hoc outcomes (stage 1 and 2 combined)

Trial arm	SOC	ST only	ST+$3	ST+$10	ST+ Lottery†	ST+ Reminder‡
Number of clusters	13	13	13	13	6	13
Eligible women	408	442	380	512	155	452
Primary outcome*	56	85	155	266	30	84
Geometric mean	13.0%	17.5%	40.9%	51.7%	18.6%	22.3%
Unadjusted RR	1	1.35	3.15	3.98	1.43	1.71
95% CI		0.90; 2.01	2.11; 4.70	2.66; 5.95	0.96; 2.13	1.15; 2.55
p-value§	NA	0.332	< 0.001	< 0.001	0.332	0.079
Adjusted RR#	1	1.45	3.01	3.72	1.53	1.58
95% CI		0.99; 2.13	1.63; 5.57	1.85; 7.48	0.93; 2.52	1.07; 2.33
p-value§	NA	0.130	< 0.001	< 0.001	0.211	0.021
Outcomes at MFC						
HIV-positive	3/56 (5.4%)	11/85 (12.9%)	11/155 (7.1%)	14/266 (5.3%)	4/30 (13.3%)	3/84 (3.6%)
Started ART	3/3 (100%)	10/11 (90.9%)	10/11 (90.9%)	13/14 (92.9%)	4/2 (100%)	2/3 (66.7%)
HIV-negative	53/56 (95.6%)	74/85 (87.1%)	144/155 (92.9%)	252/266 (94.7%)	26/30 (86.7%)	81/84 (96.4%)
Already circumcised	38/56 (67.9%)	43/85 (50.6%)	97/155 (62.6%)	168/266 (63.2%)	20/30 (66.7%)	42/84 (50.0%)
Uncircumcised	15/56 (26.8%)	31/85 (36.5%)	47/155 (30.3%)	84/266 (31.6%)	6/30 (20.0%)	39/84 (46.4%)
Circumcised	11/15 (73.3%)	17/31 (54.8%)	29/47 (61.7%)	55/84 (65.5%)	3/6 (50.0%)	20/39 (51.3%)
Post-hoc outcomes						
Referred for ART or VMMC	18/408 (4.4%)	42/442 (9.5%)	58/380 (15.3%)	98/512 (19.1%)	10/155 (6.5%)	42/452 (9.3%)
Unadjusted RR	1	1.64	3.45	3.38	1.37	1.87
95% CI		1.00; 2.68	2.10; 5.64	2.06; 5.53	0.83; 2.24	1.14; 3.07
Adjusted RR#	1	1.41	3.06	3.76	1.87	1.68
95% CI		0.79; 2.50	1.43; 6.57	1.76; 8.03	0.58; 6.01	0.90; 3.15
p-value§	NA	0.088	< 0.001	< 0.001	0.297	0.104
Started ART or were circumcised	14/408 (3.4%)	27/442 (6.1%)	39/380 (10.3%)	68/444 (13.3%)	7/155 (4.5%)	22/452 (4.9%)
Adjusted RR#	1	2.30	4.53	4.40	2.91	2.81
95% CI		1.06; 5.00	1.01; 20.39	1.55; 12.48	0.53; 15.88	1.15; 6.88
p-value§	NA	0.035	0.049	0.005	0.220	0.023

SOC: standard of care; ST: self-test; ART: antiretroviral therapy; VMMC: voluntary medical male circumcision; RR: risk ratio; CI confidence interval; MFC male friendly clinic

† 10% chance of winning $3 times number of men achieving the primary outcome; this arm was dropped at interim analysis (end of stage 1). ‡ phone call. * Primary outcome: evidence of testing and linking to male friendly clinic within 28 days (regardless of HIV test result). § Adjusted for multiple comparisons using the Dunnett test. # Adjusted for male partner history of HIV testing as reported by the woman, recruitment clinic (n=2233)

Figure 6.2-2: Cluster-level proportion for the primary outcome of evidence of testing and linking to MFC within 28 days, by trial arm



MFC: male friendly clinic; SOC: standard of care; ST: self-test. Lottery and reminder arms also had ST

Red horizontal line = geometric mean of cluster-level proportions.

Table 6.2-3: Secondary outcome of male partner HIV testing as reported by women and adverse events within 28 days (stage 1 and 2 combined)

	SOC	ST only	ST + $3	ST + $10	ST + Lottery*	ST + Reminder
Total women eligible (N = 2349)	408	442	380	512	155	452
Male partner had an HIV test†‡	71 (17.4%)	407 (92.1%)	345 (90.9%)	483 (94.3%)	135 (87.0%)	431(95.4%)
Risk ratio (95% CI)	1	5.29 (4.28; 6.55)	5.22 (4.21; 6.46)	5.42 (4.38; 6.70)	5.00 (4.02; 6.24)	5.48 (4.43; 6.78)
p-value	NA	<0.001	<0.001	<0.001	<0.001	<0.001
# Adjusted risk ratio (95% CI)	1	2.75 (1.64; 4.63)	4.84 (3.18; 7.37)	6.69 (3.46; 12.94)	3.56 (2.19; 5.79)	4.85 (2.62; 8.99)
p-value	NA	<0.001	<0.001	<0.001	<0.001	<0.001
Women experiencing an adverse event‡	0 (0.0%)	2 (0.6%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)

SOC: standard of care; ST: self-test kits

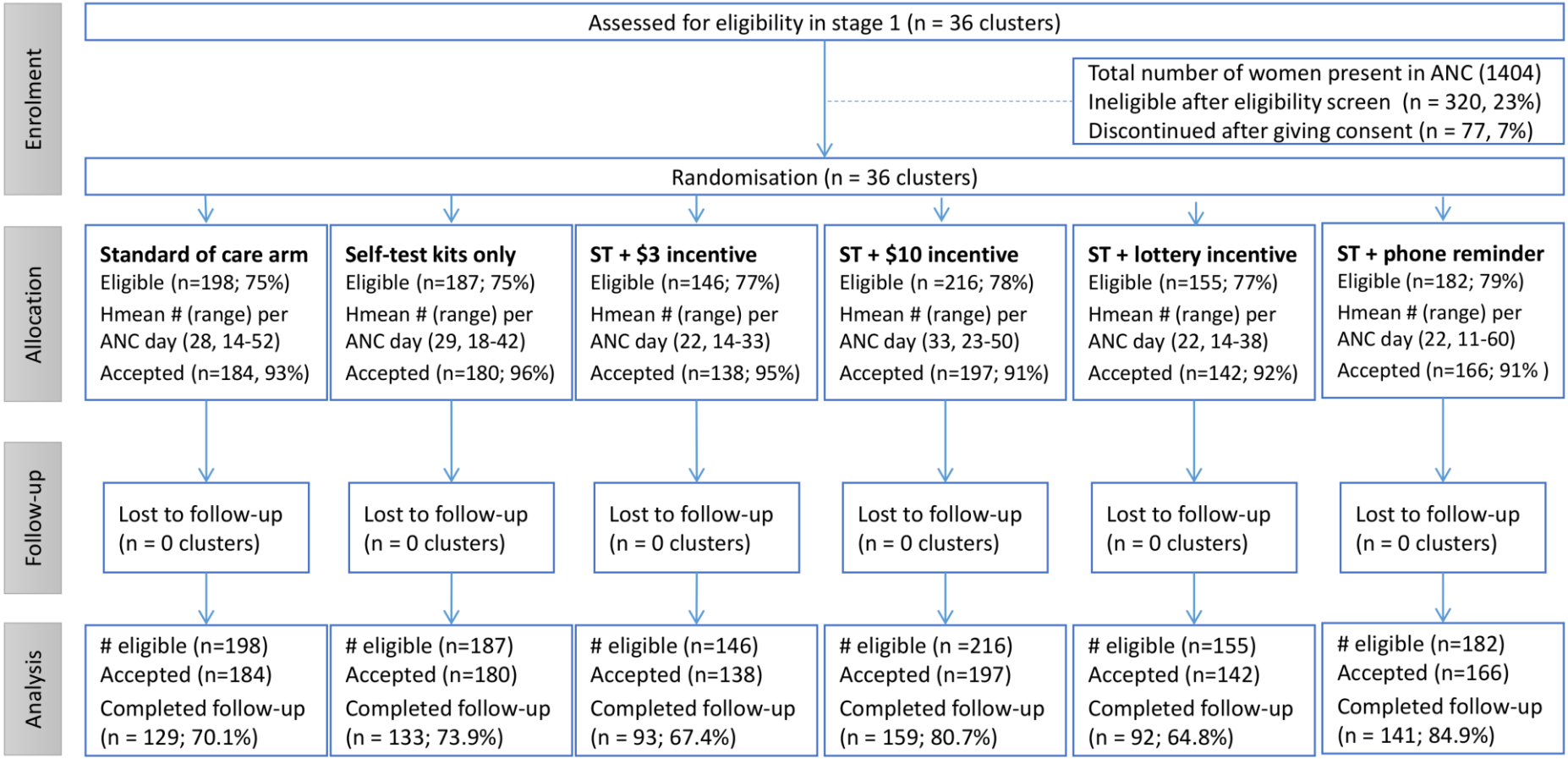
* Contributed to stage 1 only

† Male partner went to have a test in SOC arm and self-tested in intervention arms as reported by the woman

‡ Reported by women through audio computer-assisted self-interview (ACASI) four weeks after enrolment

Adjusted for male partner history of HIV testing as reported by the woman, recruitment clinic

Figure 6.2-3: Stage 1 trial profile

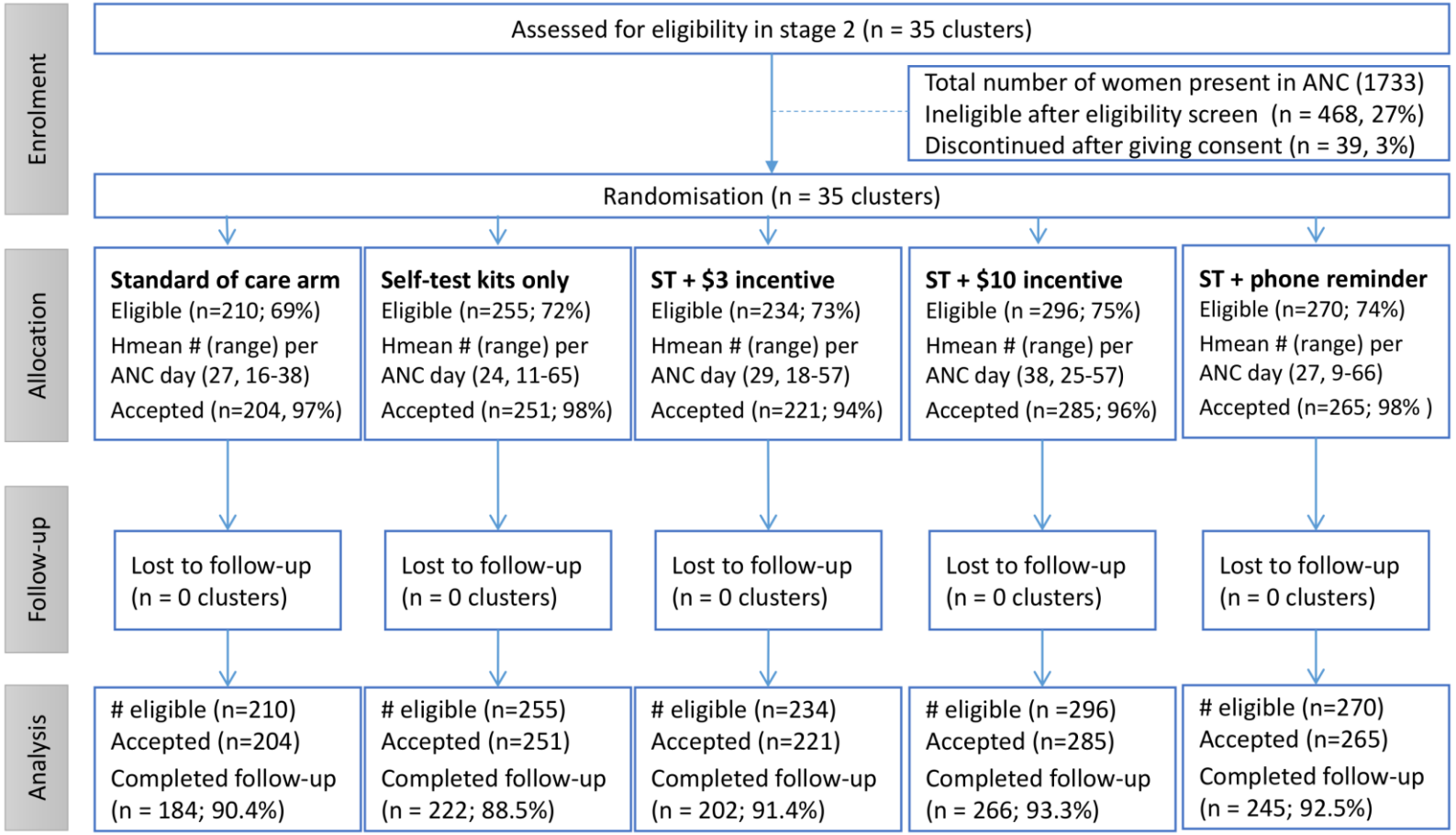


ANC: antenatal clinic; Hmean: harmonic mean

Accepted: eligible, consented and continued with the allocated arm

Completed follow-up: based on the women being interviewed 4 weeks after enrolment with data used to measure some secondary outcomes

Figure 6.2-4: Stage 2 trial profile



ANC: antenatal clinic; Hmean: harmonic mean

Accepted: eligible, consented and continued with the allocated arm

Completed follow-up: based on the women being interviewed 4 weeks after enrolment with data used to measure some secondary outcomes

Table 6.2-4: Baseline characteristic s of women (stage 1 and 2 combined)

		Trial arm					
Variable	**Characteristic**	**SOC**	**ST**	**ST + $3**	**ST + $10**	**ST + Lottery**	**ST + reminder**
Number of women per arm	n	408	442	380	512	155	452
Age (years)	Mean (sd)	25.10 (5.53)	25.16 (5.37)	24.55 (5.17)	24.96 (5.43)	24.68 (5.36)	24.53 (5.51)
Marital status	Married/cohabiting	380 (97.9)	427 (99.1)	354 (98.6)	475 (98.5)	141 (99.3)	424 (98.4)
	Never married	7 (1.8)	4 (0.9)	5 (1.4)	4 (0.8)	1 (0.7)	6 (1.4)
	Separated/Widowed	1 (0.3)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	1 (0.2)
Live together with partner?	No	17 (4.4)	27 (6.3)	16 (4.5)	19 (3.9)	12 (8.5)	22 (5.1)
	Yes	371 (95.6)	404 (93.7)	343 (95.5)	463 (96.1)	130 (91.5)	409 (94.9)
Able to read and write?	No	53 (13.7)	39 (9.0)	48 (13.4)	43 (8.9)	24 (16.9)	52 (12.1)
	Yes	335 (86.3)	392 (91.0)	311 (86.6)	439 (91.1)	118 (83.1)	379 (87.9)
Education	Never been to school	16 (4.1)	11 (2.6)	22 (6.1)	14 (2.9)	9 (6.3)	19 (4.4)
	Primary	183 (47.2)	191 (44.3)	165 (46.0)	193 (40.0)	64 (45.1)	187 (43.4)
	Secondary, no MSCE	125 (32.2)	153 (35.5)	113 (31.5)	192 (39.8)	52 (36.6)	158 (36.7)
	Secondary, MSCE	51 (13.1)	63 (14.6)	46 (12.8)	62 (12.9)	15 (10.6)	53 (12.3)
	Any tertiary	13 (3.4)	13 (3.0)	13 (3.6)	21 (4.4)	2 (1.4)	14 (3.2)
Occupation	Paid employee	25 (6.4)	29 (6.7)	48 (13.4)	38 (7.9)	17 (12.0)	29 (6.7)
	Paid domestic worker	4 (1.0)	1 (0.2)	12 (3.3)	10 (2.1)	4 (2.8)	11 (2.6)
	Self-employed	97 (25.0)	98 (22.7)	57 (15.9)	97 (20.1)	29 (20.4)	100 (23.2)
	Unemployed	261 (67.3)	295 (68.4)	238 (66.3)	331 (68.7)	91 (64.1)	289 (67.1)
	Student	1 (0.3)	7 (1.6)	3 (0.8)	5 (1.0)	1 (0.7)	2 (0.5)
	Other	0 (0.0)	1 (0.2)	1 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)
Self-rated general health	Excellent	147 (37.9)	193 (44.8)	134 (37.3)	187 (38.8)	70 (49.3)	145 (33.6)
	Good	231 (59.5)	219 (50.8)	207 (57.7)	276 (57.3)	66 (46.5)	271 (62.9)
	Fair	9 (2.3)	18 (4.2)	16 (4.5)	17 (3.5)	4 (2.8)	14 (3.2)
	Poor	1 (0.3)	1 (0.2)	2 (0.6)	2 (0.4)	2 (1.4)	1 (0.2)

SOC: standard of care; ST: self-test kits; sd: standard deviation; MSCE: Malawi school certificate of education (4 years); PHC: primary health clinic

Table 6.2-5: Unadjusted intervention effects by trial arm and trial stage for the primary outcome*

Unadjusted intervention effects for trial arm by trial stage for the primary outcome*

	Trial arm					
	SOC	**ST only**	**ST + $3**	**ST + $10**	**ST + Lottery†**	**ST + Reminder‡**
First stage						
Eligible	198	187	146	216	155	182
Outcome	27	38	61	102	30	42
Proportion**	0.124	0.179	0.428	0.473	0.186	0.316
RR	1	1.19	3.37	3.50	1.43	2.26
95% CI		0.81; 1.74	2.29; 4.97	2.35; 5.21	0.96; 2.13	1.54; 3.33
p-value	NA	0.254	<0.001	<0.001	0.332	0.010
Second stage						
Eligible	210	255	234	296	Dropped	270
Outcome	29	47	94	164		42
Proportion**	0.135	0.172	0.394	0.558		0.165
RR	1	1.27	2.91	4.12		1.21
95% CI		0.57; 2.83	1.31; 6.50	1.859.20		0.55; 2.71
p-value	NA	0.575	0.006	<0.001		0.570

* Primary outcome: evidence of testing and male friendly clinic attendance within 28 days (regardless of HIV test result)

SOC: standard of care; ST: self-test; RR: risk ratio

† 10% chance of winning $3 times number of men achieving the primary outcome

‡ phone call

** Geometric mean of the cluster proportions

Table 6.2-6: Adjusted* intervention effects by trial arm and trial stage for the *primary outcome*

	Trial arm					
	SOC	**ST only**	**ST + $3**	**ST + $10**	**ST + Lottery†**	**ST + Reminder‡**
First stage						
Eligible	198	187	146	216	155	182
Outcome	27	38	61	102	30	42
Proportion**	0.124	0.179	0.428	0.473	0.186	0.316
RR	1	1.61	3.31	3.60	1.53	1.88
95% CI		0.95; 2.73	1.43; 7.66	1.34; 9.69	0.93; 2.52	1.13; 3.13
p-value§	NA	0.211	0.001	0.001	0.211	0.039
Second stage						
Eligible	210	255	234	296	Dropped	270
Outcome	29	47	94	164		42
Proportion**	0.135	0.172	0.394	0.558		0.165
RR	1	1.13	2.61	3.83		1.51
95% CI		0.67; 1.92	1.13; 6.04	1.42; 10.31		0.91; 2.49
p-value§	NA	0.629	<0.001	<0.001		0.148

* Adjusted for male partner past HIV testing history as reported by the woman and recruitment clinic

Primary outcome: of evidence of testing and linking to male friendly clinic within 28 days (regardless of HIV test result)

SOC: standard of care; ST: self-test; RR: risk ratio

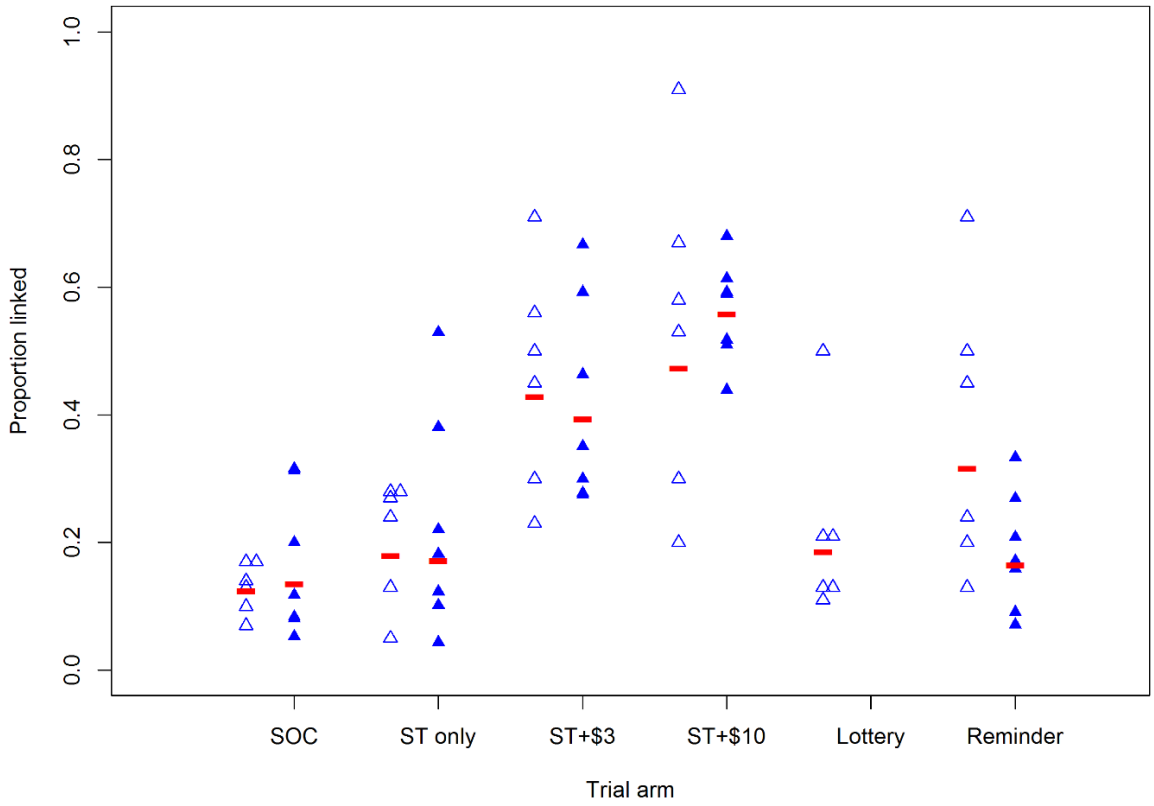
† 10% chance of winning $3 times number of men achieving the primary outcome

‡ phone call

§ Adjusted for multiple comparisons using the Dunnett's test

** Geometric mean of the cluster proportions

Figure 6.2-5: Cluster proportion for the primary outcome of evidence of testing and linking to MFC within 28 days by trial arm



MFC: male friendly clinic; SOC: standard of care; ST: self-test. Lottery and reminder arms also had ST

Notes: Red horizontal line = geometric mean of cluster proportions; Open triangles = data (proportions) from stage 1 of the trial; closed triangles = data from stage 2

Table 6.2-7: Stage 1 referral for HIV treatment and voluntary medical male circumcision by trial arm (N = 300 men linked, 128 referral for ART/VMMC)

	SOC		ST only		ST + $3		ST + $10		ST + lottery		ST + reminder		Overall	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Confirmatory testing														
HIV positive	2	7.4%	5	13.2%	6	9.8%	5	4.9%	4	13.3%	1	2.4%	**23**	**7.7%**
HIV negative	25	92.6%	33	86.8%	55	90.2%	97	95.1%	26	86.7%	41	97.6%	**277**	**92.3%**
Total linked	**27**		**38**		**61**		**102**		**30**		**42**		**300**	
Referred and started ART or were circumcised														
ART	2	100.0%	5	100.0%	6	100.0%	5	100.0%	4	100.0%	0	0.0%	**22**	**95.7%**
VMMC	4	16.0%	10	30.3%	11	20.0%	20	20.6%	3	11.5%	16	39.0%	**64**	**23.1%**
Referred but not started ART or not circumcised														
ART	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	100.0%	**1**	**4.3%**
VMMC	2	8.0%	9	27.3%	12	21.8%	12	12.4%	3	11.5%	3	7.3%	**41**	**14.8%**
No ART or VMMC indicated														
HIV-ve already circumcised	19	76.0%	14	42.4%	32	58.2%	65	67.0%	20	76.9%	22	53.7%	**172**	**62.1%**
HIV+ve already on ART	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	**0**	**0.0%**
Referred for ART or VMMC	8	29.6%*	24	63.2%*	29	47.5%*	37	36.3%*	10	33.3%*	20	47.6%*	**128**	**42.7%***
Of total eligible	198	4.0%**	187	12.8%**	146	19.9%**	216	17.1%**	155	6.5%**	182	11.0%**	**1084**	**11.8%****

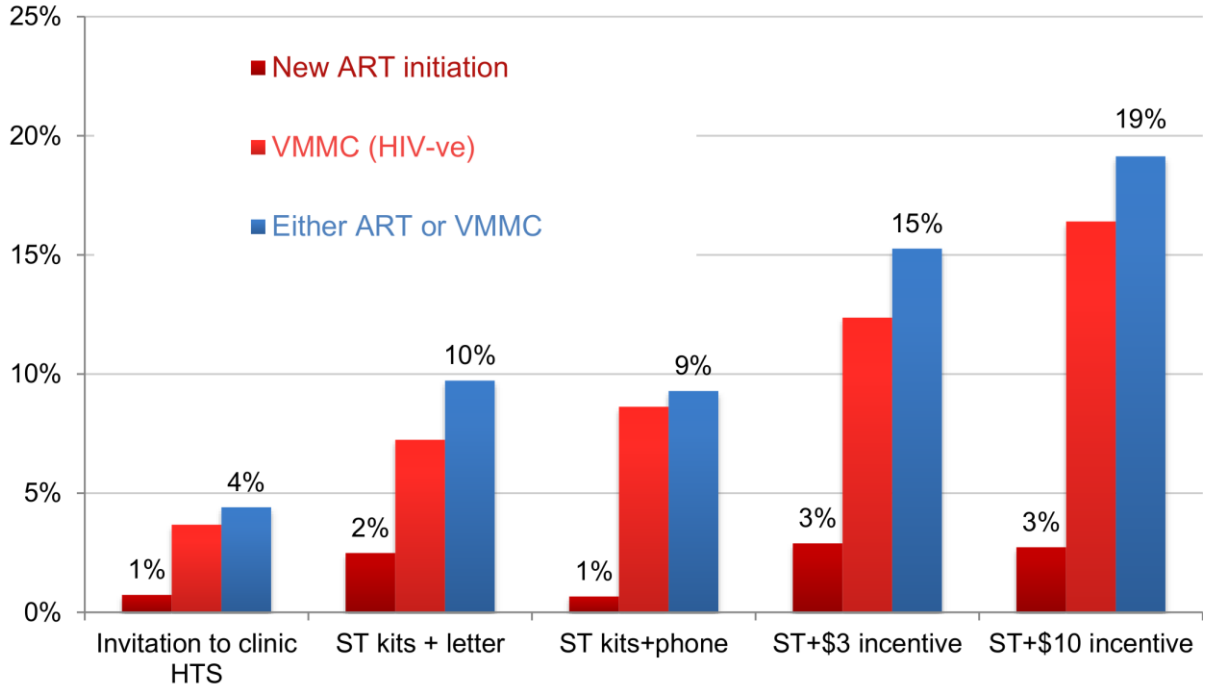
SOC: standard of care; ST: self-test kits; ART: antiretroviral therapy; VMMC: voluntary male medical circumcision
* percentage of male partners who attended the clinic; ** percentage of total women eligible

Table 6.2-8: Stage 2 referral for HIV treatment and voluntary medical male circumcision by trial arm (N = 376 men linked, 140 active events or referral for ART/VMMC)

	SOC		ST only		ST + $3		ST + $10		ST + reminder		Overall	
	n	%	n	%	n	%	n	%	n	%	n	%
Confirmatory testing												
HIV positive	1	3.4%	6	12.8%	5	5.3%	9	5.5%	3	7.1%	**24**	**6.4%**
HIV negative	28	96.6%	41	87.2%	89	94.7%	155	94.5%	39	92.9%	**352**	**93.6%**
Total linked	**29**		**47**		**94**		**164**		**42**		**376**	
Referred and started ART or were circumcised												
ART	1	100.0%	5	83.3%	4	80.0%	8	88.9%	2	66.7%	**20**	**83.3%**
VMMC	7	25.0%	7	17.1%	18	20.2%	35	22.6%	4	10.3%	**71**	**20.2%**
Referred but not started ART or not circumcised												
ART	0	0.0%	1	100.0%	1	20.0%	1	11.1%	0	0.0%	**3**	**12.5%**
VMMC	2	7.1%	5	12.2%	6	6.7%	17	11.0%	16	41.0%	**46**	**13.1%**
No ART or VMMC indicated												
HIV-ve already circumcised	19	67.9%	29	70.7%	65	73.0%	103	66.5%	20	51.3%	**236**	**67.0%**
HIV+ve already on ART	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	**0**	**0.0%**
Referred for ART or VMMC	10	34.5%*	18	38.3%*	29	30.9%*	61	37.2%*	22	52.4%*	**140**	**37.2%***
Of total eligible	210	4.8%**	255	7.1%**	234	12.4%**	296	20.6%**	270	8.1%**	**1265**	**11.1%****

SOC: standard of care; ST: self-test kits; VMMC: voluntary male medical circumcision
* percentage of male partners who attended the clinic; ** percentage of total women eligible

Figure 6.2-6: Percentage of all male partners linking to HIV treatment or circumcision, N = 2,349 eligible women*



* Intention to treat analysis using the denominator of all eligible women (assumes each woman has one male partner)
HTS: HIV testing services; SOC: standard of care; ST: self-test

Figure 6.2-7: Flow of participants from recruitment

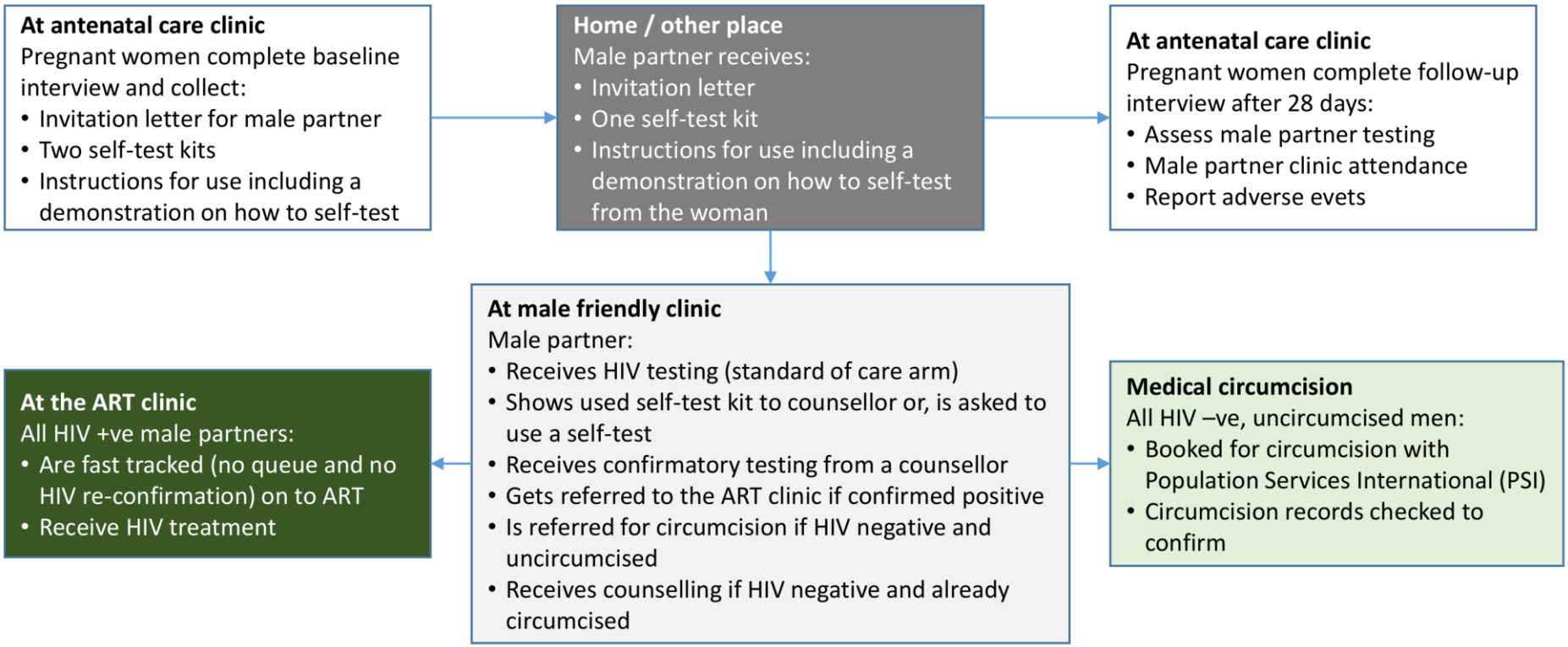


Table 6.2-9: Findings from cost analysis

	SOC (n=408)	ST only (n=442)	ST + $3 (n=380)	ST + $10 (n=512)	ST + lottery (n=155)	ST + reminder (n=452)
ANC intervention						
Personnel	US$57.52	US$67.13	US$55.92	US$75.07	US$22.12	US$67.13
Intervention cost*	US$0.01	US$2,785.98	US$2,785.58	US$5775.65	US$1,007.89	US$3,009.29
Total cost	US$57.53	US$2,853.12	US$2,841.50	US$5,850.73	US$1,030.01	US$3,076.42
MFC intervention						
Personnel	US$184.74	US$273.04	US$386.74	US$750.29	US$66.69	US$179.89
Consumables	US$226.56	US$167.61	US$233.26	US$445.90	US$42.13	US$106.59
Equipment	US$14.55	US$25.02	US$35.65	US$69.50	US$6.05	US$16.68
Overhead and other capital**	US$75.02	US$127.24	US$181.30	US$353.45	US$30.77	US$84.83
Total cost	US$499.87	US$592.91	US$836.95	US$1,619.15	US$145.64	US$387.99
Total Intervention cost***	US$557.40	US$3446.03	US$3678.44	US$7469.87	US$1,175.64	US$3,464.41
Male partners tested for HIV and attended MFC within 28 days****	56	85	155	266	30	84
Male partners started ART or circumcised	14	27	39	68	7	22
Average cost per male partner tested for HIV and attended MFC within 28 days	US$9.95	US$40.54	US$23.73	US$28.08	US$39.19	US$41.24
Average cost per male partner started ART or circumcised***	US$39.81	US$127.63	US$94.32	US$109.85	US$167.95	US$157.47
Average cost per participant randomized	US$0.14	US$6.46	US$7.48	US$11.43	US$6.65	US$6.81

SOC: standard of care; ST: self-test kits; VMMC: voluntary male medical circumcision; ART: anti-retroviral treatment

*Depending on trial arm cost includes information leaflet +/- OraQuick HIV self-test kit (US$3.23 each) +/- financial incentive +/- lottery +/- phone call reminder

** Includes clinic rental cost, utilities and refresher training for HIV counsellors

***Does not include cost of antiretroviral treatment or voluntary male medical circumcision

**** This is the primary outcome of male partner testing and male friendly clinic attendance within 28 days

Narrative

2016 US Dollars

Providing antenatal care clinic attendees a leaflet for their male partner about the male friendly clinic (MFC) least costly

In comparison to providing only an information leaflet, providing HIVST kit and a financial incentive:

- US$23-28 per additional male partner tested for HIV and linked to MFC
- US$94-110per additional male partner started ART or linked to VMMC

Higher financial incentive may offer better value for money

Appendix 6.2-1: Description of statistical analysis plan

Design and participants

This was an adaptive multi-arm two-stage cluster randomized trial randomising antenatal care (ANC) clinic days (clusters) to one of six trial arms in stage 1. At a pre-planned interim analysis conducted at the end of stage 1, adaptations included sample size re-calculation and dropping intervention arms deemed inefficacious when compared to the standard of care (SOC). New set of clusters with new ANC attendees was randomized to trial arms that proceeded to stage 2. Pregnant women accessing ANC for the first time were given a personalized clinic invitation letter only to give to their male partner (SOC). The self-test (ST) only arm offered SOC with two oral self-test kits only, the ST+$3 and ST+$10 arms offered fixed financial incentives in the local currency equivalent to $3 and $10 to male partners conditional on clinic attendance. The ST+lottery offered a 10% chance to male partners who attended the clinic to win $3 x the number of male partners attended. The final arm was ST+reminder where a phone call reminder was made to the male partner immediately the woman returned from the clinic for the man to use the self-test kits and attend the clinic, repeated after five days. It was assumed that each woman had one male partner who she named during enrollment.

Primary outcome and measurement

The proportion of male partners of ANC attendees who tested for HIV and attended the clinic within 28 days of enrolling the woman. In SOC, male partners were tested for HIV by an HIV counsellor while in all intervention arms men had to present a used self-test kit or were asked to use it on spot by an HIV counsellor to confirm that HIV testing had occurred. All men with a positive HIV test received additional testing to confirm their results before being referred to a nurse for initiation of HIV treatment. Men who had a negative HIV test result and reported uncircumcised were referred for voluntary medical male circumcision. Already circumcised HIV negative men were counselled. Data collection was done with each trial procedure in order to ascertain the trial outcomes.

Statistical analysis of primary outcome

Analysis was by intention-to-treat taking eligible women as the denominator and male partners who achieved the primary outcome as the numerator. Analysis was by cluster-level summaries using the geometric mean of the proportion achieving the primary outcome in each cluster. This was to account for the clustered design given the small number of clusters per arm, but also all analysis adjusted for multiplicity using the Dunnett's test. A two-stage analysis approach was used to adjust for covariates that showed imbalance on baseline characteristics: male partner history of HIV testing and recruitment clinic. Firstly, a logistic regression model was fitted with the two covariates to

obtain an expected outcome. Secondly, the cluster-level ratio of observed:expected outcomes were compared by arm. A t-test was used to compute a p-value for each comparison with degrees of freedom reduced by 2 to account for the cluster-level variable of recruitment clinic, followed by a Dunnett's test to correct for multiple comparisons.

Deviation from original statistical analysis plan

The original analysis plan assumed that the two trial stages were independent. Therefore, each stage was analysed separately with estimates and p-values combined. However, the current analysis is based on combined data from both trial stages. This was done because there were no major differences in results between the two analytical approaches and the combined analysis easier to understand for readers.

Appendix 6.2-2: Cost analysis

This section was completed by Dr Hendramoothy Maheswaran as part of the costing work for the adaptive multi-arm multi-stage cluster randomized trial.

Cost analysis was undertaken from the health provider perspective. For each of the six trial arms we estimated the total cost of providing the intervention to all participants randomised to that arm. This included the costs of providing the intervention at the antenatal clinic and the costs of providing care at the male friendly clinic. We did not include the cost of receiving ART or performing the male circumcision.

For each trial arm we recorded all resources used by those randomised to that arm. We then costed each resource use item to estimate the total costs. The cost of delivering the intervention at the ante-natal clinic included time with an HIV counsellor and invitation letter, and depending on the trial arm, the cost of HIV self-test kits, financial incentives or phone call reminders. As the interventions were delivered to pregnant women during their routine ante-natal clinic visits we did not include the healthcare resources utilized by the pregnant woman. The cost of the male friendly clinic included the cost of: staff salaries; training of staff; consumables and equipment; and overheads. Data from the World Bank were used to adjust all costs to 2016 US Dollars.

We estimated the cost per male partner tested for HIV and attended the male friendly clinic by dividing the total cost of providing the trial intervention to those randomised to that trial arm by the total number of men who tested for HIV and attended the male friendly clinic. We estimated the cost per male partner tested for HIV and either started onto ART or underwent VMMC. We did this by dividing the total cost of providing the trial intervention to those randomised to that trial arm by the total number of men who started ART or referred for VMMC.

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6.3 Additional trial analyses

Eligibility, trial participation and follow up

Of the 3137 women screened for eligibility, 2349 (74.9%) were eligible and gave initial consent. The main reasons for ineligibility in order of frequency were: the woman being underage (<18y old), 39%; having already tested together with the male partner in this pregnancy, 35%; the woman or the partner were not going to be present in Blantyre in the next 28 days, 29%; Not resident in the recruiting district of Blantyre, 21%. Other reasons for ineligibility were: the male partner is already on ART, 8%; not being the first antenatal care (ANC) visit for the woman, 6%; already recruited in the trial, 3%.

At enrolment, a total 116 (4.9%) of 2,349 women who initially consented to participate in the trial discontinued participation immediately after learning their allocated trial arm across the two trial stages (Table 6.3-1). Women who discontinued participation did not take the male partner clinic invitation letter and HIVST kits. Discontinuation from participation after initial consent was similar across trial arms. Among 2233 women who remained in the trial, 1866 (83.6%) completed the follow-up audio computer assisted self-interview (ACASI) four weeks after recruitment. In general, follow-up was similar across the trial arms (Figure 6.2-1) although it was lower in the self-testing + lottery arm, 64.8%, compared to > 67% in all other arms in stage 1 of the trial. Follow-up interview participation improved substantially from 74.2% in stage 1 to 88.8% in stage 2 of the trial.

Table 6.3-1: Women participation by trial arm and stage (N = 2349)

		Trial arm					
	Total	**SOC**	**ST only**	**ST + $3**	**ST + $10**	**ST+ Lottery**	**ST+ Reminder**
Stage 1							
Eligible	**1084**	198	187	146	216	155	182
Consented	**1084**	198	187	146	216	155	182
Discontinued	**77**						
by trial arm	7.1%	14 (7.1%)	7 (3.7%)	8 (5.5%)	19 (8.8%)	13 (8.4%)	16 (8.8%)
Stage 2							
Eligible	**1265**	210	255	234	296	dropped	270
Consented	**1265**	210	255	234	296		270
Discontinued	**39**						
by trial arm	3.1%	6 (2.9%)	4 (1.6%)	13 (5.6%)	11 (3.7%)		5 (1.9%)

SOC: standard of care; ST: self-test kits

Challenges with follow-up / retention in stage 1 of the trial

We note that although retention of women for follow-up interviews was sub-optimal in stage 1 of the trial, it did not affect the measurement of the primary outcome. The primary outcome was measured at the time a male partner presented to the male friendly clinic and so did not require follow-up of the woman, however, this was required for our safety and self-reported HIV testing outcomes that were measured from women at follow-up. For men, retention was equivalent to attending the MFC which also implied satisfying the primary outcome.

Lower retention (overall across all arms 74.2%) was observed among women in stage 1 (Figure 6.2-3) due to a number of challenges relating to the design and clinic logistics.

a) ***Design:*** the trial was exclusively clinic-based with no intended household follow-up. The ANC clinic day unit of randomisation meant that all women were recruited on the same day, which posed challenges with staffing for the follow-up visit.
b) **Clinic logistics:** The trial gave one standard date, 28 days after enrolment, for the follow-up visit to all women recruited on the same day while the clinic gave next ANC visit date depending on the woman's gestation. This implied that two different dates, in some cases a few days apart, were given to the woman who unsurprisingly prioritised the clinic date over the trial date.

Efforts to improve retention

A number of strategies were employed to improve retention of women for follow-up interviews. Firstly, there was harmonisation of ANC and study follow-up dates as far as possible such that trial staff extracted the next ANC day given during the first visit by the Ministry of Health personnel to avoid confusion. Secondly, weekly list of women who were (over) due for follow-up interview was produced for each clinic for trial staff to use in tracking all women for follow-up interviews. Thirdly, for women with telephone numbers as identified through our screening log or the ANC register, the follow-up interview was completed by phone in which case the women did not use ACASI. This strategy was also suggested during the first data safety monitoring board meeting. Fourthly, all health passports of women attending ANC were checked for the study barcode by trial staff who was present during routine ANC service delivery. Finally, reminders were sent to women through their male partners who presented at the male friendly clinic for the follow-up interview.

Who presented at the male friendly clinic (MFC)?

The MFC was set-up by the trial within the physical space of the main clinic. An HIV counsellor staffed the MFC and was responsible for conducting HIV tests including confirmatory testing following the National algorithm. The counsellor also verified used or unused oral HIV self-tests in all the five intervention arms, and provided the financial incentives to clients.

Of 2349 women who were eligible at ANC during enrolment, 676 (28.8%) male partners attended the MFC within 28 days of enrolling the woman (Table 6.2-2). The mean age was 31.2 (standard deviation: 6.0), with the majority reporting that they were married (667, 98.7%). About a 1/3rd had not tested for HIV before (201, 30.6%) with 55.6% of those who tested doing so in the last 12 months. Nearly half (335, 49.6%) presented at the MFC with their female partner, and self-reported HIV prevalence among male partners who attended the MFC was 6.7% (n=44). Men who were in intervention arms expressed high satisfaction with their HIV self-testing experience with the majority 531 (96.4%) indicating that it was not at all hard to self-test. Overall, most men 647 (95.7%), regardless of strategy felt that they would definitely recommend their allocated approach to their friends and family.

Table 6.3-2: Description of men who linked to the male friendly clinic as reported by the man (N = 676)

Variable	Characteristic	Estimate
Age (Years)	Mean (SD)	31.2 (6.0)
Marital Status	Married/cohabiting	667 (98.7%)
	Never married	9 (1.3%)
Currently lives together with partner	Yes	658 (97.3%)
Able to read and write	Yes	653 (96.6%)
Education	Never been to school	10 (1.5%)
	Primary	163 (24.1%)
	Secondary	440 (65.1%)
	Higher	63 (9.3%)
Occupation	Paid employee	433 (64.0%)
	Self-employed	200 (29.6%)
	Unemployed/student	43 (6.4%)
Tested for HIV before	Never	201 (30.6%)
Tested for HIV in the last 12 months	Yes	10 (55.6%)
Came as a couple	Yes	335 (49.6%)
Self-reported result	Positive	44 (6.7%)
	Negative	613 (93.2)
	Not sure	1 (0.1)
Describe your HIV self-testing experience	Not at all hard to do	531 (96.4%)
	Somewhat hard to do	19 (3.4%)
	Very hard to do	1 (0.2%)
Can recommend strategy to friends & family	Definitely yes	647 (95.7%)
	Not sure	5 (0.7%)
	Definitely no	24 (3.6%)

SD: standard deviation

Differences between men who attended and men who did not attend the male friendly clinic: In terms of characteristics of women

Additional analysis was undertaken in order to understand the characteristics of pregnant women that may influence distribution of self-test kits. Two-way tabulation, unadjusted and adjusted random effects logistic regression to account for potential clustering by clinic day was used in this analysis.

Generally, in unadjusted analysis, characteristics of women associated with male partner MFC attendance were: older age; having tested for HIV testing in this pregnancy; living together with the male partner; higher education; being in paid employment; and having better self-rated general health status (Table 6.2-3). The mean age of women whose male partners attended the clinic was higher than that of women whose partners did not attend the clinic, mean 25.3 (standard deviation [SD]: 5.37) years vs. 24.7 (SD: 5.41). In simple logistic regression analysis (Table 6.2-4) every additional year in age of the woman was associated with 3% increased odds of male partner linkage on average odds ratio (OR) 1.03 (95% CI: 1.01; 1.04). If a woman was living together with her partner, this was associated with 68% increased odds of male partner linkage OR 1.68 (95% CI: 1.02; 2.78). Male partner linkage increased 14% on average by with every additional level of education completed by the woman OR 1.14 (95% CI: 101; 1.29); p=0.040. The odds of male partner linkage were lower for women who were either self-employed OR 0.53 (95% CI: 0.37; 0.77) or unemployed OR 0.64 (95% CI: 0.46; 0.88) compared to women who reported being in any kind of paid employment. Similarly, male partner linkage was 50% lower for women had did not have an HIV test in their current pregnancy compared to those who did OR 0.47 (95% CI: 0.29; 0.82).

Overall, significant associations with male partner linkage that were observed in unadjusted analysis remained significant in adjusted analysis even having accounted for intervention effects (Table 6.2-4). However, reporting that a woman underwent HIV testing in her current pregnancy was associated with significantly decreased odds of male partner linkage adjusted OR (aOR) 0.52 (95% CI: 0.31; 0.87) compared to unadjusted analysis OR 0.57 (95% CI: 0.28; 1.13).

Table 6.3-3: Differences between men who attended the male friendly clinic and those who did not attend by characteristics of women (N = 2349)

Woman characteristic	Category / level	Male friendly clinic status Did not attend n = 1,673	 Attended n = 676
Age (years)	Mean (sd)	24.7 (5.41)	25.3 (5.37)
Tested for HIV in this pregnancy			
	No	54 (57.54)	40 (42.6)
	Yes	1505 (70.4)	634 (29.6)
Marital status			
	Married/cohabiting	1534 (69.7)	667 (30.3)
	Never married	22 (81.5)	5 (18.5)
	Separated/Widowed	3 (60.0)	2 (40.0)
Lives together with partner			
	No	89 (78.8)	24 (21.2)
	Yes	1470 (69.3)	650 (30.7)
Able to read and write			
	No	200 (77.2)	59 (22.8)
	Yes	1359 (68.8)	615 (31.2)
Highest level of education			
	Never been to school	72 (79.1)	19 (20.9)
	Primary	710 (72.2)	273 (27.8)
	Secondary, no MSCE	531 (67.0)	262 (33.0)
	Secondary, MSCE	193 (66.6)	97 (33.4)
	Any tertiary	53 (69.7)	23 (30.3)
Occupation			
	Paid employee	135 (59.2)	93 (40.8)
	Self-employed	357 (74.7)	121 (25.3)
	Unemployed	1067 (69.9)	460 (30.1)
General health self-rating			
	Excellent	572 (65.3)	304 (34.7)
	Good	62 (72.8)	25 (27.2)
	Fair / poor	925 (71.3)	345 (28.7)

sd: standard deviation

MSCE: Malawi school certificate of education (O-level equivalent)

Table 6.3-4: Unadjusted and adjusted risk factors (woman) for clinic attendance (N = 2349)

		Unadjusted			Adjusted		
Woman characteristic	**Category / level**	**OR**	**95% CI**	**p-value***	**OR**	**95% CI**	**p-value***
Age (years)	Every additional year	1.03	1.01; 1.04	0.005	1.03	1.02; 1.05	<0.001
Tested for HIV in this pregnancy	No	1.00			1.00		
	Yes	0.47	0.29; 0.82	0.007	0.52	0.31; 0.87	0.013
Marital status	Married/cohabiting	1.00			1.00		
	Not currently married	0.54	0.21; 1.36	0.192	0.96	0.32; 2.88	0.940
Lives together with partner	No	1.00			1.00		
	Yes	1.68	1.02; 2.78	0.039	1.48	0.94; 2.33	0.092
Able to read and write	No	1.00			1.00		
	Yes	1.44	1.03; 2.01	0.031	1.38	1.00; 2.33	0.053
Highest level of education	Never been to school /Primary	1.00		0.236	1.00		0.045
	Secondary, no MSCE	1.25	1.00; 1.55		1.34	1.07; 1.68	
	Secondary, MSCE	1.13	0.83; 1.55		1.22	0.88; 1.68	
	Any tertiary	0.92	0.53; 1.62		0.85	0.46; 1.51	
Occupation	Paid employee	1.00		0.003	1.00		0.005
	Self-employed	0.53	0.37; 0.77		0.56	0.39; 0.82	
	Unemployed	0.64	0.46; 0.88		0.70	0.51; 0.98	
General health self-rating	Excellent	1.00		0.402	1.00		
	Good	0.87	0.69; 1.09		0.81	0.64; 1.02	
	Fair / poor	0.79	0.46; 1.37		0.76	0.44; 1.31	
Trial arm	Standard of care	1.00		<0.001	1.00		<0.001
	Self-test (ST) kits only	1.56	0.89; 2.71		1.48	0.94; 2.32	
	ST + $3 incentive	4.72	2.76; 8.10		4.81	3.21; 7.19	
	ST + $10 incentive	7.62	4.50; 12.90		7.59	5.20; 11.08	
	ST + lottery	1.54	0.76; 3.14		1.62	0.98; 2.69	
	ST + phone reminder	1.59	0.91; 2.76		1.56	1.05; 2.32	

* Random effects logistic regression to account for potential clustering by clinic day. ND: not done i.e. Not included in the model. ** Every additional education level OR 1.14 (95% CI: 101; 1.29); p=0.040

Differences between men who attended and men who did not attend the male friendly clinic: In terms of men's characteristics as reported by women

In order to assess the kind of male partners of pregnant women who ultimately tested for HIV and linked to the MFC for post-test services, additional analysis was undertaken. This analysis may contribute to improvements in the messages that may be given to women to enhance linkage following testing. Two-way tabulation, unadjusted and adjusted random effects logistic regression to account for potential clustering by clinic day was used in this analysis.

Men who attended the male friendly clinic were older: mean age 30.4 (SD: 6.22) than men who did not attend the clinic mean age 28.9 (SD: 6.49) (Table 6.3-5). Of the 1674 men who did not attend the clinic, 730 (43.7%) were from Ndirande recruitment site compared to 192/675 (28.4%) among men who attended the clinic.

In adjusted analysis (Table 6.3-6), odds of linkage increased by 4% for every additional year in age of the male partner OR 1.04 (95% CI: 1.02; 1.07). There was marginal evidence that the odds of linkage increased by 11% for every additional level of education attained by the male partner OR 1.11 (95% CI: 1.00; 1.24). Male partner linkage was significantly lower in Bangwe OR 0.29 (95% CI: 0.17; 0.50) and Zingwangwa OR 0.45 (95% CI: 0.26; 0.76), compared to Ndirande primary health centre. Adjusted results were similar to unadjusted results for this analysis (Table 6.3-6).

Table 6.3-5: Differences between men who attended the male friendly clinic and those who did not attend (characteristics of men as reported by women during baseline interview; N = 2349)

		Male friendly clinic status	
Variable	**Characteristic**	**Did not attend n = 1,673**	**Attended n = 676**
Age (years)	Mean (sd)	28.9 (6.49)	30.4 (6.22)
Able to read and write			
	No	28 (68.3)	13 (31.7)
	Yes	1531 (69.8)	661 (30.2)
Education			
	Never been to school	12 (57.1)	9 (48.8)
	Primary	339 (71.8)	133 (28.2)
	Secondary, no MSCE	499 (72.8)	253 (27.2)
	Secondary, MSCE	577 (66.4)	216 (33.6)
	Any tertiary	132 (67.7)	63 (32.3)
Occupation			
	Paid employee	989 (69.2)	440 (30.8)
	Self-employed	467 (71.8)	183 (28.2)
	Unemployed	103 (66.9)	51 (33.1)
Ever tested for HIV			
	Never tested before	680 (70.4)	286 (29.6)
	Tested > 12m ago	499 (70.2)	176 (29.8)
	Tested ≤ 12m ago	380 (68.4)	212 (31.6)
Recruitment PHC			
	Ndirande	244 (54.8)	201 (45.2)
	Bangwe	730 (79.2)	192 (20.8)
	Zingwangwa	700 (71.3)	282 (28.7)

sd: standard deviation

MSCE: Malawi school certificate of education (O-level equivalent)

PHC: primary health clinic

Table 6.3-6: Unadjusted and adjusted risk factors (man as reported by woman) for clinic attendance (N = 2349)

		Unadjusted			Adjusted		
Woman characteristic	**Category / level**	**OR**	**95% CI**	**p-value***	**OR**	**95% CI**	**p-value***
Age (years)	Every additional year	1.04	1.02; 1.07	<0.001	1.04	1.02; 1.07	<0.001
Able to read and write	No	1.00		0.353	ND		
	Yes	0.71	0.34; 1.47				
Highest level of education **	Never been to school / Primary	1.00		0.488	1.00		0.216
	Secondary, no MSCE	0.89	0.68; 1.17		0.77	0.54; 1.09	
	Secondary, MSCE	1.08	0.82; 1.42		0.76	0.52; 1.12	
	Any tertiary	0.93	0.63; 1.39		0.53	0.27; 1.06	
Occupation	Paid employee	1.00		0.894	ND		
	Self-employed	0.96	0.76; 1.19				
	Unemployed	1.04	0.70; 1.54				
Ever tested for HIV	Never tested before	1.00		0.383	ND		
	Tested > 12m ago	1.10	0.87; 1.40				
	Tested ≤ 12m ago	1.19	0.92; 1.54				
Recruitment PHC	Ndirande	1.00		<0.001	1.00		<0.001
	Bangwe	0.29	0.17; 0.50		0.31	0.21; 0.46	
	Zingwangwa	0.45	0.26; 0.76		0.38	0.25; 0.56	
Trial arm	Standard of care	1.00		<0.001	1.00		<0.001
	Self-test (ST) kits only	1.56	0.89; 2.71		1.84	1.03; 3.27	
	ST + $3 incentive	4.72	2.76; 8.10		4.94	2.84; 8.59	
	ST + $10 incentive	7.62	4.50; 12.90		7.81	4.63; 13.19	
	ST + lottery	1.54	0.76; 3.14		1.48	0.66; 3.35	
	ST + phone reminder	1.59	0.91; 2.76		1.93	1.07; 3.42	

* Logistic regression with robust standard errors to account for potential clustering by clinic day

ND: not done i.e. Not included in the model

** Every additional educational level completed 1.11 (95% CI: 1.00; 1.24)

6.4 Important qualitative observations during trial conduct

A number of observations were made during the conduct of the trial that may improve the design of similar trials in the future. Similarly we believe that the observations may benefit design of programmatic implementation of distribution of self-test kits through ANC. We highlight these observations in the sections below:

6.4.1 Discordance

It was noted anecdotally through verbal reports from HIV counsellors that nearly half of the 46 men who tested HIV positive and attended the male friendly clinic were in a discordant relationship. The accuracy of this estimate may not be accurate because we were unable to directly link the HIV status of the man and that of the woman. By design, our baseline data collection did not include a question on HIV results of the woman. This reduced potential stigma. Additionally, women were simply distributors and not the main target, and thus were not excluded on the basis of being HIV positive themselves.

The manner in which discordant couples were easily identified in this, and perhaps other self-testing studies [1,2] targeting partners is interesting. Discordant couples are seldom identified in routine HIV testing although the literature suggests that nearly half of HIV positive individuals are in discordant relationships [3,4]. The HIV services offered in most countries including Malawi seem to have very minimal focus on discordance as a third potential status for people in relationships besides negative and positive statuses. Therefore, we found albeit anecdotally that most of our discordant couples were less prepared to continue with their relationship but changed their position following targeting couple counselling focusing on treatment as prevention. We have previously described this lack of coping ability and marital consequences in a qualitative study following community-based HIVST [1].

Therefore, future studies and programs must anticipate discordance when targeting couples with HIVST and should have strong couple-oriented counselling.

6.4.2 Potential contamination

The unit of randomization for the PASTAL trial was an antenatal care clinic (ANC) day. At trial design stage, it was suggested that this unit of randomization may lead to contamination as opposed to randomizing the entire health facility. We thus closely monitored events that may constitute contamination in during the trial implementation. The two key scenarios would be where:

participants in the standard of care (SOC) arm accessed the intervention (s), or people not eligible to be part of the trial benefited from trial services [5].

In general, the ANC day unit of randomization appeared to be robust enough with only one key event reported which may constitute contamination. A man in the SOC arm attended the male friendly clinic together with men who were in a $10 incentive arm. They discussed their invitation letters and the man in the SOC arm came a day later to claim a $10 incentive after correctly receiving SOC services from the trial in Zingwangwa recruitment clinic. It was possible to reduce any such contamination due to the robust design of the trial. All men had to present a written invitation letter delivered to them by their partners, which clearly identified the trial arm [6]. Thus, we highly recommend this approach as opposed to giving verbal invitation which may allow individuals to switch services.

There were a few non-serious events that may be regarded as contamination where peers of men in intervention arms asked to be given self-test kits so they can test themselves. This has become a norm where HIVST is offered in a restricted fashion i.e. study context and is simply indicative of the high acceptability of the HIVST intervention [7]. By design, we only provided trial services to men with invitation letters as an identity for trial participation [6].

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7. Summary discussion, recommendations and conclusions

7.1 Introduction

This chapter begins by giving a recap of the main findings of the thesis. In the summary, each of the three thesis aims are re-stated and briefly discussed in the context of the results observed in the studies that have been presented in the previous chapters. This is followed by a global reflection of the 90-90-90 targets [1] with a focus on progress, key gaps, and the role of HIV self-testing (HISVT) in the 90-90-90 targets including global policy changes. A detailed discussion of HIVST secondary distribution through antenatal care clinics is given, focusing on future direction aiming for large scale implementation. I then reflect on some outstanding questions from the thesis before discussing the role of multi-arm multi-stage trial designs in public health research. Finally, I give recommendations considering the design and implementation of studies in the thesis, and conclusions.

7.2 Summary of main findings of the thesis

The first research aim was to assess the effectiveness of *demand-side* (given to users) financial incentives in increasing linkage into voluntary male medical circumcision (VMMC) and antiretroviral treatment (ART). Chapter 3 presented results relating to this aim through a systematic review which highlighted studies that were conducted in low and middle income countries. Although only a few studies were found, they showed that demand-side financial incentives had an impact on increasing the proportion of newly diagnosed HIV positive people who started ART, or the proportion of uncircumcised men who did. This effect seemed to depend on the size of the fixed financial incentive with incentives which compensated for both out of pocket costs as well as opportunity cost showing larger effects. However, incentives that were administered as lottery did not seem to significantly increase either ART initiation or VMMC uptake. At the end of this review, fixed and lottery financial incentives (which have shown promise in an HIV prevention cohort in Lesotho) were identified as potential interventions to test in a trial.

The second research aim was to conduct a formative qualitative study to refine candidate interventions to include in the proposed trial. In this study [2], focus group discussions (FGDs) were conducted with pregnant women attending antenatal care (ANC) in urban Blantyre, Malawi. Additional FGDs with male partners of women attending ANC (not necessarily those who previously participated in FGDs) were conducted. FGD participants were later invited to participate in in-depth interviews (IDIs). Participants in the FGDs were presented with a number of interventions as identified through the systematic review or from the literature. These interventions included: providing oral self-test kits only to pregnant women to deliver to their male partners, additionally provide $3 and $15 fixed financial incentive or provide the incentive as a lottery, remind the male

partner to take action after receipt of the test kits. Participants could also suggest other interventions.

This study highlighted key barriers that deter men from testing either alone or together with their partners at ANC or at other conventional HIV testing sites, as also previously found in other studies [3]. Chief among these barriers were inconvenience men face when accessing ANC with their partners including lost economic time, lack of confidentiality and privacy, individual fear of own and their partner's HIV result. Both men and women agreed that allowing women to collect self-test kits when attending ANC would mitigate most barriers. In turn this would allow men to test themselves for HIV while being able to perform the breadwinner role in their household. Indeed many studies offering HIV self-testing kits report high uptake, most of which is attributable to the convenience and enhanced privacy as well as confidentiality that this approach offers compared to the standard approach of having an HIV counsellor perform the test [4,5].

Providing a financial incentive to compensate for out of pocket costs and opportunity cost, at minimum to refund transport money, was thought as an important addition to providing self-test kits. This was said to be likely encourage men to attend the clinic regardless of their self-test result for follow on services such as confirmatory testing, ART initiation or VMMC. Linkage after self-testing (or indeed after any HIV testing modality) remains a challenging but a key step in the continuum of HIV care or prevention [6]. In summary, this formative study led to important modifications to the originally planned interventions, such as revision of the $15 fixed incentive down to $10 due to concerns that $15 would be unduly coercive for men, from sending short messaging service (SMS) to making a phone call because of the current high volume of junk SMSs. Thus, the final choice of interventions that were to be tested in the trial were: provide HIV self-test kits only (ST), ST + $3, ST + $10, ST + lottery, ST + phone reminder [7].

The final research aim was to design and conduct a Phase II adaptive multi-arm multi-stage (MAMS) cluster randomised trial (CRT) to investigate interventions for increasing the uptake of HIV testing and linkage into care or prevention for male partners of pregnant women attending ANC. This aim was addressed through two components. First, the statistical design, explored through simulation of the adaptive MAMS CRT to identify the required sample size, type I and type II error and key trial assumptions including harmonic mean number of participants eligible for enrolment [7]. Secondly, the interventions finalised through the formative study were formally tested in PASTAL, a Phase II MAMS trial using antenatal clinic-day as the (clustered) unit of randomisation. The two-stage design allowed a pre-planned interim analysis to be conducted, at which point adaptations to the initial

design (specifically, dropping arms for safety or futility) were allowed through an independent Data Monitoring Safety Board.

PASTAL results showed that, compared to simply writing a letter to the male partner, providing HIVST kits plus a fixed financial incentive of $3 or $10 to men via their female partners increased attendance to the clinic 3-fold. These two interventions also had a significant effect on the proportion of male partners who started ART or were circumcised. Similar results were observed for referral for ART or VMMC, which included male partners who may not have finally received the service due to supply side issues. One previous study showed that providing two weeks of ART in the community before patients enter formal HIV care significantly increased demand for ART 3-fold [8]. This adaptive MAMS CRT extends this by investigating different types of interventions such as financial incentives and reminders combined with self-testing. Furthermore, this is the first study to formally investigate the role financial incentives and self-testing have on the uptake of VMMC among men in established relationships. The lottery vs. the standard of care comparison resulted in p-value >0.2 at interim analysis and so the lottery arm was dropped, while four other interventions continued to stage 2 of the trial. This result strengthens the existing body of work within the African region, suggesting that lotteries may not be effective for increasing the uptake of VMMC and may be less acceptable in extremely poor settings [9,10].

7.3 Reflection on the UNAIDS Fast Track Strategy – the 90-90-90 targets

The UNAIDS Fast Track Strategy states that by 2020, 90% of all people living with HIV should be aware of their status, 90% of those diagnosed should start ART, and 90% of those starting ART should be virally suppressed [1]. The ultimate goal is to effectively end the HIV epidemic by 2030 [1]. Good progress has been made globally towards these targets with 70% of all PLWH aware of their status in 2017, 77% of PLWH who were diagnosed started on ART, and 82% of those who started ART virally suppressed [11]. The cornerstone to achieving these ambitious targets is HIV testing in order to diagnose PLWH: vis-à-vis the first 90%. The key remaining “testing gaps” for the first 90% are highest among men, adolescents and key populations for a range of reasons including stigma, masculine gender norms, discrimination and criminalization [11].

7.4 Effect of simple clinic invitation on HIV testing among male partners of antenatal care attendees

HIV programmes in high HIV prevalence settings have been attempting to improve coverage of male partners of ANC attendees with HTS for some time culminating in obvious gaps in meeting the UNAIDS targets [11]. Simple personalised invitation letters to men have been shown to increase male involvement in clinic attendance to receive pregnancy-related education but not HIV testing

[12]. Such male involvement appears to improve newborn and maternal outcomes [13]. However, HIV testing is more psychologically fraught for the male partner than merely receiving information about pregnancy, birth and care of the neonate. While an invitation maybe taken up to show commitment by the man to his partner and unborn child, accepting a request to undergo HIV testing requires the man to accept that his sexual behaviour may already have placed them in danger [14,15]. For example: in this project, only 17% of women reported that their male partners tested for HIV following receipt of a personalised invitation letter [16].

Other effective interventions for increasing HIV testing among male partners of pregnant women include more labour intensive approaches such as home visits [17,18], or less targeted interventions, such as invitation to HTS provided in bars or churches [14]. These types of interventions are logistically difficult to scale up due to the high needs for staff and other implementation costs.

7.5 Role of HIV self-testing in the Fast Track Strategy

HIVST offers a key moment of privacy in a way that no other testing method does [19]. This explains the observations that most health care workers who have access to HIV test kits self-test [19]. Thus, HIVST has potential to contribute to the first 90% of the UNAIDS targets by allowing testing by people who would otherwise be unable or unwilling to visit formal HIV testing facilities. More importantly, there is growing evidence showing that HIVST is highly acceptable to men [16,20,21,22,23], adolescents [24], and key populations [25,26,27], thereby directly addressing the current gaps in the 90-90-90 targets [11]. In 2016 WHO strongly recommended HIVST as a complementary strategy to current HIV testing services (HTS) for increasing the coverage and frequency of testing, especially in men [28].

By April 2018, 43 countries either had policies in place allowing HIVST or had policies under development [29]. This signals a real and rapid global change in policies around HIVST, as in 2011 only a handful of countries, notably Kenya, allowed HIVST [19]. The funding of the self-testing Africa (STAR) initiative in 2015 catalysed the market for HIVST by generating multi-country evidence leading up to most country policy changes around HIVST.

While there is strong evidence to suggest that HIVST can increase the uptake of testing (Table 7.5-1) there are challenges with measurement of linkage to care or prevention. These challenges relate both to uncertainty about denominators, and to the difficulties of capturing those linkage events that do occur and relating them to HIVST. The main barrier to capturing linkage events following HIVST is lack of automatic disclosure to the kit distributor of a positive self-test. Thus, the service providers do not know how many positive clients they have to confirm linkage for. Additional challenges may include unwillingness to discuss next steps to the kit distributor and lack of

knowledge of where to access post-test services for example if kits are obtained without direct interaction with the distributor. However, there are currently no studies that have investigated if linkage to care or prevention is poor following HIVST irrespective of measurement challenges.

Table 7.5-1: Evidence and research gaps concerning HIV self-testing globally

Outcome of interest	Population	Overall estimate (s)	Research gap (s)
HIVST uptake	General population e.g. community-based testing	>70% [20,30]	Engaging men routinely and affordably
HIVST uptake among men when targeted	Male partners of pregnant women in ANC	>80% [5]	Post-test linkage
HIVST uptake among key populations e.g. FSW and MSM	Female sex workers, and men who have sex with men	>80% [25,26,27]	Post-test linkage
Linkage to care following a positive HIVST result	Newly diagnosed and existent people living with HIV	Less than 20% to 55% over one month or undefined time period [5,8,16,20]	Poorly measured, hard to measure, suboptimal if no additional interventions are provided
Retention in care 6m following a positive HIVST result	People living with HIV started on ART through HIVST at home	71% for HIVST 76% for standard HTC [8]	Not reported in many studies
Accuracy with oral fluid self-test, direct distribution with support	Adolescents and adults (>10 years)	Sensitivity: 94.3% (CI 95% 90.6-96.7) Specificity: 99.4% (CI 95% 98.6-99.8) [31]	Secondary accuracy under secondary distribution models
Accuracy in HIV positive re-testers on ART	People living with HIV who are on ART	Poor from anecdotal data	Not known
Provider cost per person tested in urban Malawi	Facility and general population	Range US$7.53 to 10.57 for facility testing US$8.78 for HIVST [32]	Secondary distribution with one self-test kit
Provider cost per HIV positive identified in urban Malawi	Facility and general population	Range US$28.30 to 67.33US$ for facility testing US$97.50 for HIVST [32]	Costs for linkage to prevention following a negative self-test

HIVST: HIV self-testing, ANC: antenatal care clinic, FSW: female sex workers, MSM: men who have sex with men, ART: antiretroviral therapy, HTC: HIV testing and counselling

7.6 Secondary distribution of HIV self-test kits through antenatal clinics

The model of HIVST considered in this thesis, distribution of self-test kits to male partners through antenatal care (ANC) attendees is a variant of models termed *secondary distribution* [21]. These models involve distribution of self-test kits to the immediately available surrogate who then delivers to the ultimate user. Three trials of ANC secondary distribution of HIVST kits, including the one detailed in chapters 5 and 6, have showed very high uptake of HIV testing among male partners

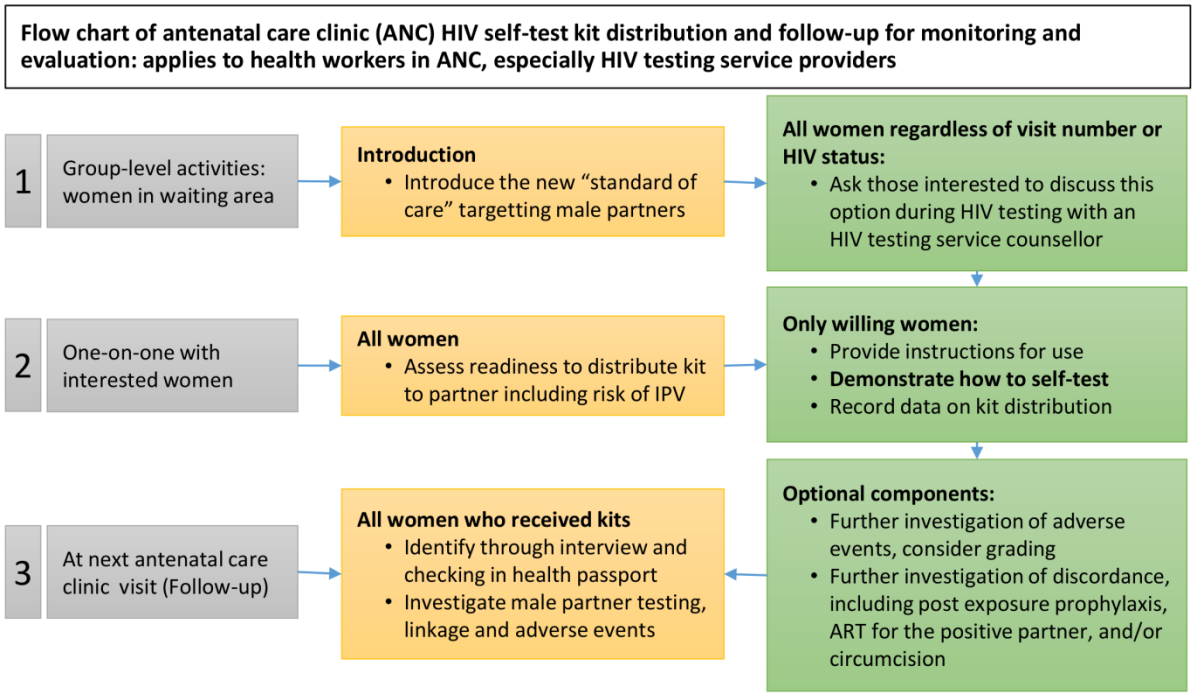
(uptake >80% in all trials) [16,21,23]. These trials have led to direct adoption of ANC secondary distribution by Ministries of Health in Kenya, Uganda and Malawi (where the trials were conducted) as well as by other countries within the African region. Therefore, ANC secondary distribution of HIVST kits should be considered a highly promising candidate for a new "standard of care" for increasing the uptake of testing among male partners of ANC attendees.

By extension, secondary distribution could also be implemented through other channels, including through people accessing HTS at testing clinics, or people attending clinics for other investigations at the out-patient department. The key elements for successful secondary distribution include demonstration of how to self-test by the health worker to the distributor, provision of instructions for use, and leaflets describing available post-test services and where to access these services. ANC secondary distribution, regardless of the HIV result or status of the woman (as adopted in this project), aligns well with potential large scale implementation. Some investigators have excluded women with a history of intimate partner violence (IPV). While this ensures higher safety in a study context it may not be feasible to apply this when secondary distribution is scaled up.

7.7 Way forward for ANC secondary distribution in Malawi, regionally and globally

In the context of large scale implementation of ANC secondary distribution by Ministries of Health in Malawi, other African countries and globally, it is essential to map out the flow of women and how services would be provided. In our model, and in the context of Malawi, women presenting for their first ANC visit were informed about the study in a group while they waited for their ANC services (Figure 7.7-1). This needs to be done as a sensitization process, and to allow women to decide on whether or not to consider taking kits for their partner before their one-on-one session. The main discussion on secondary distribution should ideally take place with an HTS provider during HIV testing of the woman with a demonstration of how to self-test in sufficient detail for her to be able to guide her partner effectively as one of the key components. Ideally, leaflets describing the process, and where to access post-test services should be provided as well as the manufacturer's translated instructions for use that are context specific.

Figure 7.7-1: Description of ANC secondary distribution



IPV: intimate partner violence
ART: antiretroviral therapy

Previous costing estimated the direct cost per individual tested through routine facility HTC clinics in urban Blantyre, Malawi is US$7.53 compared to US$8.78 for self-testing when one kit per person was delivered in the community [32]. I found similar costs in the trial: in the standard of care arm the average cost per male partner tested for HIV within 28 days was US$9.85 and for self-testing US$12.58 (or US$9.58 if HIVST kit prices are assumed to be US$2.00 as per current unit cost, rather than US$3.50 as paid in 2016) in the self-testing arms with two self-test kits provided to the pregnant woman. These costs imply that ANC secondary distribution has potential to be cost-saving, particularly with very high uptake of testing among the male partners; economies of scale may be achieved [33]. One approach for minimizing the costs of ANC secondary distribution would be to target settings (districts) with high HIV prevalence (≥5%). With 600,000 births every year, Malawi, just like other countries in the region, has a real opportunity to reduce the gap in HIV testing among men whose partners are accessing ANC.

7.8 Outstanding questions arising from thesis for immediate and future consideration

Firstly, it was observed through our trial that over 50% of all men who self-tested HIV positive were in discordant relationships. Fear of discordant results is one of the biggest barriers to HIV testing for men [2,34]. Within the wider body of HIVST research studies in Malawi, qualitative studies have

shown repeatedly that couples are simply not prepared to deal with discordance, with a variety of misconceptions leading them to view their relationship as one that simply cannot last [34]. The mere concept of discordance was biologically perplexing, with couples failing to understand how HIV could fail to be transmitted during unprotected sex. Couples were also unaware that treatment-as-prevention could enable them to resume unprotected sex six months after the positive partner was started on (and remained adherent to) ART. Moreover, health-workers staffing routine HTC and ART clinics were also unsure how to explain or manage discordance. Without these understandings, couples assumed that HIV must have been introduced very recently (implying infidelity), and were advised that condoms would be required indefinitely, precluding a healthy sex-life or children. Importantly, correcting these misconceptions led to some couples reconciling.

Thus, there is need to consider a third HIV status called discordant, additional and distinct to positive and negative for couples, and needing its own health education and management approach. Hence discordance needs to be included in the training of HIVST kit distributors and clinic staff, and should be anticipated as both a special HIV prevention opportunity and a special responsibility with high risk of adverse events for ANC HIVST secondary distribution, with the joint aims of maximising HIV prevention and for making HIVST safer and less risky to relationships on per case basis.

Secondly, while ANC secondary distribution trials have showed promising results in getting male partners tested, there is need to clearly define and optimise the role this intervention may have on other HIV prevention strategies currently on offer, including prevention of mother to child transmission. The integration component is very important for Ministries of Health considering the scale-up of this intervention. Potential areas for strengthening include data capture, confirmatory testing for male partners with a positive self-test, and managing patients starting ART.

Finally, linkage to voluntary medical male circumcision (VMMC) is important because VMMC reduces the risk of female to male HIV transmission by 60% [35]. Uptake of VMMC remains disappointingly low in Malawi at 5% with uptake in older men the lowest [36]. My trial showed that conditional cash transfers may be effective at increasing the uptake of VMMC among men in sexual relationships. This replicates findings from other parts of Africa where conditional voucher-based incentives seemed to improve the uptake of VMMC in Kenya and Tanzania [10,37]. However, our incentives were monetary as these were preferred by the participants [2] and so present logistical and ethical challenges to policy makers.

Thus, there is need to investigate alternatives that are as effective as monetary incentives given that “distributing” money is viewed as unsafe and susceptible to corruption. Critically, our study

population was a hard to reach group of breadwinners living “hand-to-mouth” and reliant on spending money raised that very day. Men in this situation cannot simply take time off their economic activities, especially when their partner is pregnant. Therefore, it is important to offer interventions that are not only acceptable to governments but interventions that are cost-effective and affordable for the man. That is, is it ethically acceptable for governments or programmes to deny men the offer of financial incentives as intervention to achieve linkage to care or prevention, despite cost-effectiveness and lower implementation costs than alternatives? In this case, does the government have a special responsibility to identify and implement an equally effective alternative?

7.9 Application of multi-arm multi-stage (MAMS) trial designs in public health research

Adaptive trial designs allow timely, efficient and cost-saving evaluation of multiple interventions in a single study [38,39,40]. In multi-arm multi-stage designs, several interventions are compared to a control arm using interim analysis [41,42], providing an unbiased approach to investigating and selection of multiple Phase II candidates under consideration for Phase III trial [41,43]. Adaptive trial designs have predominantly been used in the pharmaceutical industry, primarily to improve timeliness of trial results while maintaining statistical properties of the design [44,45,46]. My thesis was arguably the first to investigate the use of an adaptive trial design to address a public health question involving behavioural interventions, with the idea that a definitive Phase III trial would follow a Phase II trial.

While the methodology for designing individually randomized adaptive trials has improved and matured over the years [44], this thesis did not find any other adaptive trials that randomized groups or clusters. However, statistical approaches that control for clustering are commonly required in public health interventions, which are often delivered at clinic- or community-level [47]. In particular, our project aimed to investigate multiple interventions delivered on a clinic-day followed by an interim analysis to eliminate interventions no better than the standard of care [7]. Therefore, an adaptation was made to the sample size calculation for cluster randomized trials [48] to allow for the two-stage design. The two-stage design allowed a pre-planned interim analysis to be conducted at which point adaptations to the initial design were allowed through an independent Data Monitoring Safety Board. In particular, the main adaptation considered was dropping arm (s) but not including new arms.

In summary, this project successfully designed and implemented the first adaptive MAMS cluster randomized trial investigating public health interventions. Given the pressing needs to achieve the 90-90-90 UNAIDS targets [1], application of MAMS designs to address questions on the HIV cascade

of services should be considered. My trial recruitment and follow-up was completed within seven months during which around 3,100 ANC attendees were screened and around 2,500 recruited to six arms. This was achieved on a budget of less than £50,000. In contrast to a conventional parallel design, we posit that time, sample size and costs could have risen substantially to complete the five independent trials. Thus, the adaptive design appeared to be efficient in terms of number of participants enrolled, cost-saving in terms of costs incurred and extremely timely as we were able to get results of all five comparisons in seven months.

7.10 Recommendations

Increasing coverage of testing among male partners of antenatal care attendees

The findings from this project demonstrate that ANC secondary distribution is not only feasible but acceptable to both men and women, and may achieve high HIV testing coverage among the male partners [16] (Table 7.10-1). Current HTS approaches have achieved success in increasing coverage of testing and reducing the gap in the proportion of PLWH who know their status to 30% [11]. However, gaps remain particularly among men and other target populations. Therefore, we recommend that oral HIV self-test kits should be provided routinely to pregnant women who are attending ANC for the first time to deliver to their male partners. This project replicates findings of high uptake of male partner testing also observed in other studies within the region, suggesting that the results are robust and may be generalisable in different cultural environments.

This recommendation is supported by two key international policy changes as well as ANC secondary distribution being a low cost intervention that can easily be integrated into national HTS programmes. Firstly, WHO strongly recommended HIVST as a complementary strategy for increasing the coverage of testing particularly among men. The data generated here lend weight to this recommendation. Secondly, the test kit used in the project received WHO prequalification which implies that governments may now procure the test kit for national use. This is important as it supports efforts for national scale implementation of the strategy.

Using Malawi as an international case study, globally commendable results have been achieved with a recent population survey showing that 73% of all PLWH reported knowing their HIV status in 2016 [49]. An extremely decentralized HTS programme delivers three million HIV tests every year, most of which is achieved through facility-based testing. However, there is suboptimal testing among populations with barriers to facility-based HIV testing including men and key populations. More importantly, we found previously undiagnosed HIV prevalence of 7% among male partners who were tested in the trial and attended the MFC, which is very high. The Malawi Ministry of Health is

planning to scale up ANC secondary distribution to increase coverage of testing among male partners of ANC attendees as a direct result of this project.

Achieving linkage to post-test services among male partners of ANC attendees following secondary distribution

This thesis showed that without an additional intervention, only 18% of male partners would be expected to achieve timely linkage (within 28 days) to post-test services such as ART and VMMC following ANC HIVST secondary distribution. Thus, we recommend that ANC HIVST secondary distribution of HIVST kits be offered along with another intervention conditional on linkage to care or prevention. In this trial, I found fixed financial incentives to be highly effective at increasing clinic attendance post self-test as well as starting ART or undergoing VMMC (Table 7.10-1). Moreover, the use of lottery incentive or phone call reminder did not improve linkage following ANC secondary distribution in this project.

For very hard to reach groups that potentially drive the HIV epidemic, such as male partners of pregnant women, linkage to care or prevention is crucial to reduce transmission. Although financial incentives may not be readily accepted by policy makers, alternatives with comparable effectiveness are urgently needed. Our results are the first to investigate such a combination intervention (HIVST plus incentives), and so the results ideally need to be replicated in other settings. Given that the majority of people will self-test negative, linkage to prevention services is critical in order to achieve cost-effectiveness of ANC secondary distribution [50].

Policy makers may feel that no additional interventions may be required to achieve timely linkage, particularly for people who self-test. This view is supported by population based surveys in Malawi, Zambia and Zimbabwe that showed that linkage to care improves over a year of testing HIV positive [49]. However, this approach is not fully consistent with the test-and-treat strategy, which advocates immediate ART for people who test HIV positive on the basis of improving individual patient outcomes and to reduce transmission [1].

Use of novel trial designs including adaptive multi-arm multi-stage designs

This project demonstrated that the use of adaptive multi-arm multi-stage cluster randomized trials to investigate key pressing public health problems is feasible. More importantly, the trial design may have contributed to high efficiency, low costs and extremely timely results. Thus, we recommend that such novel designs be applied in public health although there are still areas of improvement needed for the design, particularly hypothesis testing for multi-stage trials that randomize groups as

opposed to individuals. Areas of improvement include accounting for multiple comparisons during sample size calculation and computing 95% CIs for a multi-stage design.

Table 7.10-1: Summary of key recommendations and future directions

Description	What is known?	Policy viewpoint	References
Impact of clinic invitation only for men			
Clinic attendance without HIV testing i.e. male involvement	Up to 30% of men attend ANC pregnancy related services. This intervention does not necessarily increase HIV testing for men.	Policy makers are willing to implement this intervention because it is low cost and easy to implement.	[12]
Impact of providing oral HIV self-tests through ANC for men			
Increased self-reported HIV self-testing	Between 80-95% of women report that their male partner self-tested during follow-up interviews. These uptake figures are impressive, but caution is needed because measurement is by self-report (hence liable to social desirability bias).	There is general acceptability to implement this model nationally by many policy makers. Key concerns are around intimate partner violence, secondary accuracy, and monitoring and evaluation.	[16,21,22,23]
Suboptimal linkage to care or prevention	Only two studies have attempted to measure linkage during ANC secondary distribution. Linkage measurement is not easy. Without additional interventions linkage is suboptimal.	Few data available for policy decisions around linkage. Certain additional interventions such as financial incentives are very effective but policy makers are unwilling to implement.	[16,21]
No serious adverse events reported	No ANC secondary distribution studies have reported any serious adverse events (SAEs) from the male partner. Other settings report ~1 SAEs per 10,000 HIVST episodes, mainly separations of discordant couples.	Strong opposition to HIVST early reflected concerns about SAEs. With more emerging data showing that SAEs are rare, policy makers are now willing to consider HIVST as an additional model.	[16,21,22,23]

ANC: antenatal care clinic; HIVST: HIV self-testing; SAE: serious adverse events

Table 7.10-2 (ct'd): Summary of key recommendations and future directions

Description	What is known?	Policy viewpoint	References
Impact of fixed financial incentives on linkage to care or prevention			
Without HIVST but conditional on achieving pre-specified outcomes	Conditional incentives increased the proportion of uncircumcised men undergoing circumcision in Kenya.	Many policy makers are unwilling to implement incentives.	[37]
With HIVST conditional on clinic attendance:	Conditional incentives increase the proportion of men who link to care or prevention following self-testing.	Many policy makers are unwilling to implement incentives.	[16]
What is the right dose and form of incentive?	Monetary incentives are preferred though logistically difficult to implement. Underlying economic conditions of the local setting should dictate the amount to be offered, which will differ from setting to setting.	Non-monetary incentives may be considered over monetary incentives.	[2]

ANC: antenatal care clinic; HIVST: HIV self-testing; SAE: serious adverse events

7.11 Strengths and limitations of the thesis

Strengths

The key strength of this project is the combination of a systematic review, a formative study and a trial to address a public health question. This unique combination means that the interventions that were found to be effective may be more likely to be acceptable at population level. It is because of this unique combination that the results of this project have been globally discussed and the approach is being considered for wide scale implementation in Malawi and regionally.

Additionally, this thesis utilized a novel trial MAMS design which implied that results from all five comparisons were realized in a timely fashion compared to conducting five independent trials. This has allowed rapid evaluation of the results by policy makers in Malawi followed by a policy change to include HIVST in the national guidelines as well as national potential national scale up of the model.

Limitations

Although the work contributing to this thesis was generally successfully implemented, some key limitations that may not have been described in each chapter of the thesis need to be highlighted. In the systematic review described in chapter 3, a study that investigated the effect of a subsidy type of financial incentive was included. A subsidy covers whole or part of user fees and may differ substantially from an incentive that is offered directly to the user. Therefore, combining this subsidy study together with other non-subsidy studies may have been problematic.

The formative study described in chapter 4 may have lacked full depth because a planned participatory workshop with key stakeholders (Ministry of Health officials) was not conducted due to time and budgetary constraints. The workshop could have allowed the health workers at the clinics participating in the trial and who ultimately assist with ART initiations and overall ANC education to have in-depth understanding of the project components and interventions. One way this resulted in logistical problems for the main trial was the different follow-up dates given to women during the trial by ANC and the study staff. This resulted in only 74% of women being followed up at day 28 in stage 1. Follow-up increased to 91% in stage 2 after health workers were familiar with the trial components and participated more in guiding participants to the trial staff for recruitment, follow-up and post test services.

The clinic-day unit of randomization was potentially liable to spill over effect or contamination. For instance, a man who was in the standard of care arm may have waited for the trial HIV counsellor

together with a man who was in a $10 incentive arm. The two men are likely to have shared information about the study leading to confusion for the man in the non-incentive arm as to what he was supposed to get at the end of his clinic attendance. A better choice of cluster would have been the whole clinic as opposed to the clinic day as this would have more effectively prevented contamination. Randomisation of the entire facility to one arm would have eliminated presentation to the same clinic for different interventions. However, this design was beyond the scope of a PhD project.

A composite primary outcome including ART initiation, undergoing VMMC and receipt of any other HIV prevention e.g. counselling was used for the primary outcome. The HIV status of the male partner was unknown at the point of delivery of HIVST kits to the woman. This means that male partners would link to care or prevention with either an HIV positive or HIV negative result. Indeed this programmatic approach is likely to be followed by HIVST programmes at scale. However, the weight for each linkage component (ART, VMMC, counselling only) is not the same. Linkage to care is the main linkage component that has been emphasized over the years. However, given that we are closer to the first 90% [1] there is more need to emphasize linkage to prevention for HIV negative individuals [6]. For HIVST in particular, the majority of people will test HIV negative and so linkage for people self-testing HIV negative is the biggest driver of cost-effectiveness [50].

In general, the literature emphasises the combination of individual components with similar importance or consequences in a composite outcome [51]. In this thesis, starting ART was obviously more important and with more serious consequences than undergoing VMMC, or simply receiving counselling if HIV negative. The other important aspect of individual components of a composite outcome is the frequency with which it occurs [51]. Clearly with any HIV testing project or program there are more people testing HIV negative than HIV positive. This implies that the frequency of linkage to ART will be different, and was indeed different from the frequency of linkage to HIV prevention.

The primary outcome for the trial was measured at the male friendly clinic i.e. men had to present with a pre-allocated letter to count in the numerator. Audio computer assisted self-interviews (ACASI) with women four weeks after recruitment suggested that more male partners tested but did not attend the male friendly clinic. The discrepancy between the proportion of men who attended the male friendly clinic (MFC) and the proportion of men who tested as reported by the female partners may suggest reporting bias despite the use of ACASI. The men who may have tested but did not attend the MFC may have gone elsewhere for care (if HIV positive) or HIV prevention (if HIV negative) [20]. This problem is inherent in the HIV self-testing intervention because the enhanced

privacy and confidentiality means people make their own choices when it comes to disclosure [20]. Similarly, men in the HIVST arms may have tested for HIV and if negative and already circumcised, they may have perceived that there was no need to attend the MFC as there would be no relevant interventions.

The trial analysis accounts for multiple comparisons with a common standard of care through the Dunnett's test [52] but the sample size calculation does not. The literature is generally not clear about adjusting for multiple comparisons at sample size calculation stage. One approach is to use a much smaller Type I error i.e. conventional Type I error e.g. 0.05 divided by the number of hypothesis tests, known as the Boniferroni correction [53]. Clearly this approach will lead to very large sample size. Some statisticians have argued that this type of adjustment may lead to unnecessarily large sample sizes [46]. Given the large effect sizes observed in the project it is not clear how this problem affected the trial.

The trial analysis does not take into account the fact that an interim analysis was conducted i.e. the two-stage design because the final analysis combined stage 1 and stage 2 data. However, a sensitivity analysis assuming that the two stages were independent yielded similar results to those from combining the two trial stages. There were additional challenges with computation of 95% CIs for the analysis that involved each stage independently and then combined using the weighted inverse normal (WIN) combination function [42,54]. The WIN function was used to combine p-values from each of the two stages of the trial but a method for combining the estimates (risk ratios) and the 95% CIs was not available.

7.12 Conclusions

The systematic review presented for this thesis found very few studies that investigated the effect of demand-side financial incentives in increasing the percentage of people starting HIV treatment or undergoing circumcision in low and middle income countries. A rigorous approach to identifying potential interventions for increasing the uptake of HIV testing and clinic attendance, regardless of HIV results, led to five interventions that were then tested in a novel MAMS CRT.

The trial results showed that HIV testing was substantially increased in all the five HIV self-testing arms compared to enhanced standard-of-care. Attendance at the clinic regardless of HIV result within 28 days (timely linkage) increased 3-fold using fixed financial incentives plus partner-delivered HIV self-test kits in a hard to reach and high priority group.

This thesis has also demonstrated that novel trial designs such as adaptive MAMS CRT can be applied to rapidly address pressing public health problems in Africa. The approach I adopted, combining a systematic review, a qualitative study and a trial is very meticulous and recommended where interventions may have varying effects from setting to setting such as financial incentives.

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8. Appendices

8.1 Information sheets and consent forms

Appendix 8.1-1: Information sheet and consent for focus group discussions

PQ20a: Participant Information and Consent Form for Focus Group Discussion Participants v0.4; 6th August 2015

Partner-provided self-testing and linkage (PASTAL)

Malawi-Liverpool-Wellcome Trust Clinical Research Programme
P.O Box 30096, Chichiri, Blantyre 3, Malawi.
Tel. +265 1 876444 Fax +265 1 875774

Title: Developing contextually acceptable candidate interventions for increasing uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in Antenatal clinics in Blantyre, Malawi: a cross-sectional qualitative study

Principal Investigator: Mr. Augustine Choko

[The following text must be read to the participant, who must have their own copy to take home]

Introduction

Hello. My name is ……, and I am working with Malawi Liverpool Wellcome Trust (MLW) on behalf of Mr. Augustine Choko and colleagues. We are conducting a study to develop interventions for increasing uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in antenatal care (ANC). We would like to understand the contextual features and attributes that should be included in a number of HIV self-testing (HIVST) models and linked interventions to make them more acceptable to men.

Request for your Voluntary Participation

I would like to ask you to voluntarily participate in this study. You have been identified because you are attending ANC services at a public primary healthcare facility in Blantyre / your partner is attending ANC services at a public primary healthcare facility in Blantyre. We consider that your views about HIVST for male partners of ANC attending women will provide some insights of community perceptions about this approach and would help us to develop interventions that are culturally acceptable and are aligned to the needs of the male partners of the ANC attending women.

Procedure
I would like to have a discussion with you and other members who are attending ANC clinics / their partners are attending ANC services as a group. The discussion will not exceed 2 hours. I will be talking to the group about your views on approaches for introducing HIVST to the male partners of ANC attending women. I would like to understand how these approaches could be implemented in a manner that is acceptable, safe and effective to both partners.

Your participation is entirely voluntary. If you decide to take part, you may withdraw from the discussions at any time if you do not want to continue. You also have a right not to answer any particular question or questions that will be asked. Declining to participate in the study will not affect any health services that you or any person related to you may be currently receiving or may require in future.

While discussing with the group, I will write down everything that the group will be discussing. However, it is usually very difficult to keep pace taking notes with the discussion. With your permission, I would like to record the group discussion using a recorder in order to capture everything that you say.

Confidentiality
All personal information collected in this study will be kept strictly confidential. I will not share the information you provide with anyone who is not part of this research. But it may be shared with fellow researchers and may also be published through meetings or journals in a manner that does not reveal your identity. Before sharing in this manner, the information from you will be combined with that from other research participants. Information which could identify you or anyone related to you will never be released. This also means that names of study participants, including your own will not be included when sharing the data. Recording equipment, recorded information and transcribed data will be kept with identifiers, locked, and only accessible to people that have authorised access.

Risks
You may be uncomfortable with some of the questions that I will ask. You are perfectly entitled to refuse discussing issues that you do not want to.

Benefits
There are no direct benefits to you in your taking part in this interview. There is a possibility though that you may feel better talking about it if you are having issues about HIV testing for male partners of ANC attending women. What we learn from this discussion would help develop ways of offering HIVST to the male partners of ANC attending women. It would also help us inform health authorities in the Ministry of Health regarding how people really feel about HIVST for the male partners of ANC attending women in Blantyre.

Compensation
You will not receive payment for participating in the focus group discussions. You will however, be offered a transport refund of K1,000 and refreshments.

Contact details

This research has been approved by the College of Medicine Research Ethics Committee (COMREC) and the London School of Hygiene and Tropical Medicine Research Ethics Committee. If you have any questions regarding your rights as a research participant, or concerns on how you have been treated in the study, please feel free to contact **Mr. Augustine Choko** [+265 (0) 999 577 452] or [augutc@gmail.com]. If you have any questions regarding your rights as a research participant, or concerns on how you have been treated in the study, please feel free to contact COMREC Secretariat, College of Medicine, Private Bag 360, Chichiri, Blantyre 3 or call on 01877 245or 01 877 291.

Consent Declaration

If you agree to voluntarily participate in the study, please sign or write your initial or your thumb print below to show that you understand the information above and that your consent is given voluntarily.

1. I have received and read or had read to me the information sheet provided by the Researcher that explains in detail the reasons for the study.
2. I have understood the purpose of the research.
3. I have asked all the questions that I have about the purpose of the research and feel that I have enough information about it.
4. I understand the reasons for this group discussion.
5. I am willing to take part in the group discussion.
6. I understand what I will be required to do if I participate in the discussion.
7. I know that I have the right to leave the discussion at any time or to refuse to answer any questions.
8. If I do not agree to take part in this discussion I understand that I will not be penalized for doing so by the researcher nor by any medical service providers in the future.
9. **I voluntarily agree to take part in this focus group discussion**

---------- -------/--------/-------

Signature/thumb print of participant Date

---------- -------/--------/-------

Signature of person obtaining consent Date

If the participant gave verbal consent, please enter the name of person who witnessed the consent here, and their signature:

---------- -----/-------/-------- ----------

Name of Witness (BLOCK CAPITALS) Date Signature or thumb print

Appendix 8.1-2: Information sheet and consent for in-depth interviews

PQ22a: Participant Information and Consent Form for In-depth Interview Participants v0.2; 21st September 2015

Partner-provided self-testing and linkage (PASTAL)

Malawi-Liverpool-Wellcome Trust Clinical Research Programme
P.O Box 30096, Chichiri, Blantyre 3, Malawi.
Tel. +265 1 876444 Fax +265 1 875774

Title: Developing contextually acceptable candidate interventions for increasing uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in Antenatal clinics in Blantyre, Malawi: a cross-sectional qualitative study

Principal Investigator: Mr. Augustine Choko

[The following text must be read to the participant, who must have their own copy to take home]

Introduction

Hello. My name is ……, and I am working with Malawi Liverpool Wellcome Trust (MLW) on behalf of Mr. Augustine Choko and colleagues. We are conducting a study to develop interventions for increasing uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in antenatal care (ANC). We would like to understand the contextual features and attributes that should be included in a number of HIV self-testing (HIVST) models and linked interventions to make them more acceptable to men.

Request for your Voluntary Participation

I would like to ask you to voluntarily participate in this study. You have been identified because you previously participated in the focus group discussions for this study which involved women attending ANC services at a public primary healthcare facility in Blantyre/male partners of women attending ANC services at a public primary healthcare facility in Blantyre. We consider that your views about HIVST for male partners of ANC attending women will provide some insights from you as an individual regarding this approach and would help us to develop interventions that are culturally acceptable and are aligned to the needs of the male partners of the ANC attending women.

Procedure

I would like to have an interview with you and our discussion will not exceed 1 hour. I will be talking to you about your views on approaches for introducing HIVST to male partners of ANC attending women. I would like to understand how these approaches could be implemented in a manner that is acceptable, safe and effective to both partners.

Your participation is entirely voluntary. If you decide to take part, you may withdraw from the interview at any time if you do not want to continue. You also have a right not to answer any particular question or questions that will be asked. Declining to participate in the study will not affect any health services that you or any person related to you may be currently receiving or may require in future.

While discussing with you, I will write down everything that you will be saying. However, it is usually very difficult to keep pace taking notes with the interview. With your permission, I would like to record the interview using a recorder in order to capture everything that you say.

Confidentiality
All personal information collected in this study will be kept strictly confidential. I will not share the information you provide with anyone who is not part of this research. But it may be shared with fellow researchers and may also be published through meetings or journals in a manner that does not reveal your identity. Before sharing in this manner, the information from you will be combined with that from other research participants. Information which could identify you or anyone related to you will never be released. This also means that names of study participants, including your own will not be included when sharing the data. Recording equipment, recorded information and transcribed data will be kept with identifiers, locked, and only accessible to people that have authorised access.

Risks
You may be uncomfortable with some of the questions that I will ask. You are perfectly entitled to refuse discussing issues that you do not want to.

Benefits
There are no direct benefits to you in your taking part in this interview. There is a possibility though that you may feel better talking about it if you are having issues about HIV testing for male partners of ANC attending women. What we learn from this discussion would help develop ways of offering HIVST to the male partners of ANC attending women. It would also help us inform health authorities in the Ministry of Health regarding how people really feel about HIVST for the male partners of ANC attending women in Blantyre.

Compensation
You will not receive payment for participating in the interview. You will however, be offered a transport refund of K1,000.

Contact details
This research has been approved by the College of Medicine Research Ethics Committee (COMREC) and the London School of Hygiene and Tropical Medicine Research Ethics Committee. If you have any questions regarding your rights as a research participant, or

concerns on how you have been treated in the study, please feel free to contact **Mr. Augustine Choko** [+265 (0) 999 577 452] or [augutc@gmail.com]. If you have any questions regarding your rights as a research participant, or concerns on how you have been treated in the study, please feel free to contact COMREC Secretariat, College of Medicine, Private Bag 360, Chichiri, Blantyre 3 or call on 01877 245or 01 877 291.

Consent Declaration

If you agree to voluntarily participate in the study, please sign or write your initial or your thumb print below to show that you understand the information above and that your consent is given voluntarily.

10. I have received and read or had read to me the information sheet provided by the Researcher that explains in detail the reasons for the study.
11. I have understood the purpose of the research.
12. I have asked all the questions that I have about the purpose of the research and feel that I have enough information about it.
13. I understand the reasons for this group discussion.
14. I am willing to take part in the group discussion.
15. I understand what I will be required to do if I participate in the discussion.
16. I know that I have the right to leave the discussion at any time or to refuse to answer any questions.
17. If I do not agree to take part in this discussion I understand that I will not be penalized for doing so by the researcher nor by any medical service providers in the future.
18. **I voluntarily agree to take part in this focus group discussion**

---------- -------/--------/-------

Signature/thumb print of participant Date

---------- -------/--------/-------

Signature of person obtaining consent Date

If the participant gave verbal consent, please enter the name of person who witnessed the consent here, and their signature:

---------- -----/-------/-------- ----------

Name of Witness (BLOCK CAPITALS) Date Signature or thumb print

Appendix 8.1-3: PQ03 Socio-demographics, partner testing and ranking: English & Chichewa v0.2 29/07/2015 [Implemented in Teleform software]

Partner-provided self-testing and linkage (PASTAL)

Malawi-Liverpool-Wellcome Trust Clinical Research Programme
P.O Box 30096, Chichiri, Blantyre 3, Malawi.
Tel. +265 1 876444 Fax +265 1 875774

- *Question numbers: G01-GXX*
- *Show numeric codes on the choices i.e. number then box [annotated questionnaire]*
- *Use less than 1o character variable names. 01-10 take from SH13*
- *Translate where possible including the leading statement "Now I would ...", 01-10 take translations from SH13*
- *Choices in vertical order*

A. Socio-demographics

Now I will ask you a few questions about you

1. ID [numeric; 001:200]
2. ANC clinic ID [numeric; 1=Ndirande, 2=Zingwangwa, 3=Bangwe]
3. Date [DD-MON-YYYY]
4. DOB [DD-MON-YYYY]
5. Age (years) [numeric; 18+]
6. Sex [numeric; 1=male, 2=female]
7. Highest level of education attained [1=never been to sch, 2=primary, 3=sec sch without MSCE, 4=sec sch with MSCE, 4=higher
8. Can you read and write? [numeric; 0=no, 1=yes]
9. Occupation [numeric; 1=paid employee, 2=paid domestic worker, 3=self-employed, 4=unemployed, 5=student, 6=other
10. Marital status [numeric; 1=married, 2=polygamous marriage, 3=living together as if married, 4=never married, 5=widower/widow, 6=separated, 7=divorced

B. HIV testing and HIV self-testing

Now I would like to ask you a few questions related to HIV testing and HIV self-testing.

11. Ever tested with your sexual partner? [numeric; 0=no, 1=yes]➔ *if no go to 13.*
12. [*if yes to 11*] Where did you have the test? [numeric; 1=ANC this pregnancy, 2=ANC before, 3=VCT centre/ hospital, 4=self-testing, 5=other
13. [*if no to 11*] Would you consider testing with your sexual partner if there was an opportunity in the future? [numeric; 0=no, 1=yes]

[***Women***]

14. If offered self-test kits during antenatal clinic to take home to self-test with your partner, would you be willing to take them? [numeric; 0=no, 1=yes]
15. [*if no to 14*] Why would you not accept the offer or self-test kits? [text]

[***Men***]

16. Would you self-test, alone or together with your partner if your partner returned from antenatal clinic with self-test kits and offered you? [numeric; 0=no, 1=yes]
17. [*if no to 16*] Why would you not accept the offer to self-test from your partner? [text]
18. [*if no to 16*] Would you have accepted the offer to self-test if any of the following offered you instead of your partner:-
    a. Health worker at hospital or VCT centre [numeric; 0=no, 1=yes]
    b. Health worker in the community [numeric; 0=no, 1=yes]
    c. Neighbour [numeric; 0=no, 1=yes]
    d. Researchers [numeric; 0=no, 1=yes]

C. Ranking interventions

Now I would like you to rank these interventions on a scale of 1-5 to [e.g. 1=very unacceptable, 2=unacceptable, 3=not sure, 4=acceptable, 5=very acceptable].

[Numeric: choice field with ranks as choices]

19. Standard of care - not introducing any change to HTC at ANC

Kupitiriza kupereka chithandizo chimene chimaperekedwa nthawi zonse – osasintha china chilichonse pa ndondomeko yoyezera kachirombo ka HIV ndi kulandira uphungu ku sikelo ya amayi oyembekezera.

20. Providing HIV Self-test kits (ST) only e.g. provide two self-test kits to the woman to take home to discuss so that her partner self-tests with her or without her

Kupereka zipangizo zoziyezera wekha kachirombo ka HIV zokha basi. Mwachitsanzo, kuperekeza zipangizo zoziyezera wekha ziwiri kwa mzimayi kuti apititse kunyumba kuti akakambirane ndi wokondedwa wake kuti wokondedwa wake akathe kuziyeza yekha limodzi ndi iye kapena popanda iyeyo.

21. HIVST kits plus a low amount incentive i.e. an amount that would cover transport costs to the clinic.

Kupereka zipangizo zoziyezera wekha kachirombo ka HIV ndi kandalama kochepa kokwanira transport yokafikira kuchipatala.

22. HIVST kits plus a medium amount incentive i.e. an amount that would cover transport costs to the clinic plus some little compensation of time spent off economic activity.

Kupereka zipangizo zoziyezera wekha kachirombo ka HIV ndi ndalama yokwererapo pang'ono yokokwanira transport yokafikira kuchipatala komanso kandalama kena kochepa kongowathokoza chifukwa cha nthawi yimene aononga kapena asiya ntchito zawo zowapezera ndalama.

23. HIVST kits plus a high amount incentive ie an amount over and above transport costs to the clinic plus some little compensation of time spent off economic activity.

Kupereka zipangizo zoziyezera wekha kachirombo ka HIV ndi ndalama zopitilira transport yokafikira kuchipatala komanso kupitilira ndalama yongowathokoza chifukwa cha nthawi yimene aononga kapena asiya ntchito zawo zowapezera ndalama.

24. HIVST kits plus a lottery incentive i.e. 2 in 20 people will win a reasonably large sum through a raffle draw.

Kupereka zipangizo zoziyezera wekha kachirombo ka HIV komanso mphoto kudzera mmayere oti anthu awiri mwa anthu makumi awiri adzawine ndalama yochulukirapo.

Appendix 8.1-4: PQ01 Focus Group Discussion Interview Guide: English & Chichewa
v0.3; 6th August 2015

Partner-provided self-testing and linkage (PASTAL)

Malawi-Liverpool-Wellcome Trust Clinical Research Programme
P.O Box 30096, Chichiri, Blantyre 3, Malawi.
Tel. +265 1 876444 Fax +265 1 875774

Title: Developing contextually acceptable candidate interventions for increasing uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in Antenatal clinics in Blantyre, Malawi: a cross-sectional qualitative study

Mutu: Kupeza njira zovomerezeka zochulukitsira chiwerengero cha abambo oyezetsa kachirombo ka HIV komanso kupita kolondira chithandizo choyeyenera pakati pa azibambo amene okondedwa awo amapita ku sikelo ya amayi oyembekezera mu mzinda wa Blantyre, Malawi.

General perceptions towards antenatal clinic (ANC) services

Zomwe anthu amaganiza zokhuzana ndi chithandizo chimene chimapezeka ku sikelo ya amayi oyembekezera.

1) What do people in your community say about men who attend antenatal clinic (ANC) services with their partners?

   Kodi anthu akudera kwanu amanena zotani zokhuzana ndi azibambo amene amaperekeza okondedwa awo ku sikelo ya amayi oyembekezera?

   Probe:
   a) What do community members feel about how ANC services are offered and organised?

      Kodi anthu amdera lanu akuona bwanji za mmene chithandizo chimene chimaperekedwa ku sikelo ya amayi oyembekezera?

   b) Which stories are positive and which ones are negative?

Kodi ndi zonena zake ziti zimene zili zabwino komanso ndi zonena zake ziti zimene zisali zabwino?

c) Which stories are much common?

Kodi ndi zonena zake ziti zimene zimanenedwa kwambiri?

d) What do you think makes the community members come up with these most common stories?

Kodi ndi chani chimene mukuganiza kuti chimapangitsa anthu kuti azinena zimene zimanenedwa kwambirizi?

2) What do people in your community say about men who test for HIV at ANC with their partners?

Kodi anthu akudera kwanu amati chani zokhuzana ndi azibambo amene amayezetsa kachirombo ka HIV ku sikelo ya amayi oyembekezera limodzi ndi okondedwa awo?

Probe:

a) How do you feel about how ANC services are organised?

Kodi chithandizo chimene chimaperekedwa ku sikelo ya amayi oyembekezera chimaperekedwa motani?

b) Which stories are positive and which ones are negative?

Kodi ndi zonena zake ziti zimene zili zabwino komanso ndi zonena zake ziti zimene zisali zabwino?

c) Which stories are much common?

Kodi ndi zonena zake ziti zimene zimanenedwa kwambiri?

d) What do you think makes the community members come up with these most common stories?

Kodi ndi chani chimene mukuganiza kuti chimapangitsa anthu kuti azinena zimene zimanenedwa kwambirizi?

Men's perceptions towards ANC services and HIV testing and counseling (HTC) at ANC

Zimene azibambo amaganiza zokhuzana ndi chithandizo chimene chimapezeka ku sikelo ya amayi oyembekezera komanso kuyezetsa ndi kulandira uphungu wa kachirombo ka HIV ku sikelo ya amayi oyembekezera

3) What do men say about attending ANC services with their partners?

   Kodi azibambo amanena zotani zokhudzana ndi kuperekeza okondedwa awo ku sikelo ya amayi oyembekezera?

   Probe:

   a) How do men feel about testing for HIV at ANC / how do men react towards testing for HIV at ANC with their partner?

      Kodi azibambo amaona bwanji pa zoyezetsa kachirombo ka HIV limodzi ndi okondedwa awo ku sikelo ya amayi oyembekezera?

   b) How do men feel about how HIV testing at ANC is organised?

      Kodi azibambo amaona bwanji za mmene kuyezetsa kachirombo ka HIV ku sikelo ya amayi oyembekezera kumakhalira?

   c) How do men feel about HIV care?

      Kodi azibambo amaona bwanji za chisamaliro chimene chimaperekedwa kwa anthu opezeka ndi kachirombo ka HIV?

   d) How do men feel about voluntary male medical circumcision?

      Kodi azibambo amaziona bwanji za mdulidwe wa abambo wa kuchipatala?

   e) What do you think prevents men who are escorting their pregnant women to ANC from testing for HIV?

      Kodi mukuganiza kuti ndi chani chimene chimalepheretsa azibambo kuyezetsa kachirombo ka HIV pamene akuperekeza okondedwa awo ku sikelo ya amayi oyembekezera?

Perceptions about the acceptability of HIVST provided through ANC for men
Maganizo okhuzana ndi mmene anthu

4) What do you think about a clinic linked to ANC that offers HIV services for male partners of pregnant women only i.e. a male friendly clinic in terms of encouraging male partners to test and link?

   Kodi kukhala ndi kachipatala kopeleka thandizo lokhudzana ndi kachirombo ka HIV kwa azibambo amene ali ndi amayi oyembekezera cholumikizidwa ku sikelo ya amayi oyembekezera chingalimbikitse azimbambo kuyezetsa komanso kumapita kuchipatala akapezeka ndi kachirombo ka HIV?

5) In your opinion, would HIV self-testing (HIVST) provided through ANC be accepted amongst men with ANC attending partners?

   Malingana ndi mmene mukuonera, kodi mukugaiza kuti kuziyeza wekha kachirombo ka HIV kumene kumachitikira ku sikelo ya amayi oyembekezera kungakhale kovomerezeka pakati pa azibambo amene okondedwa awo amapita ku sikelo ya amayi oyembekezera?

6) In your opinion, would HIV self-testing (HIVST) provided through the woman on behalf of her partner (s) during ANC be accepted amongst men with ANC attending partners?

   Malingana ndi mmene mukuonera, kodi mukuganiza kuti kumpatsa mzimayi oyembekezera ku sikelo zipangizo zoziyezera wekha HIV kuti akampatse okondedwa wake polimbikitsa kuyezetsa pakati pa abambo kungakhale kovomerezeka?

7) What would be the community concerns to provide HIVST through ANC?

   Kodi mukuona kuti anthu amdera lanu angakhale ndi nkhawa yotani pa zoti kuziyeza wekha kachirombo ka HIV kuzichitikira ku sikelo ya amayi oyembekezera?

   Probe:

   a) Concerns or worries amongst men with ANC attending partners.

      Nkhawa kapena madandaulo amene azibambo amene okondedwa awo amapita ku sikelo atha kukhala nawo.

8) What should be done to make HIVST offered through ANC more acceptable to men with ANC attending partners?

   Kodi chikuyenera kuchitika ndi chani kuti kuziyekha wekha kachirombo ka HIV kumene kungamachitikire ku sikelo ya amayi oyembekezera kukhale kolandiridwa ndi azibambo amene okondedwa awo amapita ku sikelo ya amayi oyembekezera?

Perceptions about PASTAL interventions

9) How do you feel about the following approaches for encouraging male partners of pregnant women to test for HIV and link for appropriate services such as ART, counselling, condoms or voluntary male medical circumcision (VMMC)?

   Kodi maganizo anu ndi otani pa njira zili mu nsimu zolimbikitsa azibambo omwe okondedwa awo akupita ku sikelo kuti ayezetse kachirombo ka HIV komanso kuti ayambe kulandira chithandizo choyenerera monga mankhwala otalikitsa moyo, uphungu wa kachirombo ka HIV, makondomu kapena mdulidwe wa abambo wa kuchipatala?

   a) Standard of care - not introducing any change to HTC at ANC

      Kupitiriza kupereka chithandizo chimene chimaperekedwa nthawi zonse – osasintha china chilichonse pa ndondomeko yoyezera kachirombo ka HIV ndi kulandira uphungu ku sikelo ya amayi oyembekezera.

   b) Providing HIV Self-test kits (ST) only e.g. provide two self-test kits to the woman to take home to discuss so that her partner self-tests with her or without her

      Kupereka zipangizo zoziyezera wekha kachirombo ka HIV zokha basi. Mwachitsanzo, kuperekeza zipangizo zoziyezera wekha ziwiri kwa mzimayi kuti apititse kunyumba kuti akakambirane ndi wokondedwa wake kuti wokondedwa wake akathe kuziyeza yekha limodzi ndi iye kapena popanda iyeyo.

   c) HIVST kits plus a low amount incentive i.e. an amount that would cover transport costs to the clinic.

      Kupereka zipangizo zoziyezera wekha kachirombo ka HIV ndi kandalama kochepa kokwanira transport yokafikira kuchipatala.

   d) HIVST kits plus a medium amount incentive i.e. an amount that would cover transport costs to the clinic plus some little compensation of time spent off economic activity.

      Kupereka zipangizo zoziyezera wekha kachirombo ka HIV ndi ndalama yokwererapo pang'ono yokokwanira transport yokafikira kuchipatala komanso kandalama kena kochepa kongowathokoza chifukwa cha nthawi yimene aononga kapena asiya ntchito zawo zowapezera ndalama.

   e) HIVST kits plus a high amount incentive ie an amount over and above transport costs to the clinic plus some little compensation of time spent off economic activity.

Kupereka zipangizo zoziyezera wekha kachirombo ka HIV ndi ndalama zopitilira transport yokafikira kuchipatala komanso kupitilira ndalama yongowathokoza chifukwa cha nthawi yimene aononga kapena asiya ntchito zawo zowapezera ndalama.

f) HIVST kits plus a lottery incentive i.e. 2 in 20 people will win a reasonably large sum through a raffle draw.

Kupereka zipangizo zoziyezera wekha kachirombo ka HIV komanso mphoto kudzera mmayere oti anthu awiri mwa anthu makumi awiri adzawine ndalama yochulukirapo.

10. How much in monetary value should the low, medium and high amount financial incentive interventions be?

Kodi ndalama zochuluka bwanji zimene zingaperekedwe pa njira zimene zatchulidwa m'mwambazi zolimbikitsira azibambo okhala ndi okondedwa oyembekezera kuti ayezetse kachirombo ka HIV (mwachitsanzo njira yokhala ndi ndalama yochepera; njira yokhala ndi ndalama yochuluka pan'gono, njira yokhala ndi ndalama yochuluka kwambiri)

11. Please rank these interventions on a scale of 1-5 to [e.g. 1=very unacceptable, 2=unacceptable, 3=not sure, 4=acceptable, 5=very acceptable].

Chonde onetsani mmene mukuonera za kuvomerezeka kwa njira zimenezi pogwiritsa ntchito manambala. Mwachitsanzo, 1 kutanthauza yosavomerezeka kwambiri; 2 kutanthauza yosavomerezeka; 3 simukudziwa; 4 yovomerezeka; yovomerezeka kwambiri.

Probe
Which mode, cash or voucher, do you think would best work to encourage male partners to test and link?)
Kodi ndi njira yiti, yopereka ndalama kapena vocha yogulira zinthu, imene yingalimbikitse kwambiri azibambo kuyezetsa komanso kupita kuchipatala akaona zotsatira zakuyezetsaku

How long do you think it would take for the whole process to complete i.e. number of days for the male partner to test and link?

Kodi pangatenge nthawi yochuluka bwanji kapena masiku angati kuchokera nthawi yimene mzibambo wazuyeza kufikira nthawi yopita kuchipatala kukapeza thandizo?

Introducing and implementing PASTAL interventions

12. Do you think ANC attending women would be able to introduce HIVST to their male partners? What do you think would be the possible consequences to these women when they introduce HIVST to their male partners?

    Kodi mukuganiza kuti amayi amene amapita ku sikelo ya amayi oyembekezera angathe kuwafotokozera okondedwa awo zokhuzana kuziyeza kachirombo ka HIV? Mukuganiza kuti chimene chingachitikire amayi amenewawa ndi chani pamene akuwafotokozera okondedwa awo za kuziyeza wekha kachirombo ka HIV?

    Probe:

    a) Issues of coercion/intimate partner violence

    Funsani zokhuzana ndi kuwumirizana kapena nkhanza zochitirana mchikondi

13. How could each of the following interventions be implemented at ANC to make it more acceptable and preferred by men with ANC attending partners?

    Kodi njira zotsatirazi zingayendetsedwe motani kuti azibambo amene okondedwa awo amapita ku sikelo ya amayi oyembekezera athe kuzivomera ndi kuzikonda kwambiri?

    a) Providing HIV Self-test kits (ST) only e.g. provide two self-test kits to the woman to take home to discuss so that her partner self-tests with her or without her

       Kupereka zipangizo zoziyezera wekha kachirombo ka HIV zokha basi. Mwachitsanzo, kupereka zipangizo zoziyezera wekha ziwiri kwa mzimayi kuti apititse kunyumba kuti akakambirane ndi wokondedwa wake kuti wokondedwa wake akathe kuziyeza yekha limodzi ndi iye kapena popanda iyeyo.

    b) HIVST kits plus a low amount incentive i.e. an amount that would cover transport costs to the clinic.

       Kupereka zipangizo zoziyezera wekha kachirombo ka HIV ndi kandalama kochepa kokwanira transport yokafikira kuchipatala.

c) HIVST kits plus a medium amount incentive i.e. an amount that would cover transport costs to the clinic plus some little compensation of time spent off economic activity.

Kupereka zipangizo zoziyezera wekha kachirombo ka HIV ndi ndalama yokwererapo pang'ono yokokwanira transport yokafikira kuchipatala komanso kandalama kena kochepa kongowathokoza chifukwa cha nthawi yimene aononga kapena asiya ntchito zawo zowapezera ndalama.

d) HIVST kits plus a high amount incentive ie an amount over and above transport costs to the clinic plus some little compensation of time spent off economic activity.

Kupereka zipangizo zoziyezera wekha kachirombo ka HIV ndi ndalama zopitilira transport yokafikira kuchipatala komanso kupitilira ndalama yongowathokoza chifukwa cha nthawi yimene aononga kapena asiya ntchito zawo zowapezera ndalama.

e) HIVST kits plus a lottery incentive i.e. 2 in 20 people will win a large sum through a raffle draw.

Kupereka zipangizo zoziyezera wekha kachirombo ka HIV komanso mphoto kudzera mmayere oti anthu awiri mwa anthu makumi awiri adzawine ndalama zambiri.

14. What would be other approaches that could be used to increase uptake of HIV testing and linkage into care or prevention for male partners of ANC attending women?

Kodi ndi njira zina ziti zimene zingathe kugwiritsidwa ntchito kuti azibambo ambiri amene okondedwa awo amapita ku sikelo ya amayi oyembekezera azitha kuyezetsa kachirombo ka HIV komanso kuyambitsidwa kulandira chisamaliro?

Partner-provided self-testing and linkage (PASTAL)

Malawi-Liverpool-Wellcome Trust Clinical Research Programme
P.O Box 30096, Chichiri, Blantyre 3, Malawi.
Tel. +265 1 876444 Fax +265 1 875774

Title: Developing contextually acceptable candidate interventions for increasing uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in Antenatal clinics in Blantyre, Malawi: a cross-sectional qualitative study

Mutu: Kupeza njira zovomerezeka zochulukitsira chiwerengero cha abambo oyezetsa kachirombo ka HIV komanso kupita kolondira chithandizo choyeyenera pakati pa azibambo amene okondedwa awo amapita ku sikelo ya amayi oyembekezera mu mzinda wa Blantyre, Malawi.

General perceptions towards antenatal clinic (ANC) services

Zomwe anthu amaganiza zokhuzana ndi chithandizo chimene chimapezeka ku sikelo ya amayi oyembekezera.

10) What do you feel about you (if male respondent) or your male partner (if female respondent) attending antenatal clinic (ANC) services?

Kodi inu mumaganiza zotani pankhani yokhuzana ndi inuyo (if male respondent) kapena wachikondi wanu (if female respondents) kukapezeka ku sikelo ya amayi oyembekezera?

Probe:

e) What do you feel about how ANC services are offered and organised?

Kodi inu maganizo anu ndi otani okhuzana ndi mmene chithandizo chimaperekedwera ku sikelo ya amayi oyembekezera?

f) What do you to feel that way about services offered at ANC?

Kodi ndi chani chimene chimabweresa maganizo amenewa pa nkhani yokhuza thandizo limene limaperekedwa ku sikelo ya amayi oyembekezera?

11) What do you feel about men who test for HIV at ANC with their partners?

Kodi mumaganiza zotani zokhuzana ndi azibambo amene amayezetsa kachirombo ka HIV ku sikelo ya amayi oyembekezera limodzi ndi okondedwa awo?

Probe:

e) How do you feel about how HIV testing services are organised at ANC clinic?

Kodi maganizo anu ndi otani pankhani yokhuzana ndi kuyezesa kachirombo ka HIV ku sikelo ya amayi oyembekezera?

Men's perceptions towards ANC services and HIV testing and counseling (HTC) at ANC

Zimene azibambo amaganiza zokhuzana ndi chithandizo chimene chimapezeka ku sikelo ya amayi oyembekezera komanso kuyezetsa ndi kulandira uphungu wa kachirombo ka HIV ku sikelo ya amayi oyembekezera

12) What do you feel (for male respondent) / your partner (for female respondents) feel about attending ANC services with their partners?

Kodi inu (for male respondent) / okondedwa wanu (for female respondents) mumaganiza/amaganiza zotani zokhudzana ndi kupitak ku sikelo ya amayi oyembekezera pamodzi ndi wachokondi?

Probe:

f) How do you (for male respondent) / your partner (for female respondents) feel about testing for HIV at ANC / how do you (for male respondent) / your male partner (for female respondents) react towards testing for HIV at ANC with their partner?

Kodi inu (for male respondent) / okondedwa wanu (for female respondents) mumaona/amaona bwanji pa zoyezetsa kachirombo ka HIV limodzi ndi okondedwa awo ku sikelo ya amayi oyembekezera?

g) How do you (for male respondent) / your partner (for female respondents) feel about how HIV testing at ANC is organised?

Kodi inu (for male respondent) / okondedwa wanu (for female respondents) mumaona/amaona bwanji za mmene kuyezetsa kachirombo ka HIV ku sikelo ya amayi oyembekezera kumakhalira?

h) How do you (for male respondent) / your partner (for female respondents) feel about HIV care?

Kodi inu (for male respondent) / okondedwa wanu (for female respondents) mumaona/amaona bwanji za chisamaliro chimene chimaperekedwa kwa anthu opezeka ndi kachirombo ka HIV?

i) How do you (for male respondent) / your partner (for female respondents) feel about voluntary male medical circumcision?

Kodi inu (for male respondent) / okondedwa wanu (for female respondents) mumaona/amaona bwanji za mdulidwe wa abambo wa kuchipatala?

j) What do you think prevents you (for male respondent) / your partner (for female respondents) who are escorting their pregnant women to ANC from testing for HIV?

Kodi mukuganiza kuti ndi chani chimene chimalepheretsa inu (for male respondent) / okondedwa wanu (for female respondents) mumaona/amaona kuyezetsa kachirombo ka HIV pamene akuperekeza okondedwa awo ku sikelo ya amayi oyembekezera?

Perceptions about the acceptability of HIVST provided through ANC for men
Maganizo okhuzana ndi kubvomerezeka kwa ndondomeko yoziyeza wekha kachirombo ka HIV ku sikelo ya amayi oyembekezera

13) What do you think about a clinic linked to ANC that offers HIV services for male partners of pregnant women only i.e. a male friendly clinic in terms of encouraging male partners to test and link?

Kodi kukhala ndi kachipatala kopeleka thandizo lokhudzana ndi kachirombo ka HIV kwa azibambo amene ali ndi amayi oyembekezera cholumikizidwa ku sikelo ya amayi oyembekezera chingalimbikitse azimbambo kuyezetsa komanso kumapita kuchipatala akapezeka ndi kachirombo ka HIV?

14) In your opinion, would HIV self-testing (HIVST) provided through ANC be accepted by you / your male partner?

Malingana ndi mmene mukuonera, kodi mukugaiza kuti kuziyeza wekha kachirombo ka HIV kumene kumachitikira ku sikelo ya amayi oyembekezera kungakhale kovomerezeka kwa inuyo (for male respondent) / Okondedwa wanu (for female respondents)?

15) In your opinion, would HIV self-testing (HIVST) provided through the woman on behalf of her partner (s) during ANC be accepted amongst men with ANC attending partners?

Mmene mukuonera, kodi mukuganiza kuti kumpatsa mzimayi oyembekezera zipangizo zoziyezera wekha HIV akapitata kusikelo kuti akampatse okondedwa wake polimbikitsa kuyezetsa pakati pa abambo kungakhale kovomerezeka?

16) What would be your concerns to provide HIVST through ANC?

Kodi muli ndi nkhawa yotani pankhani yokhala ndi ndondomeko yoziyeza wekha kachirombo ka HIV kuzezera ku sikelo ya amayi oyembekezera?

Probe:

b) Concerns or worries amongst men with ANC attending partners and ANC attending women

Nkhawa kapena madandaulo amene azibambo amene okondedwa awo amapita ku sikelo atha kukhala nawo komanso nkhawa za azimayi amene amapita kusikelo ya amayi oyembekezera.

17) What should be done to make HIVST offered through ANC more acceptable to men with ANC attending partners?

Kodi ndi chani chimene chikuyenera kuchitika kuti kuziyekha wekha kachirombo ka HIV kumene kungamachitikire ku sikelo ya amayi oyembekezera kukhale kobvomenerezeka pakati pa azibambo amene okondedwa awo amapita ku sikelo ya amayi oyembekezera?

Perceptions about PASTAL interventions

18) How do you feel about the following approaches for encouraging male partners of pregnant women to test for HIV and link for appropriate services such as ART, counselling, condoms or voluntary male medical circumcision (VMMC)?

Kodi maganizo anu ndi otani pa njira zili m'munsimu zolimbikitsa azibambo omwe okondedwa awo akupita ku sikelo kuti ayezetse kachirombo ka HIV komanso kuti ayambe kulandira chithandizo choyenerera monga mankhwala otalikitsa moyo,

uphungu wa kachirombo ka HIV, makondomu kapena mdulidwe wa abambo wa kuchipatala?

g) Standard of care - not introducing any change to HTC at ANC

   Kupitiriza kupereka chithandizo chimene chimaperekedwa nthawi zonse – osasintha china chilichonse pa ndondomeko yoyezera kachirombo ka HIV ndi kulandira uphungu ku sikelo ya amayi oyembekezera.

h) Providing HIV Self-test kits (ST) only e.g. provide two self-test kits to the woman to take home to discuss so that her partner self-tests with her or without her

   Kupereka zipangizo zoziyezera wekha kachirombo ka HIV zokha basi. Mwachitsanzo, kupereka zipangizo zoziyezera wekha ziwiri kwa mzimayi kuti apititse kunyumba kuti akakambirane ndi wokondedwa wake kuti wokondedwa wake akathe kuziyeza yekha limodzi ndi mkazi wake kapena popanda mkazi.

i) HIVST kits plus a low amount incentive i.e. an amount that would cover transport costs to the clinic.

   Kupereka zipangizo zoziyezera wekha kachirombo ka HIV ndi kandalama kochepa kokwanira transport yokafikira kuchipatala.

j) HIVST kits plus a high amount incentive ie an amount over and above transport costs to the clinic plus some little compensation of time spent off economic activity.

   Kupereka zipangizo zoziyezera wekha kachirombo ka HIV ndi ndalama zopitilira transport yokafikira kuchipatala komanso kupitilira ndalama yongowathokoza chifukwa cha nthawi yimene aononga kapena asiya ntchito zawo zopezera ndalama.

k) HIVST kits plus a lottery incentive i.e. 2 in 20 people will win a reasonably large sum through a raffle draw.

   Kupereka zipangizo zoziyezera wekha kachirombo ka HIV komanso mphoto kudzera mmayere oti anthu awiri mwa anthu makumi awiri adzawine ndalama yochulukirapo.

l) HIVST kits followed by phone call reminder
   Kupereka zipangizo zoziyezera wekha kachirombo ka HIV komanso kuti abambowo tidziwayimbira foni ndikukambirana nawo zoziyeza wekha.

Probe:

i) Should the phone be made before the woman talks to her partner?
Kodi foniyi idzyimbidwa nthawi yanji poyamba? Mzimayi asanafikitse nkhaniyi kwa a bamboo?

ii) How many times should the reminder be provided?
Kodi abambowa tidziwayimbira kangati kuphatikiza kuyimbiridwa koyamba mpaka kumaliza zonse?

15. How much in monetary value should the low, medium and high amount financial incentive interventions be?

Kodi ndi ndalama zochuluka bwanji zimene zingaperekedwe pa njira zimene zatchulidwa m'mwambazi zolimbikitsira azibambo okhala ndi okondedwa oyembekezera kuti ayezetse kachirombo ka HIV (mwachitsanzo njira yokhala ndi ndalama yochepera; njira yokhala ndi ndalama yochuluka pan'gono, njira yokhala ndi ndalama yochuluka kwambiri)

16. Which mode, cash or voucher, do you think would best work to encourage male partners to test and link?)
Kodi ndi njira yiti, yopereka ndalama kapena vocha yogulira zinthu, imene yingalimbikitse kwambiri azibambo kuyezetsa komanso kupita kuchipatala akaona zotsatira zakuyezetsaku

Introducing and implementing PASTAL interventions

17. Do you think ANC attending women would be able to introduce HIVST to their male partners? What do you think would be the possible consequences to these women when they introduce HIVST to their male partners?

    Kodi mukuganiza kuti amayi amene amapita ku sikelo ya amayi oyembekezera angathe kubweretsa kwa okondedwa awo njira yoziyeza kachirombo ka HIV? Mukuganiza kuti chimene chingachitikire amayi amenewawa ndi chani pamene abweretsa zipangizo zoziyezera wekha kachirombo ka HIV kwa okondedwa awo?

    Probe:

    b) Issues of coercion/intimate partner violence

    Funsani zokhuzana ndi kuwumirizana kapena nkhanza zochitirana mchikondi

18. How could each of the following interventions be implemented at ANC to make it more acceptable and preferred by men with ANC attending partners?

    Kodi njira zotsatirazi zingakhazikitsidwe motani kuti azibambo amene okondedwa awo amapita ku sikelo ya amayi oyembekezera athe kuzivomera ndi kuzikonda kwambiri?

    f) Providing HIV Self-test kits (ST) only e.g. provide two self-test kits to the woman to take home to discuss so that her partner self-tests with her or without her

    Kupereka zipangizo zoziyezera wekha kachirombo ka HIV zokha basi. Mwachitsanzo, kupereka zipangizo zoziyezera wekha ziwiri kwa mzimayi kuti apititse kunyumba kuti akakambirane ndi wokondedwa wake kuti wokondedwa wake akathe kuziyeza yekha limodzi ndi mkazi wake kapena popanda mkazi.

    g) HIVST kits plus a low amount incentive i.e. an amount that would cover transport costs to the clinic.

    Kupereka zipangizo zoziyezera wekha kachirombo ka HIV ndi kandalama kochepa kokwanira transport yokafikira kuchipatala.

    h) HIVST kits plus a high amount incentive ie an amount over and above transport costs to the clinic plus some little compensation of time spent off economic activity.

    Kupereka zipangizo zoziyezera wekha kachirombo ka HIV ndi ndalama zopitilira transport yokafikira kuchipatala komanso kupitilira ndalama yongowathokoza

chifukwa cha nthawi yimene awononga kapena asiya ntchito zawo zopezera ndalama.

i) HIVST kits plus a lottery incentive i.e. 2 in 20 people will win a large sum through a raffle draw.

Kupereka zipangizo zoziyezera wekha kachirombo ka HIV komanso mphoto kudzera mmayere oti anthu awiri mwa anthu makumi awiri adzawine ndalama zambiri.

m) HIVST kits followed by phone call reminder
Kupereka zipangizo zoziyezera wekha kachirombo ka HIV komanso kuti abambowo tidziwayimbira foni ndikukambirana nawo zoziyeza wekha.

19. What would be other approaches that could be used to increase uptake of HIV testing and linkage into care or prevention for male partners of ANC attending women?

Kodi ndi njira zina ziti zimene zingathe kugwiritsidwa ntchito kuti azibambo ambiri amene okondedwa awo amapita ku sikelo ya amayi oyembekezera azitha kuyezetsa kachirombo ka HIV komanso kuyambitsidwa kulandira chisamaliro?

8.2 Tools developed and used in the MAMS trial

Appendix 8.2-1: PQ22a: Participant Information and Consent Form for Trial Participants in the Standard of Care Arm v1.0; 31st March 2016

Malawi-Liverpool-Wellcome T
Clinical Research Programme
P.O Box 30096, Chichiri, Blantyre 3,
Malawi.
Tel. +265 1 876444 Fax +265 1 8757

Title: Investigating interventions to increase uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in antenatal clinics in urban Blantyre, Malawi: an adaptive Phase II multi-arm multi-stage cluster randomised trial

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You will not receive payment for participating in the study. You will however, be offered a small compensation for your time amounting to MWK1,000.

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[The following text must be read to the participant, who must have their own copy to take home]

Introduction

Hello. My name is ……, and I am working with Malawi Liverpool Wellcome Trust (MLW) on behalf of Mr. Augustine Choko and colleagues. We are conducting a study to identify interventions for increasing uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in antenatal care (ANC). We would like to find the most promising interventions, which could be further investigated in a larger study in order to address the problem of low uptake of HIV testing and linkage into care or prevention among male partners of pregnant women.

Request for your Voluntary Participation

I would like to ask you to voluntarily participate in this study. You have been identified because you are attending ANC services at a public primary healthcare facility in urban Blantyre for the first time. We consider that your participation would help us reach out to your partner but more importantly would help your partner by informing him about the services that we are offering.

Procedure

After the group information about the study, now I would like to give you some more information about the study and also ask you some questions related to you and your partner. The interview will not exceed 10 minutes and will include questions about your and your partner's personal information and HIV testing. At the end of the interview I will give you a personalised invitation letter to give to your partner so that he can use the letter to come to our "male friendly clinic" alone or together with you. I will also give you two self-test kits to take home to allow your partner to self-test alone or together with you. At this clinic we are offering free confirmatory HIV testing for people who report a positive HIV test followed by facilitated HIV treatment initiation, a chance to be circumcised if HIV negative,

and information about birth preparedness. We will call your partner tomorrow and after five days to remind him to self-test and come to the male friendly clinic.

As part of the study we will want to have a final interview with you when you come back for your next ANC visit in four weeks' time. The main aim of this follow-up interview is to check if your bringing up this discussion with your partner led to any problems and whether or not your partner tested and linked to the "male friendly clinic". We will also ask you to bring back used or unused self-test kits at your next visit so that we can reconcile our stock with our main office.

Your participation is entirely voluntary. If you decide to take part, you may withdraw from the interviews or the study any time. You also have a right not to answer any particular question or questions that will be asked. Declining to participate in the study will not affect any health services that you or any person related to you may be currently receiving or may require in future.

Confidentiality

All personal information collected in this study will be kept strictly confidential. I will not share the information you provide with anyone who is not part of this research. But it may be shared with fellow researchers and may also be published through meetings or journals in a manner that does not reveal your identity. Before sharing in this manner, the information from you will be combined with that from other research participants. Information which could identify you or anyone related to you will never be released. This also means that names of study participants, including your own will not be included when sharing the data. Data collection equipment and the data collected will be kept with identifiers, locked, and only accessible to people that have authorised access.

Risks

You may be uncomfortable with some of the questions that I will ask. You are perfectly entitled to refuse to discuss issues that you do not want to.

Benefits

There are no direct benefits to you in your taking part in this study. However, what we learn from this study would help develop ways of successfully reaching out to male partners, offer them an HIV test and link them to appropriate follow-on services. It would thus help us inform health authorities in the Ministry of Health regarding which interventions truly hold potential to reduce the problem of low uptake of testing and linkage among male partners of pregnant women.

Compensation

You will not receive payment for participating in the study. You will however, be offered a small compensation for your time amounting to MWK1,000.

Contact details

This research has been approved by the College of Medicine Research Ethics Committee (COMREC) and the London School of Hygiene and Tropical Medicine Research Ethics Committee. If you have any questions regarding your rights as a research participant, or concerns on how you have been treated in the study, please feel free to contact **Mr. Augustine Choko** [+265 (0) 999 577 452] or [augutc@gmail.com]. If you have any questions regarding your rights as a research participant, or concerns on how you have been treated in the study, please feel free to contact COMREC Secretariat, College of Medicine, Private Bag 360, Chichiri, Blantyre 3 or call on 01871911 ext 334.

Consent Declaration

If you agree to voluntarily participate in the study, please sign or write your initial or your thumb print below to show that you understand the information above and that your consent is given voluntarily.

1. I have received and read or had read to me the information sheet provided by the Researcher that explains in detail the reasons for the study.
2. I have understood the purpose of the research.
3. I have asked all the questions that I have about the purpose of the research and feel that I have enough information about it.
4. I understand the reasons for this study.
5. I am willing to take part in the study.
6. I understand what I will be required to do if I participate in the study.
7. I know that I have the right to leave the study at any time or to refuse to answer any questions.
8. If I do not agree to take part in this study I understand that I will not be penalized for doing so by the researcher nor by any medical service providers in the future.
9. **I voluntarily agree to take part in this study**

---------- -------/--------/-------

Signature/thumb print of participant Date

---------- -------/--------/-------

Signature of person obtaining consent Date

If the participant gave verbal consent, please enter the name of person who witnessed the consent here, and their signature:

---------- -----/-------/-------- ----------

Name of Witness (BLOCK CAPITALS) Date Signature or thumb print

8.3 Data collection tools

Appendix 8.3-1: PQ05: Baseline Questionnaire for Women
Version 0.6 last modified by Augustine Choko on 24th October 2016

Section A: Identifiers and eligibility screen

1. **b01date** Date of interview *[Date]*
2. **b02intid** Interviewer ID *[Numeric 01-20]*
3. **b03ancd** Clinic day # *[Numeric 01-99]*
4. **b04cid** Clinic ID *[Numeric]* ➔ *coded 1=Ndirande; 2=Bangwe; 3=Zingwangwa*
5. **b05arm** Arm *[Numeric 1-6]* ➔ *1=Standard of care; 2=HIV self-test kits only; 3=HIV self-test kits plus low amount financial incentive; 4=HIV self-test kits plus high amount financial incentive; 5=HIV self-test kits plus lottery financial incentive; 6=HIV self-test kits plus phone call reminder.*
6. **b06name** Initials of the woman *[String]* ➔ *indicate all the initials of the woman's names*
7. **b07pidw** Woman barcode *[Numeric]* ➔ *place barcode in the health passport and on the recruitment log. Then scan barcode from the health passport.*

Section B: Eligibility screen

8. **b08dob** What is your date of birth *[date: DD-MM-YYYY]*
   Kodi munabadwa mchaka chanji? Chonde tiwuzeni tsiku, mwezi komanso chaka ngati nkotheka.
9. **b09age** If date of birth is unknown, what is the age? *[Numeric; ask participant to guess their age if they say they don't know]*
   Kodi zaka zanu ndi zosaposera 18?
10. **b10testp** Have you tested for HIV together with your partner in this pregnancy? *[Numeric]* ➔ *1=yes; 0=no*
    Kodi mwayezetsa kachilombo ka HIV ndi wachikondi wanu mu uchembere uno?
11. **b11status** Is your partner already aware of his HIV positive status and receiving treatment? *[Numeric]* ➔ *1=yes; 0=no*
    Kodi wachikondi wanu akulandira ma ARV panopa?
12. **b12visit** Is this your first antenatal clinic visit? *[Numeric]* ➔ *1=yes; 0=no*
    Kodi munabwerako kale ku sikelo mu uchembere umenewu?
13. **b12recru** Were you already recruited in this trial? *[Numeric]* ➔ *1=yes; 0=no*
    Kodi munalowa kale mu kafukufuku ameneyu?
14. **b14resid** Would you and your male partner be around urban Blantyre in the next 28 days? *[Numeric]* ➔ *1=yes; 0=no*
    Kodi inu ndi wachikondi wanu mupezeka mu mzinda wa Blantyre mu masiku 28 akudzawa?

Section C: Participation in the allocated arm

15. **b15part** Will you participate in the study? *[Numeric]* ➔ *1=yes; 0=no*
    Kodi mukuvomera kutenga nawo mbali mu kafukufukuyu?
16. **B16why** Reasons for not participating in the allocated arm *[Text]* ➔ ***ask only if NO to 15***
    Kodi ndi chifukwa chiyani simukufuna kutenga nawo mbali mu kafukufukuyu?

17. **b17pidm** Male partner barcode *[Numeric]* ➔ *scan the barcode on the* ***male_partner_invitation_letter*** *for participants who accept to participate*

Section D: Woman demographics and antenatal clinic data

18. **b18mstat** What is your current marital status *[Numeric]* ➔ *1=married; 2=polygamous marriage; 3=living together as if married; 4=never married; 5=widow; 6=separated; 7=divorced; 8=married but not living together.*
    Kodi muli pa banja panopa?
19. **b19live** Are you currently living together with your partner? *[Numeric]* ➔ *Depends on answer to 18) <u>marital status.</u> 1=yes; 0=no.*
    Kodi mumakhala limodzi ndi mwamuna wanu?
20. **b20lit** Can you read a letter or a newspaper? *[Numeric]* ➔ *1=yes; 0=no*
    Kodi mumatha kulemba ndi kuwerenga?
21. **b21occ** How can you best describe your main activity or work status? *[Numeric]* ➔ *1=Paid employee; 2=Paid domestic worker; 3=Self-employed; 4=Unemployed; 5=Student; 6=Other*
    Kodi mumagwira ntchito yanji?
22. **b22edu** What was the highest level of education that you have completed? *[Numeric]* ➔ *0=Never been to school; 1=Primary school; 2=Secondary school no MSCE; 3= Secondary school with MSCE; 4=Higher*
    Kodi maphunziro anu munafika nawo pati?
23. **b23phone** Phone # *[Numeric].* ***Make this required for arm number 6: HIV test kits plus phone call reminder***
24. **b24genh** How do you rate your general health? ➔ 1=Uli bwino kwambiri (Excellent); 2=Uli bwino (Good); 3=Choncho (Fair); 4=Siwuli bwino (Poor) *[please read the responses to the participant]*
    Kodi mukuwona kuti umoyo wanu uli bwanji? Uli bwino kwambiri, Uli bwino, Choncho kapena Siwuli bwino?
25. **b25test** Have you tested for HIV in this pregnancy? *[Numeric]* ➔ *1=yes; 0=no*
    Kodi mwayezetsa kachilombo ka HIV mu uchembere uno?
26. **b26selft** Have you ever self-tested for HIV? *[Numeric]* ➔ *1=yes; 0=no*
    Kodi munayamba mwaziyezapo nokha kachilombo ka HIV?

Section E: questions about male partner

27. **b27dob** What is your male partner's date of birth *[date: DD-MM-YYYY]*
    Kodi mwamuna wanu anabadwa mchaka chanji? Chonde tiwuzeni tsiku, mwezi komanso chaka ngati nkotheka.
28. **b28age** If date of birth is unknown, what is the age? *[Numeric; ask participant to guess their age if they say they don't know].*
    Kodi mwamunayu ali ndi zaka zingati?
29. **b29lit** Can your male partner read a letter or a newspaper? *[Numeric]* ➔ *1=yes; 0=no*
    Kodi mwamuna wanu amatha kulemba ndi kuwerenga?
30. **b30occ** How can you best describe your male partner's main activity or work status? *[Numeric]* ➔ *1=Paid employee; 2=Paid domestic worker; 3=Self-employed; 4=Unemployed; 5=Student; 6=Other*
    Kodi mwamuna wanu amagwira ntchito yanji?
31. **b31edu** What was the highest level of education that your partner completed? *[Numeric]* ➔ *0=Never been to school; 1=Primary school; 2=Secondary school no MSCE; 3= Secondary school with MSCE; 4=Higher*
    Kodi mwamuna wanu maphunziro ake anafika nawo pati?
32. **b32phone** Partner's Phone # *[Numeric]*
33. **b33test** To your knowledge, has your male partner ever been tested for HIV *[Numeric]* ➔ *automatic yes if YES to tested together in this pregnancy; 1=yes; 0=no*
    Malingana ndi momwe mukudziwira, kodi wachikondi wanu anayamba wayezetsapo kachilombo ka HIV?
34. **b34test12m** To your knowledge, has your male partner tested for HIV in the last 12 months *[Numeric]* ➔ *Automatic yes if YES to tested together in this pregnancy. 1=yes; 0=no*
    Malingana ndi momwe mukudziwira, kodi wachikondi wanu wayezetsa kachilombo ka HIV mu miyezi 12 yapitayi?

Thank you
Zikomo

We will want to talk to you again in four weeks when you come for your next antenatal visit. Tikufuna kudzachezanso nanu masabata anayi akubwerawa mukazdabweranso ku sikelo ya amayi oyembekezera.

Appendix 8.3-2: PQ06: Follow-up Questionnaire for Women (Audio Computer Assisted Self-Interview)

Version 0.6 last modified by Augustine Choko on 15th June 2016

Instructions to the field worker

a) Make sure that the participant is oriented in using both the tablet and the ACASI system before leaving them to answer the questions
b) Stick around while maintaining confidentiality so that the participant can call you in case of issues
c) Fieldworker to complete the four test questions below together with the participant

Section A: Test questions

I. Did you eat when coming to the clinic? If you ate nsima, press thumbs up  or if you didn't eat nsima, press thumbs down  (back end capture as 1=yes; 0=no); if you want the question to repeat, press the white button to repeat the question

Kodi munadya pobwera kuchipatala?

[Ngati munadya nsima lero, tobwanyani chala choloza m'mwamba

Ngati simunadye nsima lero, tobwanyani chala choloza pansi

Ngati mukufuna kuti funso lifunsidwenso tobwanyani batani lobwerezera funso

To continue to the next question press the forward arrow button

Kuti mumve funso lotsatira tobwanyani batani la muvi oloza kutsogolo

II. Is it raining now?

Kodi panopa kukugwa mvula?

III. Do you live in Malawi?

Kodi m'makhala ku Malawi?

IV. Is this Mulanje district?

Kodi lino ndi boma la Mulanje?

V. Describe how you moved from home to the clinic.

Fotokozani momwe mwayendera pobwera ku chipatala lero.

Press record sound button, then another screen will come up

Kuti muyambe kufotokoza tobwanyani batani lalitali lomwe lili ndi malemba m'musimu, kenako pabwera ka sikirini kena.

Press the big circle button on this new screen to start talking

Tobwanyani batani lalikulu lozungulira lomwe liri pa ka sikirini kameneka nkuyamba kulankhula.

When done speaking press the square button

Mukamaliza kufotokozaku tobwanyani batani lalikulu lama kona anayi

Ngati mukufuna kuti funso lifunsidwenso tobwanyani batani lobwerezera funso

To continue to the next question press the forward arrow button.
Kuti mumve funso lotsatira tobwanyani batani la muvi oloza kutsogolo

Section B: Identifiers

Instructions to the field worker

a) Fill in this part before taking leave of the participant

b) Ensure that all identifiers are automatically filled before taking leave of the participant.

1. **a01idate** Date of interview *[Date]*
2. **a02start** Start time *[Time]* ➔ *automatically filled by the tablet*
3. **a03pidw** Field worker to scan woman barcode *[Numeric]* ➔ *field worker to scan from the woman's health passport*

Section C: Questions related to the activities in the allocated arm, woman specific

Now I am going to ask you about activities in the allocated study arm.

Panopa ndikufunsani zokhudzana ndi zochitika malingana ndi kafukufukuyu.

4. **a04st** Did you receive self-test kits from anybody in the last 4 weeks? *[Numeric, Y/N]* ➔ *Ask to participants in the SOC arm only*
Kodi munalandira zipangizo zoziyezera wekha kwa aliyense?
[Ngati munalandira, tobwanyani chala choloza m'mwamba
Ngati simunalandire, tobwanyani chala choloza pansi]

Ngati mukufuna kuti funso lifunsidwenso tobwanyani batani lobwerezera funso

Kuti mumve funso lotsatira tobwanyani batani la muvi oloza kutsogolo

5. **a05let** Did you deliver the letter given to you at enrolment to your male partner? *[Numeric]* ➔ *use thumbs up and thumbs down as in c) above all the questions unless stated otherwise*
Kodi munapereka kalata yomwe munalandira mu kafukufukuyu kwa wachikondi wanu?
[Ngati munapereka, tobwanyani chala choloza m'mwamba
Ngati simunapereke, tobwanyani chala choloza pansi]

Ngati mukufuna kuti funso lifunsidwenso tobwanyani batani lobwerezera funso

Kuti mumve funso lotsatira tobwanyani batani la muvi oloza kutsogolo

6. **a06kits** Did you deliver self-test kits to your male partner? *[Numeric, Y/N]* ➔ *only to participants in the intervention arms*

   Kodi munapereka zipangizo zoziyezera wekha kwa wachikondi wanu?

   [Ngati munapereka, tobwanyani chala choloza m'mwamba

   Ngati simunapereke, tobwanyani chala choloza pansi]

   Ngati mukufuna kuti funso lifunsidwenso tobwanyani batani lobwerezera funso

   Kuti mumve funso lotsatira tobwanyani batani la muvi oloza kutsogolo

7. **a07ipvl** Did you experience any social harm from your partner after bringing the letter to your partner? *[Numeric]* ➔ *Y/N*

   Kodi kupereka kalata kwa wachikondi wanu kunakubweretserani mavuto ena ali onse?

   [Ngati munakumana ndi mavuto ali onse, tobwanyani chala choloza m'mwamba

   Ngati simunakumane ndi mavuto ali onse, tobwanyani chala choloza pansi]

   Ngati mukufuna kuti funso lifunsidwenso tobwanyani batani lobwerezera funso

   Kuti mumve funso lotsatira tobwanyani batani la muvi oloza kutsogolo

8. **a08ipvk** Did you experience any social harm from your partner after delivering self-test kits to your partner? *[Numeric, Y/N]* ➔ *Hide this question for participants in the standard of care arm*

   Kodi kupereka zipangizo zoziyezera wekha kwa wachikondi wanu kunakubweretserani mavuto ena ali onse?

   [Ngati munakumana ndi mavuto ali onse, tobwanyani chala choloza m'mwamba

   Ngati simunakumane ndi mavuto ali onse, tobwanyani chala choloza pansi]

   Ngati mukufuna kuti funso lifunsidwenso tobwanyani batani lobwerezera funso

   Kuti mumve funso lotsatira tobwanyani batani la muvi oloza kutsogolo

9. **a09ipv** Please describe any kind of social harms you faced? For example: beaten, yelled at, denied sex, marriage break-up, not given money, being locked out, being neglected, or being threatened

Chonde fotokozani mwatsanetsatane mavuto a mtundu uliwonse omwe munakumana nawo kaya kumenyedwa, kukalipidwa, kukanizidwa za m'banja, kutha kwa banja, kumanidwa ndalama, kutsekeredwa panja, kusalidwa, kapena kuopsyezedwa.

Press record sound button, then another screen will come up

Kuti muyambe kufotokoza tobwanyani batani lalitali lomwe lili ndi malemba m'musimu, kenako pabwera ka sikirini kena.

Press the big circle button on this new screen to start talking

Tobwanyani batani lalikulu lozungulira lomwe liri pa ka sikirini kameneka nkuyamba kulankhula.

When done speaking press the square button

Mukamaliza kufotokozaku tobwanyani batani lalikulu lama kona anayi

Ngati mukufuna kuti funso lifunsidwenso tobwanyani batani lobwerezera funso

To continue to the next question press the forward arrow button.

Kuti mumve funso lotsatira tobwanyani batani la muvi oloza kutsogolo

Section D: Questions related to male partner testing

Now I am going to ask you about HIV testing issues related to your male partner.

Panopa ndikufunsani mafunso okhudzana ndi wachikondi wanu pa nkhani ya zoyezetsa HIV.

10. **a10mtest** Did your partner test after you explained to him about the study? I mean any kind of HIV test *[Numeric, Y'N]*

    Kodi wachikondi wanu anayezetsa kachilombo ka HIV mutamufotokozera? Ndikati kuyezetsa ndikutanthauza kuyezetsa kulikonse kaya ndi ku chipatala, ku malo ena oyezetsera, kapena kuziyeza wekha.

    [Ngati anayezetsa, tobwanyani chala choloza m'mwamba

    [Ngati sanayezetse, tobwanyani chala choloza pansi]

    Ngati mukufuna kuti funso lifunsidwenso tobwanyani batani lobwerezera funso

    Kuti mumve funso lotsatira tobwanyani batani la muvi oloza kutsogolo

11. **a11mself** Did your partner self-test? *[Numeric]* ➔ *depends on answer to did male partner test?; hide for participants in standard of care arm and NO to* ***a06 above.***

    Kodi wachikondi wanu anaziyeza yekha mutamufotokozera?

    [Ngati anaziyeza yekha, tobwanyani chala choloza m'mwamba

    [Ngati sanaziyeze yekha kapena simukudziwa, tobwanyani chala choloza pansi]

    Ngati mukufuna kuti funso lifunsidwenso tobwanyani batani lobwerezera funso

    Kuti mumve funso lotsatira tobwanyani batani la muvi oloza kutsogolo

12. **a12self2** Did you self-test together? *[Numeric]* ➔ *depends on answer to did male partner test? ; hide for participants in standard of care arm and NO to* ***a06 above.***

    Kodi munaziyeza limodzi ndi wachikondi wanu mutamufotokozera?

    [Ngati munaziyeza limodzi, tobwanyani chala choloza m'mwamba

    [Ngati simunaziyeze limodzi, tobwanyani chala choloza pansi]

    [Ngati mukufuna kuti funso lifunsidwenso tobwanyani batani lobwerezera funso]

    Kuti mumve funso lotsatira tobwanyani batani la muvi oloza kutsogolo

13. **a13sharea** Did male partner disclose result if he tested alone *[Numeric]* ➔ *depends on answer to did male partner test? Ask for participants in standard of care arm only.*

    Kodi wachikondi wanu anakuwuzani zotsatira zake ngati anayezetsa payekha?

    [Ngati anakuwuzani, tobwanyani chala choloza m'mwamba

    Ngati sanakuwuzeni kapena simukudziwa, tobwanyani chala choloza pansi]

    Ngati mukufuna kuti funso lifunsidwenso tobwanyani batani lobwerezera funso

    Kuti mumve funso lotsatira tobwanyani batani la muvi oloza kutsogolo

14. **a14shareb** Did male partner disclose result if he self-tested alone *[Numeric]* ➔ *depends on answer to did male partner test? Hide for participants in standard of care arm.*

    Kodi wachikondi wanu anakuwuzani zotsatira zake ngati anaziyeza payekha?

    [Ngati anakuwuzani, tobwanyani chala choloza m'mwamba

    [Ngati sanakuwuzeni kapena simukudziwa, tobwanyani chala choloza pansi]

    Ngati mukufuna kuti funso lifunsidwenso tobwanyani batani lobwerezera funso

    Kuti mumve funso lotsatira tobwanyani batani la muvi oloza kutsogolo

15. **a15result** What was his test result? *[Numeric]* ➔ *depends on answer to did male partner test? 1=positive; 0=negative; 2=DK*

    Kodi zotsatira za wachikondi wanu zinali zotani?

    [Ngati anati alibe kachilombo, tobwanyani chala choloza m'mwamba]

    [Ngati anati alinako kachilombo, tobwanyani chala choloza pansi]

    Ngati mukufuna kuti funso lifunsidwenso tobwanyani batani lobwerezera funso

    Kuti mumve funso lotsatira tobwanyani batani la muvi oloza kutsogolo

16. **a16hard** Did you or your partner experience any difficulties in conducting self-testing? *[Numeric*

    Kodi inu kapena wachikondi wanu munakumana ndi vuto lililonse poziyeza nokha?

    [Ngati panalibe vuto lililonse, tobwanyani chala choloza m'mwamba]

    [Ngati munakumana ndi vuto lililonse, tobwanyani chala choloza pansi]

    Ngati mukufuna kuti funso lifunsidwenso tobwanyani batani lobwerezera funso

    Kuti mumve funso lotsatira tobwanyani batani la muvi oloza kutsogolo

17. **a17link** Did your partner come to the clinic after testing regardless of result? *[Numeric]* ➔ *Y/N, depends on testing questions above*

Kodi wachikondi wanu anabwera kuno ku chipatala potsatira kuyezetsa mutamufotokozera posatengera zotsatira?

[Ngati anabwera, tobwanyani chala choloza m'mwamba

Ngati sanabwere kapena simukudziwa, tobwanyani chala choloza pansi]

Ngati mukufuna kuti funso lifunsidwenso tobwanyani batani lobwerezera funso

Kuti mumve funso lotsatira tobwanyani batani la muvi oloza kutsogolo

This marks the end of the questions, thank you for your time.

Pano ndi pa mathero pa mafunso athu, zikomo kwambiri chifukwa choyankha mafunsowa.

18. ***a18end*** *End time*

If you experienced any adverse events please inform the field worker who will be able to help you with the next steps.

Appendix 8.3-3: PQ07: Questionnaire for Men who link to male friendly clinic
Version 0.6 last modified by Augustine Choko on 15th June 2016

Section A: Identifiers & automatic fields for verification

1. **f01date** Date linked *[Date]*

Automatically populated upon scanning male partner barcode [3-8]

2. **f02pidm** Male partner barcode *[Numeric]* ➔ *counsellor to scan from the invitation letter*
3. **f03ancd** Clinic day # *[Numeric 01-99]* ➔ *counsellor to verify on the invitation letter*
4. **f04cid** Clinic ID *[Numeric]* ➔ *counsellor to verify*
5. **f05arm** Arm *[Numeric 1-6]* ➔ *counsellor to verify on the invitation letter*
6. **f06pidw** Woman barcode *[Numeric]* ➔ *automatically linked to the male partner barcode*
7. **f07name** Woman initials ➔ *counsellor to verify by asking the male partner to give all names of his partner.*

8. **f08coid** Counsellor ID *[Numeric 01-20]*

Section B: Demographics

9. **f09dob** What is your date of birth *[date: DD-MM-YYYY]*
   Kodi munabadwa mchaka chanji? Chonde tiwuzeni tsiku, mwezi komanso chaka ngati nkotheka.
10. **f10age** If date of birth is unknown, what is the age? *[Numeric; ask participant to guess their age if they say they don't know]*
    Kodi muli ndi zaka zingati?
11. **f11mstat** Marital status *[Numeric]* ➔ *1=married; 2=polygamous marriage; 3=living together as if married; 4=never married; 5=widow; 6=Separated; 7=Divorced; 8=married but not living together.*
    Kodi muli pa banja panopa?
12. **f12live** Are you currently living together with your partner? *[Numeric]* ➔ *Depends on answer to 12) <u>marital status.</u> 1=yes; 0=no.*
    Kodi mumakhala limodzi ndi mkazi wanu?
13. **f13lit** Can you read a letter or a newspaper? *[Numeric]* ➔ *1=yes; 0=no*
    Kodi mumatha kulemba ndi kuwerenga?
14. **f14occ** How can you best describe your main activity or work status? *[Numeric]* ➔ *1=Paid employee; 2=Paid domestic worker; 3=Self-employed; 4=Unemployed; 5=Student; 6=Other*
    Kodi mumagwira ntchito yanji?
15. **f15edu** What was the highest level of education that you have completed? *[Numeric]* ➔ *0=Never been to school; 1=Primary school; 2=Secondary school no MSCE; 3= Secondary school with MSCE; 4=Higher*
    Kodi maphunziro anu munafika nawo pati?

Section C: HIV testing and follow-on services

16. **f16test** Did you have an HIV test after your partner informed you about the study?
    Kodi munatengapo gawo pa zoyezetsa HIV wachikondi wanu atakufotokozerani?
17. **f17testb4** Have you ever tested for HIV before the test you just had *[Numeric]* ➔ *1=yes; 0=no*
    Kodi munayamba mwayezetsapo kachilombo ka HIV m'mbuyomu kupatula kuyezetsa kwa panopa?
18. **f18test12m** Have you tested for HIV in the last 12 months? *[Numeric]* ➔ *Depends on 16 above. 1=yes; 0=no*
    Kodi munayezetsa kachilombo ka HIV mu miyezi 12 yapitayi?
19. **f19couple** Came as a couple? *[Numeric]* ➔ *Don't ask but record accordingly. 1=yes; 0=no; don't ask participant simply record*
20. **f20test2** Did you test together with your partner in this pregnancy? *[Numeric]*
    Kodi munayezetsa limodzi ndi wachikondi wanu mu uchembere wawo wa panopa?
21. **f21modet** What was the mode of testing for the test you just had?*[Numeric]* ➔ *1=VCT at a testing service or clinic; 2=self-test alone; 3= self-test together; 4=self-test alone followed by self-testing together; 5=self-test alone followed by VCT at a testing service or clinic together; 6=other*
    Kodi kuyezaku kunali mnjira yanji?
22. **f22res** What was the result of your HIV test? *[Numeric]* ➔ *1=positive; 0=negative*
    Kodi zotsatira zakuyezaku zinali zotani?
23. **f23kit** Self-test kit returned? *[Numeric]* ➔ *1=yes; 0=no; don't ask participant simply record*
24. **f24rtn** Is the returned **s**elf-test kit (s) used? *[Numeric]* ➔*1=yes; 0=no; don't ask participant simply record*
25. **f25st** HTC Counsellor re-read of returned used self-test kit *[Numeric]* ➔ *1=positive; 0=negative; 2=invalid; don't ask participant simply record*
26. **f26hard** How hard was it for you to do the self-test correctly? *[Numeric]* ➔ *1=Not at all hard to do the test; 2=somewhat hard to do the test; 3=Very hard to do the test [If 2 or 3 specify]*
    Kunali kovuta bwanji kuti muziyeze nokha molondola?
    Ngati panali mavuto ena chonde fotokozani.
27. **f27recst** Did you receive self-test kits from anybody? *[Numeric, Y/N]*➔ *Ask to participants in the SOC arm only*
    Kodi munalandira zipangizo zoziyezera wekha kwa aliyense?
28. **f28conft** Confirmatory test result *[Numeric]* ➔ *don't ask but record accordingly. 1=positive; 0=negative; 2=refused; don't ask participant simply record*
29. **f29couns** Did the participant receive counselling *[Numeric]* ➔ *1=yes; 0=no; don't ask participant simply record*
30. **f30cond** Did the participant receive condoms *[Numeric]* ➔ *1=yes; 0=no; don't ask participant simply record*
31. **f31circum** Are you circumcised? *[Numeric]* ➔ *1=yes; 0=no*
    Kodi munapangitsa mdulidwe wa a bambo wa ku chipatala?
32. **f32vmmc** Was the participant successfully linked to voluntary male medical circumcision? *[Numeric, Y/N/Refused]* ➔ *1=yes; 0=no, refused; 2=HIV positive; don't ask participant simply record*
33. **f33art** Was the participant successfully linked to ART? ➔ *1=yes; 0=no; 2=no, already on ART*
34. **f34recom** Would you recommend this *strategy* to other men? *[Numeric]* ➔ *1=definitely yes; 2=not sure; 3=definitely no.*
    Kodi mungawalimbikitse azibambo ena za njira imeneyi?

Thank you
Zikomo

1.4.1.1 **1.4.1.1.2** Participant ID ☐☐☐☐☐

1.4.1.1 **1.4.1.1.4** Date of report ☐☐/☐☐☐/☐☐☐☐

D D M O N Y Y Y Y

1.4.1.1 **1.4.1.1.6** Staff ID ☐☐

1.4.1.1 **1.4.1.1.8** Clinic ID

1= NDIRANDE
2= ZINGWANGWA
3= BANGWE ☐

1.4.1.1 **1.4.1.1.1** Sex

1 = MALE
2 = FEMALE ☐

E08 Type of adverse event

1 = NEW
2 = CHANGE IN GRADE/SEVERITY
3 = RESOLUTION ☐

E07 OCC Grade of the adverse event reported *[take from Table 1 on PQ55 SOP]*

1 = GRADE 1
2 = GRADE 2
3 = GRADE 3
4 = GRADE 4
5 = GRADE 5 ☐

E08

Adverse event related to HIV self-test kits?

1 = DEFINITELY YES

2 = PROBABLY

3 = POSSIBLY

4 = UNLIKELY/NO

☐

E09

Adverse event related to financial incentives?

1 = YES

2 = PROBABLY

3 = POSSIBLY

4 = NO

☐

E10 EVENT

Describe the exact nature of

the adverse event.

E11 ACT

Describe the action taken

E12

Adverse event reported as a serious adverse event?

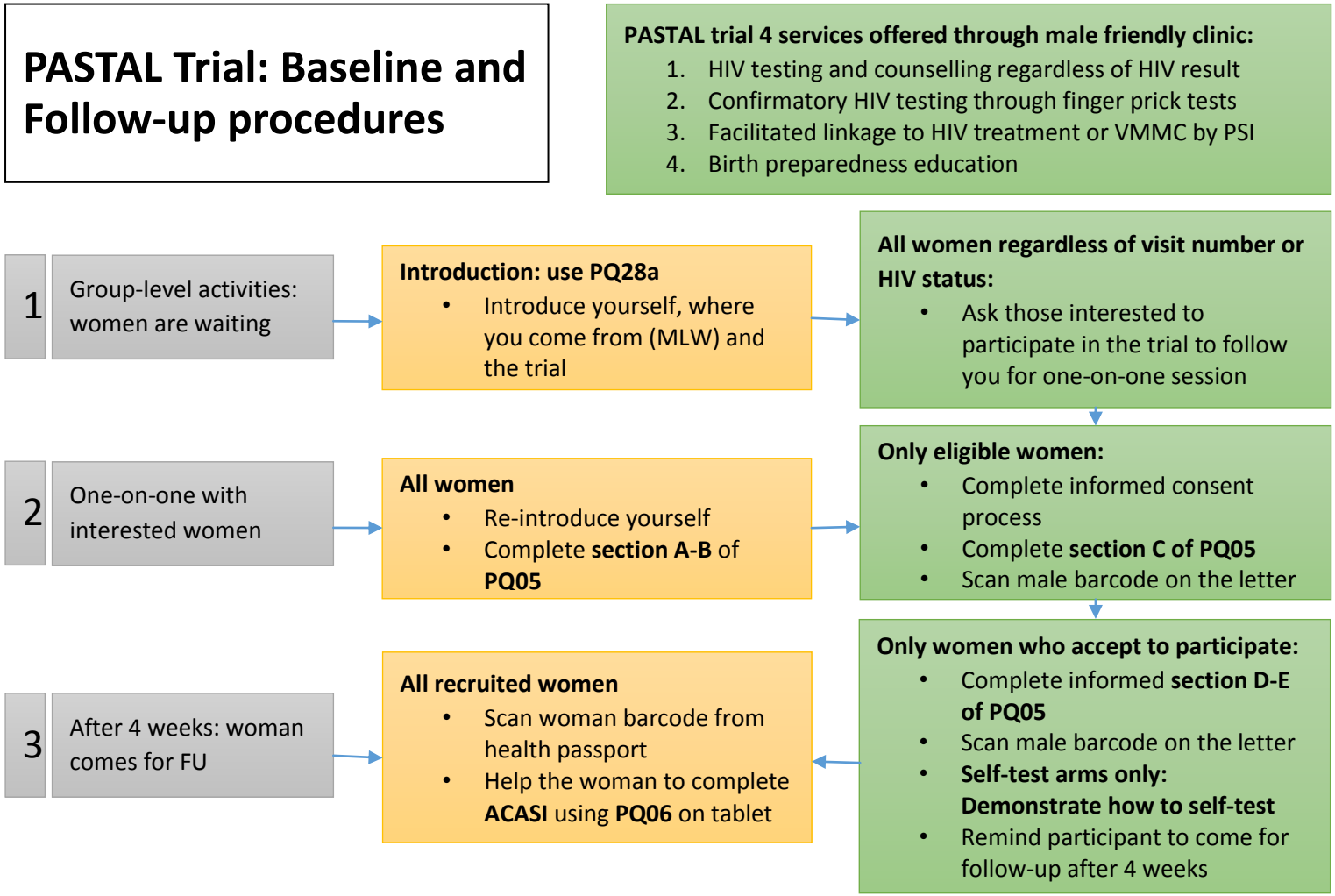
1 = YES

2 = NO

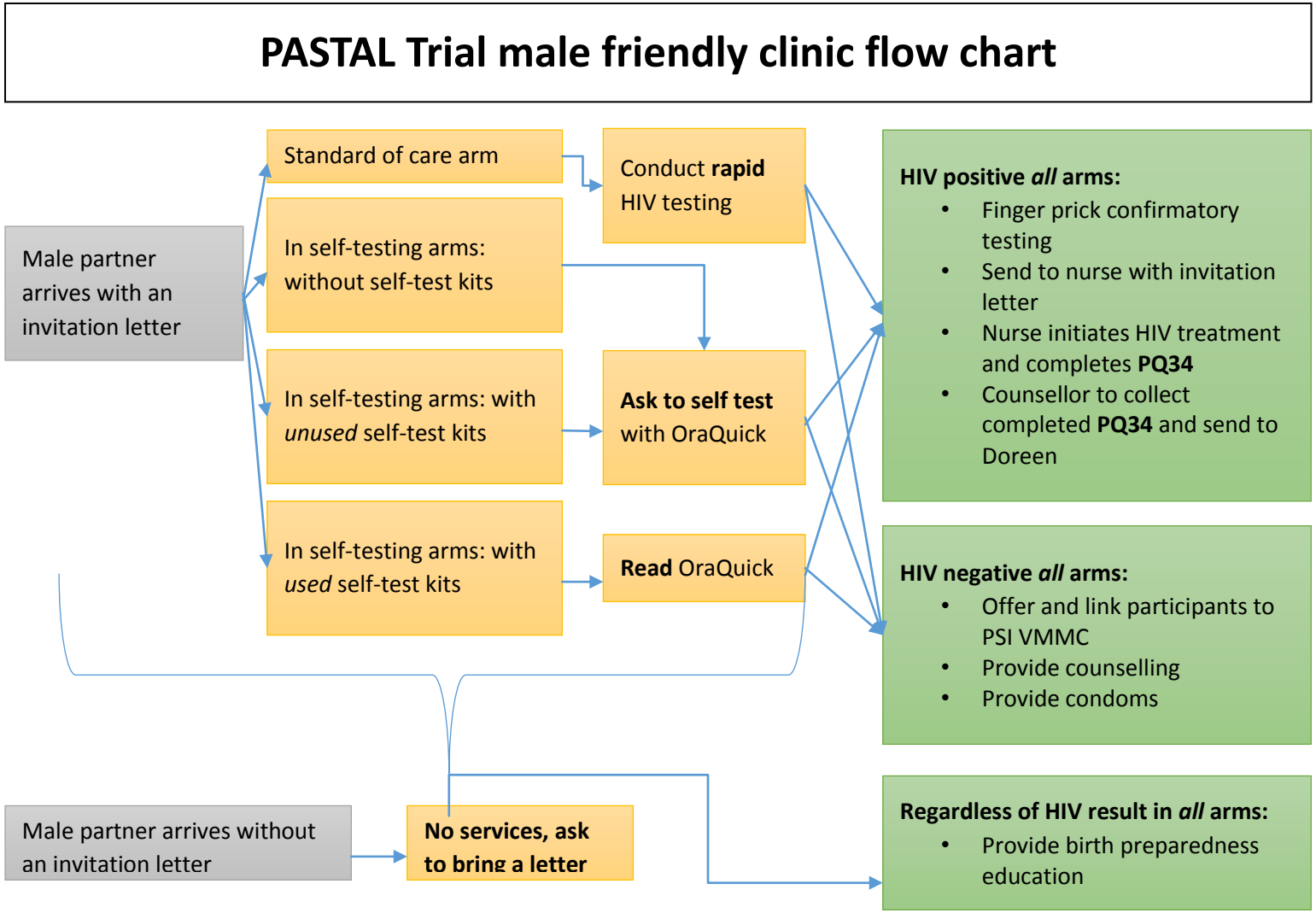
☐

8.4 Flow charts of standard operating procedures

Appendix 8.4-1: Antenatal clinic recruitment flow chart



Appendix 8.4-2: Male friendly clinic flow chart



8.5 SPIRIT Checklist and statistical analysis plan for the trial

Appendix 8.5-1: SPIRIT 2013 Checklist

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

Section/item	Item No	Description
Administrative information		
Title	1	**Effect of partner-provided HIV self-testing on HIV testing and linkage among male partners of antenatal clinic attendees in Malawi: study protocol for an adaptive Phase II cluster randomised trial (PASTAL)**
Trial registration	2a	**Trial registry name:** ISRCTN. **Number:** ISRCTN18421340. **Date registered:** 31 Mar 2016
	2b	See attached Table (Item 2b: SPIRIT.doc)
Protocol version	3	**Protocol:** version 1.5; 31 October 2016 **Revision chronology** Version 1.2, 13 May 2016 Version 1.5, 31 October 2016 Primary reason for amendment: change in the definition of the primary outcome.
Funding	4	Funder: Wellcome Trust, UK

Roles and responsibilities	5a	Augustine T. Choko*[1,4], Katherine Fielding[4], Nigel Stallard[5], Hendramoorthy Maheswaran[5], Aurelia Lepine[4], Nicola Desmond[1,2], Moses K. Kumwenda[1,3], Elizabeth L. Corbett[1,3,4]

1. Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, Malawi
2. Liverpool School of Tropical Medicine, Liverpool, United Kingdom
3. College of Medicine, Blantyre, Malawi
4. London School of Hygiene & Tropical Medicine, London, United Kingdom
5. School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
6. Warwick Medical School, Coventry, United Kingdom

Corresponding author*

Malawi Liverpool Wellcome Trust Clinical Research Programme

P.O Box 30096

Chichiri

Blantyre 3

augutc@gmail.com

+265999577452

Protocol contributors

Grant holder: ATC
Conceived of the study: ATC and ELC
Provided statistical expertise in trial design: KF and NS
Provided expertise in interventional design: ATC, HM, AL, ND, MKK, and ELC
Implemented the trial: ATC and MKK
Conducting primary statistical analysis: ATC and KF
All authors contributed to refinement of the study protocol and approved the final manuscript.

5b The trial sponsor is London School of Hygiene & Tropical Medicine (Ref, No.: QA844), WC1E 7HT, Keppel Street, +44 20 7636 8636, London, United Kingdom. Contact person: patricia.henley@lshtm.ac.uk.

5c The funder and the sponsor played no role in the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

5d **Trial Steering Committee**

- Members: KF, ND, ELC.
- Agreement of final protocol.
- Recruitment of study participants.
- Reviewing study progress and agreeing changes to the protocol if necessary.
- Making final decision to drop arms following recommendation from Data Safety and Monitoring Board (DSMB) recommendation.

Data Safety and Monitoring Board

- Independent members from the trial investigators. Prof Frances Cowan (Chair), University College London; Prof Victor Mwapasa (College of Medicine, Malawi); and Dr Patrick Phillips (University College London and MRC, UK).
- Reviewing interim analysis results including safety data.
- Recommending that trial arms be dropped.

Independent statistician

- Dr Mavuto Mukaka (Wellcome Trust, Thailand).
- Responsible for randomisation of trial units.

Introduction

Background and rationale

6a **Research question:** What are the most promising candidate interventions for increasing uptake of HIV testing and linkage into care or prevention for partners of pregnant women attending antenatal clinic in Blantyre, Malawi?

Sub-Saharan Africa (SSA) accounts for 70% of the global HIV burden despite rapid scale up of HIV services including testing. Analysis of the HIV care cascade indicates a striking fall-off in numbers between testing and linkage into HIV care or prevention. Men regularly feature among populations with lower uptake of HIV testing across SSA and lower rates of linkage into care or prevention in the era of extremely ambitious targets for HIV. The 90-90-90 targets aim to diagnose 90% of all HIV cases, start 90% of diagnosed HIV cases on treatment, and achieve viral suppression in 90% of those started on HIV treatment[1]. Awareness of HIV status amongst male partners of antenatal clinic (ANC) women attendees is low with less than 35% undergoing HIV testing when invited through their partner.

A number of strategies have been found to increase uptake of HIV testing among male partners of ANC attendees, including home-based testing, provider initiated testing and counselling (PITC), couples testing during antenatal visits and home-based couple or partner testing. Key limitations of these strategies include: logistical difficulties of wide scale implementation where home visits are required, lack of convenience, costs, lack of confidentiality and failure to prioritise men's own health. HIV self-testing (HIVST) is an alternative approach with potential to increase couple or partner testing and has been found to be highly acceptable to men in Malawi. Here we define *HIVST-plus* as offering HIV self-testing along with an additional intervention aimed at improving linkage into HIV care or prevention. Such additional interventions include facilitated linkage, financial incentives (FI), and short messaging services (SMS).

6b **Comparator:** personalised male partner invitation letter given to the pregnant woman at enrolment at antenatal clinic

Objectives	7	Primary objective 1) To identify the most promising interventions for increasing both the uptake of HIV testing and linkage into HIV care or prevention among male partners of pregnant women attending ANC. Secondary objectives 2) To identify the most promising interventions for increasing the uptake of HIV testing among male partners of pregnant women attending ANC. 3) To assess the acceptability of partner-provided HIVST-plus, as defined by willingness to deliver HIVST kits to male partners among women attending ANC. 4) To investigate the risk of intimate partner violence among women attending ANC who participate in the study. 5) To provide the cost associated with implementation of the service for each study arm
Trial design	8	This is a Phase II adaptive multi-arm multi-stage (MAMS) cluster randomised trial using antenatal (ANC) day as the unit of randomisation. Each ANC day was randomised to any one of the six trial arms using a randomised permuted block design in a ratio of 1:1:1:1:1:1.

Methods: Participants, interventions, and outcomes

Study setting	9	The study will recruit participants from Ndirande, Zingwangwa and Bangwe primary health clinics (PHC) in urban Blantyre, Malawi.

Eligibility criteria 10 **Inclusion criteria**

i) Women attending antenatal clinic for the first time at Ndirande, Zingwangwa and Bangwe PHC in urban Blantyre and their male partners.
ii) ≥ 18 years old.
iii) Have not had couple or partner testing in this pregnancy.
iv) Male partner is unaware of being HIV positive.
v) Not already recruited in this trial.
vi) Urban Blantyre resident.

Exclusion criteria

i) Have had couple or partner testing in this pregnancy.
ii) <18 years old.
iii) The man is already aware of their HIV positive status and receiving treatment.
iv) Subsequent ANC visit
v) Already recruited in this trial.
vi) Not present in urban Blantyre in the next days after the woman is enrolled in the trial.

Interventions 11a Intervention arm 1: Women receive a letter and two self-test kits to deliver to their male partners during their first antenatal clinic (ANC) visit.

Intervention arm 2: Women receive a letter and two self-test kits to deliver to their male partners who will get a financial incentive of $3 when they link into male friendly clinic and receive HIV care or HIV prevention services.

Intervention arm 3: Women receive a letter and two self-test kits to deliver to their male partners who will get an incentive of $10 when they link into male friendly clinic and receive HIV care or HIV prevention services.

Intervention arm 4: Women receive a letter and two self-test kits to deliver to their male partners who will be entered into a lottery with a 10% chance of winning $30 when they link into male friendly clinic and receive HIV care or HIV prevention services.

Intervention arm 5: Women receive a letter and two self-test kits to deliver to their male partners who will receive a phone call to remind them to test and link into male friendly clinic to receive HIV care or HIV prevention services.

11b Participants can withdraw at any time.

	11c	Participants are given trial information to improve participation in follow-up interviews with women four weeks after enrolment.
	11d	No drugs administered in the trial
Outcomes	12	**Primary and secondary outcomes** The primary outcome is the proportion of male partners of ANC attendees who test for HIV and link into HIV care or prevention within 28 days of enrolling the woman. Thus, the primary outcome is defined as presentation of the male partner at the MFC with a used self-test kit (if in the intervention arm) or undergoing on spot HIV testing with a study HIV counsellor within 28 days AND being referred for HIV care if HIV positive or VMMC if HIV negative and uncircumcised or being counselled on HIV prevention if HIV negative and already circumcised. There are four secondary outcomes: the proportion of male partners who test for HIV within 28 days; the proportion of women who accept to participate in their allocated trial arm; risk of serious adverse events (SAEs) by males and females in the study; and the total cost of implementing each trial arm. Exploratory outcome: a male partner with evidence of HIV testing within 28 days [either presenting with a used self-test kit or undergoing on spot HIV testing with a study HIV counsellor] AND being in pre-ART, received ART, received condoms, or undergone voluntary male medical circumcision (VMMC).
Participant timeline	13	Women are enrolled during their first antenatal clinic visit. Uptake of HIV testing and linkage to the trial-run male friendly clinic for HIV treatment if positive and voluntary male medical circumcision (VMMC) if negative are measured within 28 days among male partners of the pregnant women being recruited. Follow-up interviews are conducted with women four weeks after enrolment to measure safety outcomes and other outcomes.

Sample size	14	We assumed that each antenatal clinic day (cluster) will have at least 40 women attending for the first time, 90% would satisfy the eligibility criteria and at least 60% would consent to participate, so having a cluster-size of at least 21. We also assumed that in the standard of care (SOC) arm 25% of male partners will satisfy the definition of the primary outcome. For the first stage six antenatal clinic days per arm (36 days in total) would be needed to detect an absolute difference of 15% in linkage compared to 25% in the SOC arm using a family-wise error rate (FWER) of 0.2 with 80% pair-wise power and a coefficient of variation (k) of 0.10. Sample size for the second stage will be re-calculated based on empirical estimates at interim analysis with FWER of 0.1 and 80% power.
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size include group-based information while women wait for their antenatal care services followed by one-one information about each trial arm.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	The allocation sequence was obtained using computer-generated random numbers with the three clinics as factors for stratification. Random permuted block randomisation was used to reduce predictability of a random sequence.
Allocation concealment mechanism	16b	Telephone to the field team on the morning of recruitment was used as a mechanism of implementing the allocation sequence.
Implementation	16c	Dr Mavuto Mukaka (Wellcome Trust, Thailand) was responsible for randomisation and intervention assignment of trial units. Field workers will enrol the participants.
Blinding (masking)	17a	This is an unblinded trial although the trial investigators (outcome assessors) will only have aggregate data until the interim analysis.
	17b	The trial is unblinded

Methods: Data collection, management, and analysis

Data collection methods	18a	All the data will be collected using open data kit (ODK) running on Nexus tablets.

Outcome measurement

All male partners who present at the male friendly clinic in the SOC arm will be offered a single finger prick HIV test with Determine 1/2™ as per Malawi national testing algorithm. An HTS counsellor will re-read a used self-test kit if the participant returns one as evidence of self-testing in the intervention arms. Participants who return with unused self-test kits or without self-test kits will be requested to self-test in the presence of the counsellor. All HIV results will be recorded on a data form followed by confirmation of HIV positive results in parallel using Determine 1/2™ and Uni-Gold, with facilitated linkage to HIV care. All men who test HIV negative and report to be uncircumcised will be offered VMMC to be conducted by Population Services Internal (PSI). Thus, measurement of primary outcome includes evidence of an HIV test, confirmatory testing, and referral to HIV care or VMMC as appropriate within 28 days of the woman being recruited.

The secondary outcome of HIV testing among male partners will also be measured though proxy reporting by the woman using audio computer-assisted self-interview (ACASI) during her next ANC visit four weeks later. Participation in the allocated trial arm will be measured by computing the proportion of women who accept to participate after receiving trial-arm specific information using the denominator of the total number of women who are eligible. All women will be asked to report any adverse events through ACASI at their next ANC visit while men who present to the MFC will be asked to report any adverse events. A costing tool validated in urban Blantyre[2] will be used to capture the costs associated with providing the service in each trial arm. The cost and outcome data will be used to estimate the cost per male partner tested for HIV, and cost per male HIV-positive identified through all SOC and intervention arms.

18b In order to retain participants and to complete follow-up interviews with women we plan to:

- Check health passports of all women attending antenatal clinic (ANC) on days other than the first ANC.
- Conduct telephone follow-up interviews for women with phone numbers who give prior consent during enrolment.
- Inform male partners who link into the trial-run male friendly clinic to remind their partners about the follow-up visit.

Participants who discontinue from the trial will have a short version of the follow-up interview to measure trial outcomes.

Data management

19 Data will be managed through infrastructure set up within Malawi-Liverpool-Wellcome Trust Clinical Research Programme (MLW). Data collection and processing will be as detailed in the data management plan (DMP) included in Appendix R. Data will be collected using tablets running Open Data Kit (ODK) and will be downloaded onto a server running a MySQL Relational Database. Data quality assurance will be implemented within the electronic form so that out of range values, inconsistent values and required variables will be checked at the time of data collection. All tablets will have full log-in details of the person collecting the data including a password. Access to the study database will be protected by a password known only to the PI (Augustine Choko) and the IT systems administrator in MLW. Data for study monitoring will be periodically exported into comma separated values (CSV) from the study database on the MLW server for analysis and to raise plus resolve data queries.

Protocols for managing data without breach of confidentiality are in place within MLW. Access to the final data set will be limited to the PI (Augustine Choko), the Trial Steering Committee (TSC) and the Data Safety and Management Board (DSMB). Sensitive information (including HIV results) will not be linked to personal identifiers in the final data set. All devices and paper-based tools containing data will be kept in locked offices at MLW during data processing and in a locked data repository room for longer term storage. All data will be backed up daily by the MLW Data Office, with offsite back up once weekly. Backup data will be stored in a locked filing cabinet away from the office by the PI.

Statistical methods	20a	Baseline characteristics will be computed as proportions or median (interquartile range [IQR]), as appropriate, by arm in each of the two stages of the trial. Any variables that show imbalances will be adjusted for when analysing the trial outcomes at the end of the second stage. All analyses will be by intention-to-treat taking as the denominator the number of women who were eligible and take into account the clustered design. Given the small number (six) of clusters per arm in the first stage, analysis will be by cluster-level summaries using mean of proportion of male partners per clinic day who link to care or prevention in each arm. The proportion of male partners who link into care or prevention will be computed per clinic day for each arm with number of men achieving the primary outcome and the number of women eligible and recruited in ANC on enrolment day as denominator. A log transformation of the clinic day proportions will be applied if a positive skew is observed[3]. The harmonic mean of clinic day proportions in each of the five intervention arms will be compared to the SOC arm using unpaired t-test. An estimate of the risk ratio (RR) and a 95% CI will also be computed for each comparison. The Dunnett test[4] will be applied to the t-statistics generated from the unpaired t-test to control the stage-wise FWER. Final results will then be based on combined p-values from both the first stage and the second stage using the weighted inverse normal (WIN) method.
	20b	Any variables that show imbalances will be adjusted for when analysing the trial outcomes at the end of the second stage using logistic regression with random effects.
	20c	Analysis of the primary outcome will be by intention-to-treat.

Methods: Monitoring

Data monitoring	21a	Data Safety and Monitoring Board (guided by DAMOCLES Charter) • Independent members from the trial investigators. Prof Frances Cowan (Chair), University College London; Prof Victor Mwapasa (College of Medicine, Malawi); and Dr Patrick Phillips (University College London and MRC, UK). • Reviewing interim analysis results including safety data.
	21b	Interim analysis at the end of stage 1 will assess whether any of the five intervention arms should be dropped as recommended by an independent data monitoring and safety board (DSMB) based on a 3-part criteria. First, an arm whose statistical comparison to the SOC arm yields a p-value>0.2 will be considered for dropping for futility. Second, any intervention arm with *high* incidence of SAEs i.e. grade 3, 4 or 5 (Table 1) compared to SOC will be considered for dropping. Thirdly, an arm may be maintained after taking into account the costs associated with providing the service in light of the p-value from statistical analysis. For this cost analysis, we will provide the DSMB estimates of the incremental cost per male partner tested, and incremental cost per male HIV positive identified through the intervention arms in comparison to the SOC arm.
Harms	22	There is potential for intimate partner violence (IPV) particularly to women although evidence from similar studies in Kenya suggest this approach is unlikely to increase this problem. All women will be asked through audio computer assisted self-interview (ACASI) if they experienced any adverse event including IPV four weeks after enrolment. Male partners who link into the trial-run male friendly clinic will also be asked to report if they experienced any adverse events particularly being coerced to have an HIV test. All adverse events will be captured and graded using tools developed as part of the trial.
Auditing	23	The trial will be independently audited according to standard operating procedures (SOPs) laid down by the Malawi Liverpool Wellcome Trust Clinical Research Programme (MLW) Clinical Trial Support Unit (CTSU) internal monitoring committee and the University of Malawi-College of Medicine Research Support Centre (RSC) monitoring process.

Ethics and dissemination

Research ethics approval	24	Ethics approval was obtained locally from the College of Medicine Research Ethics Committee (COMREC) in Malawi (approval number P.04/16/1932) and from the London School of Hygiene & Tropical Medicine Ethics Committee (approval number 11308).
Protocol amendments	25	Important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) will be communicated first to IRBs for approval before implementation.
Consent or assent	26a	Field workers (data collectors) will obtain informed consent or assent from potential trial participants or authorised surrogates. All trial participants will give written or witnessed (with thumb print for illiterate participants) consent before undergoing any trial procedures. Written consent for male partners was waived by the two ethics committees because the first contact is with the woman.
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies (**not applicable**).
Confidentiality	27	Only authorised personnel will handle the study data with password protection of both the computer and the study database. Final data will be fully anonymised to remove any participant identifying information to uphold confidentiality.
Declaration of interests	28	All principal investigators declare no other competing interests for the overall trial and each study site.
Access to data	29	All trial investigators and DSMB members will have access to the final trial dataset. There are no contractual agreements that limit access for investigators. The final fully anonymised data from the study will be made publicly available through the LSHTM data repository (http://datacompass.lshtm.ac.uk/.
Ancillary and post-trial care	30	There are no ancillary and post-trial care, and for compensation to those who suffer harm from trial participation.

Dissemination policy	31a	Findings from the trial will be disseminated to the Blantyre District Health Office (DHO) and officials in Ministry of Health (MoH) through presentations and final copy of the report. Further local dissemination will be done at the National AIDS Commission (NAC) / College of Medicine (COM) annual dissemination conference. Findings will also be presented at peer-reviewed regional and international conferences. Copies of the final report, published peer-reviewed paper (s) and abstracts will be made available to the COM Library, and to College of Medicine Research Ethics Committee (COMREC).
	31b	ICMJE authorship eligibility guidelines will be followed during publication.
	31c	The final fully anonymised data from the study will be made publicly available through the LSHTM data repository (http://datacompass.lshtm.ac.uk/.The trial registration number is ISRCTN18421340 and the full protocol can be shared with no restrictions on request.

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates (See attached Information sheet and consent form—**PQ23a**)
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, (**Not applicable**)

*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.

Appendix 8.5-2: Statistical analysis plan

Investigating interventions to increase uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in antenatal clinics in Blantyre, Malawi: an adaptive Phase II multi-arm multi-stage cluster randomised trial (ISRCTN18421340)

Statistical Analysis Plan

(Linked to Protocol v1.5; 29/10/2016)

Last modified by Augustine T. Choko on 30th May 2017

Principal investigator: Augustine Talumba Choko (LSHTM, MLW)

Co-investigators:

Katherine Fielding	London School of Hygiene & Tropical Medicine (LSHTM)
Elizabeth L Corbett	LSHTM & Malawi Liverpool Wellcome Trust Clinical Research Programme (MLW)
Nicola Desmond	MLW & Liverpool School of Tropical Medicine (LSTM)
Moses Kumwenda	MLW & College of Medicine (COM)
Aurelia Lepine	LSHTM
Hendramoothy Maheswaran	University of Warwick
Nigel Stallard	University of Warwick
Simon Makonbe	HIV Unit, Lilongwe-Malawi

Institutions:

Malawi-Liverpool-Wellcome Clinical Research Programme (MLW), Blantyre, Malawi
Malawi Ministry of Health (MoH), HIV unit (DoHIV/AIDS)
Blantyre District Health Office (DHO), Blantyre, Malawi
Liverpool School of Tropical Medicine (LSTM)
London School of Hygiene and Tropical Medicine (LSHTM), UK

Date: 30th May 2017

1. Overview of study design, setting and recruitment

The aim of this cluster randomised trial (CRT) is to investigate whether providing HIV self-test kits alone or with an additional intervention through pregnant women who are accessing antenatal care (ANC) for the first time can increase male partner HIV testing and linkage into HIV treatment or prevention services. This is a Phase II trial intended to investigate *safety outcomes*, to provide an estimate of *acceptability* to the woman and *efficacy* relating to uptake of testing and subsequent HIV services by the male partner. The trial involved testing 5 different interventions for improving linkage to the "male friendly" clinic regardless of male partner HIV result including financial incentives and reminders compared to the standard of care (SOC) of giving a personalised letter only to the male partner (annex - Fig. 1). The trial is a multi-arm multi-stage (MAMS) adaptive design with 6 arms (5 intervention and 1 SOC) in the first stage with a planned interim analysis at the end of that stage of recruitment aiming to drop arms and re-calculation of sample size. Enrolment continued in stage two and analysis conducted for participants enrolled into stage two, as well as combing effect estimate across the two stages, where appropriate.

2. Outcomes

Primary outcome

6) The proportion of male partners of ANC attendees who test for HIV and link into HIV care or prevention within 28 days of enrolling the woman.

Secondary outcomes

1) Proportion of male partners of ANC attendees who test for HIV within 28 days.
2) Proportion of women who accept to participate in their allocated study arm.
3) Risk of serious adverse events within 30 days of enrolment associated with each study arm.
4) Total cost of implementing the service per study arm.

<u>Adverse events and safety reporting:</u>

Adverse events will be reported using terms and definitions outlined below

Grade 3 events, any of the following within 30 days:

- Intimate partner violence that leads to pain, bruising or marks within 24hrs.
- Threat of life-threatening violence (e.g. statement of intent to kill, mock strangulation, threatened with a knife or gun
- Physically coercive sex
- Reports fearing for her life
- Marriage break

- **Grade 4 events, any of the following within 30 days:**

    - Intimate partner violence leading to hospitalisation or death
    - Suicide or attempted suicide
    - Attack using potentially lethal force (e.g. knife, gun, hammer, kicks to the head)

- **Grade 5, death.**

3. Randomisation

Block randomisation was used to allocate the ANC days across the trial arms in either trial stage. Although recruitment was done from three PHCs no stratification was applied because the PHCs are very similar. The allocation sequence was only communicated to the field workers on the day of recruitment to minimise selection bias.

4. Description of each trial arm

1) Standard of care (SOC): Women will receive personalised letters to give their male partners inviting them to come to the male friendly clinic.
2) Self-test kits only: Women receive a letter and self-test kits to deliver to their male partners.
3) Self-test kits + a $3 financial incentive: Women receive a letter and self-test kits to deliver to their male partners who will get an incentive of $3 conditional on attending the male friendly clinic.
4) Self-test kits + a $10 financial incentive: Women receive a letter and self-test kits to deliver to their male partners who will get an incentive of $10 conditional on attending the male friendly clinic.
5) Self-test kits + lottery incentive: Women receive a letter and self-test kits to deliver to their male partners who will be entered into a lottery with a 10% chance of winning $30 conditional on attending the male friendly clinic.
6) Self-test kits + phone call reminder: Women receive a letter and self-test kits to deliver to their male partners who will receive up to two phone calls to remind them to test and link into male friendly clinic to receive HIV care or HIV prevention services.

5. Sample size justification

Sample size for primary outcome (stage 1)

The choice of 36 clusters provided 80% power to detect a 15% difference from an assumed 25% HIV testing plus linkage for male partners in the SOC arm, assuming a 0.1 value for the coefficient of variation (k).

6. Trial profile

A trial profile figure based on the extension of the CONSORT for cluster randomised trials[5] (annex-Figure 2) will be produced for each of the two trial stages illustrating the following:

i. Number of ANC days (clusters) in each randomisation group
    a. Total number of women and men across clusters
    b. Median number of women and men per clusters by trial arm
ii. Number of clusters lost to follow up
iii. Number of clusters and individuals analysed for each trial outcome, by arm

7. Baseline enrolment characteristics

Analyses will be done in R [6] and Stata 14.0 (Stata Corp, Texas, USA). Baseline characteristics will be computed as proportions or median (interquartile range [IQR]), as appropriate, by arm in each of the two stages of the trial. We will examine baseline characteristics of men as reported by the woman (annex - Table 1 & 2), as well as baseline characteristics of women (annex - Table 3 & 4).

Individual level characteristics

- Age
- Literacy
- Highest level of education
- Occupation
- Marital status
- HIV testing history

8. Statistical analysis of primary outcome

We will assume that the two stages of the trial are independent [7] and will proceed to carry out a test of the null hypothesis of no difference in effectiveness of each intervention compared to the SOC. We will do this by analysing data from the first stage first followed by interim decisions to drop arms; then we will conduct and analyse data from the second stage (no overlap of participants from the first stage). The primary outcome analysis of the whole trial will thus combine p-values and estimates from the each separate stage[7]. The p-values from either stage will be combined using the weighted inverse normal (WIN) method [8] for arms that are not dropped at interim. A weighted average of the log (risk ratio [RR]) will be computed for each intervention arm vs SOC, for the whole trial using estimates from each trial stage (Table 5). The estimates will be weighted using the inverse of the variance. All analyses will be by intention-to-treat taking as the denominator the number of women who were eligible and take into account the clustered design.

Alternatively, we will analyse the stage 1 data first as a planned interim analysis. Decisions to drop trial arms will be based on this analysis. At the completion of the second stage, data from each stage will then be combined and analysed as a single trial. This approach will be simpler and likely to enhance statistical power as more clusters will now be available for analysis.

In each cluster the proportion of male partners with the primary outcome will be calculated as:

$$\frac{\text{number of male partners who have an HIV test + linked to male friendly clinic}}{\text{number of women recruited in that antenatal clinic day}}$$

The distribution of these cluster-level estimates will be examined graphically by trial arm in each stage and a logarithm of the cluster-level summaries applied prior to further analysis if the distributions are right-skewed[3]. The geometric mean of clinic day proportions in each of the five intervention arms will be compared to the SOC arm using unpaired t-test [3]. An estimate of the RR and a 95% CI will also be computed for each comparison by dividing the geometric mean of proportions in each intervention arm and the geometric mean of proportions in the SOC arm[3]. Any variables that show imbalances will be adjusted for using a 2-stage analytical approach for both stages. First, a logistic regression model will be fitted to obtain a residual for each cluster; then these residuals will be analysed in place of the observed estimates.

This analysis involves more than two comparisons with a single control arm which can lead to higher than the specified family wise error rate (FWER) or significance level. Therefore, a Dunnett test [4] will be applied to the t-statistics generated from the unpaired t-test to control the stage-wise FWER. Final decision-making at interim analysis will compare the Dunnett-corrected p-values to stage 1 FWER of 0.2. Since the two stages are assumed to be independent, cluster level summaries approach analogous to stage 1 analysis will also be followed in stage 2 comparing intervention arms that proceed to stage 2 with the SOC arm.

Adaptations at interim analysis (end of stage 1)

Interim analysis at the end of stage 1 will assess whether any of the five intervention arms should be dropped as recommended by an independent data monitoring and safety board (DSMB) based on a 3-part criteria. First, an arm whose statistical comparison to the SOC arm yields a p-value>0.2 will be considered for dropping for futility. Second, any intervention arm with *high* incidence of SAEs i.e. grade 3, 4 or 5 compared to SOC will be considered for dropping. It is the discretion of the DSMB to decide based on absolute number of SAEs in each intervention trial arm whether they are high or not. Such an observation and recommendation will then be shared with the investigators who will make the final decision. Thirdly, an arm may be maintained after taking into account the costs associated with providing the service in light of the p-value from statistical analysis. For this cost analysis, we will provide the DSMB estimates of the incremental cost per male partner tested, and incremental cost per male HIV positive identified through the intervention arms in comparison to the SOC arm. The investigators will access the first stage data only after the last follow-up visit for participants has occurred in order to perform interim analysis.

Descriptive analysis

We will explore intervention effects on the absolute number of male partners who started ART or got linked to VMMC by trial arm and trial stage (annex – Table 6). The components of the primary outcome will further be broken down into a) men who completed linkage i.e. started ART or got circumcised b) men whose linkage was incomplete: linked to ART or VMMC but did not start ART or were not circumcised.

We will explore if results differ by the self-reported HIV status of the woman; age of the man, recent HIV testing (<12 months); education level.

An estimate of the between-cluster variation, *k*, will be provided for each stage.

9. Analysis of secondary outcomes

The four secondary outcomes are listed as follows:

i) Proportion of male partners who test for HIV within 28 days (as reported by the woman). This will be measured through audio computer assisted self-interview (ACASI) with the woman after her enrolment in the trial. The proportion and 95% Binomial Exact confidence interval (CI) of male partners reported to have had a test following the woman reenrolment will be computed using the number of women eligible at enrolment as the denominator.

ii) Proportion of women who accept to participate in their allocated trial arm. Measured by acceptance of the woman to continue participation in the allotted trial arm after knowing the activities in that particular arm. The proportion and 95% Binomial Exact CI of women who continue participation will be computed using the number of women eligible as the denominator, and shown by trial arm (Table 8).

iii) Risk of serious adverse events (SAEs) by males and females in the study; and the total cost of implementing each trial arm **(see Section 10).**

10. Safety analysis

The total number of participants experiencing serious adverse events (SAEs) will be given as absolute numbers per arm. We expect these to be small hence no formal comparisons to the SOC will be made (annex- Table 7).

11. Sources of bias and contamination

Potential sources of bias which will be examined include:

- Contamination between clusters: it is possible for women or men from the SOC to benefit from the interventions such as by getting self-test kits. We will examine the proportion of participants in the SOC arm who report having received a self-test kit.

- We will check the fidelity of the phone call reminder by examining the proportion of participants who were successfully reached by the study staff

Annex: Figures and Tables

Figure 1: Trial schema

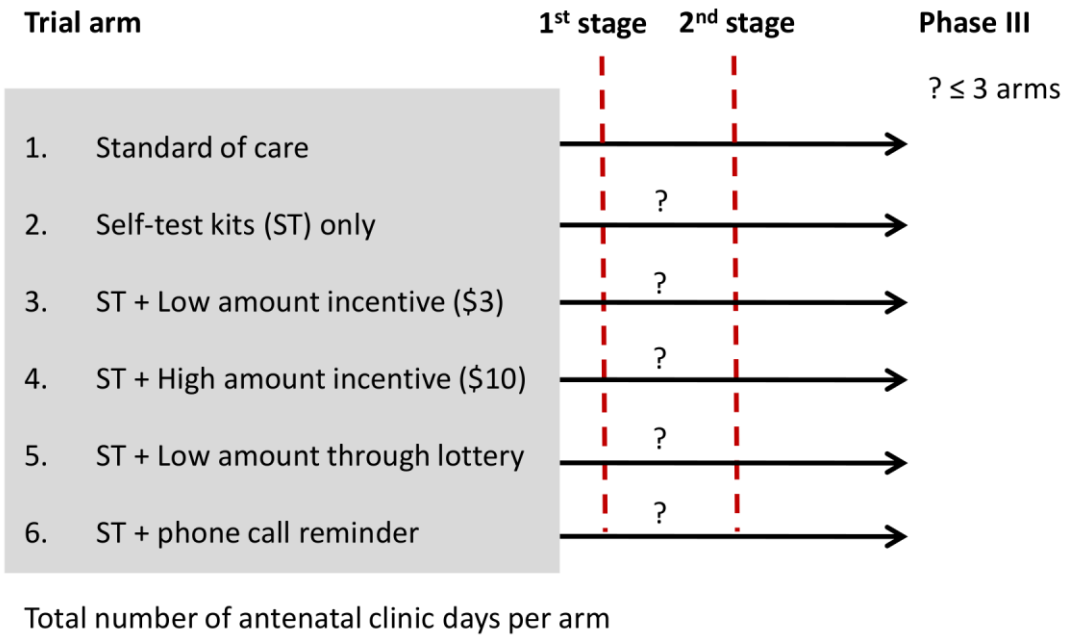


Figure 2. Stage 1 & 2 trial profile

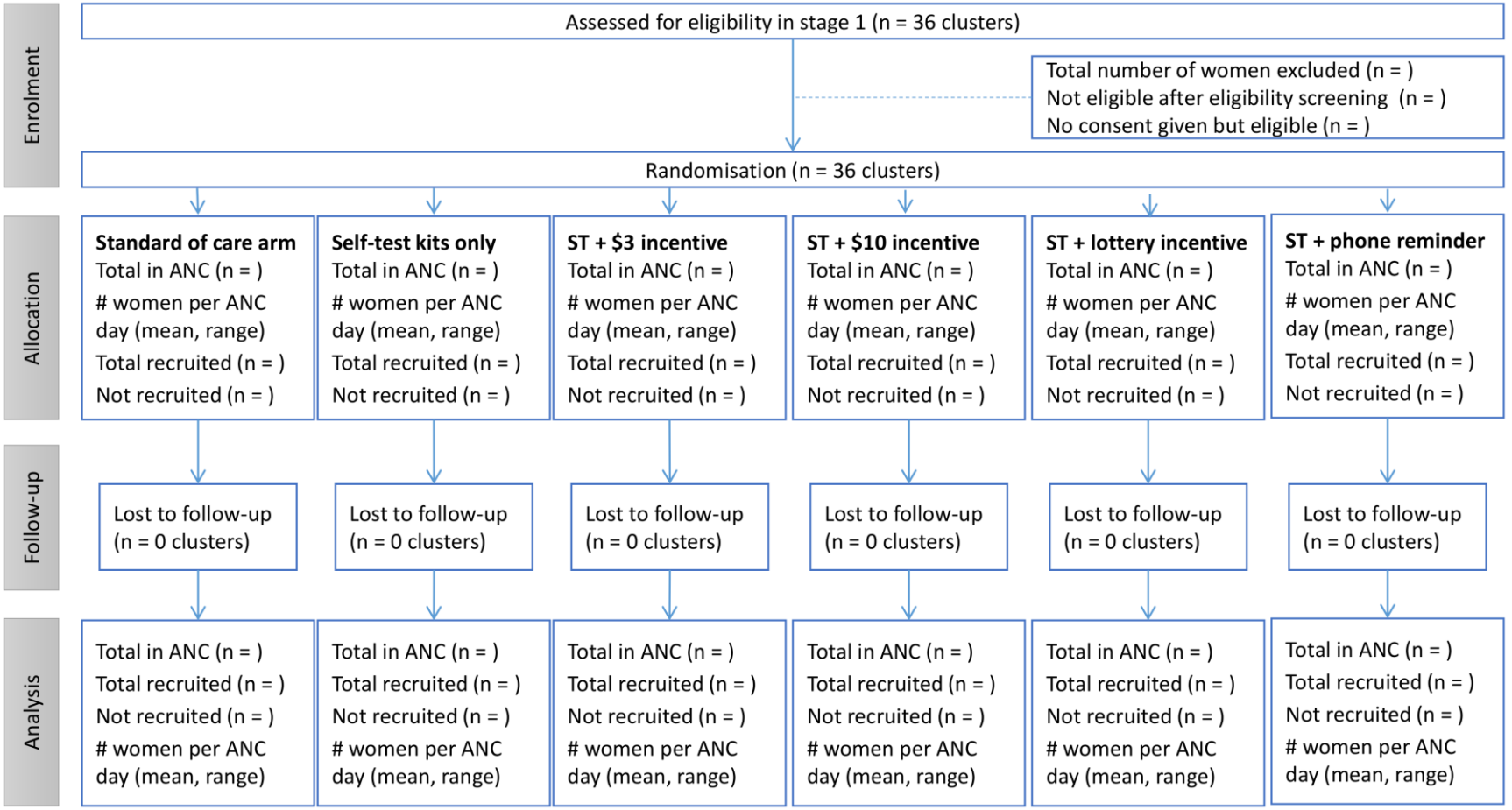


Table 1 & 2: Stage 1 & 2 baseline characteristics of men as reported by the woman (N = XXXX)

		Trial arm					
Variable	**Characteristic**	**SOC**	**ST**	**ST + $3**	**ST + $10**	**ST + Lottery**	**ST + reminder**
Number responded	n						
Age (years)	Mean (sd)						
Age group	18-19						
	(20,30]						
	(30,60]						
Able to read and write	No						
Education	Never been to school						
	Primary						
	Secondary						
	Higher						
Occupation	Paid employee						
	Self-employed						
	Unemployed						
Ever tested for HIV	No						
Tested for HIV in the last 12m	No						
Recruitment PHC	Ndirande						
	Bangwe						
	Zingwangwa						

SOC: standard of care; ST: self-test kits; sd: standard deviation; MSCE: Malawi school certificate of education (4 years); PHC: primary health clinic

Table 3 & 4: Stage 1 & 2 baseline characteristics of women (N = XXXX)

		Trial arm					
Variable	**Characteristic**	**SOC**	**ST**	**ST + $3**	**ST + $10**	**ST + Lottery**	**ST + reminder**
Number responded	n						
Age (years)	Mean (sd)						
Age group	18-19						
	(20,30]						
	(30,60]						
Able to read and write	No						
Education	Never been to school						
	Primary						
	Secondary						
	Higher						
Occupation	Paid employee						
	Self-employed						
	Unemployed						
Ever tested for HIV	No						
Tested for HIV in the last 12m	No						
Recruitment PHC	Ndirande						
	Bangwe						
	Zingwangwa						

SOC: standard of care; ST: self-test kits; sd: standard deviation; MSCE: Malawi school certificate of education (4 years); PHC: primary health clinic

Table 5: Intervention effects by trial arm and trial stage

	Trial arm					
	SOC	**ST only**	**ST + $3**	**ST + $10**	**ST + Lottery†**	**ST + Reminder‡**
First stage						
Eligible						
Outcome*						
Proportion**						
RR	1					
95% CI						
p-value	NA					
Second stage						
Eligible					Dropped	
Outcome*						
Proportion**						
RR						
95% CI						
p-value						
First stage + second stage						
RR#						
95% CI						
p-value§						

SOC: standard of care; ST: self-test; RR: risk ratio

† 10% chance of winning $3 times number of men achieving the outcome

‡ phone call

* Evidence of testing and linked to clinic within 28 days regardless of test result

** Geometric mean of the cluster proportions

Inverse variance weighted risk ratio

§ Using weighted inverse normal method

Table 6: Starting HIV treatment or linkage to male circumcision by trial arm across the two stages

	SOC		ST only		ST + $3		ST + $10		ST + lottery		ST + remin	
	n	%	n	%	n	%	n	%	n	%	n	%
Confirmatory testing												
HIV positive												
HIV negative												
Total linked												
Completed linkage												
ART												
VMMC												
Linkage referred (incomplete)												
ART												
VMMC												
No ART or VMMC indicated												
HIV-ve already circumcised												
HIV+ve already on ART												
Referred for ART or VMMC												
Of total eligible												

SOC: standard of care; ST: self-test kits; VMMC: voluntary male medical circumcision

Table 7: Adverse events and ACASI participation in women by trial arm and trial stage

	Trial arm						
	SOC	**ST**	**ST+$3**	**ST+$10**	**ST+Lottery**	**ST+reminder**	**Total**
First stage							
Total number eligible for ACASI*							
Number interviewed at follow-up							
% of those eligible for ACASI							
Reported on an adverse event							
Through ACASI							
Direct report							
Through male friendly clinic							
Second stage							
Total number eligible for ACASI*							
Number interviewed at follow-up							
% of those eligible for ACASI							
Reported on an adverse event							
Through ACASI							
Direct report							
Through male friendly clinic							

ACASI: audio computer-assisted self-interview; SOC: standard of care; ST: self-test kits

* Excluding number of women who discontinued after giving consent

Table 8: Stage 1 & 2 women participation by trial arm stage

		Trial arm					
	Total	**SOC**	**ST**	**ST + $3**	**ST + $10**	**ST + Lottery**	**ST + reminder**
Stage 1							
Eligible							
Consented							
Discontinued by trial arm							
Stage 2							
Eligible							
Consented							
Discontinued by trial arm							

SOC: standard of care; ST: self-test kits

References

1. UNAIDS (2014) 90-90-90: An ambitious treatment target to help end the AIDS epidemic. Geneva, Switzerland.

2. Maheswaran H, Petrou S, MacPherson P, Choko AT, Kumwenda F, et al. (2016) Cost and quality of life analysis of HIV self-testing and facility-based HIV testing and counselling in Blantyre, Malawi. BMC Med 14: 34.

3. Hayes JR, Moulton LH (2009) Cluster Randomised Trials: Chapman and Hall/CRC.

4. Dunnett CW (1955) A multiple comparison procedure for comparing Several Treatments with a control. Journal of the American Statistical Association 50: 1096-1121.

5. Campbell MK, Piaggio G, Elbourne DR, Altman DG, Group C (2012) Consort 2010 statement: extension to cluster randomised trials. BMJ 345: e5661.

6. R Core team (2015) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

7. Bretz F, Schmidli H, Konig F, Racine A, Maurer W (2006) Confirmatory seamless phase II/III clinical trials with hypotheses selection at interim: general concepts. Biom J 48: 623-634.

8. Bauer P, Kohne K (1994) Evaluation of experiments with adaptive interim analyses. Biometrics 50: 1029-1041.

Appendix 8.5-3: Adverse events grading table

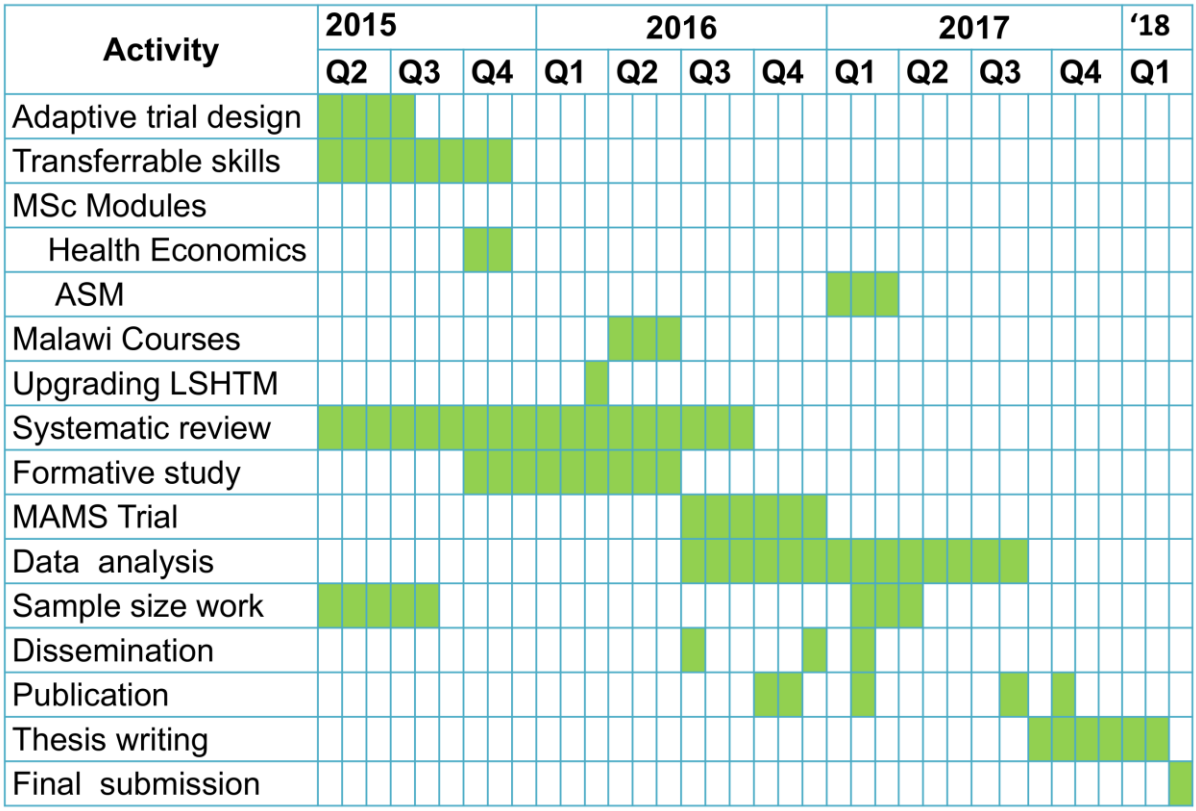
	GRADE 1 (Mild)	**GRADE 2** (Moderate)	**GRADE 3** (Severe) (Within 30 days)	**GRADE 4** (Potentially life-threatening) (Within 30 days)
	1.Verbal, emotional or psychological Intimate-partner violence (IPV) 2.Denying access to household resources 3.Being ignored 4.Being controlled (e.g. not allowed to leave house)	1.Coercion to self-test. 2.Coercion to disclose a self-test result 3.IPV that includes pushing, or slapping with an open hand that does not result in pain, or visible marks >24hrs 4.Severe or prolonged psychological or emotional IPV leading to disruption of daily activities 5.Psychologically coercive sex	1. IPV that leads to pain, bruising or marks >24hrs. 2.Threat of life-threatening violence (e.g. statement of intent to kill, mock strangulation, threatened with a knife or gun 3.Physically coercive sex 4.Reports fearing for her life 5.Marriage break-up	1.IPV leading to hospitalisation or death 2.Suicide or attempted suicide 3.Attack using potentially lethal force (e.g. knife, gun, hammer, kicks to the head)
STEPS TO BE FOLLOWED	Refer to community based institutions for assistance. e.g Church leaders and marriage counsellors	Refer to community-based gender-based violence (GBV) support organisations (One Stop Centre and Queen Elizabeth Central Hospital Counselling Centre)	• Facilitate urgent referral to Queen Elizabeth Central Hospital • Refer to One Stop Centre for psycho-social support • Facilitate relocation to a safe environment	• Facilitate urgent referral to Queen Elizabeth Central Hospital • Ensure safe alternative abode before discharge • Refer to One Stop Centre for psycho-social support • Report to police (Suicide / Murder)

Grade 1 indicates a mild event
Grade 2 indicates a moderate event
Grade 3 indicates a severe event

Grade 4 indicates a potentially life-threatening event
Grade 5 indicates death. Not indicated on the table

8.6 Timelines and support letters

Appendix 8.6-1: PhD Timeline



Appendix 8.6-2: Local district health office support letter

Telephone: Blantyre 01875332 / 01877401
Fax: 01872551/01 878 539

Communication should be addressed to:

The District Health Officer

In reply please quote No. .....

MINISTRY OF HEALTH AND POPULATION
DISTRICT HEALTH OFFICE
P/BAG 66
BLANTYRE
MALAWI

Ref. No. DHO/MED/19

23rd July, 2015

Mr Augustine T. Choko
Malawi Liverpool- Welcome Trust
Clinical Research Programme
P.O Box 30096,
BLANTYRE 3

Dear Sir,

PARTNER-PROVIDED HIV SELF-TESTING AND LINKAGE (PASTAL)

I am pleased to inform you that you have been granted permission to conduct your study entitled "**Investigating interventions to increase uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in antenatal clinics in Blantyre, Malawi**", subject to approval by the College of Medicine Research Ethics Committee.

However, note that the office advises its participation in the study for ownership and use of findings.

Yours sincerely,

[redacted]

Dr. Medson Matchaya
DISTRICT HEALTH OFFICER

8.7 Ethical approvals and data safety monitoring board charter

This section presents the letters of ethical approvals from the local institutional reiew board, College of Medicine Research Ethics Committee (COMREC) and the London School of Hygiene & Tropical Medicine Research Ethics Committee. These approvals are for the formative study described in chapter 3 and the adaptive multi-arm multi-stage cluster randomized trial described in chapter 5.

Appendix 8.7-1: Local ethics approval for the qualitative study: College of Medicine Research Ethics Committee

COLLEGE OF MEDICINE

Principal
M. H. C. Mipando MSc PhD

Our Ref:

Your Ref: P.08/15/1784

College of Medicine
Private Bag 360
Chichiri
Blanytre 3
Malawi
Telephone: 01 871911
01 874107
Fax: 01 874 700

5th October 2015

Mr. Augustine T. Choko
Malawi Liverpool Welcome Trust
P.O Box 30096
Blantyre 3

Dear Mr. Choko,

RE: P.08/15/1784 – Developing contextually acceptable candidate interventions for increasing uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in antenatal clinics in Blantyre, Malawi: a cross-sectional qualitative study version 2

I write to inform you that COMREC reviewed the above captioned proposal which you resubmitted for review. I am pleased to inform you that COMREC granted you conditional approval. Full approval will be granted when you address the following:

- Regarding the response to comment number 2, you have insisted that being a qualitative study, it is not applicable to define and operationalise variables. With this stance, the specific objectives of the study still remain wordy and non-specific. In addition, it remains unclear as to which variables will be used to meet which study objectives or how the study activities will meet the objectives of the study. Please address this issue.

Please note that implementation of the study may not commence unless Full approval has been granted.

Yours sincerely,

[redacted]

Dr. C. Dzamalala
Chairperson, COMREC
CD/ck

UNIVERSITY OF MALAWI
COLLEGE OF MEDICINE
05 OCT 2015
COMREC
PRIVATE BAG 360
CHICHIRI, BLANTYRE 3

Appendix 8.7-2: Local ethics approval for the qualitative study: London School of Hygiene & Tropical Medicine Research Ethics Committee

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Mr Augustine Choko
LSHTM

3 November 2015

Dear Augustine

Study Title: Partner-provided self-testing and linkage (PASTAL); Part 1

LSHTM Ethics Ref: 10332

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Investigator CV	J Chikovore CV Signed	17/07/2015	1.0
Local Approval	BT DHO letter PASTAL	23/07/2015	1.0
Investigator CV	Nic_CV_May 2015	01/08/2015	1.0
Information Sheet	PQ21a_Info_sheet_SPW_english_v0.4	06/08/2015	0.4
Information Sheet	PQ21b_Info_sheet_SPW_chichewa_v0.4	06/08/2015	0.4
Investigator CV	CV_Mkumwenda	10/08/2015	1.0
Investigator CV	cv_kfielding	11/08/2015	1.0
Investigator CV	Augustine Choko shortCV	24/08/2015	1.0
Local Approval	AUGUSTINE CHOKO	28/08/2015	1.0
Information Sheet	PQ20a_FGD_Info_sheet_english_v0.5	09/09/2015	0.5
Information Sheet	PQ20b_FGD_Info_sheet_chichewa_v0.5	09/09/2015	0.5
Information Sheet	PQ22a_IDI_Info_sheet_english_v0.2	21/09/2015	0.2
Information Sheet	PQ22b_IDI_Info_sheet_chichewa_v0.2	21/09/2015	0.2
Protocol / Proposal	PASTAL Qualitative protocol v1.2	25/09/2015	1.2
Covering Letter	Augustine_Cover_letter_PASTAL qualitative_v0.3	21/10/2015	0.3

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

Appendix 8.7-3: Local ethics approval for the adaptive multi-arm multi-stage cluster randomized trial: College of Medicine Research Ethics Committee

CERTIFICATE OF ETHICS APPROVAL

This is to certify that the College of Medicine Research and Ethics Committee (COMREC) has reviewed and approved a study entitled:

P.04/16/1932 – Investigating interventions to increase uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in antenatal clinics in Blantyre, Malawi: an adaptive Phase II multi-arm multi-stage cluster randomized trial by Augustine Choko

On 30th June 2016

As you proceed with the implementation of your study, we would like you to adhere to international ethical guidelines, national guidelines and all requirements by COMREC as indicated on the next page

[redacted]

Dr. C. Dzamalala- Chairperson (COMREC)

Approved by
College of Medicine
30 JUN 2016
(COMREC)
Research and Ethics Committee

30th June, 2016
Date

Appendix 8.7-4: Local ethics ammendment for the adaptive multi-arm multi-stage cluster randomized trial: College of Medicine Research Ethics Committee

COLLEGE OF MEDICINE

Principal
M. H. C. Mipando MSc PhD

Our Ref:

Your Ref: P.04/16/1932

College of Medicine
Private Bag 360
Chichiri
Blanytre 3
Malawi
Telephone: 01 871911
01 874107
Fax: 01 874 700

2nd December 2016

Mr. A. Choko
Malawi-Liverpool Wellcome Trust
P.O Box 30096
Chichiri
BT 3

Dear Mr. Choko

RE: P.04/16/1932 – Investigating interventions to increase uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in antenatal clinics in Blantyre, Malawi: an adaptive Phase II multi-arm multi-stage cluster randomized trial

I write to inform you that COMREC reviewed the amendments to the above mentioned study which you submitted for review. I am pleased to inform you that COMREC **approved** the following requests:

1. To revise the eligibility criteria on questionnaire PQ05, Section B to include a more complete question with regards to both women and the male partner being present within the next 28 days following enrolment of the woman
2. To revise the primary outcome

As you proceed with the implementation of your study we would like you to take note that all requirements by the college are followed as indicated on the attached page.

Yours sincerely,

Dr. C. Dzamalala
COMREC CHAIRMAN
CD/ck

Appendix 8.7-5: Approval for the adaptive multi-arm multi-stage cluster randomized trial from the London School of Hygiene & Tropical Medicine Research Ethics Committee

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Mr Augustine Choko
LSHTM

10 June 2016

Dear Augustine,

Study Title: Investigating interventions to increase uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in antenatal clinics in Blantyre, Malawi: a MAMS CRT

LSHTM Ethics Ref: 11308

Thank you for responding to the Interventions Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Local Approval	PASTAL COMREC APPROVAL	10/11/2010	1.0
Investigator CV	E_Corbett_Biosketch Dec HIVST 2014	01/12/2014	1.0
Local Approval	BT DHO letter PASTAL	23/07/2015	1.0
Investigator CV	Lepine_A_cv_short	10/08/2015	1.0
Investigator CV	cv_kfielding	11/08/2015	1.0
Investigator CV	Augustine Choko shortCV_1.0	24/08/2015	1.0
Information Sheet	PQ22a_Info_sheet_consent_women_english_v0.1	28/03/2016	0.1
Information Sheet	PQ22b_Info_sheet_consent_women_chichewa_v0.1	28/03/2016	0.1
Information Sheet	PQ23a_Info_sheet_consent_women_english_v0.1	28/03/2016	0.1
Information Sheet	PQ23b_Info_sheet_consent_women_chichewa_v0.1	28/03/2016	0.1
Information Sheet	PQ24a_Info_sheet_consent_women_english_v0.1	28/03/2016	0.1
Information Sheet	PQ24b_Info_sheet_consent_women_chichewa_v0.1	28/03/2016	0.1
Information Sheet	PQ25a_Info_sheet_consent_women_english_v0.1	28/03/2016	0.1
Information Sheet	PQ25b_Info_sheet_consent_women_english_v0.1	28/03/2016	0.1
Information Sheet	PQ26a_Info_sheet_consent_women_english_v0.1	28/03/2016	0.1
Information Sheet	PQ26b_Info_sheet_consent_women_english_v0.1	28/03/2016	0.1
Information Sheet	PQ27a_Info_sheet_consent_women_english_v0.1	28/03/2016	0.1
Information Sheet	PQ27b_Info_sheet_consent_women_chichewa_v0.1	28/03/2016	0.1
Other	PQ42_DSMB_Charter_v0.1	28/03/2016	0.1
Investigator CV	Nigel_Stallard_shortCV_1.0	30/03/2016	1.0

Sponsor Letter	Choko_sponsor_QA844_26052016	26/05/2016	QA844
Covering Letter	LSHTM_Ethics_response_v0.1	03/06/2016	0.1
Protocol / Proposal	PASTAL_MAMS_protocol v0.5_TRACKED	03/06/2016	0.3
Protocol / Proposal	PASTAL_MAMS_protocol v0.5_CLEAN	03/06/2016	0.5
Protocol / Proposal	PQ55_Adverse_Events_Handling_Procedures_SOP_v0.3	03/06/2016	0.3
Protocol / Proposal	PQ08_Adverse_Events_Reporting_v0.3	03/06/2016	0.3
Protocol / Proposal	Critical Incident Interview Guide	03/06/2016	0.2

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Improving health worldwide

Appendix 8.7-6: Ammendment approval for the adaptive multi-arm multi-stage cluster randomized trial from the London School of Hygiene & Tropical Medicine Research Ethics Committee

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Mr Augustine Choko
LSHTM

5 December 2016

Dear Augustine,

Study Title: Investigating interventions to increase uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in antenatal clinics in Blantyre, Malawi: a MAMS CRT

LSHTM Ethics Ref: '11308 - 1'

Thank you for your application for the above amendment to the existing ethically approved study and submitting revised documentation. The amendment application has been considered by the Interventions Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above amendment to research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval for the amendment having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Other	PQ05_Baseline_qn_women_v0 6_CLEAN-fsedtd 25oct2016	25/10/2016	0.6
Other	PQ05_Baseline_qn_women_v0 6_Tracked_fsedt 25oct2016	25/10/2016	0.6
Other	Cover_letter_MAMS_amendment_v0.1.docx	25/10/2016	0.1
Other	PASTAL_MAMS_protocol v1.5_CLEAN	29/10/2016	1.5
Other	PASTAL_MAMS_protocol v1.5_TRACKED	29/10/2016	1.5
Other	Cover_letter_MAMS_amendment_v0.2	31/10/2016	0.2

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

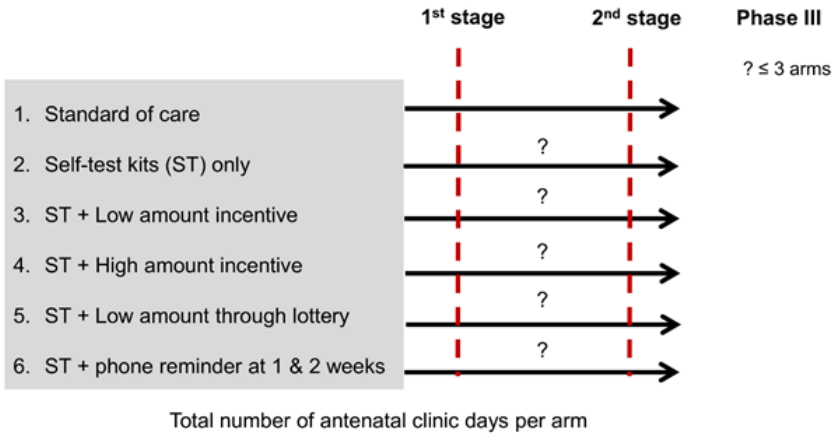
Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Appendix 8.7-7: Data Safety Monitoring Board (DSMB) Charter

Partner-provided HIV self-testing and linkage Phase II adaptive trial
DAMOCLES Charter for Data Safety Monitoring Board (DSMB)

Content	Description
1. Introduction	
Partner-provided HIV self-testing and linkage (PASTAL).	The PASTAL Phase II trial is a multi-arm multi-stage adaptive cluster randomised trial (ISRCTN: ISRCTN18421340) funded by Wellcome Trust, UK as a Training Fellowship in Public Health & Tropical Medicine. It will be conducted in urban Blantyre, Malawi and will be based at Malawi Liverpool Wellcome Trust Clinical Research Programme (MLW).
Objectives of trial, including interventions being investigated	The objectives of PASTAL are as follows: **Primary objective** 7) To identify the most promising interventions for increasing both the uptake of HIV testing and linkage into HIV care or prevention **among male partners of pregnant women attending antenatal clinic (ANC)**. **Secondary objectives** 8) To identify the most promising interventions for increasing the uptake of HIV testing among **male partners of pregnant women attending ANC.** 9) To assess the acceptability of partner-provided HIVST-plus, as defined by willingness to deliver HIVST kits to male partners **among women attending ANC.** 10) To investigate the risk of intimate partner violence **among women attending ANC** who participate in the study. 11) To provide the cost associated with implementation of the service for **each study arm** The interventions will be investigated in two stages aiming to select ≤3 interventions to proceed to a potential Phase III trial (Figure 1). An antenatal clinic day will be randomised to any one of the six arms, with women requested to deliver HIV self-test kits to their male partners in the 5 intervention arms. **Fig. 1:** Schema of the Phase II adaptive MAMS CRT and interventions

Content	Description
	
Outline of scope of charter	The purpose of this document is to describe the roles and responsibilities of the independent DSMB for the PASTAL trial, including the timing of meetings, methods of providing information to and from the DSMB, frequency and format of meetings and statistical issues.
2. Roles and responsibilities	
A broad statement of the aims of the committee	"To protect and serve [trial] participants, particularly women who may be at risk of social harms (especially re: safety) and to assist and advise Principal Investigators so as to protect the validity and credibility of the trial." "To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial."
Terms of reference	The DSMB should receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the Trial Investigators. The DSMB should inform the Investigators if, in their view: (i) An intervention arm should be dropped from the trial because of being less efficacious compared to the standard of care. (ii) Notwithstanding (i), an intervention arm should be dropped because of safety concerns by reviewing safety data. a) Comparison of SOC to all intervention arms on the incident cases of intimate partner violence preceding the introduction of interventions; b) Comparison of SOC and each intervention arm separately.
Specific roles of DSMB	Interim review of the trial's progress including updated figures on recruitment, main outcomes and safety data (Figure 2. Specifically, the DSMB will:- • Monitor recruitment figures. • Monitoring evidence for intervention differences in the main efficacy outcome measures. • Monitor evidence for social harms i.e. intimate partner violence (IPV) precipitated by the introduction of the interventions. IPV includes *any* abuse experienced by the woman after delivering HIV self-test kits to the male partner and directly linked to HIV self-testing.

Content	Description
	• Decide whether to recommend that an intervention arm (s) of the trial be dropped at interim analysis. • Suggest additional data analyses. • Advise on pre-planned adaptations including sample size re-calculation. • Assess the impact and relevance of external evidence
3. Before or early in the trial	
Whether the DSMB will have input into the protocol	All potential DSMB members were invited to be part of the DSMB and received a concept note of the trial. The members listed in this Charter fully agreed to be part of the DSMB.
Whether the DSMB will meet before the start of the trial	The DSMB will meet before the trial starts to discuss the protocol, the trial, any analysis plan, future meetings, and to have the opportunity to clarify any aspects with the principal investigators. A "dummy" report with empty shell tables will be presented to familiarise the DSMB members with the format that will be used in the reports. The second DSMB meeting will be within a month of completing first stage follow-up to review the accumulating data. All DSBM meetings will be held by Teleconference arranged by the Investigators in Blantyre, Malawi.
4. Composition	
Membership and size of the DSMB	The DSMB will comprise three independent members with expert knowledge in HIV self-testing, adaptive trial designs and the local HIV context namely; Prof Frances Cowan (University College London/LSHTM), Dr Patrick Phillips (Medical Research Council, UK) and Prof Victor Mwapasa (College of Medicine), respectively.
The Chair, how they are chosen and the Chair's role. (Likewise, if relevant, the vice-Chairman)	Prof Frances Cowan will chair the DSMB, was chosen by the investigators and has served on DSMBs before. She will facilitate and summarise discussions.
The responsibilities of the DSMB statistician	Dr Patrick Phillips is the DSMB statistician with special expertise in adaptive trial design and provide independent statistical expertise.
The responsibilities of the trial statistician	The trial statistician, Mr. Augustine Choko will produce the report to the DSMB with oversight provided by Dr Katherine Fielding and Prof Nigel Stallard all of whom will participate in DSMB meetings. Mr Choko will guide the DSMB through the report and will take notes.
5. Relationships	
Relationships with Principal Investigators	The DSMB will interact directly with the Investigators through Mr Choko (the Principal Investigator).
Clarification of whether the DSMB are advisory (make	The DSMB will play an advisory role in this trial and the investigators will make the final decisions based on the recommendations of the

recommendations) or executive (make decisions)	DSMB. Recommendations of the DSMB will be communicated in written format to the Investigators through Dr Katherine Fielding.
Payments to DSMB members	There will be no payments to the DSMB members other than costs related to logistics of attending the Teleconference meetings, if any.
The need for DSMB members to disclose information about any competing interests	All DSB members will be required to disclose any Competing interests (Annex 1).
6. Organisation of DMC meetings	
Expected frequency of DSMB meetings	The trial is expected to complete recruitment and follow-up within a 10 months. Two DSMB meetings are planed; i) to review the trial protocol ii) at 4-5 months to review the data.
Whether meetings will be face-to-face or by teleconference	All meetings will be by teleconference.

How DMC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session	A mixture of open and closed sessions will be organised as follows:- 1. Open session: Introduction and any "open" parts of the report attended by Trial Investigators available. 2. Closed session: DSMB discussion of "closed" parts of the report with Dr Katherine Fielding representing all the Investigators and, if necessary, 3. Open session: Discussion with other attendees on any matters arising from the previous session(s). 4. Closed session: extra closed session
7. Trial documentation and procedures to ensure confidentiality and proper communication	
Intended content of material to be available in open sessions	Open sessions: Accumulating information relating to recruitment, number of women experiencing intimate partner violence and total numbers of events for the primary outcome measure and other outcome measures may be presented, at the discretion of the DSMB.
Intended content of material to be available in closed sessions	Closed sessions: In addition to all the material available in the open session, the closed session material will include efficacy and safety data by trial arm.
Will the DSMB be blinded to the treatment allocation	The DSMB will not be blinded.
Who will see the accumulating data and interim analysis	The following Investigators will see the accumulating data and interim analysis: 1. Mr Augustine Choko (Principal Investigator) 2. Dr Katherine Fielding 3. Prof Liz Corbett 4. Prof Nigel Stallard

	DSMB members do **not** have the right to share confidential information with anyone outside the DMC, including the PI.
Who will be responsible for identifying and circulating external evidence (eg from other trials/ systematic reviews)	The Trial Investigators will be responsible for identifying and circulating external evidence (eg from other trials/ systematic reviews).

To whom the DSMB will communicate the decisions/ recommendations that are reached	The DSMB will report its recommendations in writing to the Principal Investigator (Mr Augustine Choko), copied to Dr Katherine Fielding.
Whether reports to the DSMB be available before the meeting or only at/during the meeting	The DSMB report will be made available to the DSMB members via e-mail at least 2 weeks before any meetings.
What will happen to the confidential papers after the meeting	The DSMB members should store the papers safely after each meeting so they may check the next report against them. After the trial is reported, the DSMB members should destroy all interim reports.
8. Decision making	
What decisions/recommendations will be open to the DSMB	Possible recommendations could include:- • No action needed, trial continues as planned • Early stopping due to futility, harm (intimate partner violence), or external evidence • Stopping recruitment within a subgroup • Extending recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences) or extending follow-up • Stopping a single arm of a multi-arm trial • Sanctioning and/or proposing protocol changes
The role of formal statistical methods, specifically which methods will be used and whether they will be used as guidelines or rules	We assume that the two trial stages are independent. Total number of clinic days per arm will be provided along with summary statistics and proportions for continuous and categorical baseline variables as appropriate. Total number of male partners linking into care or prevention, and the total number of women reporting intimate partner violence will be computed overall (for the open session) and per arm (for the closed session). Following the intention-to-treat principal, the proportion of male partners linking into care per clinic day per arm will be computed. A cluster-level summary approach to analysis will be followed considering the mall number of clusters per arm for the trial. Proportion estimates from each arm will form a sample from which a mean proportion (standard deviation) will be computed followed by a comparison for each intervention arm and the standard of care (SOC) arm using the unpaired t-test. A log transformation of the clinic day proportions will be applied if a positive skew is observed. Analysis will take into account the clustered design with the Dunnett test used to control for multiple comparisons. **As a rule, any intervention arm whose p-value <0.2 will be dropped** from the trial at interim analysis. Randomisation for the second stage will be to those arms that remain in the trial after interim analysis. Thus, the final analysis will use the Weighted Inverse Normal combination method to combine p-values for the two stages of the trial. **As a rule, any intervention arm whose p-value <0.1** in the second stage will not be recommended for a potential Phase III trial.

How decisions or recommendations will be reached within the DSMB	The decision to recommend that an intervention arm be dropped will be reached by:- • Examining the evidence (p-value and confidence intervals) for each intervention compared to the SOC. • Examining the data relating to IPV, specifically focussing on the number of events in the SOC and the rest of the intervention arms; and the SOC and the each intervention arm separately. This examination may reveal two patterns i) suggesting that delivering HIV self-test kits to male partners puts women at high risk of IPV or ii) the use of financial incentives as interventions precipitates IPV in this population. • Considering the points above, an intervention arm deemed less efficacious and also with increased IPV compared to SOC will be recommended to be dropped right away. The DSMB will deliberate and vote for or against dropping an intervention arm which is more efficacious but also has increased IPV compared to the control. • The Chair will summarise discussions and encourage consensus and will break the tie during voting. Details of the voting will not be part of the DSMB meeting to avoid conveying information about the state of the trial data.
When the DSMB is quorate for decision-making	All three members of the DSMB must be present to form a quorum.

9. Reporting	
To whom will the DMC report their recommendations/decisions, and in what form	The DSMB will write a formal letter (Annex 2) to Mr Augustine Choko (Principal Investigator) following the DSMB meeting at interim analysis within 3 weeks after the meeting copied to Dr Katherine Fielding.
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	Mr Augustine Choko will take minutes for the open sessions and will file these accordingly. The Chair will appoint a member to take minutes for the closed session and she will sign off any minutes or notes.
What will be done if there is disagreement between the DSMB and the Investigators	In case of disagreement between the DSMB and the trial Investigators a further committee comprising some senior Investigators (Dr Katherine Fielding, Prof Liz Corbett and Prof Nigel Stallard) and an independent external expert may be convened to adjudicate. If the DSMB has serious problems or concerns with the Investigators' decision a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DSMB's concerns. Depending on the reason for the disagreement confidential data will be revealed to all those attending such a meeting. The meeting will be chaired by the external expert.
10. After the trial	
Publication of results	At the end of the trial there may be a meeting to allow the DSMB to discuss the final data with principal trial investigators and give advice about data interpretation
The information about the DSMB that will be included in published trial reports	DSMB members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DSMB meetings will be included in the body of the paper.

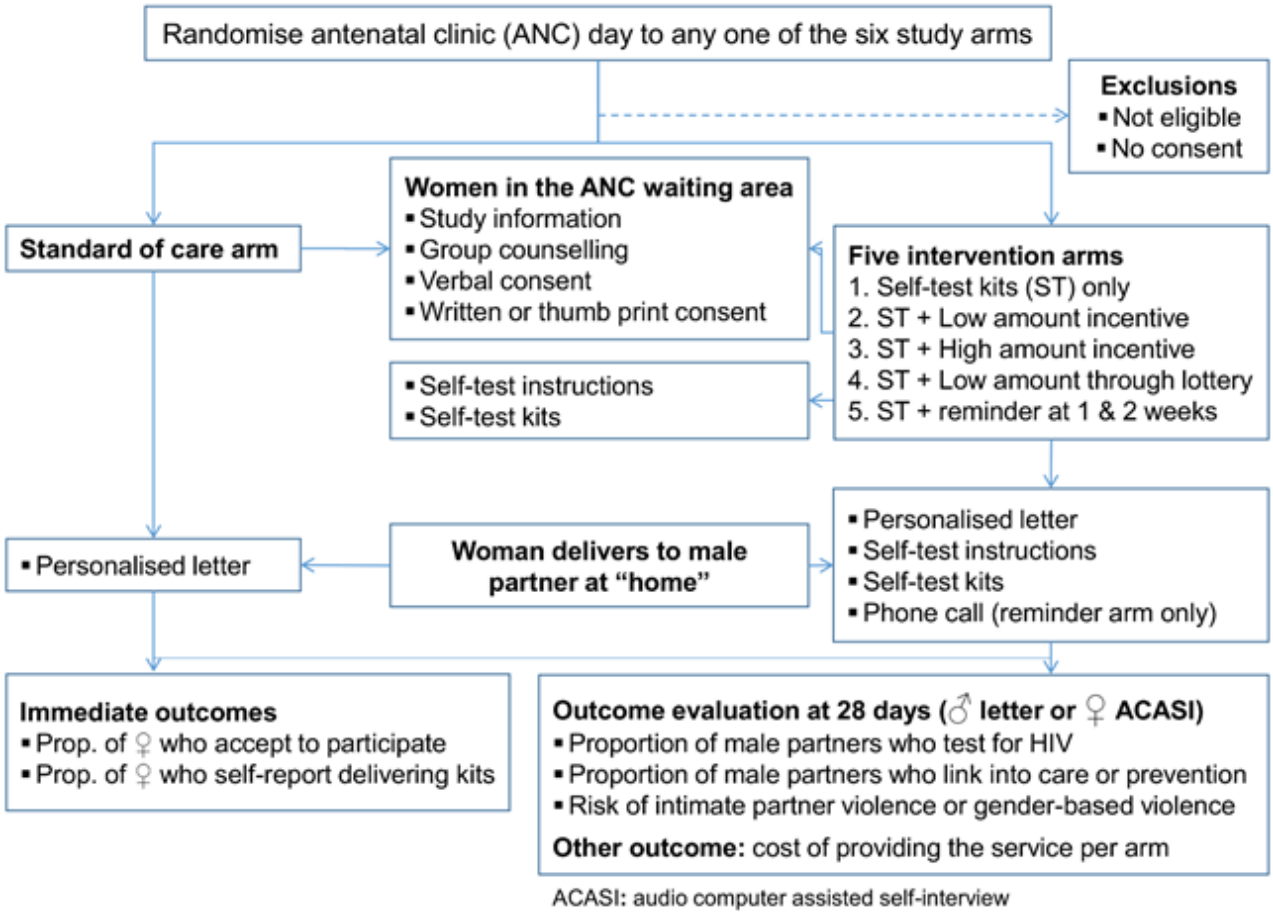
Figures and appendices

Figure summarising trial

Annex 1: Competing interest form

Annex 2: Suggested letter from DSMB to Trial Investigators

Figure 2: Randomisation, recruitment, follow-up and outcome evaluation



ACASI: audio computer assisted self-interview

Annex 1: Suggested competing interests form

Potential competing interests of Data Safety Monitoring Board members for *PASTAL*

The avoidance of any perception that members of a DSMB may be biased in some fashion is important for the credibility of the decisions made by the DMC and for the integrity of the trial.

Possible competing interest should be disclosed by informing the trial investigators. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) DSMB member should remove the conflict or stop participating in the DSMB. Table 1 lists potential competing interests.

Table 1: Potential competing interests

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the sponsor
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict eg strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) in competing products
- Involvement in the publication

Please complete the following section and return to the trials office.

☐ **No,** I have no competing interests to declare

☐ **Yes,** I have competing interests to declare (please detail below)

Please provide details of any competing interests:

_____

_____

Name: _____

Signed: _____ Date: _____

Annex 2: Suggested report from DSMB to the Trial Investigators where no recommendations are being made

[Insert date]

To: Chair of Trial Steering Committee

Dear [Investigators' representative]

The Data Safety Monitoring Board (DSMB) for the PASTAL trial met on [meeting date] to review its progress and interim accumulating data. [List members] attended the meeting and reviewed the report.

We congratulate the trial organisers and collaborators on the progress and conduct of the trial and the presentation of the data. The trial question remains important and, on the basis of the data reviewed at this stage, we recommend continuation of the trial according to the current version of the protocol [specify protocol version number and date] with no changes.

We shall next review the progress and data [provide approximate timing]

Yours sincerely,

[Name of meeting Chair]
Chair of Data Safety Monitoring Board

On behalf of the DSMB (all members listed below)

DSMB members:
(1) [Insert name and role]
(2) [Insert name and role]
(3) [Insert name and role]

8.8 Data safety monitoring board report and data management plan

Appendix 8.8-1: Data safety monitoring board report
This report includes the key decisions made by the independent data safety monitoring board for the PASTAL trial at the end of stage 1 (pre-planned interim analysis).

PASTAL Trial 2nd Data Monitoring and Safety Board (DSMB) Meeting minutes & recommendations January 13, 2017

Attendees

Present: **Investigators:** Mr Augustine Choko, Prof Liz Corbett and Prof Katherine Fielding

DSMB Members: Prof Frances Cowan (DSMB Chair) and Prof Victor Mwapasa

Apologies: Dr Patrick Phillips (DSMB member)

Agenda

Old agenda points

1. None

New Business

1. Presentation of trial interim data by the investigators
2. Questions for the DSMB members
3. Recommendations regarding trial arms to drop/maintain
4. AOB

Old agenda points

1. None

New agenda points

1. **Presentation of trial interim data by the investigators**
   a) Investigators presented the key interim data (Recruitment, primary outcome, and adverse events data) to the DSMB members led by Augustine (PI).
      - It was noted that the trial had achieved the intended sample size with high participation across all the six arms. There was no concern from the DSMB members with regards recruitment or sample size attained.
      - DSMB members noted that there was need to focus on part b of the primary outcome (proportion of male partners who started ART or were HIV negative and referred for circumcision). This was emphasised after noting differences between the primary outcome (% of male partners who linked to male friendly services) and % of men requiring ART or VMMC referral who linked to male friendly service in the self-testing intervention arm where incentives were not offered (illustrated in Report tables 3 and

4). It was suggested that investigators consider this difference and the importance of the linkage outcome for necessary referral as opposed to the primary outcome of linkage to the male friendly clinic only (regardless of whether this was necessary or appropriate).

- There were no particular concerns around adverse events given reasonable retention and only three events were reported.

b) Questions for the DSMB members

There was a discussion regarding the need to maintain a standard of care (SoC) arm in phase two as effectiveness in that arm was much lower than anticipated during the first phase. DSMB members felt that despite low linkage in the SoC arm, that arm should be maintained in phase two (both because there had been no prior plan to drop the SoC arm in phase two and because it may be difficult to convince policy makers of the relevance of self-testing +/- incentive approach if only 6 clinic days of SoC were included in the trial overall).

c) **Recommendations regarding trial arms to drop/maintain**

i) *Drop the lottery arm:* low effectiveness on both the primary outcome and part b of the primary outcome

ii) *Maintain the self-test only arm:* more events needed to have high precision

2. **AOB**

a) The investigators will attempt to have another meeting with Dr Patrick Phillips to present the report and also to discuss additional design elements to consider for the second stage of the trial.

b) The investigators will consider submitting an abstract of the data to the International AIDS Society Meeting in Paris (July 2017). The submitted abstract will be shared with the DSMB members.

Next Meeting: NA

Signed: 

Prof Frances Cowan (on behalf of the DSMB Members)

Date: 12 May 2017

Data Management Plan
for Research Projects

Project Name	PASTAL: Partner-provided self-testing and linkage
Funder	Wellcome Trust, UK
Project End Date	December 2018
Principal Investigator	Mr. Augustine T. Choko
Contact e-mail	Augustine.Choko@lshtm.ac.uk

Support

Information on writing a Data Management Plan can be found at
http://www.lshtm.ac.uk/research/researchdataman/plan/

One-to-one advice is available through the RDM Support Service
researchdatamanagement@lshtm.ac.uk

DATA DESCRIPTION

1) What data will you collect or create?

Describe the data that you are collecting or creating in your project. Relevant information to provide includes:

- The type of information that will be contained. E.g. MRI scans, interview transcripts, spatial data, etc.
- Methods of capture. E.g. face-to-face interview, web survey, etc.
- Amount of data. E.g. 100 patients will undergo an MRI scan, 500 people will be interviewed.

- Face-to-face interviews with structured paper-based questionnaires with 1,600 participants at baseline and at 4 weeks follow-up
- Audio computer assisted self-interviews (ACASI) using tablets with 1,600 participants at 4 weeks follow-up
- Data will include numerically coded values and an audio-captured field from ACASI

2) Briefly describe the key activities that will be performed on your data, from its creation/capture to its eventual archiving or deletion.

Consider the lifecycle of your research data and the actions that will be performed during that time. For example, data may be captured using a web form, anonymised to remove personal information using software X, cleaned using Tool Y to enable it to be analysed, analysed using software Z, and so on. The lifecycle may be written as text or pictorial form (e.g. a gantt chart).

In addition, it's useful to consider the approximate time period when you will perform each action (e.g. data capture in month 2, data cleansing in month 4, etc.).

- The data captured using paper-based questionnaires will be transported at the end of everyday using project vehicles to Malawi Liverpool Wellcome Trust Clinical Research Programme (MLW) data office for subsequent processing including immediate quality check, scanning, verifying and committing into a MS Access database.
- Tablets running Open Data Kit (ODK) will be used to administer the audio computer assisted self-interview (ACASI) questionnaire. The data on the tablets will be sent to a server AT MLW running MySQL via a secure mobile network with direct download onto the server as a back-up strategy.

3) What data formats or standards will you use to store data produced by your project?

Outline the data formats, encoding standards, or software tools that you will use to create, analyse, or use data. E.g. data will be captured using a MySQL database and analysed using STATA and MS Access.

- Paper-based questionnaires will be scanned using Teleform Optic Mark Reading (OMR) software into an electronic database in MS Access (.mdb). Thereafter, the data will be exported into comma separated values (.csv) for importation into Stata for cleaning and immediate descriptive analysis.
- Data captured using audio computer assisted self-interview (ACASI) will be deposited into a server running MySQL on a daily basis during the study. Thereafter, the data will be exported into comma separated values (.csv) for importation into Stata for cleaning and immediate descriptive analysis.
- The cleaned dataset will be saved in .csv format and will be imported into R software for final analysis.

4) What quality controls and thresholds will you establish to ensure that your data is fit for purpose?

Quality controls may be applied prior, during and following data capture and processing. Possible QC practices include: testing instrumentation to ensure it is correctly calibrated, recording multiple measures, double-entry of information, checking validity of entered values

- All the tools to be used in this trial will be tested in a pilot involving participants from an antenatal clinic that will not be used as a recruitment site.
- All paper-based questionnaires will be checked by a field supervisor at the recruitment site for obvious omissions or errors.
- The completed questionnaires will also be checked before scanning into the Teleform system and during data verification to ensure that correct values are recorded and committed into the study database.
- The participant identifier will be set to be a non-empty field at the design of the questionnaires.
- Inbuilt quality control will be implemented for the data collected using tablets. Skip patterns, range checks and consistency checks will be programmed in open data kit (ODK) to ensure quality data are collected.

5) What documentation or metadata is needed to understand your data?

Describe the documentation or metadata that you will create to enable the data to be understood and used by your future self and others. It is helpful to consider the following questions:

- What information is needed to understand the content and context of its creation?
- What documentation and metadata standards will be used?
- How will potential users find out about your data?

- Each dataset, variable and values will be labelled with separate additional documentation in a data dictionary to be held in MS Word.
- The data will be made publicly available by publication on the Loondon School of Hygiene & Tropical Medicine Data Campus (http://datacompass.lshtm.ac.uk/).

DATA STORAGE AND MANAGEMENT

1) Where will you store data during the project lifetime? (tick one or more)

School PC local drive (drive C: or D:)		**Personal area on School network (drive H:) Yes**		LSHTM Shared Network drive (e.g. I: drive)		**Dedicated server maintained at partner institution Yes**	
LSHTM-based project server		**School laptop or tablet (Yes)**		LSHTM Secure Data Server (for confidential data)		LSHTM Novell Filr	
For-cost cloud service (e.g. Amazon S3)		Free cloud service (e.g. Dropbox, Google Docs)		Portable storage (e.g.USB disk or memory stick)		Other. Please indicate	

Other

2) How will you organise and label your data?

Describe the approach you will take to structure and label your data. E.g. files and folders on a storage device, database tables and labels.

A password-protected folder containing the study database and datasets will be created on the H Drive on the school's network with a similar copy kept on a personal school laptop and on a server at MLW in Malawi.

3) What security measures, if any, will you apply to protect data? (tick one or more)

Controlled access limited to authorized users only (Yes)		**Physical security**		**Remove identifiable information (e.g. anonymisation)**	
Data storage encryption (7 zip)		**Data transfer encryption**		**Password protection**	
Process on isolated machine in secure room		Secure deletion following analysis			
Avoid use of third party storage, such as Dropbox		Other			

Other

DATA ARCHIVING AND SHARING

1) What data do you need to keep after your project ends and for how long?

The paper-based questionnaires will be kept for a minimum of 10 years before being destroyed.

2) Where will data be kept after your project has finished (tick one or more)

Research data may be submitted to a data repository or data archive, which will handle the process of curation, preservation and sharing on your behalf.

I will keep the data myself		My supervisor will look after the data		It will be looked after by the project team	
Held in the LSHTM Research Data Repository		Held in a LSHTM-maintained project system		Held in a 3rd party data repository. Please specify in Other field	

Other

The data will be kept within the MLW archiving system in Blantyre, Malawi.

3) Can data be made available to anyone? If not state the reason it needs to be restricted and criteria for gaining access.

Can data be made freely available to anyone or do restrictions need to be applied? This question will help you to consider whether access controls need to be applied to limit data access. Potential reasons for restriction include the need to comply with consent agreements, which state:

- Data can only be used by specific users, e.g. researchers working in an academic environment, a specific skill set, etc.
- Data can be analysed only for specific purposes compatible with the consent agreement.

If data does need to be restricted, state the reason and the criteria that users would need to meet to gain access

Yes, the data will be made freely available conformant with the funder requirements (Wellcome Trust, UK).

4) What actions will be performed to prepare your data for access? (tick one or more)

Removal of personal information (Yes)		Add synthetic data (e.g. pseudonyms)		Copyright clearance	
Establish participant consent (Yes)		Develop an access agreement			

Other

RESOURCING

1) What do you consider to be the primary data management challenges in your project?

What problems or issues do you need to address in your project.

Potential for network failure which may affect daily data transfer from tablets to the server at MLW. However, the field supervisor will ensure that all failed data transfers are done manually by connecting the tablets to the server at MLW.

2) What resources would it be helpful for the School to provide to help deliver your plan?

How can the School help you to manage your data? E.g. training, specific IT Services, etc.

Storage space for large datasets as currently only have 500MB allocated on the H Drive.

8.9 Overview of dissemination activities

Date (s)	Description of dissemination activity
November 2016	The 21th International AIDS Conference in Durban, South Africa (abstract number TUPED429)
10th July 2017	Invited meeting with His Royal Highness Prince Harry of Wales at London School of Hygiene & Tropical Medicine, United Kingdom. Briefing on the impact of HIV self-testing on the uptake of HIV testing linkage for men and the youth
23-26 July 2017	19th International AIDS Society Conference on HIV Science Paris, France. Invited speaker at the Self-Testing Africa non-commercial satellite.
August 2017	PhD project work highlighted in UNAIDS Science now, HIV THIS MONTH for August 2017.
November 2017	Malawi Ministry of health policy brief and wide scale implementation of project results. See policy brief below highlighting the trial results in antenatal clinic oral self-test kits distribution model targeting male partners.
November 2017	Case study selected for oral presentation at the Wellcome Trust-Bill and Melinda Gates Foundation funded Global Forum on Bioethics Research meeting: Bangkok, Thailand.