WITHOUT DIRECTLY OBSERVED SEX, WHAT'S A MICROBICIDE TRIALIST TO DO?

ADHERENCE AND ADHERENCE MEASUREMENT AS A CLINICAL TRIAL DESIGN ISSUE IN VAGINAL MICROBICIDE TRIALS FOR HIV PREVENTION

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Thesis submitted in accordance with the requirements for the degree of
Doctor of Philosophy
University of London
2016

FINANCIAL OR IN-KIND SUPPORT FOR THIS PHD RESEARCH WAS PROVIDED BY:

Economic and Social Research Council
Tropical Epidemiology Group, LSHTM
HIV Prevention Unit's Capacity Development Programme of the South African Medical Research Council
Mwanza Intervention Trials Unit
Tongaat Child Welfare
Anonymous donors
Self-funding

ABSTRACT

Background

This research examined past microbicide effectiveness trials to better understand how adherence and adherence assessment could be improved in future vaginal microbicide trial design. No product is currently available despite decades of clinical trials of candidate microbicides, yet the need for women to have a method to reduce their risk of sexual transmission of HIV that does not rely on male partner agreement remains urgent. Low product adherence and inaccurate adherence reporting has inhibited the ability of trials to accurately assess the biological efficacy of candidate products.

Methods

Three different studies were conducted to examine adherence as a clinical trial design issue. The comparative study examined how five trials measured, calculated, and reported microbicide adherence. The quantitative study used latent class and latent profile analysis and multinomial logistic regression to examine if patterns of adherence could be identified in four trials and, if so, what individual-level factors were associated with the patterns. The qualitative study sought opinions from former trial participants about how to improve adherence and adherence reporting in future microbicide trials through focus group discussion workshops in South Africa and Tanzania.

Results

There was diversity in methods used to collect and calculate adherence among the included trials. Two methods to calculate averages of overall adherence were identified. Trial documentation and publications lacked clarity in exact methods used to calculate adherence estimates.

Latent structure analysis identified different patterns of adherence in all included trials, and these patterns were similar. Multinomial logistic regression identified factors associated with adherence patterns in all trials.

Women join and stay in microbicide trials for their own needs, which are not necessarily related to interest in using the investigational product. Key reasons for joining and staying in trials included access to health care and financial reimbursements. Fear of adverse

effects from the investigational product was the most important reason why participants did not use the gel. Participants reported that male partners can act as barriers to gel use and the key reason for inaccurate reporting of gel use was fear of removal from the trial. This study demonstrated that trial teams and participants can work together to develop improved trial designs.

Recommendations

There are improvements to be made in how trialists plan, conduct, analyse and report results of microbicide trials. Trial teams can improve the clarity of their trial materials, and use analysis methods to identify patterns of adherence. To improve adherence and trial implementation, trials can test applicators for evidence of vaginal insertion and report results to participants, better engage male partners, develop a less watery gel, and create an atmosphere of transparency and respect between research teams and participants.

Identifying HIV prevention products for women requires better understanding of the lives of women asked to join these trials, and application of that understanding to collaboratively develop innovative trial designs that meet both the needs of the research and the needs of participants.

ACKNOWLEDGEMENTS

First I would like to acknowledge my supervisor, Richard Hayes. Thank you for your thoughtful input, sense of perspective, and support over these years. Thanks to James Carpenter and Tim Clayton for your assistance with securing ESRC funding, and for your support at the start of this PhD journey.

A big thanks to Sheena McCormack, Mitzy Gafos, and Angela Crook for your support whenever I needed it. Thanks to Salim Abdool Karim, Quarraisha Adbdool Karim, and Leila Mansoor. Thanks to Barbra Richardson and Cliff Kelly. Thanks to Barbara Friedland and Marlena Plagianos. Thanks to Gustavo Doncel, Lut van Damme, Doug Taylor, and Vera Halpern. Thanks to the investigators, trial teams, and participants of HPTN 035, MDP 301, Carragard, the CS CONRAD, CAPRISA 004, and VOICE. A special thanks to Kathy Baisley for orienting me to the world of data management, for our discussions about LCA, for always thoughtfully and thoroughly answering my questions, and for your careful review of my LCA chapter.

Thank you to the participants in South Africa and Tanzania who were willing to join my study. Thank you for opening your minds and hearts, for giving candid feedback, and for sharing the realities of your lives with me. Thanks to Shelley Lees for your support and feedback. Thanks to Caroline Turley for your detailed comments on my FGDW guide. To Gita Ramjee, Renee Street, and Neetha Morar: I am filled with gratitude. Each of you went above and beyond to help me, and I feel lucky to have worked closely with you. Thanks to Dhevium Govender and Nonwakazi Mnquonywa. Thanks too to the administrative team at the MRC HIV Prevention Unit in Durban and the clinic team in Tongaat, whose sense of professionalism sets the standard for the rest of the world. Thanks to Nozipho Vilakazi, Funeka Mthembu, Sizah Sukazi, Duduzile Dlamini, Sicelo Mthimkhulu, Winnie Hlophe, and Fanele Ntombela. To Saidi Kapiga: Thank you for your thoughts, support, and inspiration. Thank you to the warm and welcoming team at MITU, who cared for me and helped me. To Veronica Celestine: Thank you for your diligent work. Thanks to Happiness Ng'habi and Stanslaus Shitindi. Thanks to John Changarucha, Thabitha Daudi, Gaga Lupande, and the administrative team.

Thanks to Jenny Fleming, always a voice of reason. Thank you to Anne Schoeneborn for assisting with some of my tables, and to Kay Robin Alexander for proofreading this thesis.

I am grateful to my friends and family. Infinite thanks to David, for genuinely supporting me through this entire process and being available to help whenever I needed it. Thanks to my teachers at Parker and Grinnell, who are with me every day. Thanks to my friends around the globe who have encouraged me and provided love and support. To my beloved PhD mates: you are the greatest gift this PhD has given me. Thanks to my parents, for everything you have taught me. And especially to my mother, a rock star, without whom this PhD journey would not have been possible.

Image Credits

- Title page photo: Microbicide Trials Network, University of Pittsburgh and Magee-Womens Research Institute.
- Chapter 5, image of Carraguard applicators: Wallace, A., Thorn, M., Maguire, R. A., Sudol, K. M. Phillips, D. M. Assay for Establishing Whether Microbicide Applicators Have Been Exposed to the Vagina. Sex. Transm. Dis. 31, 465–468 (2004).
- Chapter 5, diagrams of microbicide trials: images adapted from the VOICE informed-consent booklet.

DECLARATION

I, Lori Miller, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

ACRONYMS

ABIC Sample-size adjusted Bayesian information criterion

ACASI Audio computer-assisted self-interview

AIC Akaike information criterion

AOR Adjusted odds ratio

ARV Antiretroviral

ASPIRE A Study to Prevent Infection with a Ring for Extended Use

AVAC Global Advocacy for HIV Prevention

BAT24 Before-after-two-24; gel-use regimen for CAPRISA 004

BIC Bayesian information criterion

CAB Community advisory board

CAG Community advisory group

CAPRISA Centre for the AIDS Programme of Research in South Africa

CI Confidence interval

COL-1492 Nonoxynol-9 vaginal gel; also the name of the multi-country trial

CONRAD Formerly: Contraceptive Research and Development Program

CRFs Case report forms

CS Cellulose sulphate

CVL Cervical vaginal lavage

DNA Deoxyribonucleic acid

DSA Dye stain assay

DSMB Data and safety monitoring board

EM Expectation-maximisation

ESRC Economic and Social Research Council

FACTS Follow-on African Consortium for Tenofovir Studies

FEM-PrEP Preexposure Prophylaxis Trial for HIV Prevention among African Women

FGD Focus group discussion

FGDW Focus group discussion workshop

FHI Formerly: Family Health International

FIML Full information maximum likelihood

FTC Emtricitabine

FTFI Face-to-face interview

GCP Good clinical practice

GPP Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials

HIV Human immunodeficiency virus

HPTN HIV Prevention Trials Network

HR Hazard ratio

IC Informed consent

IDI In-depth interview

IPM International Partnership for Microbicides

iPrEx Pre-exposure Prophylaxis Initiative (iPrEx) trial

IPV Intimate partner violence

LCA Latent class analysis

LPA Latent profile analysis

LRT Likelihood ratio test

LSHTM London School of Hygiene and Tropical Medicine

MAR Missing at random

MDP Microbicides Development Programme

MIRA Methods for Improving Reproductive Health in Africa trial

MITU Mwanza Intervention Trials Unit

MRC Medical Research Council

MTN Microbicide Trials Network

N-9 Nonoxynol-9

OR Odds ratio

pH Potential of hydrogen

PhD Doctor of Philosophy

PK Pharmacokinetic

PrEP Pre-exposure prophylaxis

PSA Prostate-specific antigen

RA Research assistant

RR Relative risk

RRR Relative risk ratio

RSID-Semen Rapid Stain Identification of Human Semen

SA South Africa

SAP Statistical analysis plan

SOP Standard operating procedures

STI Sexually transmitted infection

TDF Tenofovir disoproxil fumarate

TVF Tenofovir gel

TZ Tanzania

UK United Kingdom

UNAIDS Joint United Nations Programme on HIV/AIDS

US United States of America

UTC University of Cape Town

UTI Urinary tract infection

UVL Ultraviolet light

VIREA Visual inspection of returned empty applicators

VOICE Vaginal and Oral Interventions to Control the Epidemic

WHO World Health Organization

ZAR South African Rand

THIS WORK IS DEDICATED TO MY MOTHER

I am woman, hear me roar
In numbers too big to ignore
And I know too much to go back and pretend
Cause I've heard it all before
And I've been down there on the floor
No one's ever going to keep me down again
Oh, yes, I am wise
But it's wisdom born of pain
Yes, I've paid the price
But look how much I gained
If I have to I can do anything
I am strong
I am invincible
I am woman
You can bend but never break me
Cause it only serves to make me
More determined to achieve my final goal
And I'll come back even stronger
Not a novice any longer
Cause you've deepened the conviction in my soul
Oh, yes, I am wise
But it's wisdom born of pain
Yes, I've paid the price
But look how much I gained
If I have to I can do anything
I am strong
I am invincible
I am woman
I am woman, watch me grow
See me standing toe-to-toe
As I spread my loving arms across the land
But I'm still an embryo
With a long, long way to go
Until I make my brother understand
Oh, yes, I am wise
But it's wisdom born of pain
Yes, I've paid the price
But look how much I gained
If I have to I can face anything
I am strong
I am invincible
I am woman

*Helen Reddy, 1971

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INTRODUCTION

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INTRODUCTION

1.1 INTRODUCTION

In many places and relationships worldwide, women may not have control over how and when they have sex. Use of condoms, which prevent sexual transmission of HIV, requires the knowledge and agreement of male sexual partners. HIV continues to be a global problem, with young women aged 15–24 years, in particular, at high risk for HIV infection. Young women represent 11% of the population globally but accounted for 20% of new HIV infections in 2015.[1] Efforts to reduce sexual transmission of HIV based on abstinence, faithfulness, and correct and consistent use of condoms do not take into account the fact that individuals' risk may depend not only on their own behaviours but also on the behaviours of their sexual partners, of which they may have no knowledge or control. Such individual behaviour-based prevention messaging does not take into account gender dynamics in intimate relationships, structural factors which may put women at risk of HIV, and inequalities in how sexes are treated in societies.[2,3,4,5,6]

The concept of vaginal microbicides resulted from the need for women to have a method to reduce their risk of sexual transmission of HIV that they can control themselves and does not rely on male partner agreement.[7] The concept of a vaginal microbicide called for a topically applied product which could be developed in different formulations such as a gel, film, ring, or suppository. Preferably, the product would reduce a woman's risk of HIV acquisition as well as other sexually transmitted infections and would be available in contraceptive and non-contraceptive forms. To have the broadest impact, microbicides would be available without prescription and could be used without the need for clinical monitoring.

The field of vaginal microbicide research was born in the 1990s, when candidate products began to be tested in clinical trials in populations at risk of HIV infection. However, designing, conducting, and analysing results of clinical trials for vaginal microbicides is challenging for a complex set of reasons.[8,9,10,11,12,13,14] After 26 years of clinical trials, a mi-

crobicide product is still not available on the market.

A central challenge of microbicide trials, unlike many clinical trials that test investigational drugs, is that the end result of a late-stage microbicide trial does not give an estimate of product efficacy, or biological effect of the product. Microbicides are user-controlled products: they are used around the time of sex or inserted vaginally at specific times, during the normal lives of clinical trial participants, rather than in a controlled setting such as a research clinic. Therefore, the final result of a microbicide trial is influenced by a combination of factors. These include the biological effects of the product, participants' adherence, and other factors which may inhibit a trial's ability to detect an efficacious product; for example, anal sex, lubrication effect of the placebo gel, and time off product due to pregnancy.[11,15,16,17] In addition, rather than an estimate of efficacy, late-stage clinical trials of vaginal microbicides give an estimate of the effectiveness of the study product. Further complicating the situation are the absence of a gold standard or consistently reliable way in clinical trials to measure adherence to using microbicides or exposure to HIV. Historically, microbicide trials have largely relied on participants reporting their own sexual behaviour and microbicide use; both areas are known to be subject to recall bias and social desirability bias.[18,19]

Microbicide trials are conducted to test whether a candidate microbicide is effective at reducing HIV transmission and whether it is safe for human use. If research teams are not sure to what extent trial participants have used the candidate product, then it is difficult to interpret the results of microbicide trials. A trial result that does not indicate a beneficial effect of the product could be due to the fact that the product is actually biologically ineffective at reducing HIV transmission, or it could be due to the fact that trial participants did not use the product enough for protective properties to be detected. Conversely, it is possible that a candidate product could increase the risk of HIV if used correctly. Yet this effect would not be observed if product use by trial participants is low. Similarly, if results of a microbicide trial show an equal number of adverse events in the experimental and placebo arms, one explanation could be that the product is safe for human use. An alternative explanation could be that participants did not use the product enough for adverse events to be observed at an adequate level for detection.

In 2012, at the start of this PhD research, 12 vaginal microbicide effectiveness trials had been conducted,[20,21,22,23,24,25,26,27,28,29,30,31] with only one trial, CAPRISA 004,[31] a phase IIb study of 1% tenofovir gel, showing an effect of reducing HIV transmission (Table 1.1.1). Due to the large size and cost of microbicide trials, once a phase III trial is completed and

an investigational product is not found to be effective, it is typically discarded from the product development pipeline, even if there is lack of confirmation that it is biologically non-efficacious. This is a disadvantage to women worldwide who would benefit from a product they could use to reduce their chance of becoming infected with HIV. In the biomedical HIV prevention field, there has been great concern that low adherence may have been the cause of some of the null findings in the effectiveness trials. Thus, this significant challenge of adherence in microbicide trials has emerged as a key topic in the microbicides field.

Reference	Product	Trial/Sponsor	Key results HIV vs. Placebo [95% confidence interval]	Locations	Participants contributing to key results	Years conducted
			First generation			
Kreiss, 1992	N-9 Sponge, 1000mg vs. placebo suppository	FHI	Hazard ratio HIV 1.7 [0.9–3.0], [Genital ulcer relative risk 3.3 p<.001]	Kenya	116	January 1987–June 1990
Roddy, 1998	N-9 Film, 70 mg	FHI	Rate ratio 1.0 [0.7–1.5]	Cameroon	1170	March 1994–December 1996
Richardson, 2000	N-9Gel, 52.5 mg	FHI	Relative risk 0.7 [0.3–1.5]	Kenya	278	July 1996–February 1998
Van Damme, 2002	N-9 Gel, 52.5 mg	COL-1492 UNAIDS	Hazard ratio 1.5 [1.0–2.2] For women using >3.5 applicators per day: HR 1.8 [1.0–3.2]	Benin, Cote d'Ivoire, South Africa, Thailand	765	September 1996–June 2000
Peterson, 2007	C31G, SAVVY Gel	Savvy Ghana FHI	Hazard ratio 0.9 [0.3–2.3]	Ghana	2038	March 2004–February 2006
Feldblum, 2008	C31G, SAVVY Gel	Savvy Nigeria FHI	Hazard ratio 1.7 [0.9–3.5]	Nigeria	2082	September 2004–August 2006
			Second generation			
Van Damme, 2008	Cellulose sulphate	CS CONRAD	Hazard ratio 1.61 [0.86–3.01], final analysis; Interim result at independent data monitoring committee: HR 2.3 [1.05–5.03]	Benin, India, South Africa, Uganda	1398	July 2005–March 2007
Halpern, 2008	Cellulose sulphate	CS FHI	Hazard ratio 0.8 [0.3–1.8]	Nigeria	1506	November 2004–March 2007
Skoler-Karpoff, 2008	Carraguard	Carraguard Population Council	Hazard ratio 0.87 [0.69–1.09]	South Africa	6004	March 2004–March 2007
Abdool Karim, 2011	BufferGel, 0.5 % PRO 2000	HPTN 035	Hazard ratio 1.10 [0.75–1.62] Hazard ratio 0.70 [0.46–1.08]	Malawi, South Africa, Zambia, Zimbabwe, US	3087	February 2005–September 2008
McCormack, 2010	0.5% PRO 2000, 2% PRO 2000	MDP 301	Hazard ratio 1.05 [0.82–1.34]	South Africa, Tanzania, Uganda, Zambia	8859 (6268 for 0.5% + placebo)	October 2005–September 2009 (2% dropped February 2008)
			Third generation			
Abdool Karim, 2010	1% tenofovir gel	CAPRISA 004	Hazard ratio 0.63 [0.42–0.94]	South Africa	889	May 2007–March 2010

Table 1.1.1: Microbicide effectiveness trials through 2012

With the completion of each trial, more experience is gained and that knowledge is shared within the field so future trials can be improved.[8,10,11,32] However, despite concerns around adherence, the study design of microbicide trials has largely remained the same. Improvements in trial design have been incremental and have not looked fundamentally at the design of the trials in the context of the needs of trial participants or in terms of how best to understand and report adherence-related data.

Clinical trials are bound by the realities of science and donor budgets, and must be conducted within the context of research ethics. Healthy individuals volunteer their bodies, their lives, and their time to participate in trials. They are exposed to potential risks of the study product and study participation. In the case of effectiveness or late-stage microbicide trials, tens of millions of dollars, often from taxpayers, are invested in these multicountry, multiyear studies.[33,34] These trials are bound by the ethical obligation of scientific quality. Trials must be designed in a way that maximises, to the best extent possible, the ability to achieve their research objectives. If adherence is known to be an important issue in interpreting results of microbicide trials, then it is an ethical obligation to understand how to facilitate good adherence and more accurate adherence estimation in these trials.[35] There is a scientific and ethical need to fully consider adherence as a critical microbicide trial design issue so that future trials will be better able to answer their research questions and equipped to identify an efficacious vaginal microbicide.[8,13,19,24,25,26,32,36,37,38]

1.2 PURPOSE OF THIS PHD RESEARCH

The GOAL of this PhD research was to critically examine, from different perspectives, experiences of past vaginal microbicide effectiveness trials to better understand how adherence and adherence assessment can be improved in future microbicide trial design. In this context, adherence assessment refers to the measurement of adherence and sexual behaviour, and to the analysis and reporting of those data. The goal of this PhD research was accomplished by conducting three different studies, each with a different objective and methodology, to examine adherence as a clinical trial design issue from a different perspective.

OBJECTIVE ONE of this PhD research was to critically examine how five completed effectiveness microbicide trials measured, calculated, and reported microbicide gel adherence. To accomplish this objective, trial-related materials were systematically reviewed and comparative analysis methods were used to identify how trial teams collected adherence and

sexual behaviour data and how trial teams reported adherence in their primary results manuscripts. Trial materials were also reviewed to identify the specific choices and calculations that trial teams used to characterise adherence.

Objective two of this PhD research was to examine, using self-reported adherence data from four completed effectiveness microbicide trials, if longitudinal patterns of adherence are evident, and if so, what individual level factors are associated with these patterns of adherence. This objective was accomplished using quantitative methods to conduct latent class and latent profile analysis, followed by multinomial logistic regression.

Objective three of this PhD research was to use the expertise of former microbicide trial participants to understand barriers to adherence and accurate adherence reporting, and to seek their opinions about how to improve adherence and adherence reporting in future microbicide trials. Qualitative methods were used to conduct focus group discussion workshops to engage former participants in concepts around microbicide trial design, adherence, and their own experiences of trial participation. Eight focus group discussion workshops were conducted in Tongaat, Durban, South Africa, and Mwanza, Tanzania.

Table 1.2.1 provides a summary of this PhD research by listing each objective as well as corresponding research questions and methods.

The goal of this PhD research was to critically examine, from different perspectives, experiences of past vaginal microbicide effectiveness trials to better understand how adherence and adherence assessment can be improved for future microbicide trial design.		
Objective	**Research questions**	**Methods**
To critically examine how five completed effectiveness microbicide trials measured, calculated, and reported microbicide gel adherence.		**Comparative study**
	A. How are overall adherence estimates reported in primary trial results publications?	• Obtain protocols, CRFs, and statistical analysis plans from trial teams.
	B. What are the different adherence and sexual behaviour adherence measures used to collect source data?	• Review primary results publications and extract overall adherence estimates.
	C. How are adherence and sexual behaviour data used to calculate overall adherence estimates?	• Extract source questions used for adherence and sexual behaviour measurement from CRFs.
		• Analyse overall adherence estimates, statistical analysis plans, and CRFs to determine exact methodology used to calculate adherence measures; summarize findings in diagrams.
		• Conduct survey with trial teams to check results of analysis, clarify specific methods, and provide rationale for measurement and analysis methods used.
To examine, using self-reported adherence data from four completed effectiveness microbicide trials, if longitudinal patterns of adherence are evident and, if so, what individual-level factors are associated with patterns of adherence.		**Quantitative study**
	A. Can longitudinal patterns of adherence be identified in self-reported data in four completed effectiveness trials?	• Review CRFs and protocols from trials to determine appropriate variables to request for quantitative study.
	B. If patterns can be identified, how do patterns of adherence compare across the trials?	• Obtain and manage data sets for analysis.
	C. If patterns are identified, what individual-level factors are associated with the different patterns of adherence, and how do these compare across trials?	• Conduct latent class and latent profile analysis on data from four trials to identify patterns of adherence.
		• Conduct multinomial logistic regression with latent trajectories as outcome using data from four trials.
To use the expertise of former microbicide trial participants to understand barriers to adherence and accurate adherence reporting and seek their opinions about how to improve adherence and adherence reporting in future microbicide trials.		**Qualitative study**
	A. What are the reasons why women join and stay in microbicide trials?	• Develop participatory tools to engage former trial participants in thinking about microbicide trial design, the importance of adherence, and factors affecting adherence and adherence reporting in microbicide trials.
	B. What are former participants' experiences with regard to barriers to product use?	• Obtain required ethical approvals for qualitative study.
	C. What are former participants' experiences with regard to barriers to accurate adherence reporting?	• Recruit former microbicide trial participants in Tongaat, Durban, South Africa; and Mwanza, Tanzania.
	D. What are former participants' feelings and needs?	• Conduct focus group discussions workshops with former microbicide gel trial participants.
	E. What are former participants' perceptions of trial staff and the research?	• Gain former participants' feedback on how to improve adherence and adherence reporting in future microbicide trials.
	F. How would former participants design future microbicide trials with respect to improving adherence and adherence reporting?	

Table 1.2.1: PhD research

1.3 THESIS STRUCTURE

CHAPTER 2 provides background and context to the field of microbicides at the start of this PhD research in 2012. It describes microbicide trial design and its challenges, gives a brief history of effectiveness trials completed through 2010, and provides an overview of the primary methods used to measure adherence and sexual behaviour in those trials.

CHAPTERS 3, 4, AND 5 comprise the research content of the thesis, which was designed in 2012. Each chapter includes one study which corresponds to a particular PhD research objective. Research chapters are written in paper style, meaning that specific study results are contextualised within the format of an introduction, methods, results, and discussion.

CHAPTER 3, "What do we really mean by adherence? A comparative study of measuring, calculating, and reporting adherence in five microbicide effectiveness trials," contextualises and reports results of the comparative study to address the first objective of this PhD research.

CHAPTER 4, "Hidden heterogeneity: Uncovering patterns of adherence in microbicide trials," contextualises and reports results of the quantitative study, using latent class and latent profile analysis and multinomial logistic regression to address the second objective of this PhD research.

CHAPTER 5, "Design your own microbicide trial: Opinions of former microbicide trial participants on how to improve adherence and adherence reporting in future microbicide trials," contextualises and describes results of the qualitative study to address the third objective of this PhD research.

CHAPTER 6, the overall discussion, contains a summary of the key findings of this PhD research as well as an update on the microbicide field, and provides a discussion of the PhD research results contextualised within research results published through 2015.

2

BACKGROUND

2

WHY ARE MICROBICIDE TRIALS SO COMPLICATED?

Chapter 2 gives overall background on the complexities of phase IIb and phase III vaginal microbicides. The first section, 2.1, provides a general description of how microbicide trials are designed and implemented. The following section, 2.2, explains why phase IIb and phase III trials are unable to test product efficacy, and the importance of sexual behaviour measurement for interpreting trial results. Section 2.3 gives a brief history of microbicide effectiveness trials up to the start of the PhD research in 2012. Section 2.4 provides an overview of methods to measure adherence used in those trials. The final section, 2.5, provides a brief summary of the microbicide trials that are included in this PhD research.

2.1 VAGINAL MICROBICIDE CLINICAL TRIAL DESIGN AND METHODOLOGY

As with other biomedical HIV prevention trials, microbicide trials must be conducted in populations of healthy HIV-negative individuals where incidence of HIV is high. The difference between HIV seroconversion rates among the group of trial participants assigned to the investigational product and the group of trial participants assigned to the control product is how investigational products are evaluated. If trials are conducted among populations in which HIV incidence is low, trials would not be feasible due to the time it would take to answer their research questions. Even within populations where there is high HIV incidence, HIV seroconversion is a rare event. Effectiveness trials typically enrol 800–9000 women and follow them for 1–3 years to accrue the required number of HIV seroconversions in order to have suitable power to detect a difference between the experimental and control arms.

From an ethical standpoint, it is important that investigational products be tested for safety and efficacy in populations that need and will use the products.[39] For these reasons, the majority of microbicide trial participants are located in sub-Saharan Africa. Economic, social, educational, and other structural factors which put women at risk for HIV are the same factors which make them vulnerable in other important ways.[40] Women who

may be interested and eligible to join microbicide trials may lack economic independence, and may have limited access to education and other opportunities where they live. Thus, women who enrol in microbicide effectiveness trials are a particular population with particular needs and circumstances that are different from the circumstances and needs of those who fund, design, and conduct the microbicide trials.

To achieve the number of required seroconversions, microbicide trials are generally multisite studies and usually involve collaboration between several countries. Donors are often from the United States (US) or United Kingdom (UK); partnerships are formed across countries to design, conduct, and analyse results from the trials.[40] Conducting microbicide trials to meet the needs of all the stakeholders requires extensive planning and coordination. Trials also require regulatory and ethical approval from multiple bodies before recruitment is allowed to commence. The power inequalities and cultural and linguistic differences between stakeholders add further layers of complexity. Research teams recruit healthy populations of people to volunteer to use investigational products that may be harmful. Understandably, without careful consideration of how trials are communicated to local communities, controversy can emerge, especially around concerns of exploitation. Such controversies can put the research at risk if not addressed sensitively.[41,42,43]

Recruitment of trial participants requires liaising with local authorities and communities. Community advisory boards or groups (CABs or CAGs) are developed or engaged with to help bridge trial sites and local communities. Populations of sexually active, healthy HIV negative women are identified and recruited. As it takes time to enrol the required number of participants at each site, screening and enrolment of participants is staggered and can take place over long periods of time until accrual targets are met. Because enrolment in microbicide trials includes eligibility requirements that require clinical and laboratory tests, there is typically a two-stage informed consent process. Generally, prospective participants are invited to provide informed consent to complete the screening procedures, which include asking participants about themselves and their sexual history as well as conducting clinical and laboratory procedures to check their health, pregnancy, HIV, and STI status. Once participants are deemed eligible per pre-defined protocol criteria, they are invited to enrol in the clinical trial.

The informed consent process for enrolment in microbicide trials is lengthy. Key aspects of the process include informing participants about the voluntary nature of participation, the investigational nature of the product, that ability to protect against HIV is not known, that adverse effects are not all known, how the product is expected to be used, trial pro-

cedures, clinical and laboratory tests, collection of behavioural data, protection of data, reimbursement, and their rights as participants.[44] Reimbursement varies from site to site and must be approved by local ethics committees. The reason for local approval is to help ensure that the reimbursement amount is not coercive, meaning that, it is not so large that individuals in the local population would feel compelled to join a trial that exposes them to potential adverse effects of an investigational product because the amount of money being offered is so attractive. In most sub-Saharan countries, the value of the amount is not substantial. South Africa, however, requires that clinical trial participants receive 120 ZAR per trial visit,[45] which may be a significant motivating factor for women in South Africa to join microbicide trials.

Participants who enrol are randomly assigned to one of the arms of the trial, where they receive the intervention or control plus an HIV risk reduction package. The HIV risk reduction package changes as new ways to prevent HIV are discovered. Microbicide trials through 2012 have typically included HIV risk reduction counselling, provision of condoms, and STI screening and treatment. In some trials, participants are encouraged to invite their partner or partners to come to the clinic for HIV testing and counselling, or to learn about the study itself.

Participants who consent to enrol are expected to use the study product per the required regimen. At the start of this PhD research, all regimens of completed effectiveness microbicide trials required use of the product around the time of sex, referred to as a "coitally dependent" regimen. Participants are generally asked to return to the study clinic monthly for product refills, adverse event reporting, pregnancy tests, HIV and STI screening, risk reduction counselling, and to report product use and sexual behaviour. Trials may divide some of the procedures into "shorter" (monthly) visits, and "longer" (quarterly) visits. Regular visits are generally scheduled on a particular day each month, and there is an allowable "window period" around that day (for example, 7 days before or after the scheduled date) for which attendance during that time would be considered a successful visit and data collected at that visit would be entered into the database as that month's data for that participant. If a participant has a visit outside of the allowable window for a particular period, then the visit may be considered "missed." As clinical trials must minimise loss to follow-up, when participants do not show up for their appointment, dedicated staff typically follow up with them to remind them about the missed appointment. Once a participant has completed the amount of time required for her participation, or the trial has stopped for other reasons, she will attend a final visit. Some trials have included special exit questionnaires to ask more detailed questions about trial participation, product

use and acceptability, and behavioural or other information.

Trials are monitored by independent safety and data committees[44] which are composed of experts who are not staff on the particular trial. The committees check the progress of the trial at designated time points and will make recommendations that a trial continue as planned, be stopped for futility, be stopped for harm, or in the case of a substantial benefit, be stopped as it would no longer be ethical to provide participants with the control product.

Main trial results are typically reported at large international conferences, which may or may not be coordinated with publication of the primary results manuscripts in journals. Further analyses are then conducted and published. Trial results, either at the planned end of a trial or following important findings from an independent data and safety monitoring committee meeting, need to be disseminated quickly as results are relevant to both ongoing trials in the field and planned trials. Clinical trials are conducted within the context of equipoise; if a product is found to be harmful, trials testing that product may need to stop. If a product is found to be highly effective, it may no longer be ethical to continue ongoing trials of that product. Results of other biomedical interventions for HIV are also relevant. If another HIV prevention method is found to be effective, this may affect the informed consent process and package of HIV prevention options potentially offered to trial participants.

2.2 Specific methodological challenges in microbicide trials: effectiveness versus efficacy and how to interpret trial results

Phase III clinical trials traditionally assess biological efficacy of an investigational product in a population of healthy human volunteers. In an ideal scenario, any difference in HIV incidence between participants using the investigational product and those using the placebo product would be due to the biological effect of the investigational drug. Phase IIb and phase III trials of vaginal microbicides for the prevention of sexual transmission of HIV are faced with a number of unique methodological challenges, discussed below, that affect the ability of a trial to detect a difference in HIV incidence between the arms, and to identify a potentially efficacious (or harmful) product.[8,10,11,12,13,16,46,47,48] Therefore, phase IIb and phase III trials are unable to provide results that indicate biological efficacy of an investigational product; rather, results provide an estimate of product effectiveness.

As microbicide trials estimate effectiveness rather than efficacy, it is particularly important to measure the factors which limit the ability of trials to estimate product efficacy, to the best extent possible, in order to optimise results interpretation. These methodological challenges, which affect how phase IIb and phase III trials are designed and conducted, and how results can be interpreted, are briefly summarised below.

2.2.1 PREGNANCY

As candidate microbicides are investigational, the effects of the drugs on a foetus are unknown. For this reason, trial protocols usually require that if a participant has a positive pregnancy test, she not use the study product until a negative pregnancy test is observed. This means that a substantial period of time during a woman's follow-up may be without product use, especially in locations where fertility is high, thereby decreasing the power of the trial.[8,11,46]

2.2.2 PLACEBO GEL

Microbicide gel trials use placebo gels in the comparator arm. Due to the lubricating and possible barrier effects of a placebo gel, the "placebo" used in microbicide trials may not be truly inert and may have some ability to reduce HIV transmission for participants using the placebo gel.[8,11,46] Also relevant is that some placebo gels and investigational products have different pH levels and ingredients,[23] such as preservatives which may affect vaginal flora. Presence of a gel in the vagina will also dilute semen—which, if the partner is HIV positive, will contain HIV. For these reasons, placebo gels may affect the incidence of HIV in the control arm compared to no use of gel at all. This is the reason that the HPTN 035 trial team chose a clinical trial design with two control arms: one blinded with a placebo gel, and the other unblinded with no gel intervention, using only condoms for HIV prevention.[12]

2.2.3 ANAL SEX

Vaginal microbicide effectiveness trials to date have only tested products that were designed for vaginal use. Participants were instructed not to use the microbicides rectally when engaging in anal sex. If all participants used their study products exactly as instructed, but also engaged in anal intercourse without condoms, it is likely that some of the HIV seroconversions in the trial would be due to anal rather than vaginal transmis-

sion of HIV, thus limiting the ability to detect a protective effect of the investigational product on vaginal HIV transmission of HIV.[8,11,48] This possibility is particularly likely given the higher rate of HIV transmission associated with anal sex, despite lower rates of anal sex than vaginal sex in most microbicide trial populations.[48]

2.2.4 CONDOM

Another dilemma faced in microbicide trial design is that, from an ethical standpoint, participants must be provided with risk reduction counselling and condoms,[49] yet exposure to HIV while using the investigational product versus the placebo is how a difference is detected between the two products. If intact condoms are used correctly during each sex act, no HIV transmission will take place, and it will not be possible to test the effect of a microbicide. As long-term perfect condom use within a population is rare, and indeed is one of the reasons microbicides are needed, most populations recruited into microbicide trials will experience HIV serocoversions over time. However, the patterns of condom use, in combination with the study product, may be important for interpretation of results.[11,13] If participants tend to use condoms and the study products together, and use of the gel alone during sex is rare, it will be difficult for a trial to detect a difference in HIV rates in the trial arms.

2.2.5 PRODUCT ADHERENCE

The most significant threat to trial results and their interpretation is adherence to the study product. If women do not use the study products to a sufficient extent, HIV rates in the different trial arms will be similar and it will not be possible for a trial to detect a protective effect of a truly efficacious drug.[10,11,13,16] There are multiple reasons why women might not use study products, including the fact that women enrolled in trials are aware that they might be assigned to the placebo gel which has no active drug. Therefore, some form of measurement of product adherence is critical in microbicide trials so that trial results can be interpreted optimally.

In order to interpret results, a microbicide trial should measure product use, condom use, vaginal sex, and anal sex. Coitally dependent microbicides create an even more challenging situation because gathering data on product use, by definition, also requires gathering data about sexual behaviour. This translates into collecting data about each vaginal sex act, each anal sex act, condom use for each vaginal sex act, condom use for each anal sex

act, and gel use for each vaginal sex act.[32,50]

Sexual behaviours are private, often stigmatised for women to discuss, and are not directly observable in a trial setting; these realities comprise another major challenge to conducting and analysing microbicide trials. Research teams, not able to directly observe behaviours around exposure to HIV and use of the study product, must therefore seek alternative ways to gain as much information as possible about those behaviours. Multiple methods to gather these data have been developed and continue to be developed, but these data, for the most part, cannot be fully validated because of the private and complicated nature of the behaviours being studied.[50] Different methods for measuring adherence used in effectiveness trials prior to the start of this PhD research are described in Section 2.4.

2.3 SUMMARY OF MICROBICIDE EFFECTIVENESS TRIALS THROUGH 2012

At the start of this PhD research, 12 effectiveness trials of candidate microbicides had been completed (Table 1.1.1). Eleven of the trials used a coitally dependent regimen that asked participants to use one dose of microbicide prior to sex. CAPRISA 004, the last trial to be completed before this PhD research, used a coitally dependent regimen with a pre-sex and a post-sex dose of microbicide. Microbicide trials began with products that had already been developed and marketed as spermicides.[51] Most products tested in trials completed by 2012 were gels applied vaginally with applicators. Different products had different properties, including different viscosities, volume, and applicator types. The first generation of products were surfactants whose method of action was disruption of cell membranes of sperm and pathogens causing sexually transmitted infections, including HIV.[33,51] Between 1987 and 2000, the four trials testing the effectiveness of Nonoxynol-9 (N-9), a licenced spermicide, in reducing transmission of HIV were conducted.

The first trial tested an N-9-infused sponge against a placebo suppository among sex workers in Kenya.[20] The trial did not find a significant difference in HIV infections between the active product and placebo arms (hazard ratio 1.7; 95% CI 0.9–3.0).[20] The trial team did, however, observe a trend towards increased risk of HIV and of genital ulcers among participants using the 1000 mg N-9 sponges. For these reasons, in July 2002, the data and safety monitoring committee recommended termination of the trial. N-9 was then tested as a vaginal film among a sex worker population in Cameroon.[21] This trial, which used a 70 mg dose, did not find a significant reduction in HIV (rate ratio 1.0; 95% CI 0.7–1.5).[21] The next trial used 52.5 mg of nononoxyl-9 (N-9) in a gel formulation to test the effect

of N-9 in reducing STIs, including HIV, among a population of sex workers in Kenya.[22] This trial did not find a difference in the incidence of genital ulcers between the N-9 and placebo groups and was unable to find a difference in HIV transmission due to lack of power.[22] The final clinical trial to test N-9 as an HIV microbicide was the COL-1492 study, a phase II/III trial which enrolled sex workers in Benin, Cote d'Ivoire, South Africa, and Thailand.[23] This study found an increased risk of HIV infection among women randomised to N-9 gel (hazard ratio 1.5; 95% CI 1.0–2.2), and this risk was higher among women who used more applicators of N-9 gel per day.[23] Based on results of the COL-1492 trial, N-9 was discarded as a possible vaginal microbicide for preventing sexual transmission of HIV.

The second drug to be tested as a possible vaginal microbicide was C3IG, an amphotetric surfactant, called SAVVY. Two phase III trials were conducted in West Africa: SAVVY Ghana and SAVVY Nigeria.[24,25] Both trials used 1.0% C31G in the form of a coitally dependent gel and both were stopped early due to futility as the HIV incidence was much lower than anticipated.[24,25] However, the SAVVY Nigeria team noted that their results could not be interpreted as confirmation of no harm because a trend towards harm was observed (hazard ratio 1.7; 95% CI 0.9–3.5). In both trials there was concern, based on self-reported behaviour of participants, that adherence to the gel when no condom was used was low. Trialists also suspected that self-reported data on gel use and condom use were inaccurate because pregnancy rates did not correspond with behavioural reports of participants given the contraceptive effects of condoms and C31G.[52] The SAVVY Ghana team suggested that future microbicide trials require participants to use effective non-barrier methods of contraception to increase the ability of future trials to answer their research questions. Surfactants as vaginal microbicides for HIV prevention were thus discarded for further evaluation.

The second generation of microbicides subsequently went into late-stage trials; this generation included polyanions, negatively charged polymers which were shown to inhibit HIV-1 replication,[51,53,54,55] and buffering agents which aimed to maintain a high pH in the vagina, thereby potentially inactivating HIV and preventing entry into lymphocytes and macrophages.[51,56,57,58,59,60,61,62]

Cellulose sulphate (CS) was tested in two phase III effectiveness trials: a multi-country trial sponsored by CONRAD and a trial conducted in Nigeria, sponsored by FHI.[27,28] The CS CONRAD trial, which was conducted in Benin, India, South Africa, and Uganda, tested 6% CS gel against a placebo gel. An independent data monitoring committee re-

viewed data after 35 incident HIV cases and found a hazard ratio of 2.23 (95% CI 1.0–5.03). They recommended that the trial be halted due to harm. The final results included 6 additional HIV infections, giving a hazard ratio of 1.61 (95% CI 0.86–3.01). Due to results of the multi-country CS CONRAD results, the CS Nigeria study was also halted over concern for potential harm, although their results did not suggest harm (hazard ratio 0.8; 95% CI 0.3–1.8). As with previous studies, trial teams were concerned that use of the gel during condom-less sex was low. Pregnancy rates were similar in both groups, despite CS having contraceptive properties.[63]

The CS CONRAD trial team noted that there are potentially two mechanisms of biological effect with candidate microbicides. The first is the biological effect of the candidate gel related to HIV prevention used during a specific sex act. The second biological effect of a candidate gel might be related to the candidate gel's effect on the vaginal environment with repeated use over time, which could degrade the vaginal epithelium and thus put a participant at greater risk of HIV infection over time, with more product use. The trial team noted that although a per sex act-specific effect of a candidate gel would be difficult to identify if adherence was low, this difficulty would not preclude a cumulative adverse effect of product exposure which could lead to an increased risk of HIV.[28] The CS CONRAD trial team raised the question of the need to assess microbicides in different populations: those who have very high use, for cumulative exposure, and those with less coital frequency.[28]

The CS FHI trial team suggested that phase I trials test candidate products at greater exposure rates than the typical 1–2 doses per day for 14 days, to help identify the potential adverse effects of high frequency use.[27] The CS FHI team noted that by recruiting women who were at high risk for HIV, they were also selecting a population that was highly mobile. They lost one-third of their participants from each study arm to follow-up. This loss, although non-differential, highlights the dilemma in microbicide trials between recruiting populations of women with high HIV incidence versus women who are less mobile and more able to fulfil study procedures, but may have lower rates of HIV.

Carraguard (PC-515), a second-generation, seaweed-derived product, is a sulphated polysaccharide[33,51] developed by the Population Council. A phase III trial tested Carraguard gel against a placebo gel in South Africa. The trial did not find a protective effect of the investigational product (hazard ratio 0.87; 95% CI 0.69–1.09).[26] Carraguard was the first microbicide effectiveness trial in which a novel technology was developed to assess product adherence without relying solely on participant self-report. This technology, a dye

stain assay (DSA),[64,65] which tests if used applicators have been vaginally inserted, involves identifying, by a staining procedure, a mucosal enzyme's presence on the gel applicator. Presence or absence of the characteristic blue pattern indicates if the applicator was "used" or not. There are limitations with the DSA: a woman can insert the applicator vaginally but still expel the gel externally; a positive dye pattern indicating vaginal use does not confirm if the gel was expelled in the correct participant's vagina; and the assay was not validated in the context of applicators being washed by participants before returning them to the clinic.[66] Self-reported data from trial participants indicated 96.1% gel use at last sex act. Results of the DSA, however, together with self-reported sexual behaviour data, indicated that participants used the gel in approximately 42.1% of sex acts. Results from the Carraguard trial had a large impact on the microbicide community, as it was the first trial to confirm that self-reported adherence data were significantly overreported and also highlighted the extent to which participants might not be using the study products.

PRO 2000, a synthetic naphthalene sulphonate derivative,[51,67,68,69] was tested in two different microbicide trials. The first trial was a phase II/IIb trial, HIV Prevention Trials Network (HPTN) 035, which tested 0.5% PRO 2000 gel. HPTN 035 found an indication of a protective effect (hazard ratio 0.7; 95% CI 0.46–1.08)[29] when compared to a placebo gel. However, the larger phase III trial, Microbicides Development Programme (MDP) 301,[30] did not find a protective effect (hazard ratio 1.05; 95% CI 0.82–1.34). The MDP 301 trial, in addition to testing a 0.5% formulation, also tested a 2% formulation of PRO 2000 gel. This arm was discontinued early, however, due to futility.

BufferGel, an acid-buffering product, was also tested in the HPTN 035 trial. It was also not found to reduce HIV transmission in the phase II/IIb trial (hazard ratio 1.10; 95% CI 0.75–1.62).[29] MDP 301 and HPTN 035 were the last effectiveness trials to test products within the second generation of microbicides. While trial participants in both studies reported high adherence, it is possible that low adherence may have played a role in the null results observed. HPTN 035 measured adherence by asking participants about their product use in face-to-face interviews. MDP 301 asked participants about their adherence in face-to-face interviews and requested that participants return their applicators to study clinics. MDP 301 also conducted an intensive social-science sub-study, which included asking a subsample of participants to complete coital diaries and participate in in-depth interviews and a reconciliation process for discrepant adherence data. Based on those studies, the MDP 301 trial team estimated that product use was high.[30,70] However, there was no way to verify the actual adherence of either the HPTN 035 or MDP 301 trial participants. The microbicide field then shifted focus to specific acting antiretroviral (ARV)

drugs in vaginal formulations for the prevention of HIV.

Tenofovir gel, a nucleotide reverse transcriptase inhibitor, was the first ARV to reach effectiveness trial testing in the third generation of candidate microbicides. ARVs have the advantage of being specific and potent, and have demonstrated safety in the context of clinical use. An ARV-based microbicide, however, would not likely meet the original call for a female-controlled product that would be available without a prescription. Users of ARVs need to be tested regularly for HIV, monitored for HIV drug resistance should they seroconvert while using the ARV microbicide, and also monitored for long-term adverse effects of the ARV. While ARVs are highly potent against HIV, they do not provide broad protection from transmission of other STIs (although the CAPRISA 004 trial, discussed below, did find a 51% reduction of Herpes simplex virus type 2 transmission[31]). An advantage of ARV-based microbicides is that biomarkers are available to detect the drug in biological samples, which can greatly aid the interpretation of trial results.

The CAPRISA 004 trial, which began in May 2007, tested 1% tenofovir gel against a placebo gel in South Africa.[31] The phase IIb trial was the first effectiveness trial to test both an ARV microbicide and a coitally dependent regimen that included a pre and post coital dose of gel. The regimen was called "BAT24" because trial participants were instructed to use an applicator of gel before sex and after sex, and not to use more than two applicators of gel in a 24-hour period. The trial results, released in 2010, were the first to show a statistically significant reduction in HIV transmission (hazard ratio 0.63; 95% CI 0.42–0.94). Analyses of self-reported adherence, along with applicator assessments, indicated a dose effect with participants having higher adherence achieving greater protection from HIV transmission.[31]

At the start of this PhD research, a number of new microbicide trials were in the field or the planning stage. Results of those trials are discussed in Chapter 6.

2.4 METHODS FOR ADHERENCE MEASUREMENT IN MICROBICIDE TRIALS

As discussed in Section 2.2, a critical reason to measure adherence and sexual behaviour in microbicide trials is to help interpret trial results. This section provides a brief overview of some of the adherence and sexual behaviour measurement methods available for microbicide studies prior to the start of this PhD research in 2012.

While adherence data can support interpretation of research results, there are other important reasons to have accurate estimates of adherence in microbicide trials. If research teams can identify issues around poor product adherence or inaccurate reporting of adherence, there may be ways to adjust study procedures to improve those outcomes prospectively, during trial implementation, thus increasing the chance of finding an effect of the study product if it is indeed efficacious. Understanding the issues around participant adherence and participant reporting of adherence in completed trials can be used to improve the design of future trials. Although trial participants who use an experimental product which is not yet known to be effective, and their motivations and behaviour, are likely different from populations who use already licensed products, it is useful to understand factors which affect product adherence in a clinical trial so that programmatic rollout of the product can be designed in an optimal way, thereby increasing the likelihood of product uptake in the population.[8,32]

2.4.1 SELF-REPORT

Measures of adherence in microbicide trials have relied heavily on self-report data about sexual behaviour and product use.[20,21,22,23,24,25,26,27,28,29,30,31] With self-report measurements, the participant directly provides information about her use of the study product and sexual behaviours, including condom use. Self-report is a simple and inexpensive method, but relies on a participant's ability to remember her behaviour accurately and thus is subject to recall bias. The amount of detail requested and the length of time over which a participant is asked to recall behaviour will affect the accuracy of a participant's self-reported information.[18,32,71] Microbicide trials, which often employ coitally dependent regimens, are particularly challenging because measuring adherence requires a participant to recall specific past sex acts and to recall for each of those sex acts whether she used the study gel, or a condom, or both.

Self-report is also subject to social desirability bias because individuals are asked to answer sensitive questions about sexual behaviour and stigmatised behaviours.[18,71] Participants responding to questions may not feel comfortable telling the truth and may give answers they think will be more acceptable to the interviewer and less likely to cause a negative effect, such as jeopardising their participation in the trial, or answers that they think describe themselves in a way with which they are more comfortable.

How to reduce both recall bias and social desirability bias is critical to obtaining more accurate measures of sexual behaviour and product adherence. Different time periods of

recall and modes of seeking self-reported data can potentially facilitate or hinder a participant's ability to remember details and to feel comfortable reporting her behaviours accurately.[18,71,72,73,74]

2.4.1.1 FACE-TO-FACE INTERVIEWS (FTFIS)

Fate-to-face interviews (FTFIs) with structured questionnaires have been the most common format of self-report in microbicide trials. With this method, for coitally dependent regimens, participants are asked about their product and condom use in relation to sexual activity by study staff, during monthly or quarterly visits. Face-to-face interviews are easy to integrate into trial visits as staff collect other data using case report forms (CRFs). The quantitative data can easily be tabulated for one participant across her study participation or aggregated with data from other study participants to summarise adherence data over the entire trial.

Face-to-face interviews, however, may increase the chance of social desirability bias as participants are asked to answer very personal questions directly to members of research teams. Overall measures of adherence from data obtained from FTFIs in microbicide trials have been consistently high, ranging from 70% to 96.2%.[75] These data cannot be directly validated, however; thus it is difficult to know if and by how much those estimates differ from the truth.

One small study (n=132),[72] conducted within the context of a phase II trial of Carraguard, attempted to assess if microbicide trial participants intentionally misreported behaviours in FTFIs during the trial. Seventy-nine percent (79%) of participants in the study reported they had misled interviewers at least once. Reasons given for misreporting were politeness (34%), seeking approval or fear of criticism (24%), and embarrassment (18%).[72]

As trials have integrated additional methods of adherence measurement into trial designs, they have shown discrepancies in results of the different adherence measurement tools, demonstrating the limitations of relying solely on FTFIs.[36,31]

2.4.1.2 AUDIO COMPUTER-ASSISTED SELF-INTERVIEW (ACASI)

Audio computer-assisted self-interview (ACASI) is a method of data collection that allows a participant to use a computer to answer the same types of questions that would be asked in FTFIs. Typically, the participant is seated alone; the computer speaks the question audibly and can show pictures on the screen to help the participant understand the

question and choose answers. Microbicide research teams have been interested in ACASI as a method to reduce social desirability bias due to some of the successes observed with increased reporting of sensitive behaviours using this mode.[76,77,78,79,80] As trial participants do not give their answers directly to another human, ACASI may be a better format for asking sensitive questions. ACASI provides perceived greater privacy and thus may reduce participants' feelings of embarrassment or stigma, facilitating their comfort in answering questions accurately.

ACASI, however, has limitations. Trial teams may believe a system like ACASI might provide more privacy, but trial participants may not be confident that their answers are truly confidential and may, therefore, not change how they report their information in ways that trial teams hope. ACASI requires financial investment in software and hardware and is dependent on electricity; source data are recorded electronically and can be lost if there is a system failure. A self-administered, electronic system can also increase the chance that participants provide answers without actually understanding the questions, an event which would be difficult to identify. Most importantly, ACASI might not be appropriate or easy to implement in settings where trial participants have low literacy or exposure to electronic devices. Successful use of ACASI may require substantial orientation of trial participants to facilitate proper use of the device and ability to answer questions using it.

One study[73] specifically attempted to compare the accuracy of ACASI versus FTFIs in reporting sensitive behaviours in a simulated microbicide trial using a placebo gel. Responses from questions about sexual behaviour and product adherence were validated by an applicator stain test and a test for the presence of semen, Rapid Stain Identification of Human Semen (RSID-Semen). Results indicated that participants were more likely to report sexual behaviours accurately via ACASI; however, this difference diminished over time. Importantly, results from questions about product adherence did not show a difference between ACASI and FTFI modes.[73]

2.4.1.3 COITAL DIARIES

Coital diaries are paper-based tools that a participant is given to take home and use to record sexual behaviour and product use as they occur. Participants are oriented on how to complete them and, at specified intervals, the diaries are collected so that the information can be transferred into databases by research staff. Coital diaries may be advantageous in reducing recall bias as they allow participants to record their behaviours as they occur.

Social desirability bias may also be reduced because a participant can complete the diary independently and is not required to directly report answers to a research staff member, a situation that potentially facilitates greater comfort.

Coital diaries, however, are dependent on participants being at least semi-literate and require that participants be taught how to use them. The pictures used in the diaries, and how to complete the diaries, may be complicated and understood in different ways. It can be difficult to know if diaries have been completed in a way that is consistent with how the research team understands the diary and intends it to be completed. An additional concern about coital diaries is that participants might not complete the diaries as sex acts occur but may instead complete them immediately before they are collected by research staff, which means they are not necessarily documenting an accurate record of their ongoing behaviours.[23] It is also possible that while participants fill out coital diaries privately, they are aware that their answers will be reviewed by research staff and that this awareness may influence the answers they provide.

Data from three studies examining the utility of coital diaries in the context of microbicide trial populations indicate that coital diaries may decrease social desirability bias compared to FTFIs.[81,82,83] Sexual activity was reported more frequently, gel use less frequently, and stigmatised behaviours such as sex during menstruation and lack of vaginal washing more frequently in coital diaries than in FTFIs.

2.4.1.4 IN-DEPTH INTERVIEWS (IDIS)

An IDI is a type of face-to-face interview that typically produces qualitative data. In microbicide trials, quantitative data can also be gathered with IDIs, but in a conversational manner rather than by asking questions in a structured format as with the case report forms used in FTFIs. In-depth interviews can therefore facilitate greater rapport between the trial participant and the staff member. This style of interviewing may put participants more at ease and thus they may feel freer to provide candid information about their circumstances. In-depth interviews can be used to collect information on sexual behaviour and product use, and to reconcile discrepant answers from other modes of data collection. The phase III MDP 301 trial used IDIs as a method in a subsample of trial participants to collect sexual behaviour and product use data.[30,70,74] As with FTFIs, IDIs are still subject to social desirability and recall biases. IDIs are labour intensive and thus expensive to complete; they require highly trained staff members; and they produce data that are more

difficult to extract and analyse compared to more structured interviews.

2.4.1.5 RECALL TIMING

An important consideration in determining the optimal way to ask for self-reported behaviours is recall timing. Time periods commonly used in microbicide trials are last sex act, last 7 days, and last 30 days. There are benefits and drawbacks to different time frames. Asking about last sex act will likely diminish recall bias, as it is easier to remember behaviours that were recent rather than further back in time. However, participants might be inclined to change their behaviour just before attending a study visit, as they know they will be asked about use of the study product. Last sex act also captures information about one sex act as opposed to usage over time. Longer periods of recall might provide a less biased estimate, as they can capture more typical behaviour, but might be difficult for participants to remember.[32]

2.4.2 NON SELF-REPORT METHODS

Non self-report methods entail methods of collecting adherence data, such as applicator counts and biomarkers, that do not rely on the participant directly providing verbal or written report about her behaviour.

2.4.2.1 APPLICATOR COUNTS

Some effectiveness microbicide trials[36,30,31] asked participants to bring their unused, or used and unused gel applicators back to the clinic to be counted. Theoretically, applicator counts can provide some indication about how much study product a participant has used since her last study visit. As a further example of social desirability bias, however, a participant might choose which applicators to bring back, or expel study product from applicators not used vaginally around the time of sex. In addition, participants can insert the gel vaginally without having sex and can choose to share their study product with other people. Thus, counts of applicators are also not an objective or a highly reliable measure of product adherence. Applicator counts for coitally dependent regimens must be paired with data on sexual behaviour to obtain estimates of adherence, a requirement which adds additional complexity and opportunity for bias. Another consideration is that in settings where microbicide trials are typically conducted, keeping and returning applicators may be difficult for some participants.

2.4.2.2 APPLICATOR DYE STAIN ASSAY (DSA)

For their Carraguard trial, the Population Council developed a unique method which involved using an assay to try to determine which applicators were inserted vaginally.[26] Using a staining procedure, the assay identifies a mucosal enzyme's presence on the applicator thus indicating that the applicator has been vaginally inserted. According to tests by the developers, the assay has 97.5% sensitivity and 96% specificity.[26,64,65] However, the DSA cannot confirm whose vagina it was inserted into, and was not validated in the context of washed applicators.[66] It also cannot determine if gel was inserted per regimen instructions, around the time of sex.

2.4.2.3 BIOMARKERS FOR SEXUAL INTERCOURSE

In the context of microbicide trials, biomarkers for sexual intercourse can provide information about a participant's sexual behaviour, in the form of exposure to semen. Tests for the presence of semen can help corroborate reports of vaginal sex or condom use. The most commonly used assays are prostate specific antigen (PSA), Rapid Stain Identification of Human Semen (RSID-Semen) and Y-chromosome DNA.[8,32,50,73] While all can be used to detect the presence of semen, positive results of the Y-chromosome DNA assay may be due to sources of male DNA other than semen which may enter the woman's vagina. The limitation of these assays is that they are only able to detect markers of semen exposure for relatively short periods of time: about 48 hours for PSA, 3 days for RSID-Semen, and 4–15 days for Y-chromosome DNA.[50,84]

2.4.2.4 BIOMARKERS FOR USE OF MICROBICIDE PRODUCTS

The fact that biomarkers were not available for first- and second-generation microbicides is one of the reasons for heavy reliance on self-reported data in those trials. Biomarkers for ARVs, as well as other technologies specific to measuring adherence in microbicide trials, are currently being developed. ARV-based microbicides, such as tenofovir, can be detected in the human body using biological specimens. Both plasma and cervico-vaginal fluid can be used to detect levels of tenofovir from vaginal dosing of 1% tenofovir gel.[85,86]

ARV-based biomarkers for microbicides tend to provide information about use very proximate to a sample being collected.[85] This information, however, does not provide direct information about whether the drug was biologically available at the right location at the time of exposure to HIV. With coitally dependent microbicides, adherence measurement will always need to include information about sexual behaviour, which at this time in effectiveness trials is achieved by asking a woman about her behaviour. Collection and

analysis of specimens can be expensive and time-consuming. Moreover, some biomarkers can be manipulated by the participant, in that participants can alter their use of the study product in anticipation of a specimen being collected.[50,85,87] As biomarker assays improve and become less expensive, they will undoubtedly greatly aid the understanding of adherence in future microbicide trials.

In the context of microbicide effectiveness trials, specimens are generally taken at study visits. As specimens at visits can only be collected episodically, biomarkers may tend to cover either very specific points in time such as hours preceding a study visit, or general periods in time such as a period of weeks or months. Because of the complicated nature of sexual behaviour—which includes specific sexual acts, use of product and condoms, and how all of these behaviours play out in an individual act of sexual intercourse or rounds of sexual intercourse—data from specimen analysis will not provide a complete set of data with which to examine exposure to study product and exposure to semen.[50]

Finally, if one of the objectives of biomarker use is to prospectively utilise information about adherence to improve study outcomes, then biomarkers that identify the investigational product will compromise double blinding if done on an individual basis. Analyses using biomarkers which identify the study product must be done retrospectively, after data collection has completed. Alternatively, biomarker data used to alter study procedures to improve adherence during follow-up can be examined at the group (often site) level.

2.4.3 OTHER STRATEGIES

2.4.3.1 MIXED METHODS

A mixed methods approach can refer to a trial design that gathers data about sexual behaviour and product adherence using several different sources such as quantitative and qualitative methods.[32,70,74] This term can also be used to describe the use of different sources to measure adherence. Examples of mixed methods could include using FTFIs and applicator counts, FTFIs and a biomarker, or FTFIs, ACASI, and applicator returns. As no gold standard exists to measure sexual behaviour and product adherence in microbicide trials, employing mixed methods is a useful way to attempt to gauge the level of adherence. In the Carraguard trial, self-reported product use was 96% at last sex act.[26] However, the applicator DSA indicated that overall product use for the study was only 42%.[26] A mixed methods approach will not ensure accurate adherence data; however, it

can help research teams better understand and interpret the data they do have. While it is more expensive to use several methods to collect sexual behaviour and adherence data, utilisation of mixed methods is likely to be the most successful approach in the absence of a gold standard.[38,70,74]

2.4.4 TRIANGULATION OF DATA

Data triangulation occurs when results from different methods of data collection are compared and discrepancies examined and reconciled to produce an improved estimate of sexual behaviour and product adherence.[74] The inclusion of qualitative methods in the triangulation process can also help research teams have a greater understanding of how their questions are being understood by the trial participants, which may be different from how the questions are understood by the research team.[70,74]

MDP 301[30] pioneered this methodology in microbicide trials, creating a comprehensive approach of mixed methods and triangulation of data for a subsample of the trial population. MDP 301 used FTFIs, applicator returns, coital diaries, and IDIs to compare and reconcile responses about sexual behaviour and product adherence.[30,70,74] Incorporating a substantial social science component in a trial takes time, money, and extremely skilled interviewers. While the extensive social science component used in MDP 301 is not likely feasible in all or even most microbicide trials, it is quite possible that reconciliation of different methods of adherence measurement could be done at standard interviews with participants at regular clinic visits.[74]

2.5 TRIALS INCLUDED IN THIS THESIS

This PhD research includes data from six effectiveness microbicide trials. A brief summary of each trial is given below. Table 2.5.1 provides a summary of the trials included in this PhD research.

Trial	Product	Number of participants	Locations	Years conducted
HPTN 035	BufferGel, 0.5% PRO 2000	3101	Malawi, South Africa, Zambia, Zimbabwe, US	February 2005–September 2008
MDP 301	0.5% PRO 2000, 2% PRO 2000	9385	South Africa, Tanzania, Uganda, Zambia	October 2005–September 2009 (2% dropped February 2008)
Carraguard Population Council	Carraguard	6202	South Africa	March 2004–March 2007
CS CONRAD	Cellulose sulphate	1398	Benin, India, South Africa, Uganda	July 2005–March 2007
CAPRISA 004	1% tenofovir gel	889	South Africa	May 2007–March 2010
VOICE	1% tenofovir gel (plus oral tenofovir disoproxil fumarate, oral tenofovir–emtricitabine)	5029 (all regimens)	South Africa, Uganda, Zimbabwe	September 2009–August 2012

Table 2.5.1: Trials included in this PhD research

HPTN 035 was a four-arm phase II/IIb randomised placebo-controlled trial testing 0.5% PRO 2000 gel and BufferGel for the prevention of sexual transmission of HIV against a placebo gel and a condom-only arm. The three gel arms were double-blinded; the condom-only arm was not blinded. A total of 3101 women were enrolled in Malawi, South Africa, Zambia, Zimbabwe, and the US. Results indicated no preventive effect for BufferGel and a non-significant 30% reduction in HIV for 0.5% PRO 2000. HPTN 035 is included in the comparative and latent structure studies of this PhD research (Chapters 3 and 4).

MDP 301 was a three-arm phase III randomised, double-blind placebo-controlled trial testing 0.5% and 2% PRO 2000 for the prevention of sexual transmission of HIV against a placebo gel. In total, 9385 women were enrolled in South Africa, Tanzania, Uganda, and Zambia. The 2% PRO 2000 arm was closed early due to futility. Trial results for 0.5% PRO 2000 did not indicate an effect on HIV incidence. MDP 301 is included in the comparative, latent structure, and qualitative studies in this PhD research (Chapters 3, 4, and 5).

Carraguard was a phase III randomised, placebo-controlled, double-blind trial to test the effect of Carraguard gel for the prevention of sexual transmission of HIV. It enrolled 6202 women in South Africa. Carraguard was not shown to reduce HIV transmission in this trial. Carraguard is included in the comparative and latent structure studies in this PhD research (Chapters 3 and 4).

CS CONRAD was a phase III randomised, placebo-controlled, double-blind trial to test the effect of cellulose sulphate gel for the prevention of sexual transmission of HIV. CS CONRAD enrolled 1398 women in Benin, India, South Africa, and Uganda. CS CONRAD was halted early due to evidence that CS increased the risk of HIV transmission. Final trial results, however, did not show a statistically significant increase in HIV transmission for participants using the CS gel. CS CONRAD is included in the comparative and latent structure studies within this PhD research (Chapters 3 and 4).

CAPRISA 004 was a phase IIb randomised, placebo-controlled, double-blind trial to test 1% tenofovir gel for the prevention of sexual transmission of HIV. CAPRISA 004 enrolled 889 women in South Africa. Trial results showed that 1% tenofovir gel reduced HIV acquisition in the tenofovir arm by about 39%. CAPRISA 004 is included in the comparative study of this PhD research (Chapter 3).

VOICE (Vaginal and Oral Interventions to Control the Epidemic) was a 5-arm, randomised, placebo-controlled phase IIb trial to assess daily use of 1% tenofovir (TFV) vaginal gel, or oral tenofovir disoproxil fumarate (TDF), or oral tenofovir–emtricitabine (TDF/FTC) against HIV infection. Women in South Africa, Uganda, and Zimbabwe were enrolled. At the start of this PhD research, VOICE was an ongoing trial actively collecting data. At the start of the qualitative study for this PhD research, the VOICE trial had completed its follow-up and its study participants had exited; therefore, former VOICE gel trial participants were eligible for inclusion in the qualitative study conducted for this PhD research (Chapter 5).

3

WHAT DO WE REALLY MEAN BY ADHERENCE?

MEASURING, CALCULATING AND REPORTING ADHERENCE IN FIVE TRIALS

OBJECTIVE

To critically examine how five completed effectiveness microbicide trials measured, calculated, and reported microbicide gel adherence

INCLUDED TRIALS

HPTN 035
MDP 301
Carraguard
CS CONRAD
CAPRISA 004

3

WHAT DO WE REALLY MEAN BY "ADHERENCE"?

3.1 INTRODUCTION

Trial population adherence to the investigational product regimen is a critical factor in interpreting results of microbicide trials. How adherence is measured and calculated is, therefore, equally critical. In the field of biomedical HIV prevention research, trial teams determine study procedures and methods of analysis. Consequently, each microbicide trial team may choose different ways to assess adherence and calculate adherence estimates. Each trial team also chooses how to report adherence findings in their primary trial results publication. Because methods of data collection, modes of analysis, and ways of reporting results are not standardised, comparisons across trials can be challenging. This difficulty can be compounded when adherence information provided in publications is minimal or lacking clarity. Lack of ability to make comparisons across trials is particularly problematic when the same experimental product is tested. The importance of implementing common methods of measurement and analysis so that results can more easily be compared has been recognised as an issue in the field.[38,32,37,88,89]

To understand the extent of the similarities and differences in adherence assessment across different trials, it is necessary to look in detail at the methods trial teams used. The purpose of this study was to critically examine and compare how five effectiveness trials of coitally dependent microbicide gels collected adherence data, how the summary estimates of adherence in primary results manuscripts were reported and characterised, and how those summary estimates of adherence were actually calculated.

3.2 METHODS

Eligibility criteria for included trials in this study were post-surfactant microbicide candidates being tested in effectiveness trials (phase IIb or later) and willingness and ability of

trial teams to provide required information about their trial. Trial teams from six completed microbicide gel trials were invited in the spring of 2012 to participate in this comparative study. Five trials were able to participate: HPTN 035, MDP 301, Carraguard, CS CONRAD, and CAPRISA 004[29,30,26,28,31] (Table 3.2.1). All trials included in this study tested coitally dependent regimens of vaginal microbicide gels, meaning that participants were instructed to use the gel each time they had vaginal sex. Trial protocols, case report forms (CRFs), and statistical analysis plans (SAPs) were provided by each trial team. These trial materials, as well as the primary results publications for each trial, were examined for this study.

Trial	Product	Number of participants	Locations	Years conducted
HPTN 035	BufferGel, 0.5 % PRO 2000	3,101	Malawi, South Africa, Zambia, Zimbabwe, US	February 2005 – September 2008
MDP 301	0.5 % PRO 2000, 2 % PRO 2000	9,385	South Africa, Tanzania, Uganda, Zambia	October 2005 – September 2009, (2% dropped February 2008)
Carraguard Population Council	Carraguard	6,202	South Africa	March 2004 – March 2007
CS CONRAD	Cellulose sulphate	1,398	Benin, India, South Africa, Uganda	July 2005 – March 2007
CAPRISA 004	1% Tenofovir gel	889	South Africa	May 2007 – March 2010

Table 3.2.1: Trials included in the comparative study

As the purpose of this study was to accurately report how the included trials collected adherence data, how adherence estimates were reported in publications, and how those estimates were actually calculated, care has been taken in the results section to report information using the terminology and language that the trial teams used. The discussion section provides interpretation and criticism of terminology, methods, and language used by the trial teams.

The sections below describe the methods used to determine trial teams' methods for collecting adherence data, how overall estimates of adherence were reported in primary results publications, and how source data were specifically used to calculate the reported adherence estimates.

3.2.1 SOURCE DATA

The term "source data" refers to specific pieces of information collected from participants and used by trial teams as the foundation of calculations to estimate adherence to study products and exposure to HIV. Because all of the trials in this study tested coitally dependent microbicides, adherence must be calculated by combining information about the occurrence of specific sex acts and whether gel was used as directed for those sex acts. Information on the occurrence of sex acts can only be provided by participants, as they cannot be directly observed by trial teams. Source data are collected from participants in a number of ways that usually involve questionnaires during face-to-face-interviews (FTFIs). As discussed in Chapter 2, source data can also be collected through means such as applicator returns or biological samples that are tested for biomarkers.

For each trial, protocols and CRFs in English were examined to identify what information was collected from participants, including any information related to sex acts, gel use, and condom use. All source data for each trial were identified and placed into a common spreadsheet. Source data were categorised as self-reported or non self-reported. Recall period, frequency of the measurement, and particular wording of the questions, if relevant, were documented.

3.2.2 OVERALL ADHERENCE ESTIMATES

To understand how trial teams initially reported overall adherence to the investigational gels, first the primary results publication for each trial was reviewed. Next, written statements that provided estimates of adherence for each trial were extracted; the wording found in the publications was retained. Finally, overall adherence estimates were documented in a comparison table across all trials.

3.2.3 CALCULATIONS OF OVERALL ADHERENCE ESTIMATES IN MANUSCRIPTS

The next step in this study was to understand how source data were used to calculate the overall adherence estimates that were reported in the primary results publications. This was accomplished through a multi-step procedure. First, trial protocols, CRFs, SAPs, and the primary results publications were reviewed.

Second, a schematic figure was developed to track the information and the flow of information for each trial. The schematic figure for each trial included three sections: an area to list source data, an area to describe intermediate calculations, and an area to list the actual overall adherence estimates. Intermediate calculations refer to sums of source data or equations using source data that are subsequently used in equations to calculate overall adherence estimates. Each different piece of source data, intermediate calculation, and overall adherence estimate is presented in its own box within the schematic figure for each trial, with source variables placed at the left, intermediate calculations in the middle, and overall adherence estimates at the right.

The third step was to complete the schematic figures to represent how source data are transformed into the published overall estimates. This was accomplished by reviewing each overall estimate published and the description of how that estimate was calculated in the publication (if available), reviewing the SAP, reviewing the available source variables for the trial, and reviewing the trial protocol to understand study procedures, timing, and frequency of source data collection.

Based on this information, along with the available source data for each trial, equations were developed to characterise how source data were transformed to overall adherence estimates. These equations were placed within the schematic figures. Each piece of source data was described within an individual box, represented by a lower-case letter. Each in-

termediate calculation was represented by an upper-case letter, and an equation if applicable. Upper-case letters representing intermediate calculations were then arranged in equations, to convey how they could be used to give the final adherence estimates provided in the primary results publications.

Finally, a trial team survey was conducted to share the schematic diagrams with trial team representatives and check that the interpretations of how adherence was measured, calculated, and reported were correct. All five trial teams responded with clarifications and corrections. Last of all, schematic figures were revised based on corrections from trial teams; these are presented in the results section.

3.2.4 COMMENTS AND LESSONS LEARNED FROM TRIALISTS

In the trial team survey, trial teams were invited to provide comments about considerations and choices they made regarding adherence measures, calculations, and overall estimates. They were also invited to share lessons learned and to make recommendations on adherence in future microbicide trials.

3.3 RESULTS

3.3.1 SOURCE DATA

This section summarises the types of source data that were collected in HPTN 035, MDP 301, Carraguard, CS CONRAD, and CAPRISA 004. The types of source data described in this section are divided into three categories. The first category describes how self-reported data were collected in FTFIs. The second section describes methods that trials used to collect source data that were not verbally self-reported by participants. The third category describes methods of collecting source data that may have been novel at the time and were only used with a subset of participants within the trial using that method.

Table 3.3.1 provides a summary of all of the types of source data collected across the five clinical trials. Figures 3.3.1–3.3.5 provide a more detailed description of the type of source collected for each trial, including aspects of the specific wording of questions used to collect information in FTFIs.

Trial	Participant self-report at face-to-face interviews							Non self-report methods			Methods used with subsample			
	Last sex act	Last 7 days		Last 2 weeks		Last 30 days		Applicator count	DSA	Biomarker	Coital diary	Comparison form	In-depth interview	ACASI
	1. Gel use at last sex act 2. Condom use at last sex act (Frequency of question)	Number of sex acts (Wording of question) (Frequency of question)	1. Number of times gel used 2. Number of times condom used (Wording of question) (Frequency of question)	Number of sex acts (Wording of question) (Frequency of question)	1. Number of times gel used 2. Number of times condom used (Wording of question) (Frequency of question)	Number of sex acts (Wording of question) (Frequency of question)	1. Number of times gel used 2. Number of times condom used (Wording of question) (Frequency of question)	(Frequency of data collection)	(Frequency of data collection)	(Frequency of data collection)				
HPTN 035	1. Yes 2. Yes (Quarterly)	Yes ("Past week") (Quarterly)	1. Yes 2. Yes ("Past week") (Quarterly)	No	No	No	No	No	No	No	No	No	No	Subset
MDP 301	1. Yes 2. Yes (Monthly)	Yes ("Last week") (Weeks 4, 24, 40, 52)	1. Yes 2. Yes ("Last week") (Weeks 4, 24, 40, 52)	(Yes) (For those who had sex in the last 4 weeks but not last week) (Weeks 4, 24, 40, 52)	(1. Yes) (2. Yes) (For those who had sex in the last 4 weeks but not last week) (Weeks 4, 24, 40, 52)	(Yes) (Last 4 weeks, for those who did not have sex in the last week) (Weeks 4, 24, 40, 52)	(1. Yes) (2. Yes) (Last 4 weeks, for those who did not have sex in the last week) (Weeks 4, 24, 40, 52)	Yes (Monthly)	No	No	Subset	Subset	Subset	No
Carraguard	1. Yes 2. Yes (Month 1 + Quarterly)	No	No	Yes ("Past 2 weeks") (Month 1 + Quarterly)	1. No 2. No	No	No	Yes (Month 1 + Quarterly)	Yes (Batched)	No	No	No	No	No
CS CONRAD	No	Yes ("Past 7 days") (Monthly)	1. Yes 2. Yes ("Past 7 days") (Monthly)	No	No	No	No	No	No	No	No	No	No	No
CAPRISA 004 (One gel before sex and one gel after sex)	1. Yes 2. Yes (Monthly)	Yes (Last 7 days) (Monthly)	1. Yes, but did not ask about coverage of two doses: "How many of these sex acts had gel use?" 2. No (Last 7 days) (Monthly)	No	No	Yes (Last 30 days) (Monthly)	1. Yes: "How many study gels did you use?" 2. No (Last 30 days) (Monthly)	Yes (Monthly)	No	Yes Genital specimens (Baseline, months 3, 12, 24, exit & at time of suspected seroconversion)	No	No	No	No

Table 3.3.1: Source variables for the five trials

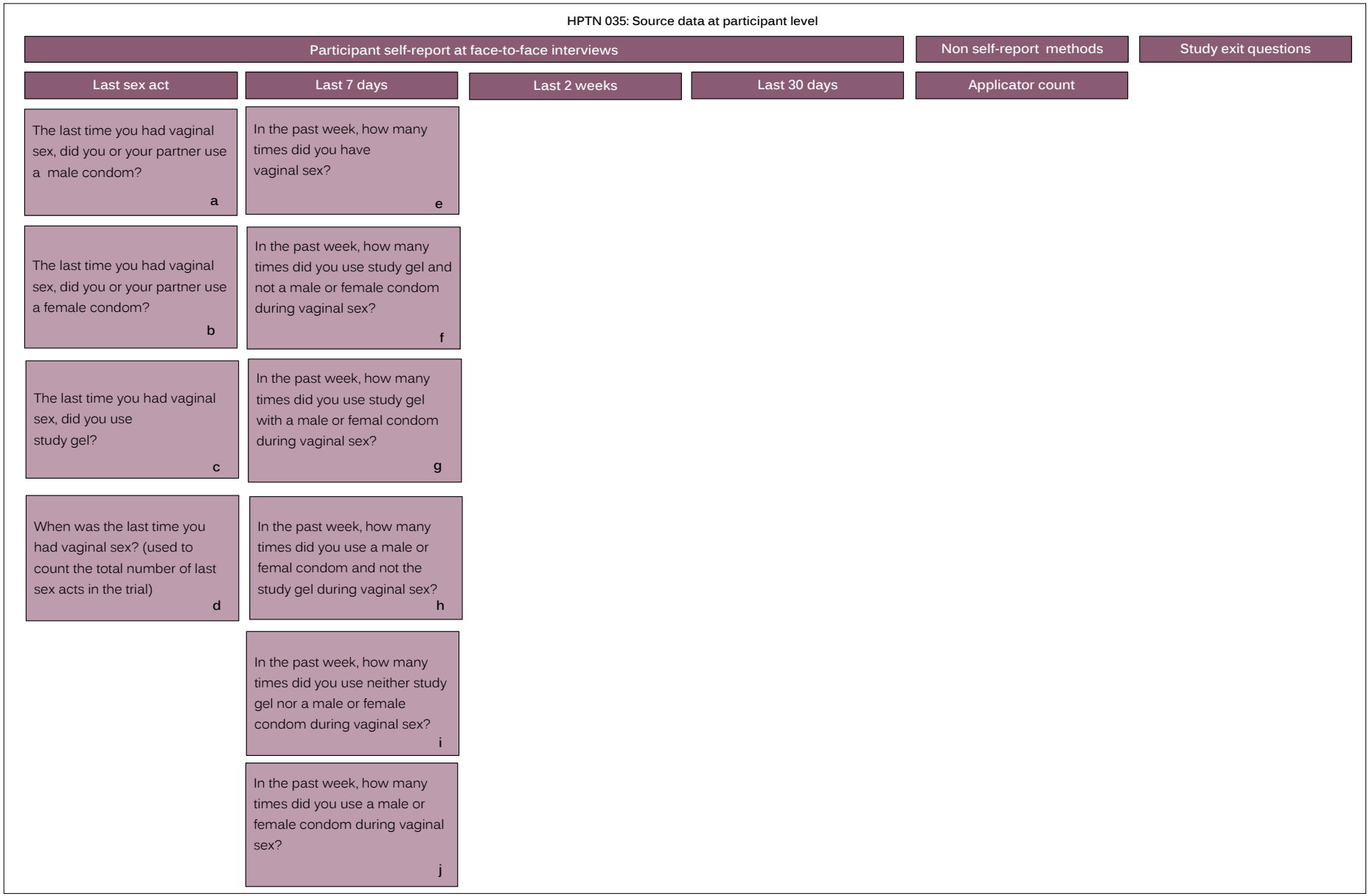


Figure 3.3.1: HPTN 035 source variables

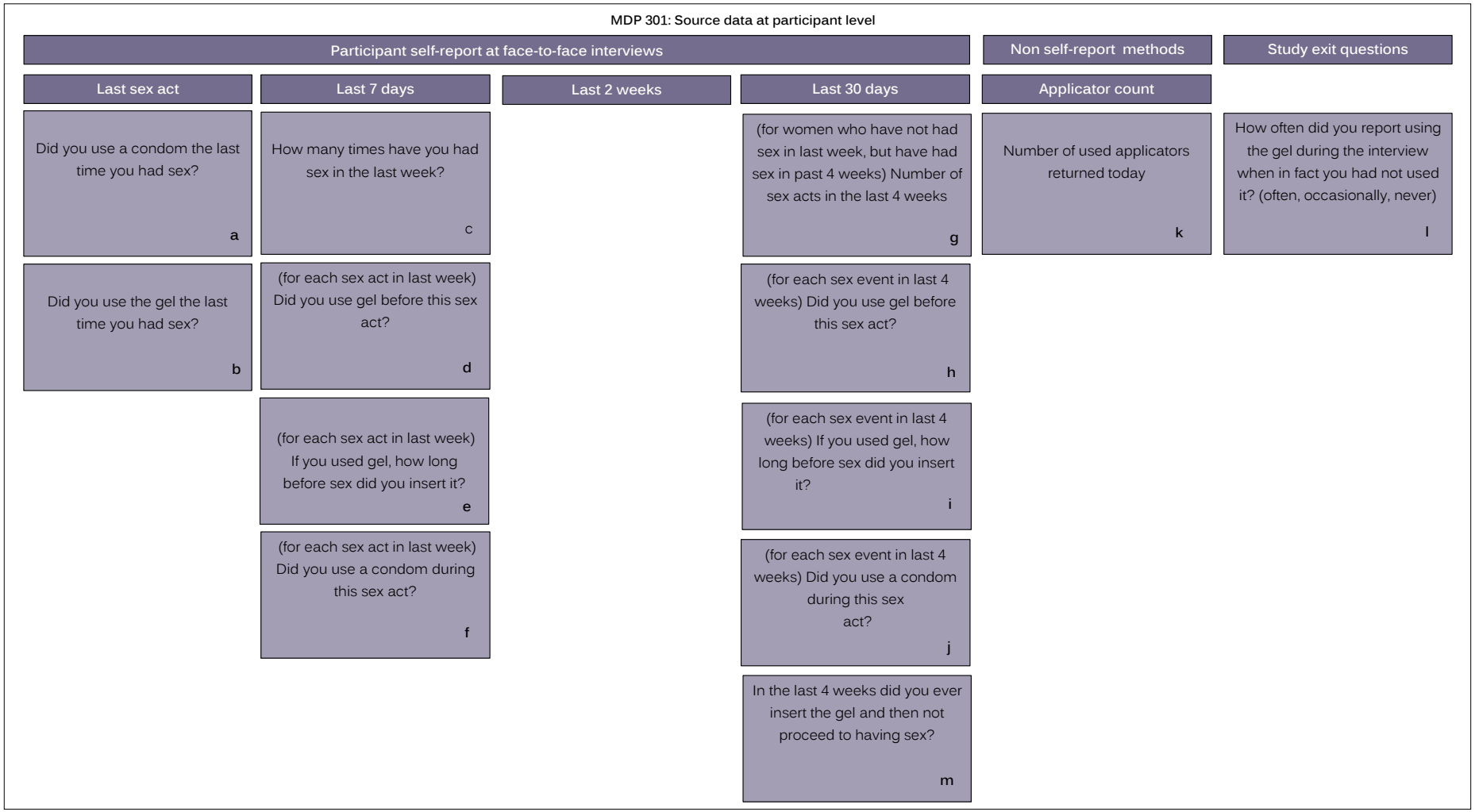


Figure 3.3.2: MDP 301 source variables

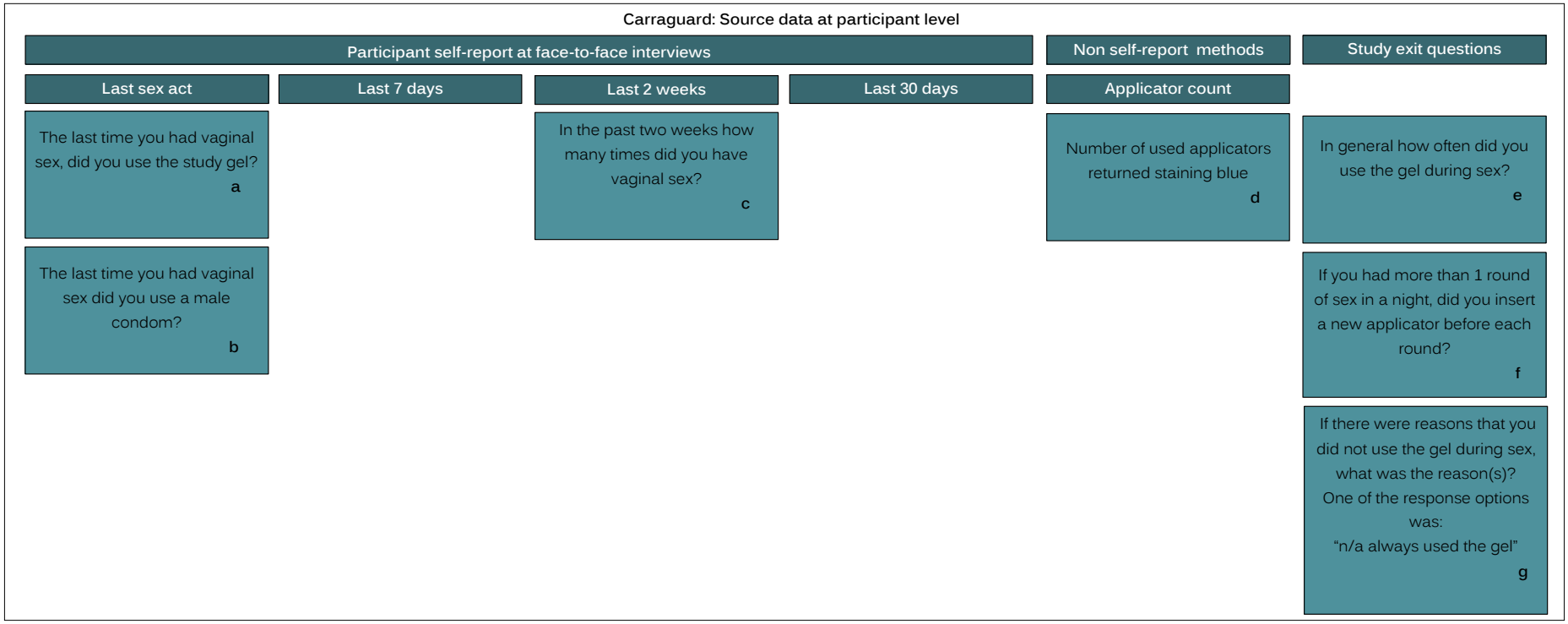


Figure 3.3.3: Carraguard source variables

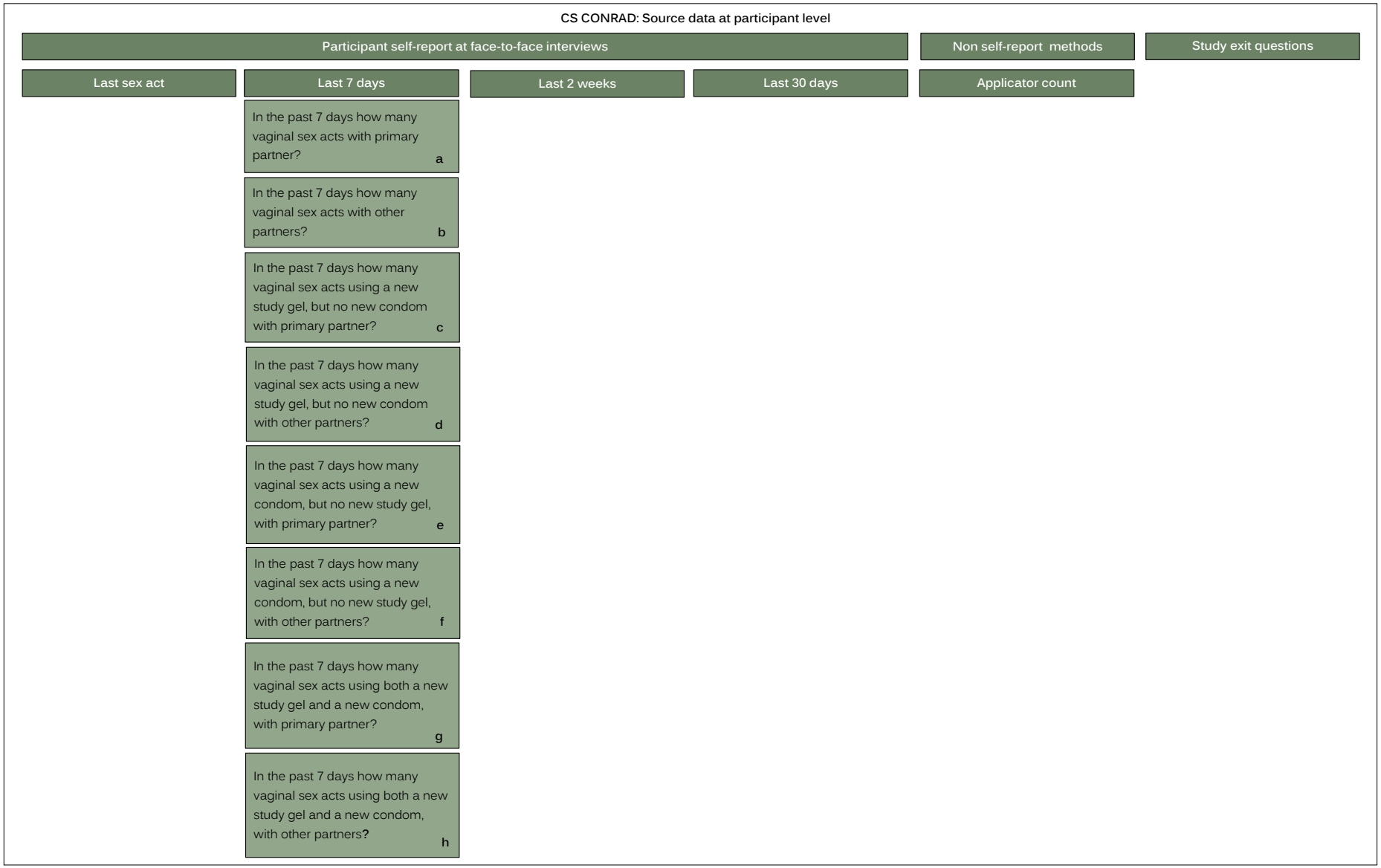


Figure 3.3.4: CS CONRAD source variables

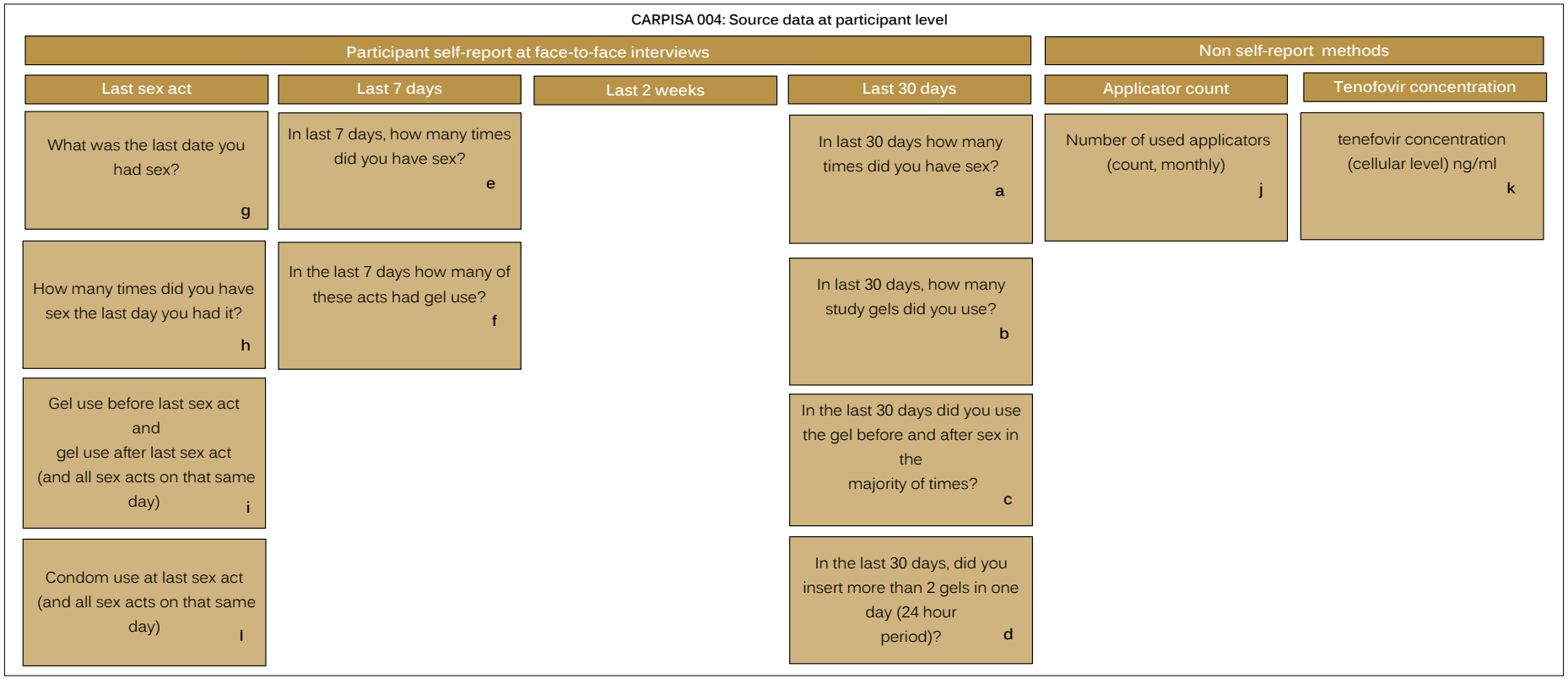


Figure 3.3.5: CAPRISA 004 source variables

3.3.1.1 SELF-REPORTED GEL AND CONDOM USE DURING SEX

All five trials included questions about sex acts, gel use during sex acts, and condom use during sex acts, gathered in FTFIs conducted by trial staff. The trials combined these questions in different manners and used different recall periods and frequency of data collection.

LAST SEX ACT

Four of the five trials asked in FTFIs about gel use and condom use at last sex act (HPTN 035, MDP 301, Carraguard, CAPRISA 004). CAPRISA 004 asked if one applicator of gel was used before sex and one applicator after sex, per the BAT24 regimen that requires an applicator of gel within 12 hours before sex, an applicator of gel as soon as possible after sex and again within 12 hours, and not more than two applicators within a 24-hour period. CAPRISA 004 also asked about all sex acts on the day of the "last sex act." Two trials (HPTN 035 and Carraguard) asked this question at quarterly visits. Two trials (MDP 301 and CAPRISA 004) asked this question at monthly visits. CS CONRAD was the only trial of the five that did not ask about last sex acts.

LAST 7 DAYS OR LAST WEEK

Four of the five trials (HPTN 035, MDP 301, CS CONRAD, CAPRISA 004) asked about the proportion of sex acts covered by gel in the last 7 days or last week. Wording of the time period varied from trial to trial, as did the format of the questioning (see example in Figure 3.3.6). CAPRISA 004 asked how many sex acts had gel use, but did not ask how many gels were used, or if a pre-dose and post-dose were used. Three trials (HPTN 035, MDP 301, CS CONRAD) also asked about the proportion of sex acts covered by condoms with and without gel. CAPRISA 004 did not ask about condom use for the 7-day recall period. Two trials (CS CONRAD, CAPRISA 004) asked this question at monthly visits; one trial (HPTN 035) asked this question at quarterly visits; and one trial (MDP 301) asked this question four times over follow-up (weeks 4, 24, 40, and 52). Carraguard did not use a 7-day recall period.

HPTN 035

I know that you are counseled to use condoms for each act of vaginal sex, but I also know that this is not always possible.

2b. In the past week, how many times did you use a male or female condom and not the study gel during vaginal sex? ..... ☐☐ *# of times*

2c. In the past week, how many times did you use study gel and not a male or female condom during vaginal sex? ..... ☐☐ *# of times*

2d. In the past week, how many times did you use study gel with a male or female condom during vaginal sex? ..... ☐☐ *# of times*

2e. In the past week, how many times did you use neither study gel nor a male or female condom during vaginal sex? ..... ☐☐ *# of times*

MDP 301

6. "Now I am going to ask you some more detailed questions about your condom and gel use each time you had sex in the last week."

Day/ date	order	sex acts	Partner	Condom	Gel	Gel timing	Vaginal Cleaning	Washing timing	Partner informed
	Order of sex acts	Sex acts in the last week	What **type** of partner was this act with?	Did you use a condom during this sex act?	Did you use gel before this sex act?	If you used the gel how long before sex did you insert it?	Did you clean inside your vagina after sex? **(This includes using a dry cloth)**	If you cleaned, how long after sex was this?	If you used the gel, did you tell your partner about it?
		Codes	1=long-term stable relationship 2=other type of partner 8=don't remember	1=yes 2=no 8=don't remember	1=yes 2=no 8=don't remember	1=less than 1 hour 2= 1 to 3 hours 3= more than 3 hours 8=don't remember 9=didn't use it	1=yes 2=no 8=don't remember	1=less than 1 hour 2= 1 to 2 hours 3= more than 2 hours 8=don't remember 9=didn't clean	1=yes 2=no 8=don't remember 9=didn't use it
		1 last sex act	☐	☐	☐	☐	☐	☐	☐
		2 sex act before that	☐	☐	☐	☐	☐	☐	☐
		3 sex act before that	☐	☐	☐	☐	☐	☐	☐
		4 etc.	☐	☐	☐	☐	☐	☐	☐

Figure 3.3.6: Wording of adherence questions in two trials

LAST 2 WEEKS

Participants in Carraguard were asked how many times they had sex in the past 2 weeks. There was no corresponding question to participants about how many of those sex acts were covered by gel with and without condom. The data on the number of sex acts in the past 2 weeks were later combined with gel applicator data to estimate adherence (see section 3.3.3.3). Number of sex acts in the past 2 weeks was asked at month 1 and at quarterly visits in Carraguard.

Questions about the proportion of sex acts covered by gel in the last 2 weeks were not explicitly asked by any of the five trials as a standard question. Sex acts covered by gel and condom use in the last 2 weeks were incidentally captured with questions about sex acts in the last 4 weeks in MDP 301 when a participant reported she had not had sex in the last week, but had had sex in the last 4 weeks. There were potentially four times over follow-up when a participant could answer this question (weeks 4, 24, 40, and 52).

LAST 30 DAYS, LAST 4 WEEKS

CAPRISA 004, at monthly visits, asked participants how many sex acts they had in the last 30 days and how many gels they used in the last 30 days. They did not ask about condom coverage for those same sex acts. The proportion of sex acts covered by gel with and without condom in the last 4 weeks were documented in MDP 301 when a participant reported she had not had sex in the last week, but had had sex in the past 4 weeks. There were potentially four times over follow-up when a participant could answer this question (weeks 4, 24, 40, and 52).

3.3.1.2 NON SELF-REPORTED SOURCE DATA

This section describes how trials collected adherence-related data in ways that did not involve participants answering questions in FTFIs.

APPLICATOR COUNTS

Three trials asked participants to return applicators to the study clinics for counting (MDP 301, Carraguard, CAPRISA 004). Carraguard collected applicators at month 1 and at

quarterly visits. MDP 301 and CAPRISA 004 collected applicators at monthly visits.

APPLICATOR DYE STAIN ASSAY (DSA)

Carraguard was the only trial of the five trials that developed a specific method for testing if the returned gel applicators had evidence of being vaginally inserted. The dye stain assay (DSA) was conducted on all returned applicators and was completed at the end of the trial.

BIOMARKERS

CAPRISA 004 collected genital specimens from participants at baseline; months 3, 12, and 24; study exit; and at the time of suspected seroconversion. Genital samples were tested for concentration levels of tenofovir, the antiretroviral drug being tested for prevention of sexual transmission of HIV. All other trials included in this study tested investigational microbicides for which no biomarkers were available.

3.3.1.3 METHODS USED WITH SUBSETS OF TRIAL POPULATIONS

The following methods were not used to collect adherence source data for all trial participants. They were used in subsets of trial participants to help understand adherence in the trials and test novel methods for adherence and sexual behaviour data collection. HPTN 035 included a sub-study with audio computer-assisted self-interview (ACASI). MDP 301 included a social science sub-study that used a number of methods to better understand adherence in the trial. MDP 301's sub-study followed a subset of 725 randomly assigned trial participants over time. Methods to assess adherence in this sub-study included use of coital diaries, in-depth interviews, the standard gel accountability forms used for all participants, the standard structured interviews used for all participants, and a special comparison form to triangulate and reconcile adherence data from the various sources.

COITAL DIARY

MDP 301 gave coital diaries to a subset of trial participants (725) to record their sexual activity and gel and condom use over a 4-week period of time prior to study visits at weeks

4, 24, and 52.

IN-DEPTH INTERVIEWS

MDP 301 used in-depth interviews (IDIs) in two ways in order to understand adherence in their social science sub-study. First, they used IDIs to ask trial participants about sexual behaviour and gel adherence for the same time periods used in the CRFs for visits at weeks 4, 24, and 52, but used open-ended questions. They then used the IDIs to reconcile discrepancies in adherence data from answers at FTFIs on CRFs, returned gel applicators, coital diaries, and answers received earlier in the IDIs.

COMPARISON FORM FOR DATA TRIANGULATION

As noted above, MDP 301 used a special step to reconcile discrepant answers from different sources. A "comparison form" linked to study visits at weeks 4, 24, and 52 was used with a subset of 725 trial participants. Prior to IDIs, data about gel use from CRFs, returned gel applicators, and coital diaries were noted on the form. During the IDI, gel use data gained through more open-ended questioning, were also recorded. Discrepancies from these four different sources were discussed with participants and resolved. The corrected gel use data was then noted on the comparison form.

ACASI

Audio computer-assisted self-interview (ACASI) was used by HPTN 035 in a subset of 663 participants from Lilongwe and Blantyre, Malawi. Hand-held devices with pictures and audio asked participants the same set of adherence and sexual behaviour questions as used in the CRFs in FTFIs.

3.3.1.4 SUMMARY OF SOURCE DATA

All trials used self-reported data to measure adherence. Different recall periods for sex were used, with four out of five trials asking about more than one recall period (HPTN 035, MDP 301, Carraguard, CAPRISA 004). Four out of five trials asked about last sex act (HPTN 035, MDP 301, Carraguard, CAPRISA 004). Frequency of questions varied, with three trials collecting adherence data at monthly visits (MDP 301, CS CON-

RAD, CAPRISA 004) and two trials collecting adherence data primarily at quarterly visits (HPTN 035, Carraguard). Three trials included applicator returns as a part of their data collection (MDP 301, Carraguard, CAPRISA 004). One trial tested returned applicators using a special assay to better differentiate applicators that were vaginally inserted from those where contents might have simply been expelled (Carraguard). One trial used an ARV-based microbicide and was able to collect genital specimens for biomarker analysis (CAPRISA 004). Two trials collected adherence data using additional methods on just a subsample within their trial populations (HPTN 035, MDP 301). MDP 301 had a significant social science component where coital diaries, in-depth interviews and reconciliation sheets were used. HPTN 035 included a sub-study where some participants answered questions about sexual behaviour and gel use via ACASI.

3.3.2 OVERALL ADHERENCE ESTIMATES IN PUBLISHED MANUSCRIPTS

This section describes the overall adherence estimates used by trial teams to describe trial adherence in primary results publications. This results section, which describes the overall adherence estimates, preserves the terminology and language chosen by trial teams used in the publications, which may not be precise. Commentary on the language is provided in the discussion section. A summary of overall adherence estimates for each trial is provided in Table 3.3.2.

Trial	Publication	Summary estimate 1	Summary estimate 2	Summary estimate 3
HPTN 035	AIDS 2011	81% last sex acts covered by gel	61.3% sex acts with gel and condom	69.1% condom free last sex acts covered by gel
MDP 301	Lancet 2010	89% mean gel use at last sex act (95% CI: 86–91)		
Carraguard Population Council	Lancet 2008	96.1% last sex acts covered by gel	Estimated average of 42.1% sex acts covered by gel	
CS CONRAD	New England Journal of Medicine 2008	87% of all sex acts covered by gel in trial (reported in the 7 days before each follow up visit)	78% of sex acts with primary partners covered by gel (reported in the 7 days before each follow up visit)	45.8% condom free sex acts covered by gel (reported in the 7 days before each follow up visit)
CAPRISA 004	Science 2010	72% (average), 60.2% (median) of self-reported sex acts in the last 30 days covered by two doses of gel	61.3% (overall median) gel adherence for women who did not aquire HIV; 59.2% (overall median) for women who did aquire HIV	About 40% of women had below 50% gel adherence

Table 3.3.2: Overall adherence estimates in primary results publications

3.3.2.1 HPTN 035

HPTN 035 reported three summary estimates of adherence in their primary results publication.[29] The first adherence summary estimate states the percentage of last sex acts covered by gel for the trial (81%). The second adherence summary estimate states the percentage of "sex acts" covered by gel and condom for the trial (61.3%). The third adherence summary estimate states the percentage of last sex acts with no condom which were covered by gel in the trial (69.1%). The methods section of their publication states that adherence estimates were calculated using self-reported data for last sex act data.

3.3.2.2 MDP 301

MDP 301 reported one summary estimate of adherence in their primary results publication.[30] The summary adherence estimate reported in the publication states the mean percentage of last sex acts covered by gel (89%). The methods section in the publication states trial participants were asked at each monthly visit about their gel use at their most recent sex act.

3.3.2.3 CARRAGUARD

Carraguard reported two summary estimates of adherence in their primary results publication.[26] The first adherence summary estimate states the average percentage of last sex acts covered by gel (96.1%). It is clear in the publication that this estimate is derived from self-reported data. The second adherence summary estimate states a different estimate of sex acts covered by gel, based on results of the DSA of gel applicators and estimated reported number of sex acts each week (42.1%). The methods section states this calculation was made by dividing the average number of applicator insertions per week (based on the DSA results) by the average number of sex acts every week (based on participant interviews).

3.3.2.4 CS CONRAD

CS CONRAD reported three summary estimates of adherence in their primary results publication.[28] The first adherence summary estimate states the percentage of all sex acts covered by gel in the trial (87%). The second adherence summary estimate states the percentage of sex acts with primary partners that were covered by gel in the trial (78%). The

third adherence summary estimate states the percentage of sex acts with no condom in the trial that were covered by gel (45.8%). It is clear in the publication that these estimates are derived from self-reported data based on the 7 days prior to each study visit.

3.3.2.5 CAPRISA 004

CAPRISA 004 reported three main summary estimates of adherence in their primary results publication.[31] The first set of summary adherence estimates stated the average and median percentage of "sex acts covered by two doses of gel in the last 30 days" (72% and 60.2%, respectively). The methods section defines the basis of these estimates as the number of returned applicators, divided by 2, divided by the number of sex acts reported that month. The second set of summary adherence estimates were calculated in the same manner as the first set of estimates, but segregated by HIV status: the median percentage of gel adherence for the last 30 days for women who did not acquire HIV (61.3%) and the median percentage of gel adherence for the last 30 days for women who did acquire HIV (59.2%). The third summary estimate of adherence states the approximate percentage of trial participants who had less than 50% adherence (40%).

3.3.2.6 SUMMARY OF ALL TRIALS

All five included trials presented summary adherence estimates for the trials as means or medians. The type of means and medians are explained in the results section that describes the calculation of published results (3.3.3) and in the discussion section under two types of averages (3.4.4.1). Some trials had up to three estimates to describe adherence; one trial reported one summary estimate of adherence. Three trials used averages based exclusively on self-reported data (HPTN 035, MDP 301, CS CONRAD). Two trials combined applicator data with self-reported data to produce summary estimates (Carraguard, CAPRISA 004).

While CAPRISA 004's publication provided the most clarity on how the estimates were calculated, in general the descriptions in the manuscripts do not provide enough specificity for the reader to understand exactly how the adherence estimates were calculated, as there are different methods that can be used to produce overall averages from the source data.

Statistical analysis plans were consulted for more detailed explanations of how the estimates were made. This resulted in less clarity, as descriptions offered in SAPs often did not match the methods described in the publications or there was not enough specificity in the SAP for the reader to understand the exact methods used for the published estimates.

3.3.3 CALCULATION OF PUBLISHED RESULTS

This section explains in detail the mathematical process that each trial team used to calculate the adherence estimates reported in their primary results publications. Review of the SAPs and primary results publications did not provide confirmation on the exact methods used to calculate the adherence estimates published. All trial teams were contacted for confirmation of their methods. Results presented below are based on trial teams' reviews and subsequent corrections and clarifications of the schematic diagrams describing the adherence calculation process sent to them. The process of using source data to calculate the overall adherence estimates is represented for each trial in figures 7–11. For completeness, the detailed process is also described in text format below.

3.3.3.1 HPTN 035

The first summary estimate of adherence reported by HPTN 035 was: 81% of last vaginal sex acts were covered by gel. Figure 3.3.7 shows how this figure was calculated from the source data. The total number of last vaginal last sex acts for the trial (D) was calculated by summing the number of responses to the question "when was the last time you had vaginal sex"? (d). The total number of last vaginal sex acts covered by gel for the trial (C) was calculated by summing the number of "yes" responses to the question "The last time you had vaginal sex, did you use study gel"? (c), aggregated across all sex acts across all participants in the trial. The total number of last sex acts covered by gel for the whole trial (C) was then divided by the total number of last sex acts for the whole trial (D), to calculate the summary estimate of percentage of last vaginal sex acts covered by gel.

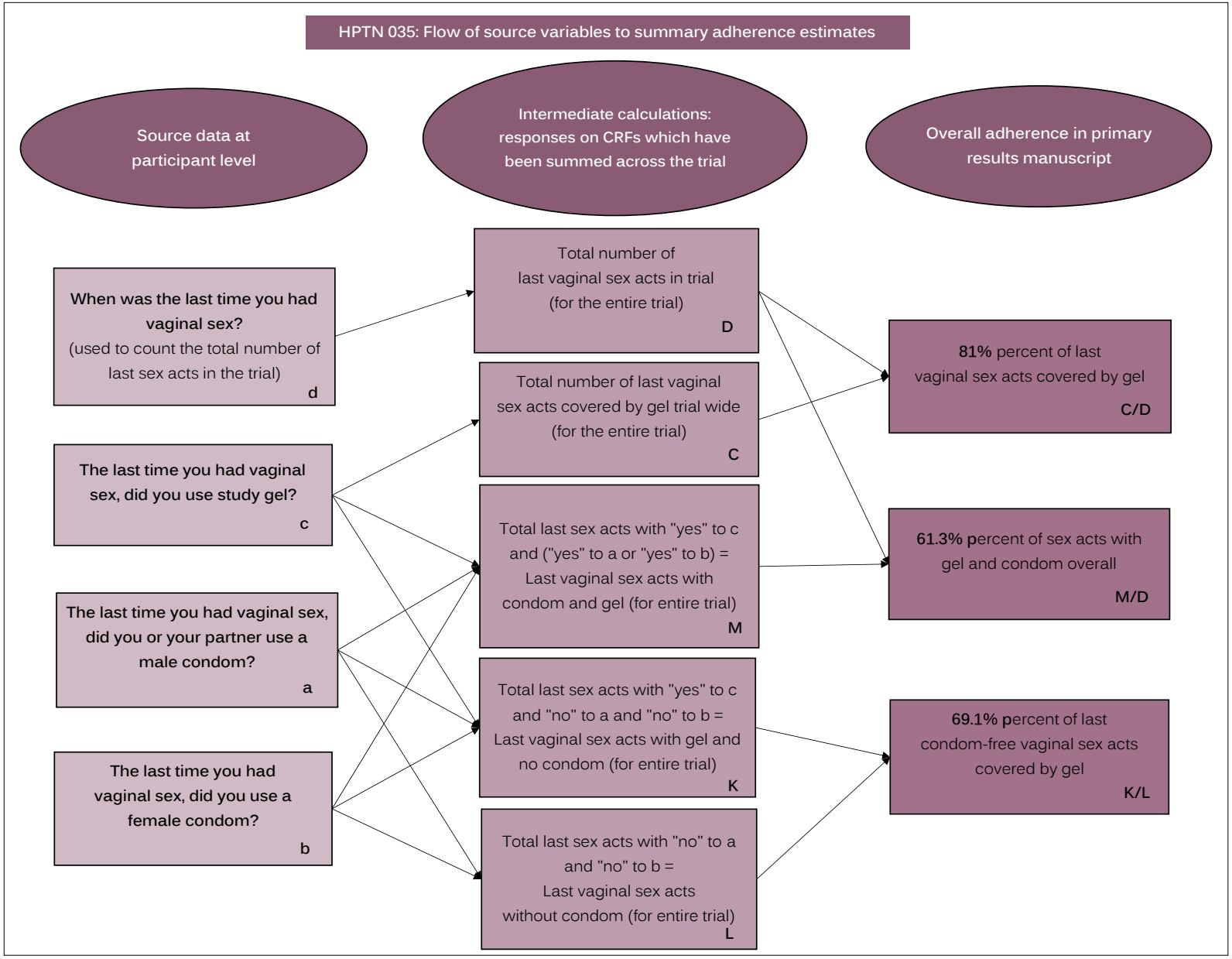


Figure 3.3.7: HPTN 035 calculation of summary adherence estimates

The second summary estimate of adherence reported by HPTN 035 was: 61.3% of vaginal sex acts were covered by gel and condom. While the estimate stated in the publication did not state which type of sex act was used to make this calculation, the trial team confirmed the source data were last sex acts. Figure 3.3.7 demonstrates how this estimate was calculated from the source data. The total number of last vaginal last sex acts for the trial (D), aggregated across all sex acts across all participants in the trial, was calculated by summing the number of responses to the question "when was the last time you had vaginal sex"? (d) and serves as the denominator for this estimate. The total number of last sex acts with condom and gel (M), the numerator of the summary estimate, was calculated by summing the total number of "yes" responses to "The last time you had vaginal sex did you use study gel"? (c) and "yes" responses to "The last time you had vaginal sex did you or your partner use a male condom"? (a) or "yes" responses to "The last time you had vaginal sex did you use a female condom"? (b). The total number of last sex acts with condom and gel (M) was then divided by the total number of last sex acts for the whole trial (D), to calculate the summary estimate of percentage of last vaginal sex acts with gel and condom for the trial.

The third summary estimate of adherence reported by HPTN 035 was: 69.1% of last condom-free vaginal sex acts were covered by gel. Figure 3.3.7 shows how this estimate was calculated from the source data. The total number of last vaginal sex acts without condom for the trial (L) was calculated by summing the total responses of "no" to the question "The last time you had vaginal sex did you or your partner use a male condom"? (a) and the total number of responses of "no" to the question "The last time you had vaginal sex did you use a female condom"? (b), aggregated across all sex acts for the trial. This comprised the denominator of the summary estimate. The numerator of the estimate, the total number of last sex acts in the trial with gel and no condom (K), was derived by summing the total number of "yes" responses to the question "The last time you had vaginal sex did you use the study gel"? (c) and "no" responses to the question "The last time you had vaginal sex did you or your partner use a male condom"? (a) and "no" responses to the question "The last time you had vaginal sex did you use a female condom"? (b). The total number of last sex acts with gel and no condom (K) was then divided by the total number of last vaginal sex acts without condom for the trial (L) to calculate the summary estimate of percentage of last condom-free vaginal sex acts covered by gel for the trial.

3.3.3.2 MDP 301

The summary estimate of adherence reported in the main trial paper for MDP 301 was 89% gel use at last sex act. Figure 3.3.8 shows how this estimate was calculated from the source data. The total number of last sex acts for each participant over her trial follow-up (W) was calculated by summing the total number of "yes" responses with the total number of "no" responses to the question "Did you use the gel the last time you had sex"? (b). The total number of sex acts covered by gel for each participant for her follow-up (Z) was calculated by adding all of the "yes" responses to the question "Did you use gel the last time you had sex"? (b). To calculate the percentage of sex acts covered by gel for each participant over her follow-up (Y), her total number of "yes" responses to using gel at last sex act (Z) was divided by her total number of sex acts over follow-up (W). To calculate the average percentage of gel use at last sex act for the whole trial, the mean adherences (Y) of the participants were added together and divided by the number of participants who contributed values to the numerator (n).

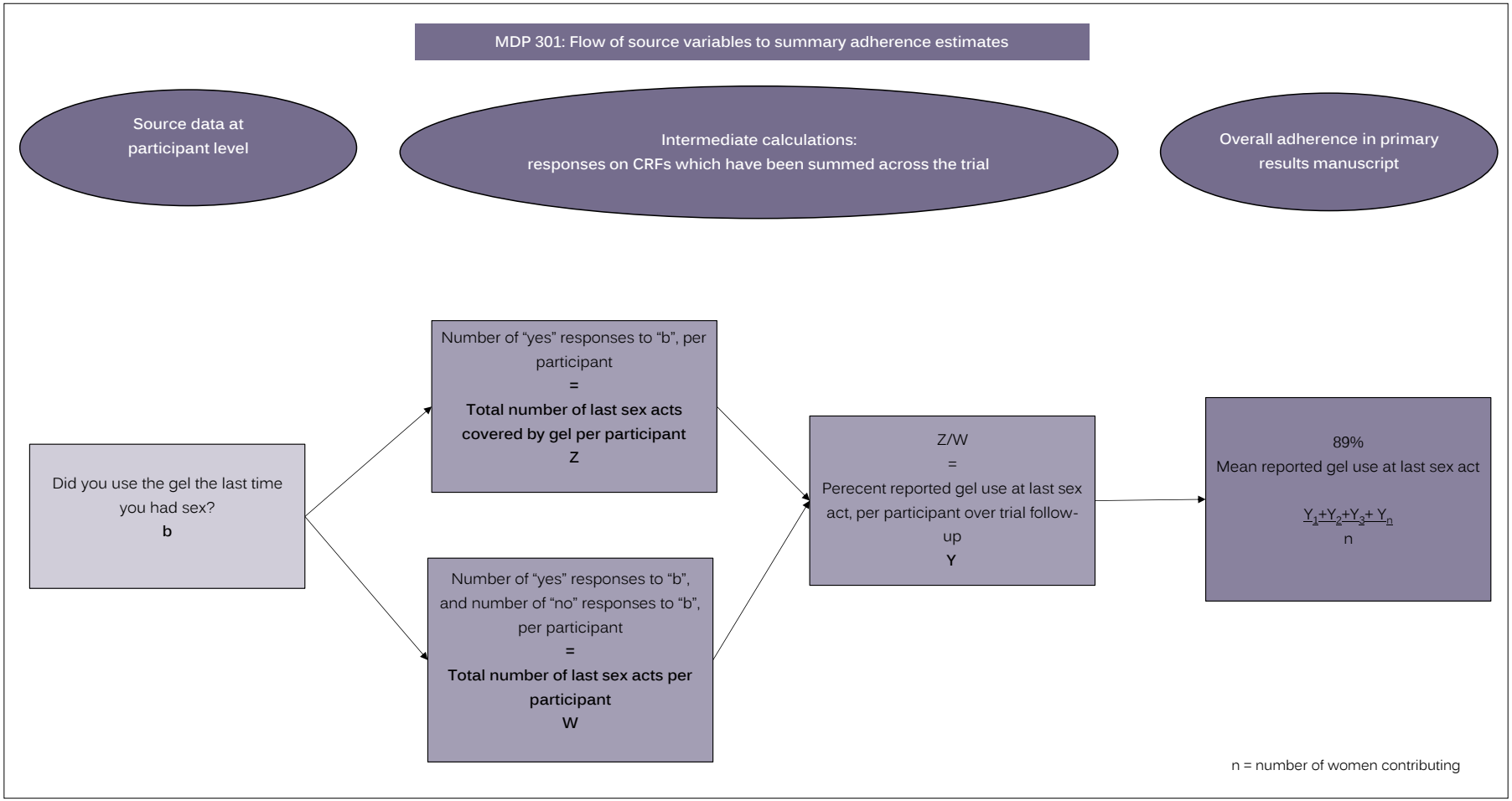


Figure 3.3.8: MDP 301 calculation of summary adherence estimates

3.3.3.3 CARRAGUARD

The first summary estimate of adherence reported by Carraguard was: 96.1% of last sex acts were covered by gel. Figure 3.3.9 shows how this estimate was calculated from the source data. The number of "yes" responses to the question "The last time you had vaginal sex, did you use the study gel"? (a) was used to calculate the total number of last sex acts covered by gel for the whole trial (G). The number of "no" responses to the same question (a) was used to calculate the total number of last sex acts not covered by gel for the trial, denoted as "H" in the figure. The total number of last vaginal sex acts for the whole trial (Z) was calculated by summing the total number of last sex acts covered by gel for the trial (G) with the total number of last sex acts not covered by gel for the trial (H). To calculate the percentage of last vaginal sex acts covered by gel for the trial, the total number of last sex acts covered by gel (H) was divided by the total number of last sex acts for the whole trial (Z).

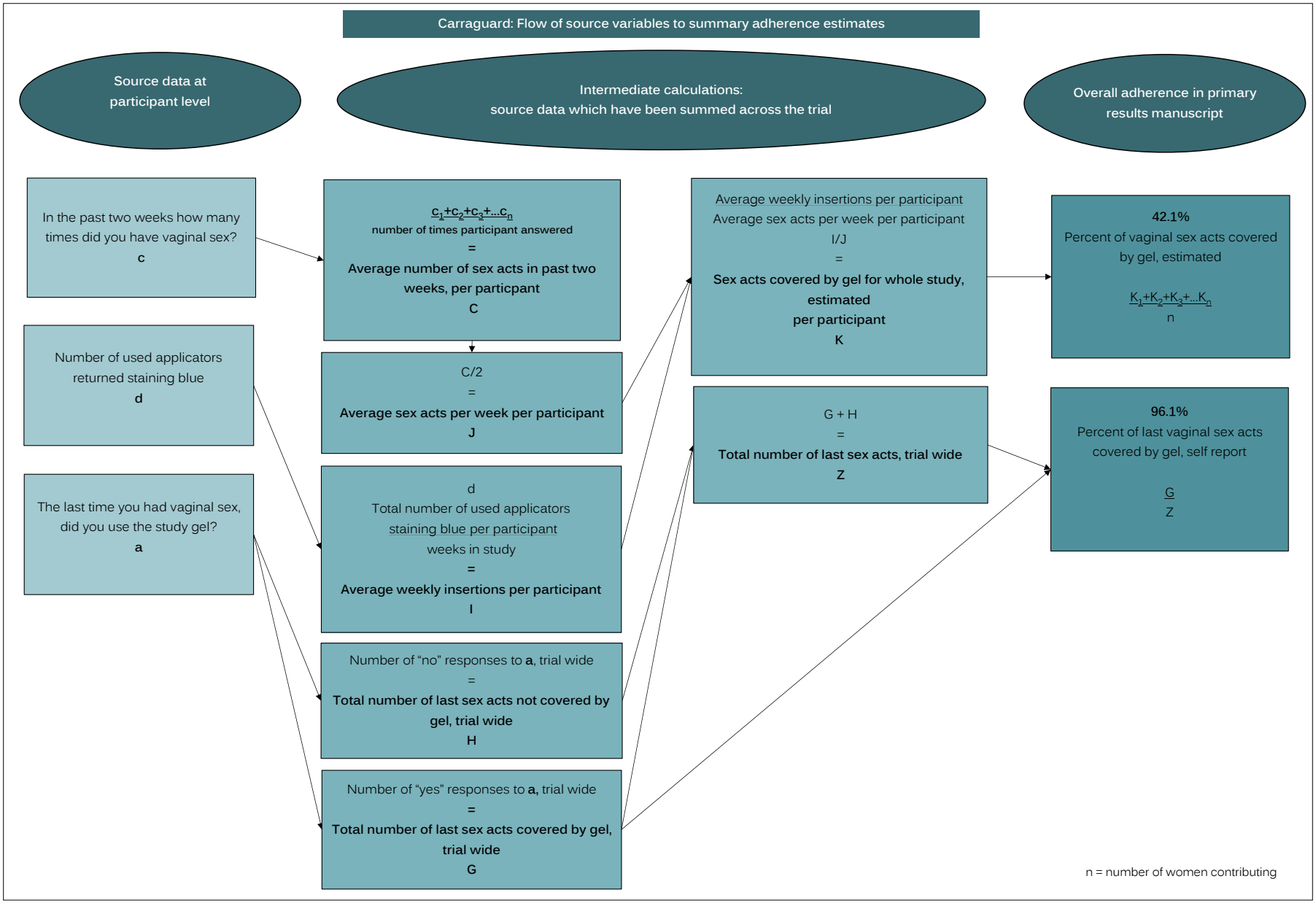


Figure 3.3.9: Carraguard calculation of summary adherence estimates

The second summary estimate of adherence reported by Carraguard was: 42.1% of vaginal sex acts coveded by gel. Figure 3.3.9 shows how this estimate was calculated from the source data. Each trial participant returned her used applicators at regular trial visits. For each participant, all returned used applicators were tested with the DSA to determine if they were inserted vaginally, according to the assay. To estimate the average weekly insertions of gel for each participant (I), the total number of used applicators staining blue (d) for a trial participant over her follow-up was then divided by the number of weeks she participated in the study. At each follow-up visit, each participant was asked "In the past two weeks how many times did you have vaginal sex"? (c). For each participant, this number was averaged over her follow-up to calculate her average number of sex acts in the last 2 weeks (C). The average sex acts per week (J) for each participant was then calculated by dividing the average number of sex acts in the last two weeks by 2. Sex acts covered by gel over the study for each participant (K) was calculated by dividing her average weekly insertions (I) by her average sex acts per week (J). To calculate the summary estimate for the trial of the 42.1% of vaginal sex acts covered by gel, the estimated proportions of sex acts covered by gel over the study for each person (K) were added together and divided by the total number of participants participating who contributed to the numerator.

3.3.3.4 CS CONRAD

The first summary adherence estimate reported in the main trial paper for CS CONRAD was: 87% of all sex acts in the trial were covered by gel. Figure 3.3.10 shows how this estimate was calculated from the source data. At every monthly visit, each participant was asked "In the past 7 days how many vaginal sex acts with a primary partner"? (a). Each participant was also asked "In the past 7 days how many vaginal sex acts with other partners"? (b). To obtain the total number of vaginal sex acts for a participant for the past 7 days, the answers to (a) and (b) were summed to give "S," the total number of vaginal sex acts in the past 7 days. To obtain the number of vaginal sex acts covered by gel in the past 7 days for an individual participant (J), the responses from the following 4 questions were summed: "In the past 7 days how many vaginal sex acts using a new study gel, but no new condom with primary partner"? (c); "In the past 7 days how many vaginal sex acts using a new study gel, but no new condom with other partners"? (d); "In the past 7 days, how many vaginal sex acts using both a new study gel and a new condom, with primary partner"? (g); and "In the past 7 days, how many vaginal sex acts using both a new study gel and a new condom, with other partners"? (h). To obtain the percentage of sex acts covered by gel for one participant's monthly visit (Q), the total number of vaginal

sex acts covered by gel (J) was divided by the total number of vaginal sex acts reported by that participant at that monthly visit (S). To calculate each participant's trial average of gel adherence (N), each participant's monthly visit's reported percentage of gel coverage was added ($Q_1+Q_2+Q_3+...+Q_n$) and divided by the number of months contributed in the numerator, to obtain an average adherence for each participant. Then all participant averages were averaged across the trial by adding each participant's contribution ($N_1+N_2+N_3+...+N_n$) and dividing by the total number of participants contributing to the numerator, to obtain the average percentage of vaginal sex acts covered by gel for all participants over the trial.

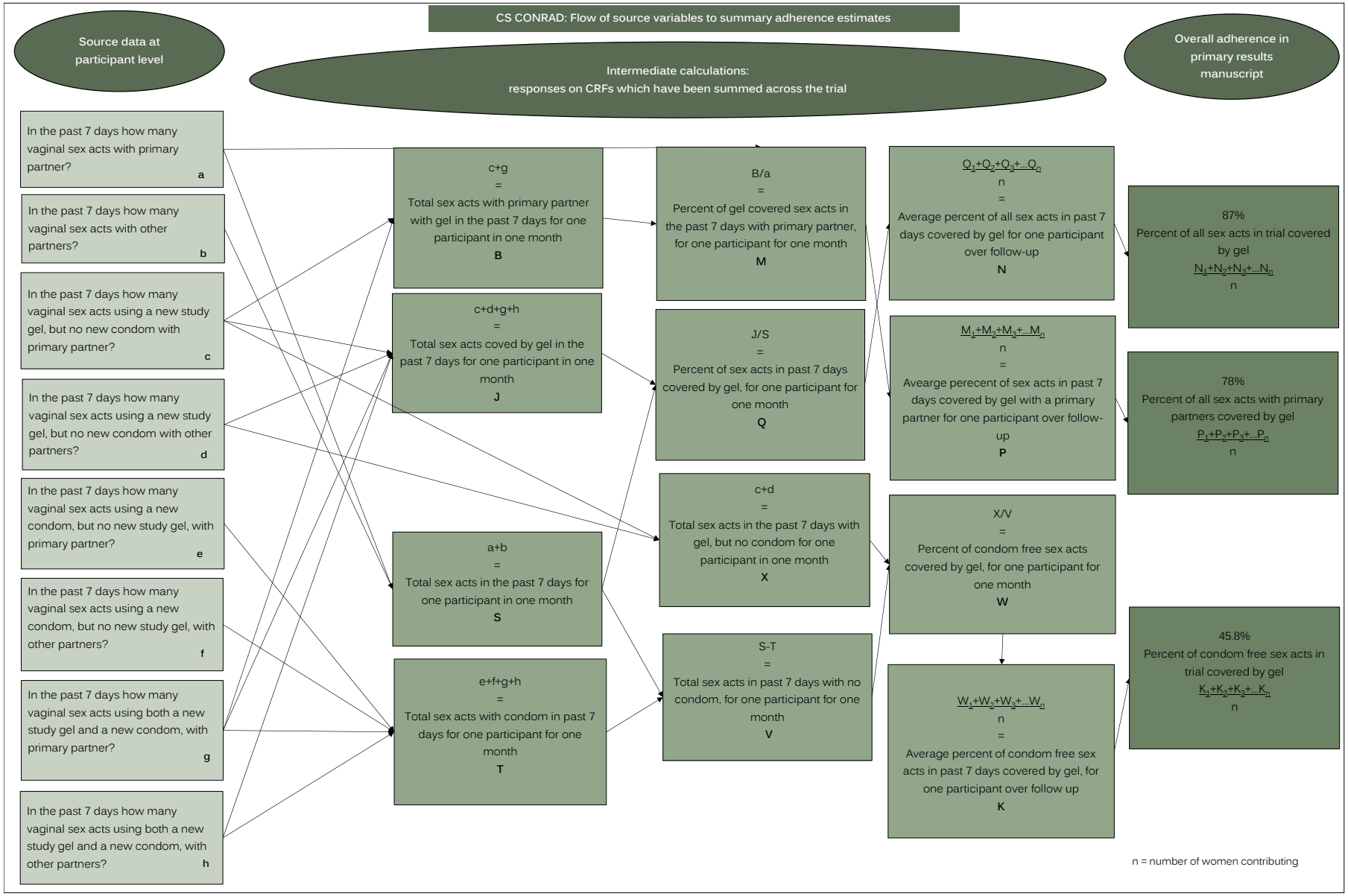


Figure 3.3.10: CS CONRAD calculation of summary adherence estimates

The second summary adherence estimate reported in the main trial paper for CS CONRAD was: 78% of all sex acts with primary partners in the trial were covered by gel. Figure 3.3.10 shows how this estimate was calculated from the source data. To obtain the number of vaginal sex acts with a primary partner when gel was used in the past 7 days for an individual participant (B), the responses from the following two questions were summed: "In the past 7 days how many vaginal sex acts using a new study gel, but no new condom with primary partner"? (c) and "In the past 7 days, how many vaginal sex acts using both a new study gel and a new condom, with primary partner"? (g). To obtain the number of sex acts with a primary partner over the past 7 days, participants at each monthly visit were asked "In the past 7 days how many vaginal sex acts with a primary partner"? (a). The number of sex acts covered by gel with a primary partner for one participant for one monthly visit (B) was divided by the total number of vaginal sex acts with a primary partner reported by that participant at that monthly visit (a), to calculate the percentage of sex acts with a primary partner covered by gel at that monthly visit (M) for one participant. Each participant's monthly gel coverage with a primary partner was then calculated by adding each monthly visit's percentage of gel coverage ($M_1+M_2+M_3+...+M_n$) and dividing by the number of monthly visits contributed in the numerator, to obtain an average gel coverage with primary partner for each participant over follow up (P). Then all participants' averages across the trial were added ($P_1+P_2+P_3+...+P_n$) and divided by the total number of participants contributing to the numerator, to obtain the average percentage of vaginal sex acts covered by gel with primary partners for the trial.

The third summary adherence estimate reported in the main trial paper for CS CONRAD was: 45.8% of condom-free sex acts in the trial were covered by gel. Figure 3.3.10 shows how this estimate was calculated from the source data. First, the number of sex acts with a condom in the past 7 days (T) was determined by adding responses to the following four questions: "In the past 7 days how many vaginal sex acts using a new condom, but no new study gel with primary partner"? (e); "In the past 7 days how many vaginal sex acts using a new condom, but no new study gel, with other partners"? (f); "In the past 7 days how many vaginal sex acts using both a new study gel and a new condom, with primary partner"? (g); and "In the past 7 days how many vaginal sex acts using both a new study gel and a new condom, with other partners"? (h), to give T. Then the total number of sex acts in the past 7 days (S) was calculated by summing responses from the following two questions: "In the past 7 days how many vaginal sex acts with primary partner"? (a) and "In the past 7 days how many vaginal sex acts with other partners"? (b). To calculate the number of sex acts in the past 7 days with no condom (V), the number of sex acts in the past 7 days with a condom (T) was subtracted from the total number of

sex acts in the past 7 days (S) for that participant for that monthly visit. To calculate the total number of sex acts in the past 7 days with gel and no condom (X), responses to the following two questions were summed: "In the past 7 days how many vaginal sex acts using a new study gel, but no new condom with primary partner"? (c) and "In the past 7 days how many vaginal sex acts using a new study gel, but no new condom with other partners"? (d). The total number of sex acts in the past 7 days with gel and no condom (X) was then divided by the total number of sex acts without a condom (V) to give one participant's percentage of condom-free sex acts covered by gel for one monthly visit (W). Each participant's percentage of condom-free, gel-covered sex acts for the trial (K) was calculated by adding together the percentages of condom-free, gel-covered sex acts across all monthly visits of observation ($W_1+W_2+W_3+...+W_n$) and dividing by the number of monthly visits contributed in the numerator. Then all participants' averages across the trial were added together ($K_1+K_2+K_3+...+K_n$) and divided by the total number of participants contributing to the numerator to obtain the average percentage of vaginal sex acts covered by gel and no condom for the trial.

3.3.3.5 CAPRISA 004

The first set of summary adherence estimates reported in the main trial paper for CAPRISA 004 were 72% (average) and 60.2% (median) of self-reported sex acts in the last 30 days covered by two doses of gel, trial-wide. Figure 3.3.11 shows how this estimate was calculated from the source data. Each month, the number of used applicators were counted for each trial participant (j). For each participant, the total number of used applicators (j) was divided by 2 to obtain "half the number of returned used applicators in the last 30 days" (L). To obtain the proportion of sex acts in the last 30 days covered by 2 gels for each participant (M), half of the number of returned used applicators for each month (L) was then divided by the answer to the question "In the last 30 days how many times did you have sex?" (a). For each participant, the median monthly adherence (N) was then calculated by taking the median "proportion of sex acts in the last 30 days covered by 2 gels" across all months of observation (M). The average percent of self-reported sex acts in the last 30 days covered by two doses of gel for the whole trial was then calculated by taking each participant's median monthly adherence (N) and dividing by the number of participants who contributed a median monthly adherence value, giving a mean of medians. The median percentage of self-reported sex acts in the last 30 days covered by 2 doses of gels for the trial was calculated by taking the median of each of the participant's median

monthly adherence estimates (N).

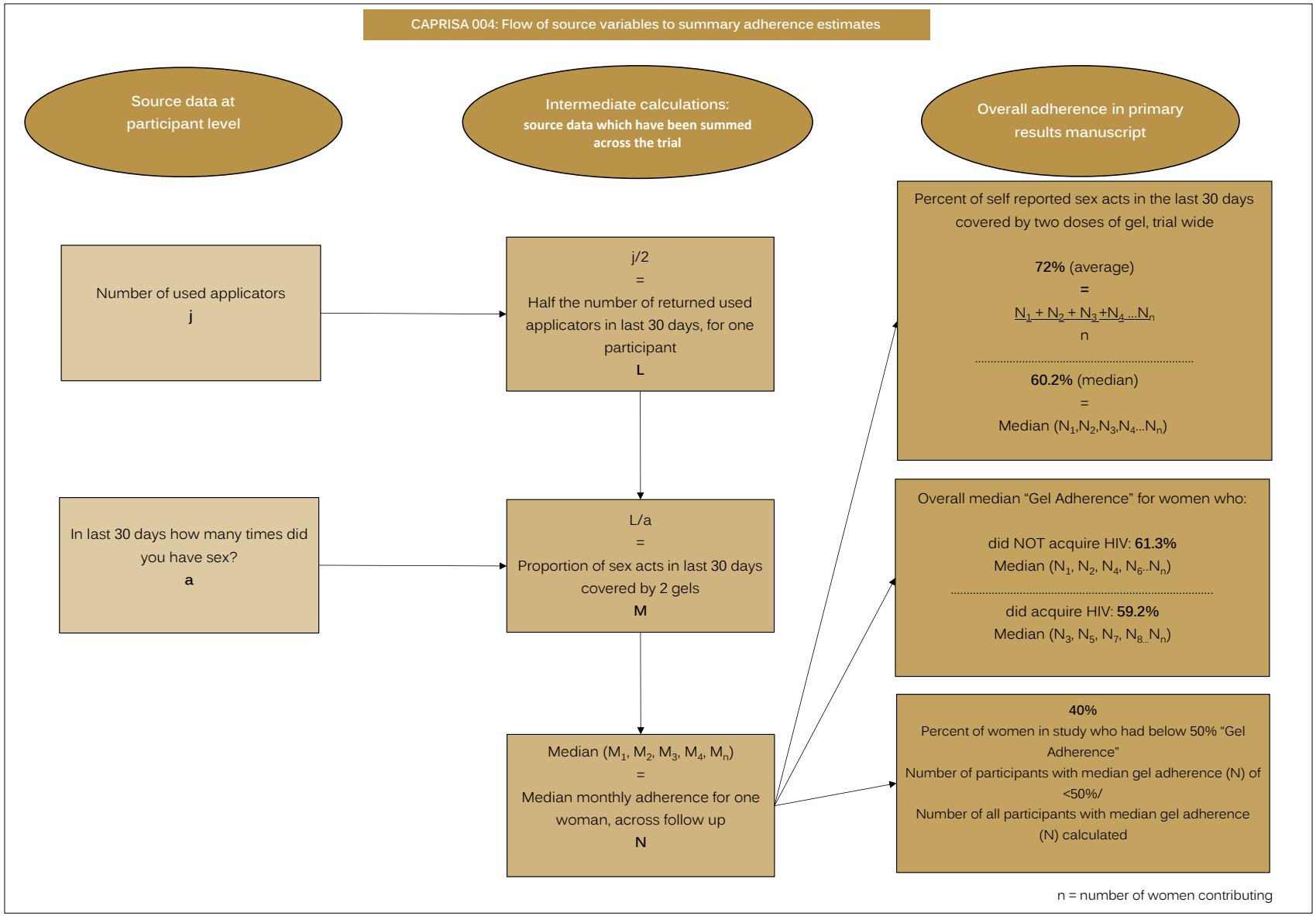


Figure 3.3.11: CAPRISA 004 calculation of summary adherence estimates

The second set of summary estimates of adherence for CAPRISA 004 includes the overall median gel adherence for women who did not acquire HIV (61.3%) and for women who did acquire HIV (59.2%). Figure 3.3.11 shows how these numbers were calculated. The median of each participant's median monthly adherence (N) for participants who did not acquire HIV was taken to obtain the 61.3% gel adherence for women who did not acquire HIV. The median of each participant's median monthly adherence (N) for participants who did acquire HIV was taken to obtain the 59.2% gel adherence for women who did acquire HIV.

The final summary estimate of adherence reported for CAPRISA 004 was 40% of women in the study had less than 50% gel adherence. This summary estimate was calculated by taking the number of participants with a median gel adherence (N), as described above, who had less than 50% adherence, and dividing by the number of all participants for whom a median gel adherence was calculated.

3.3.3.6 SUMMARY OF CALCULATIONS

Not all source data collected were ultimately used to summarise adherence in primary results manuscripts. Two different methods to summarise adherence results emerged: some trials used the total number of sex acts as the denominator, with the numerator being comprised of the total number of sex acts covered by gel in the trial; other trials used the number of participants as the denominator, with the numerator being comprised of the addition of each participant's average adherences over trial follow-up. Two trials used calculations based on the number of sex acts across the trial as the denominator for some summary estimates (HPTN 035, Carraguard). Four trials used calculations based on averages of participant adherence to characterise overall adherence (MDP 301, Carraguard, CS CONRAD, CAPRISA 004).

Three trials exclusively used self-reported data to calculate overall adherence estimates reported in primary results publications (HPTN 035, MDP 301, CS CONRAD). One trial (CAPRISA 004) used only composite measures, including self-report and applicator data, to calculate all of the overall adherence measures reported in their manuscript. One trial (Carraguard) reported overall adherence by including one estimate using exclusively self-reported data as well as one composite estimate that included a combination of self-reported data and results from the DSA.

3.3.4 COMMENTS AND LESSONS LEARNED FROM TRIALISTS

During the process of providing feedback through the trial team survey, trial teams were invited to share comments or lessons learned about trial procedures for collecting adherence data. Four of the five trial teams provided comments and feedback (MDP 301, Carraguard, CS CONRAD, CAPRISA 004). The sections below summarise some of the key points shared by these trial teams.

3.3.4.1 CHOICE OF ADHERENCE MEASURES

At the time that most of the included trials were being designed, last sex act was thought to be a good proxy for all sex acts for general populations. Because the CS CONRAD trial population included sex workers with different partner types (such as paying clients and primary partners), the trial team thought that last sex act might not be as informative as a recall period that included more sex acts. Due to the high frequency of sex acts for their population, they thought that a 30-day recall period would be too long of a duration, so a 7-day recall period was chosen to account for enough sex acts and not be too difficult for participants to recall.

Asking about adherence over multiple days better allows the opportunity to compare self-reported data with returned applicators and biomarkers. CAPRISA 004 chose a 30-day recall period so applicators from the last visit could be reconciled with participant report and because participants did not necessarily have frequent sex.

How often to ask participants about sex and gel use is another factor that must be considered. Asking adherence information at less-frequent intervals is less burdensome to trial participants and staff, and is less costly as well. Two trial teams noted that when participants have fewer times to report about adherence, it might create an environment where they are less comfortable admitting that they had not used the gel.

Trial teams were highly supportive of including biomarkers and new technologies in future trials, especially as these technologies are continuing to improve. There was also support for using different measures to assess adherence, such as composite measures and triangulation of results. Trial teams that included a strong social science component thought those elements were essential and helped improve adherence and overall trial implementation. One trial team that did not include a strong social science component thought it

should be included in future trials.

It was stressed by some trial teams that an element of self-reported adherence is essential in any microbicide trial. Asking about adherence provides an opportunity for trial staff to ascertain if trial participants understand the regimen and how to use the product. If staff members discover issues with adherence during the FTFIs, they can then provide support to participants about how to use the product correctly and manage situations where they have had difficulty using the product. This is a critical way that trials can prospectively improve product adherence.

3.3.4.2 REPORTING ADHERENCE IN PRIMARY PUBLICATIONS

All trial teams reported adherence as overall estimates that were means or medians across the trials. Space limitation was noted by some trial teams as a reason for not providing more information about adherence. One trial team noted that averages are not particularly informative for data of a time-varying nature.

3.3.4.3 RECOMMENDATIONS FOR FUTURE TRIALS

As stated earlier, trial teams recommended more reliance on biomarkers and technologies to help assess adherence in trial populations, as well as inclusion of a strong social science component. Trial teams noted that future adherence questions should be phrased to ask about non-use, with the underlying assumptions of the questionnaire being that all participants will miss some doses and that doing so is both normal and acceptable. Creating an environment where participants feel it is expected that they will not be able to adhere all of the time can improve honest reporting. One trial team noted the need for improved and innovative ways to help trial participants remember actual sex acts and gel use. Another team noted that the underlying problem in microbicide trials is low adherence, and that finding ways to ensure better adherence to study products is therefore of critical importance to the field of microbicide development.

3.4 DISCUSSION

3.4.1 LIMITATIONS AND STRENGTHS

The main limitation of this study is that four of the five trials available to be examined in this study represent second generation microbicide trials, rather than third generation microbicide trials, which is currently the direction that the microbicide field is taking. In recent years, microbicide trials have tested ARV-based products that allow biomarker source data to be collected. Biomarkers were not available for the investigational products tested in HPTN 035, MDP 301, CS CONRAD, and Carraguard. Over time, microbicide trial design has become more sensitive to the importance of adherence, and each subsequent microbicide trial draws on lessons learned from previous trials. In particular, current biomedical HIV prevention trials have focused attention on improved adherence counselling and stronger social science components which comprehensively examine adherence.[90,91,92] Another limitation of this study is that CRFs were reviewed in English and not in the local languages used at each site. It is possible that exact wordings of questions in the final local language forms were not exactly equivalent to the approved English versions, despite procedures used for translations and back translations.

Two strengths of this study are that trial-specific documents such as actual CRFs, SAPs, and protocols were used in the analysis and that results, before finalisation, were shared with trial teams for corrections and clarifications. A third strength of this study is that five post-surfactant effectiveness trials were included in the analysis, which gives a broad sense of the ways that second generation trials were measuring, calculating, and reporting adherence.

3.4.2 SOURCE DATA

The five included trials collected a variety of source data that could be used to assess adherence, although not all of the source data collected were used in the primary publications to characterise adherence.

3.4.2.1 CLARITY OF WORDING AND HOW QUESTIONS ARE ASKED

The wording of some questions was ambiguous, which created a situation where trialists may have understood the meaning of the question in one way and different trial participants may have understood it in other ways. One example would be when trialists are interested in knowing about sex acts and gel use in the last 7 days, but ask participants about the "last week." The understandings of "week" and "last week" may vary from person to person,[93] whereas "day" is a term that is likely to have more similar interpretations across different people. A trial collecting data on sex acts in the "last week" may inadvertently be including information about sex acts in different periods of time in their dataset compared to trials that ask about "last 7 days," unless each interviewer at each interview takes time to carefully and correctly define the trial team's definition of "last week" for the duration of the trial. Similar problems with meanings of words or phrases have also been identified with terms such as "sex" and "sex act," and "anal sex."[70,19] In order to better ensure that terms used in study forms are clear, unambiguous, and have the same meaning to trial staff as they do to the diversity of participants participating in the trials, it is important for leaders of trial teams to invest appropriate resources in creating study materials. Trial staff must understand their own limitations with regard to cultural understanding, and work closely with study populations to pilot forms and terminology until there is certainty that meanings are understood as intended.[93,70]

An interesting finding is that questions using the same recall period may be written in significantly different ways that may be easier or more difficult for participants to answer accurately. MDP 301 asked participants about sex acts "last week" by first asking about the last time the participant had sex and then filling in information about gel and condom use for that sex act. The sex act after that one was then identified; the participant was asked about gel and condom use for that sex act; and so on. HPTN 035, by contrast, asked participants to produce verbal statements of how many sex acts in the last week were covered by differing combinations of gel and condom use. A question that asks participants to mathematically calculate in their heads the number of sex acts in the last week covered by various combinations of gel and condom, such as "How many times did you use the study gel and not the male or female condom"? may have been challenging for some participants to answer, and may have increased the chance for error. Asking participants to remember the most recent sexual event, recall specifics of that event, and then move on to the next most recent event may make it easier for participants to recall and report more accurately.

3.4.2.2 RECALL TIME

Choosing a recall time to collect adherence data requires considering the trial population, the types of sexual partners they have, the frequency with which they have sex, and what other type of adherence data might be collected that could be combined with self-reported data to develop composite measures of adherence. Last sex act is a simple and useful recall period, especially for general population participants. For participants who have different types of partners, and potentially different gel and condom use patterns, according to partner type, asking about sex acts over multiple days may be advantageous. Asking about a recall period that includes multiple days can be helpful when combined with other types of data, such as returned applicators.

3.4.2.3 SELF-REPORTED DATA

Since the results of Carraguard were published, and showed a large discrepancy between self-reported adherence and adherence results estimated from of the applicator DSA, it has been well established that self-reported data in biomedical HIV prevention trials are likely to overestimate adherence.[26,88,94,95,96] However, there are important reasons why self-reported adherence data will continue to be an essential element within microbicide trials. Adherence to microbicide regimens that are used around the time of sex can only be assessed in the context of knowing when sexual intercourse takes place. At this time, the only way to know when participants have had sexual intercourse is to ask them. Even in the context of non-coitally dependent microbicides, where biomarkers can be used to measure adherence, it is important to ask participants about when their sex acts have occurred, so that data on exposure to HIV can be examined along with exposure to the study drug.

Asking about adherence in any microbicide trial is also of critical importance because doing so provides a platform for staff to assess if participants understand the regimen correctly and are having any problems using the product. Many of these products, such as gels, are new to trial participants and may be uncomfortable or seem strange at first. In the context of asking about adherence, staff can correct misunderstandings, provide more advice on product use, and help participants problem solve situations where adherence might have been difficult or impossible. For example, if a participant is concerned about her partner's reaction to her gel use, a staff member can suggest inviting the partner to the study clinic to learn about the gel and the trial. Engaging participants in discussions about their adherence is one of the most important ways that adherence within a trial

can be improved prospectively. It is important to note, however, that asking participants about their adherence for counselling purposes can be conducted separately from the procedures for adherence data collection.

Accuracy of self-reported adherence can be facilitated in a number of ways that relate to the study clinic environment and how questions are asked. Preceding questions with "permissive" statements that acknowledge that it is not always possible to use the study gel are being included more often in trials. As noted by some trial teams in this study, another important way to increase accuracy in self-reported data would be to create an environment where times of non-adherence are expected and considered a normal part of trial participation. Questions around product use should begin with asking about non-use, which helps the participant understand that using the gel all of the time is not usually possible.

3.4.2.4 NON SELF-REPORTED SOURCE DATA

Applicator returns were used in three of the five included trials, although they were not always included in summary adherence estimates. Returned applicator data give trial staff an additional avenue to understand participant adherence, but as with verbal self-reports, participants can manipulate their "answers" by controlling how many applicators they return as "used." The Population Council attempted to address this issue by developing their DSA, which identifies a mucosal enzyme and therefore can differentiate between vaginally inserted applicators and those that simply had the gel expelled, outside of the vagina. This assay was not validated in the context of washed applicators, however (some participants may have washed them before returning them to the clinic);[66] nor can the assay identify if the applicator contents were expelled into the correct participant's vagina. Distinct advantages of applicator assessments is that they can be used with both placebo and active products and that adherence information can be fed back to participants during trial follow-up to prospectively improve adherence.

Trial teams included in this study were enthusiastic about inclusion of biomarkers in future trials, as they can provide additional and potentially more accurate data about product use. Now that most microbicides being investigated are ARVs, collection of blood and vaginal specimens is included in trial protocols. Biomarkers do have a number of challenges, however. Analyses of biological specimens for microbicides tend to only provide information about product use proximate to sample collection, and rates of drug absorp-

tion can vary within individuals and between individuals.[85] Results of biomarker assays do not provide information about sexual activity, and thus about exposure to HIV. Results are subject to being manipulated by participants, as participants may choose to use the product immediately before attending study visits where samples are collected, but not at other times. In placebo-controlled trials, results of adherence based on study drug found in biological samples cannot be shared with participants in real time during trials to improve adherence prospectively, as this would break the blinding. Biomarker data are also not available for the placebo group, which eliminates the possibility of conducting sub-analyses of efficacy by adherence on both the investigational and control products. Finally, a current major limitation of collection of biological samples and processing for biomarkers is the high expense.

3.4.3 OVERALL ADHERENCE ESTIMATES

All five included trials presented summary adherence estimates for the trials as means or medians. Overall averages can mask important information and can paint a more positive image of adherence. For example, CAPRISA 004 reported that an average of 72% of sex acts "were covered by two doses of gel," yet another measure indicates that 40% of women had below 50% adherence. Reliance on averages is particularly a problem when trials report null results.

Overall, summary estimates also do not convey important differences between members of trial populations, such as age categories or site, which may have differences in adherence. Importantly, overall averages may not convey enough information to assist trial teams and other members of the field in interpreting the primary results of the trials. Participants use microbicide products over many months or even years, but overall averages are unable to convey how product use may vary over time and how product use may vary between different trial participants.

There are a number of possible reasons why trials have historically reported more simplistic estimates of adherence in primary results publications. One is that it has taken time for the microbicides field to learn the central role that adherence plays in these trials, and thus dedicate more resources to understanding adherence. Another is that, with no biomarkers being available for first and second generation products, adherence estimates have largely relied on participant self-report of product use. Yet another is that the objective of publications of primary results from microbicide trials is to report the main trial

findings, and more detailed analyses of adherence typically are conducted and published at a later time. Finally, journal space restrictions may have also played a role in limiting the amount of information trial teams provided about adherence. One hopes that space limitations will not continue to be a factor; journals are increasingly offering supplemental sections online to provide greater detail and clarifications for publications.

3.4.4 How calculations were made

3.4.4.1 Two types of averages

Two main differences emerged in how summary estimates were calculated: some summary estimates were based on total sex acts as the denominator, whereas other summary estimates were based on trial participants as the denominator. Both methods provide an overall summary of adherence, but numbers produced from the different estimates can be different and can provide different information. When the total number of sex acts is used as the denominator, the numerator includes the total number of sex acts that are covered by gel in the trial. In this case, the adherence estimate provides information about what proportion of sex acts within the entire trial were covered by the investigational product. Here, all sex acts are treated equally and the estimate can more directly be used to help interpret the effectiveness estimate of the trial. Overall estimates that use participants as the denominator use the addition of each participant's average adherences over trial follow-up as the numerator. In this case, the overall estimate is influenced by the adherence behaviour of participants. This type of estimate is helpful to provide information about participant adherence over follow-up.

A simple mathematical example designed to demonstrate the difference is a hypothetical trial with 10 participants. Two participants have 100 sex acts each (with no condoms) and do not use the gel during any of the sex acts. The remaining 8 participants have 6 sex acts each (with no condoms) and use the gel for each of those sex acts. In the method where overall adherence is calculated by having the total number of sex acts as the denominator, there are a total of 248 sex acts (100 + 100 + 6 + 6 + 6 + 6 + 6 + 6 + 6 + 6) over trial follow-up. The numerator is comprised of 48 sex acts which have been covered by gel (0 + 0 + 6 + 6 + 6 + 6 + 6 + 6 + 6 + 6). 48/248=19% adherence, meaning that 19% of sex acts in the trial were covered by gel. In the method where overall adherence is calculated by having the total number of participants as the denominator, there are 10 participants in the trial. The numerator is comprised of each participant's average adherence (0% + 0%

+ 100% + 100% + 100% + 100% + 100%+ 100% + 100% + 100%), which is then divided by the number of participants to yield 800%/10=80% adherence.

In this example, different methods to calculate average adherence using the same data produced very different summary estimates: 19% adherence and 80% adherence. If a trial had a null result, and adherence was reported to be 19%, it would indicate that participant use was low and that biological efficacy of the investigational drug was still unknown. If in that same trial adherence was reported to be 80%, the assumption might be that adherence was high; thus, a reasonable conclusion might be that the investigational drug is not efficacious.

In reality, these two estimates do not provide the same information. The 19% estimate provides information about how many sex acts were covered by gel, and this estimate is helpful to interpret the result of a trial result with respect to potential biological efficacy. The 80% estimate based on averages of participant adherence, however, is not necessarily helpful in interpreting the result of the trial with respect to product efficacy. Rather, the 80% estimate is an average of each participant's overall adherence over follow-up and therefore provides more direct information about participant behaviour.

3.4.4.2 ASSUMPTIONS IN CALCULATIONS

The two trials that used composite estimates to report overall adherence estimates included important assumptions in their calculations. Carraguard was unable to test applicators in real time with the DSA, and thus results of the assays are not linked to actual time periods of reported sexual activity during the trial. Averages for each participant were taken of reported sex acts over 2-week periods over follow-up, and then divided by 2. Accordingly, the trial team accurately characterised their summary composite adherence measure in their publication as "estimated." As noted earlier, the DSA was not validated in the context of washing the applicators. Thus it is not known if washing applicators may have reduced the DSA's ability to detect if an applicator was used, potentially biasing their estimate of adherence to a lower value.

CAPRISA 004, in their calculations of overall adherence, assumed that each sex act was covered by two gels even though data for pre- and post-sex applications were not collected for the 30-day recall period. In their publication, their main summary estimate is referred to as "sex acts covered by two doses of gel in the last 30 days." This calculation

was achieved by taking the number of returned used applicators, dividing by 2, and then dividing by the number of sex acts reported for that same period of time. The trial team states in their manuscript that "adjusting for multiple sex acts within 24 hours made no material difference" to the estimates made. This statement does not consider situations, however, when participants may have consistently used only one applicator of gel for each sex act. Thus, the adherence estimates reported by CAPRISA 004 may have been biased in a higher direction.

3.4.4.3 LACK OF CLARITY OF METHODS USED TO ESTIMATE ADHERENCE IN TRIAL INFORMATION

To understand how the five trial teams estimated adherence in their trials, this comparative study examined primary results publications, trial protocols, CRFs, and SAPs. Interestingly, reading those materials did not locate clear explanations on how all adherence estimates were calculated. In some cases, there was a lack of clarity in the SAP or publication as to exactly how calculations were made, particularly with respect to whether denominators were sex acts or participants. In other cases, methods may have been well defined in the SAP, but a different definition or method was used in the primary publication or vice versa. In one case, the SAP stated that trial teams were still determining how adherence would be calculated.

It appeared, in reviewing the SAPs, that some of the methods described for analysing adherence data were intended for internal purposes and that there was not necessarily clear documentation about how adherence estimates would be reported in publications. Moreover, in communicating with trial teams, it appeared that certain definitions used for "adherence" in some SAPs were intended for thorough analyses of adherence and were not included in the primary results publications. In all five trials, it was necessary to ask for clarification of the methods used to calculate adherence estimates reported in primary results manuscripts.

Good practice in clinical trials includes pre-specifying how analyses will be conducted.[44] Pre-specification helps prevent investigators from only reporting results that might be more favourable to a particular perspective—a practice which, in turn, can result in bias. If trial teams specify analytic methods for adherence estimation a priori, but use different methods for the results which are actually reported, it is important for trial teams to state

the change in analysis method and the reason for making the change.

3.4.5 GOING FORWARD

This study has looked at how five completed effectiveness trials of coitally dependent microbicide gels measured adherence, calculated adherence, and reported adherence in primary trial results publications. There was considerable variety in how trials measured, calculated, and reported adherence. Better standardisation of methods would more easily allow comparison of results across trials. There is also a need for better rigour in designing questions used on CRFs so that terms are unambiguous and have the same meaning to trialists as to trial participants. Questions about adherence should begin by asking about non-adherence as the standard. In addition, continued investment in strong social science components of trial implementation can help improve how questions are asked and improve trial conduct.[74,40,97,98]

Interpretation of trial results will be improved as ways to test biological samples and technologies to monitor adherence are developed and refined.[99,100] Despite careful reading of trial protocols, CRFs, SAPs, and primary results publications, it was not possible to understand exactly how reported adherence estimates were calculated. Methods used for calculations described in SAPs were not always the same as methods described in primary results publications. Trial teams can invest more resources in planning how adherence analyses will be conducted, as adherence is such a critical finding in microbicide trials. Deviations from pre-specified analysis plans should be included in publications. More meaningful estimates of adherence need to be utilised to report product adherence of trial participants over time.

Finally, while it is important to continue to improve accurate ways of measuring adherence, lack of adherence can be a major cause for null results in trials, and more resources should be devoted to understanding how actual adherence to study products can be improved.

4

HIDDEN HETEROGENEITY

UNCOVERING PATTERNS OF ADHERENCE IN MICROBICIDE TRIALS

OBJECTIVE

To examine, using self-reported adherence data from four completed effectiveness microbicide trials, if longitudinal patterns of adherence are evident, and if so, what individual-level factors are associated with these patterns of adherence

INCLUDED TRIALS

HPTN 035
MDP 301
Carraguard
CS CONRAD

4

HIDDEN HETEROGENEITY

4.1 INTRODUCTION

Understanding participant adherence is critical to interpretation of results from clinical trials testing vaginal microbicides to prevent sexual transmission of HIV. As vaginal microbicides are user-controlled products, women may or may not use these topically applied investigational products according to protocol instructions. Due to the vaginal microbicides being user-controlled, a trial result that does not show a reduction in HIV in the active gel arm might be due to an investigational product not having a sufficient biological effect, or it might be due to low usage by trial participants. At the start of this PhD research, none of the completed vaginal microbicide effectiveness trials identified a protective effect of the investigational microbicides[20,21,22,23,24,25,26,27,28,29,30] except for CAPRISA 004.[31] Low adherence among trial participants is thought to have contributed to some of the null findings.[8,16,11,32,36,38]

Interestingly, while adherence is a key factor in understanding vaginal microbicide trial results, primary results publications typically report adherence to microbicides as overall averages for the trial populations. Trial averages can create an impression of overall high adherence to the study product. In reality, each woman has her own trajectory of adherence over the life of a trial, and a longitudinal approach to adherence data analysis may provide a better understanding of how participants use study products over follow-up. Rather than viewing trial populations as homogeneous, it would be helpful to understand if there are typical or distinct patterns of adherence that exist among trial participants. Thus, the first objective of this study was to determine if different patterns of adherence using self-reported data within four completed coitally dependent microbicide gel effectiveness trials could be identified, and if so, how those patterns may compare across trials. While true patterns of adherence would better be reflected in data collected from biomarker specimens, these data were not available at the start of this PhD research. If a microbicide trial population is indeed composed of subpopulations with different ad-

herence patterns, it would then be useful to understand if certain individual-level factors are associated with different patterns of adherence. If factors are associated with different patterns of adherence, this information can be helpful to trial teams both during trial implementation and trial planning. Thus, the second objective was to explore which factors might be associated with different adherence patterns.

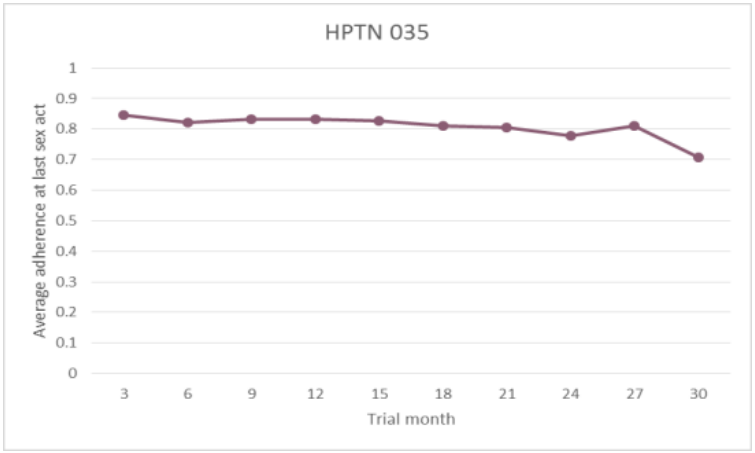
4.2 METHODS

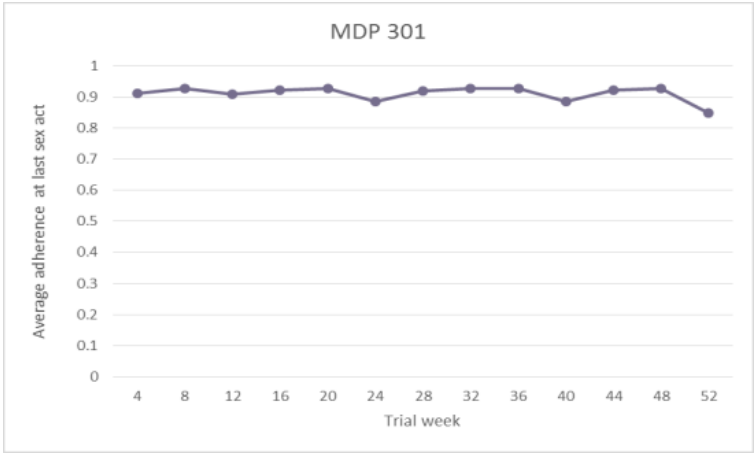
4.2.1 INCLUDED TRIALS

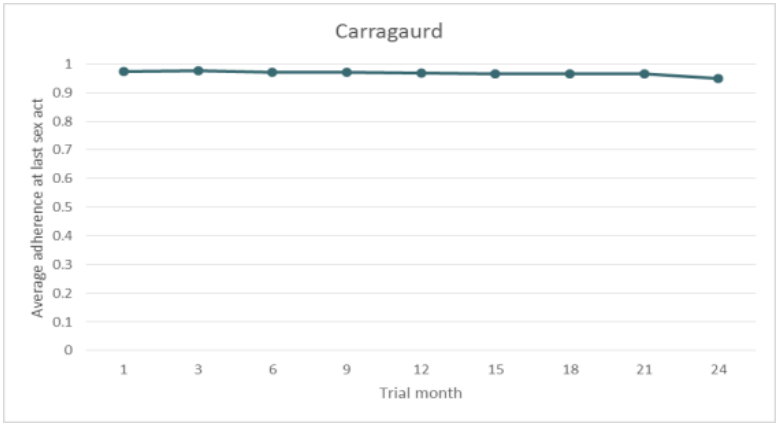
Data from four completed non-ARV based vaginal gel microbicide trials were included in this study: HIV Prevention Trials Network (HPTN) study of PRO 2000 and BufferGel (HPTN 035),[29] Microbicides Development Programme's trial of PRO 2000 (MDP 301),[30] the Population Council's trial of Carraguard (Carraguard),[26] and CONRAD's trial of Cellulose Sulphate (CS CONRAD).[28] All four trials included in this PhD study tested vaginal gels to be used around the time of sex. Self-reported adherence data were collected on a monthly or quarterly basis for each participant over her follow-up period. For this study, adherence data for three of the trials (HPTN 035, MDP 301, Carraguard) were based on asking participants about their gel use at their last sex act. Responses were yes or no, and adherence data were therefore categorical. For one trial (CS CONRAD), adherence was measured as the proportion of sex acts covered by gel over the past 7 days (all partners), with adherence being treated as a continuous variable. Two trials collected adherence data at monthly visits (MDP 301 and CS CONRAD) and two trials collected adherence data at quarterly visits (HPTN 035 and Carraguard). Table 4.2.1 provides overview information of each trial including investigational product, trial population size, locations, type and frequency of adherence data collected, and dates of trial conduct. Figure 4.2.1 provides average adherence reported for the trial, as reported in primary results publications for the trials.

Organization name Candidate product "Trial name"	Average adherence overall by self-report	Total number of participants	Type of data	Frequency of adherence data collection	Trial dates	Locations	Planned follow-up	Actual follow-up and notes
HIV Prevention Trials Network (HPTN) BufferGel PRO 2000 "HPTN 035"	81%	3,101 (This analysis: 2,282)	Categorical: Gel use at last sex act (yes/no)	Quarterly	February 2005 – September 2008	Malawi, South Africa, Zambia, Zimbabwe, US	12 – 30 months	Average follow-up was 20.4 months; trial closed as planned
Microbicides Development Programme (MDP) PRO 2000 "MDP 301"	89%	9,385 (This analysis: 6,238) (includes 0.5% gel arm + placebo to 52 weeks)	Categorical: Gel use at last sex act (yes/no)	Monthly	October 2005 – September 2009 (2% arm dropped February 2008)	South Africa, Tanzania, Uganda, Zambia	12 months for primary analysis	For 0.5% PRO 2000 and placebo gel arms, follow-up was 12 months as planned
Population Council Carraguard "Carraguard"	96%	6,202 (This analysis: 6,038)	Categorical: Gel use at last sex act (yes/no)	Quarterly	July 2005 – March 2007	South Africa	9 – 12 months	Trial closed as planned
CONRAD Cellulose Sulphate "CS CONRAD"	87%	1,398 (This analysis: 1,314)	Treated as continuous: Proportion of gel covered sex acts in past 7 days	Monthly	July 2005 – March 2007	Benin, India, South Africa, Uganda	12 months	Up to 12 months, trial halted early

Table 4.2.1: Trials included in latent structure analysis study







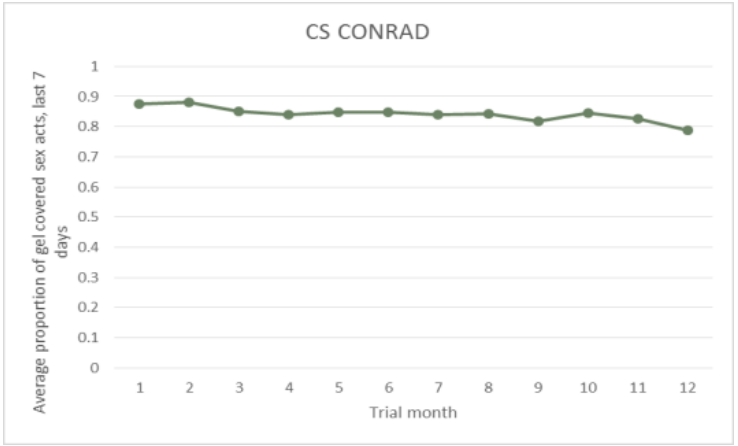


Figure 4.2.1: Average adherence in four trials

4.2.2 DATA PROCUREMENT AND ETHICAL APPROVAL

Trial teams from six completed microbicide trials were contacted and asked if they would be willing to share their data for this study. Four trial teams had data that they were able to share. Three trials requested confidentiality agreements, which were negotiated and signed. Annotated case report forms (CRFs) and study protocols were provided by trial teams and used to understand detailed trial procedures as well as to identify potential individual level variables that could be included in the analysis for each trial. Lists of requested variables were shared with trial teams, which were then approved for use in this study. Data were provided by trial teams in various formats and levels of usability. Data were examined and requests for data in more usable or appropriate formats were made. In all cases, trial teams were eventually able to provide the agreed data in a usable format.

Ethical review from London School of Hygiene Tropical Medicine (LSHTM) ethics committee was sought and a favourable opinion was granted for this study, using secondary data.

4.2.3 DATA MANAGEMENT

Data for each trial were extracted, and cleaned as necessary. For each trial, a denominator population for this study was identified in consultation with trial team representatives, based on the effectiveness populations used in the primary results analyses. Data were managed to create files with the designated denominator populations and subsequently with required adherence and covariate data.

4.2.4 IDENTIFYING PATTERNS OF ADHERENCE: LATENT CLASS AND LATENT PROFILE ANALYSIS

Data used in this analysis are self-reported adherence to vaginal gels prior to vaginal sex collected at monthly or quarterly visits over the course of trial follow-up. Latent class and latent profile analysis (LCA and LPA) are data reduction techniques that can help to simplify large amounts of data and aim to identify patterns within data. They are types of finite mixture modelling, which is a family of modelling techniques that allow subgroups within a larger population to be identified.[101] The goal of LCA and LPA is to take a

seemingly homogeneous population and "un-mix" it so that the existing constituent subgroups are identified within the larger population. Latent class analysis was initially used to better characterise "latent" concepts in the social sciences that are difficult to measure directly, such as racial prejudice, religious commitment, and authoritarianism.[102] These latent groups are often typologies or composed of categories of individuals.[103] The groups or subgroups are referred to as latent because they are not directly observable and cannot be measured directly. The latent subgroups are identified and defined by their similar response patterns to a particular set of questions or factors. Because the answers to sets of questions are directly observable, it is their particular combination of response patterns that is then able to characterise the latent group or category. These directly observable data, which are called "indicator data," are the data that are entered into the model to identify the patterns and subsequent latent subgroups. In the latent class model, it is the latent variable or concept that is believed to be the cause of the observed indicator variables.[102,103,104,105]

The term "latent class analysis" (LCA) is used when indicator data used to observe patterns are categorical, as is the case for HPTN 035, MDP 301, and Carraguard. The term "latent profile analysis" (LPA) is used to refer to the process when indicator data are continuous, as is the case for CS CONRAD. For simplicity, in this PhD research, LCA and LPA together will be referred to as "latent structure analysis." LCA and LPA are types of cross-sectional finite mixture models, as opposed to longitudinal finite mixture models that are designed to model trajectories as a function of time, such as growth mixture models or latent transition models. In this PhD research, LCA and LPA are able to model trajectories of microbicide adherence patterns over time because the indicator data, gel use during sex, were collected at regular intervals over each participant's follow-up. Using LCA and LPA rather than a longitudinal finite mixture model allows fewer assumptions to be imposed in the modelling process, which results in models that more accurately represent the observed adherence data in the trials.

The objective of latent structure analysis in this study was to use the adherence data collected over time from four trials to determine if the trial populations were actually composed of subpopulations of participants with different patterns of adherence. The identified subpopulations, using LCA and LPA, will be referred to as "latent trajectories."

4.2.4.1 MODELLING PROCESS

In latent structure analysis, it is initially not known how many latent trajectories might exist within a population and what those trajectories might look like. Indeed, learning this information is the objective of this type of latent structure analysis. This is accomplished by running a series of separate models, with the number of trajectories for each model specified by the user. The series of models typically begins with one trajectory, with an additional trajectory added for each subsequent model. Results from the various models are then examined and compared. Last, the final model which is deemed best to describe the data for the particular research purpose is selected. These steps are described in more detail in the sections below.

Once the number of desired latent trajectories is specified, the model will characterise the trajectories based on individuals' adherence data collected over time. The latent trajectories are characterised by estimating two types of overall parameters. The first parameter type estimates the probability of adherence at each point in time, conditional on belonging to that particular latent trajectory or subgroup within the population. These probabilities, known as item response probabilities, indicate the form of the particular pattern that characterises a particular latent trajectory. The second parameter type estimated by the model is the proportion of individuals in the population estimated to be in each latent trajectory, which is called the latent class or latent profile prevalence.[103]

The model also provides estimates for each individual of their probability of belonging to each of the latent trajectories specified in the model, based on how the individual's actual data pattern compares to the item response probabilities estimated by the model. The probabilities of belonging to each trajectory for each individual, called posterior probabilities, range between 0 and 1 for each trajectory and sum to 1 for each individual across all of the possible trajectories modelled. A model that is well defined will have trajectories which are distinct from each other and individuals will have one trajectory for which they have a high probability of membership (with remaining trajectories having much lower probabilities of membership).[103]

Latent structure software typically uses an iterative search algorithm such as the expectation-maximisation (EM) algorithm,[106] which is a maximum likelihood approach, to characterise the specified number of latent trajectories. The EM algorithm is designed to identify unknown data. In this case, the "unknown" data are the simplified version of gel adherence patterns or trajectories for the microbicide trial population. The EM algorithm

estimates the model parameters through an iterative approach that randomly selects adherence patterns for the specified number of trajectories and compares those patterns to actual adherence patterns of the trial population. This iterative approach continues until the search is close enough to a set of parameter estimates that maximises or nearly maximises the likelihood function, or until the maximum number of iterations is reached.[103] Once the model has converged, the maximum likelihood value is reported as the log likelihood, which increases as the number of parameters increases.

4.2.4.2 MODEL SELECTION

After fitting multiple models with a range of numbers of trajectories, a representative model can be chosen from among them. Models are typically assessed for parsimony, absolute model fit, relative model fit, and classification quality, in addition to being assessed for interpretability and usefulness in answering the research question. Output from latent structure statistical packages provides information that can assist investigators in assessing the models. There is no gold standard, however, for choosing a model with the optimal number of latent trajectories. The model selection process includes examining and weighing different information, and different individuals may disagree on which model should be deemed optimal.

PARSIMONY is the principle by which a simple explanation is preferred to a more complex explanation. In the case of latent structure modelling, with all else being equal, a model which can describe the data with fewer parameters would be preferable to a model with more parameters.[103]

ABSOLUTE MODEL FIT refers to whether a particular model provides an adequate representation of a particular set of data. It can be assessed using a goodness-of-fit test to compare the model-produced response pattern proportions to the actual response pattern proportions in the data set. Hypothesis testing may not be possible, however, if data are sparse or if the degrees of freedom are so large that the reference distribution is unknown.[103]

RELATIVE MODEL FIT refers to determining which model in a series is more optimal, with respect to balancing parsimony and adequate data representation. Relative model fit can be assessed through a likelihood ratio difference test or by examining relative fit indices,

described below.

> Relative fit indices are a set of information, provided by latent structure software packages, that can be used to compare models with different numbers of trajectories. These indices provide information that try to balance model fit and parsimony. Typical fit indices are Akaike information criterion[107] (AIC), Bayesian information criterion[108] (BIC), and sample-size adjusted Bayesian information criterion[109] (ABIC). These indices are based on the value of -2 times the log likelihood of the model, and then adjusted with a "penalty" for the number of parameters, sample size, or other factors.[103] Although the model with the smallest value for the fit indices is desired, due to the different types of penalties used to adjust each index, fit indices often do not agree on the optimal model. Therefore, fit indices are generally considered along with other criteria for model selection.[103,110]

Classification quality refers to how well a model represents the actual data from the population. It can be assessed using a number of methods which include looking at the results of the model and referring to diagnostics provided by software packages. Aspects of these concepts are described below.

> Homogeneity of latent trajectories is the extent to which members of a particular latent trajectory have the same response patterns. High homogeneity occurs when many of the members of a particular trajectory have the same response patterns. High homogeneity indicates that the model has created a trajectory for which the included individuals have similar patterns and would therefore constitute a district group when compared to other members in the population from where they came.[103]

> Latent trajectory separation is the extent to which the latent trajectories in a model are distinct from one another and truly represent different patterns. Indicators of high latent trajectory separation are that the trajectories within the model appear as distinct patterns from each other and that many of the posterior probabilities of members of each trajectory are closer to 0 and 1.[103]

> Relative entropy,[111] provided by software packages, is a type of measure of classification error based on average posterior probabilities of trajectory

membership for the population across the model. Within a particular model, relative entropy values closest to 1 indicate less classification error than values closer to 0. Error around assignment to trajectories, however, can increase as a function of increasing the number of trajectories within the model.[103] Relative entropy only provides information about a particular model and cannot be used to compare models with different numbers of subgroups.

Optimal models are those which are parsimonious, useful for answering the research question, and have good homogeneity and class separation. While no one method exists to select an optimal model, decisions around model selection are often guided by fit indices provided by software, parsimony, interpretability, usefulness of the model, and knowledge of the field.[103,112]

For this PhD study, the LCA Stata plugin[113] (Lanza and Collins) was used in Stata SE 13 (StataCorp, 2013) for LCA. For LPA, Mplus version 7.31 (Muthén and Muthén) was used. Models with 1–6 latent trajectories were fitted for each of the four included trials. All data available—for individuals with both complete and incomplete data—were used in the analysis to model the latent structures, as software packages use full information maximum likelihood (FIML).[103]

To select a model believed to best describe adherence patterns of a particular trial, the following information about the latent trajectory structures was examined: character of the trajectories, proportion of trial population belonging to each trajectory, trajectory separation, homogeneity, relative fit indices, relative entropy, parsimony, interpretability, and usefulness of the model. Relative fit indices provided by software were BIC, AIC, and ABIC. Consideration was also given to evidence that AIC has been demonstrated to overestimate the optimal number of latent groups.[112]

As the objective of this latent trajectory analysis was to reduce a large volume of data, in order to understand participant adherence patterns and then perform multinomial logistic regression to test associations of different factors with the trajectories, key aspects of model selection were parsimony and interpretability of the latent trajectory structures.

4.2.5 IDENTIFYING FACTORS ASSOCIATED WITH ADHERENCE PATTERNS: MULTINOMIAL LOGISTIC REGRESSION

The objective of the multinomial multivariable analysis was to identify independent factors which were associated with different latent adherence trajectories within each trial, as well as to examine those associations across the four trials. Three types of individual-level factors were considered in this analysis: demographic characteristics (site, age, and education), self-reported baseline behavioural characteristics collected around enrolment (number of sex partners, number of sex acts, condom use, anal sex, exchange of sex), and study exit acceptability characteristics (variables reflecting self-reported views of the microbicide gel and participants' reports of how they thought their partners viewed the gel).

Multinomial logistic regression, with latent adherence trajectory as the outcome variable, was used for this analysis. Multinomial logistic regression was chosen because the adherence trajectories are distinct entities and would not be expected to have relationships or to be ordered. The regressions were weighted by each trial participant's posterior probability of belonging to each of the latent trajectories in the model. This analysis was conducted in Stata SE 13.

For each trial, univariable multinomial logistic regression adjusted for age was conducted with each included variable to examine the relationship between that variable and latent adherence trajectory outcome. Each variable was assessed using the likelihood ratio chi-square test statistic that compares the model with age and the variable of interest to the model without the variable of interest. Variables were deemed to have evidence of an association with latent adherence trajectory based on results of likelihood ratio chi-square test of $p=0.05$ or less. Multivariable multinomial logistic regression was then conducted by adding variables one by one to the model, starting with those that had the strongest evidence of an association. Each variable was added into the model and assessed using the likelihood ratio chi-square test statistic of the full model versus the model without the variable until a final set of variables were identified which had strong evidence of an association with the latent adherence trajectory membership, based on results of likelihood ratio chi-square test of $p=0.05$ or less.

Individuals who did not have a complete set of variables in a particular model were dropped from the model during multinomial logistic regression in Stata.

4.3 RESULTS

4.3.1 ADHERENCE DATA AVAILABLE FOR LATENT STRUCTURE ANALYSIS

Trials included in this PhD study enrolled between 1428 and 9385 participants which were accrued with staggered entry; therefore, it may have taken months or years to enrol the total sample size. Table 4.2.1 provides information about the follow-up times and data available for this study. Figure 4.3.1 shows the number of participants who contributed data to latent trajectory modelling at each time point for each trial. While entry time for participants is staggered during the trials, time along the x-axis represents the first follow-up visit for each participant, not calendar time for the trial. At any given point in time, the total number of participants not contributing adherence data is due to a number of factors. Participants might not have been contributing data because they had officially exited the trial because they completed their follow-up period as per protocol or had formally withdrawn from the trial, or because the trial was halted, thus shortening their follow-up period. Participants might not have been contributing data because they were on product hold due to pregnancy or other health reasons. Participants also might not have contributed adherence information at a particular time point because their data were missing due to circumstances such as a missed visit, loss to follow-up, moving away, or death. Data used in this latent trajectory analysis included all adherence data available for the selected adherence measures for each trial population.

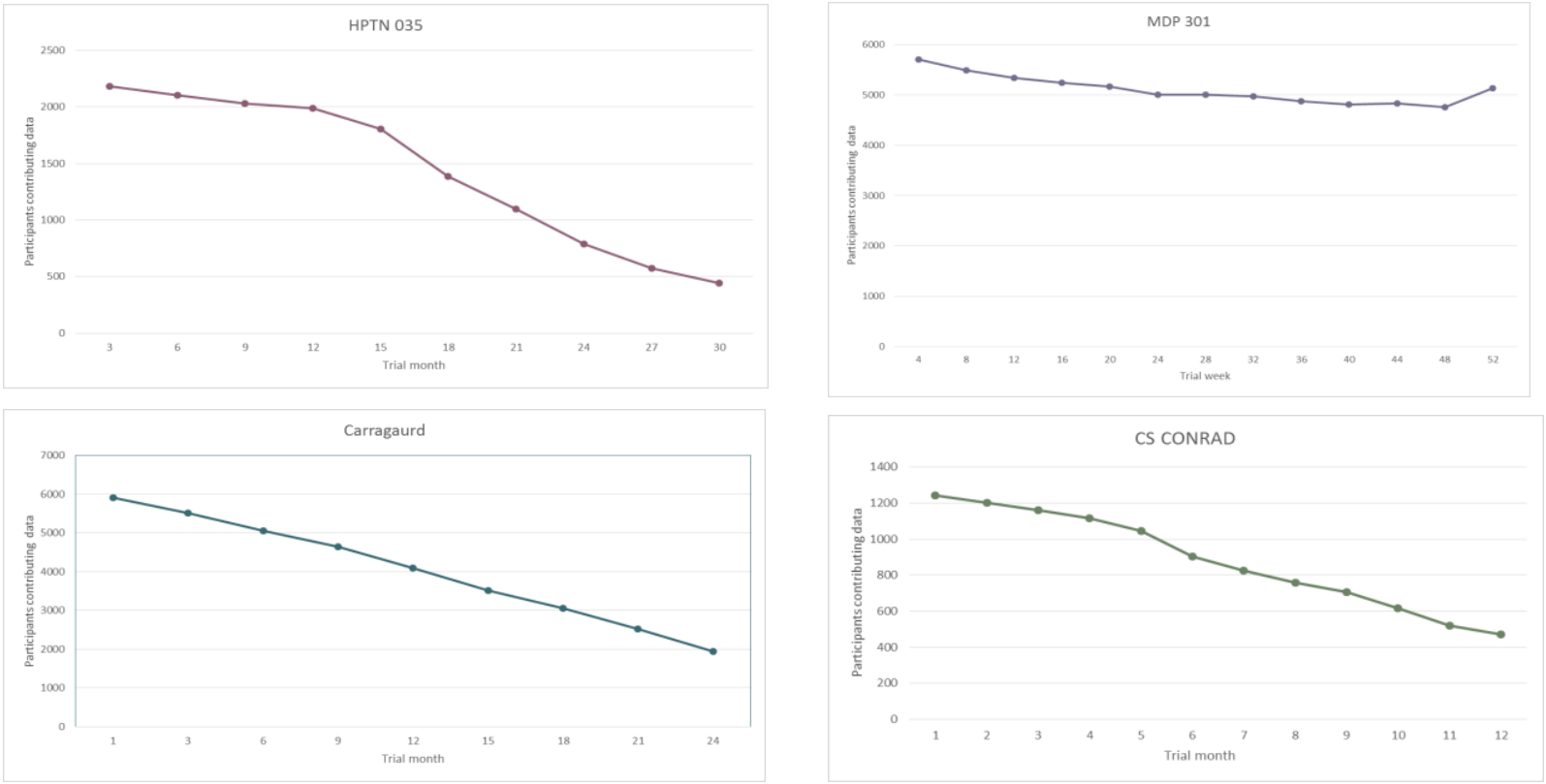


Figure 4.3.1: Adherence data contributed in four trials

HPTN 035 and Carraguard protocols were designed with varying follow-up times for different participants in the whole trial. HPTN 035 planned 12–30 months of follow-up for phase IIb participants. The actual mean adherence time for HPTN 035 participants was 20.4 months. Study retention, meaning the proportion of those enrolled who had a study exit visit with an HIV test, was 93.6%. A total of 6.1% of person-years comprised follow-up time during which study product was withheld temporarily, mostly due to pregnancy.[29] The trial closed at the planned time as per protocol.

Carraguard planned 9–24 months of follow-up for participants. A total of 14% of participants were lost to follow-up or died, and 18% withdrew early, including because of pregnancy, which was a requirement of the protocol due to the investigational nature of the study drug.[26] The Carraguard trial closed at the planned time as per protocol.

Both MDP 301 and CS CONRAD planned 12 months of follow-up for the primary analyses (MDP 301 included an extended safety subsample of serodiscordant couples for a total of up to 24 months). MDP 301 was a three-arm trial that tested two concentrations of PRO 2000 gel; the 2% arm was closed for futility during the trial. MDP 301 reported that 81% of their participants completed a week 52 visit and that 4% of women-years did not contribute to the primary analysis due to pregnancy.[30] MDP 301 data used in this PhD research include participant data for 52 weeks of follow-up for the 0.5% PRO 2000 gel arm and the placebo gel arm.

While CS CONRAD intended to follow up each participant for 12 months, the trial closed early due to concern about the investigational product causing increased HIV transmission in the CS arm. As the last enrolment took place on 25 January 2007 and the last follow-up visit on 31 March 2007, some women's official follow-up time in the study was just a few months. A total of 9.9% of participants were lost to follow-up and 1.7% discontinued the trial early.[28]

4.3.2 MODEL SELECTION AND PATTERNS OF ADHERENCE

4.3.2.1 HPTN 035

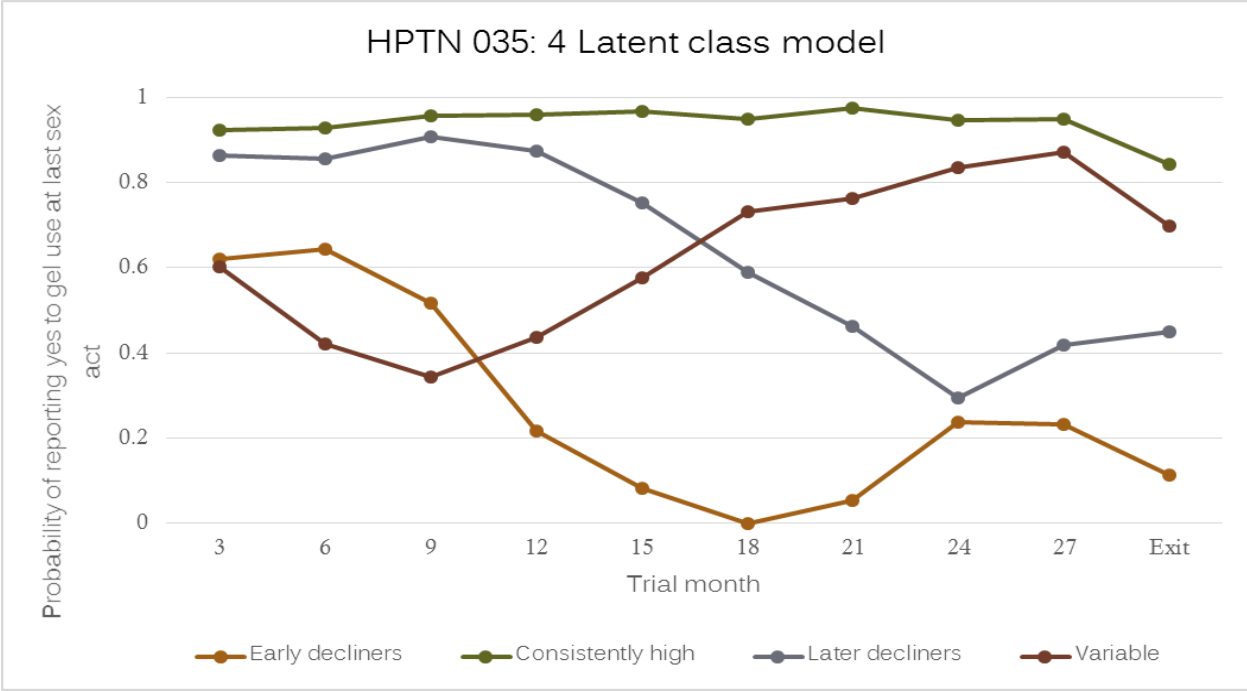
Table 4.3.1 provides information about each of the models for HPTN 035 with 1–6 latent adherence trajectories. Figure 4.3.2 shows the latent adherence trajectory chosen for HPTN 035, which was the model with four trajectories. Table 4.3.1 shows that the 5-class

HPTN 035 Latent models (n=2,282)						
Number of latent classes	Number of parameters estimated	Log likelihood	AIC	BIC	ABIC	Relative entropy
1	10	-6,751	1,929	1,987	1,955	1
2	21	-6,227	905	1,025	959	0.64
3	32	-6,138	749	932	831	0.66
4	43	-6,099	693	939	803	0.64
5	54	-6,060	636	946	774	0.66
6	65	-6,050	638	1,010	804	0.59

Table 4.3.1: HPTN 035 latent trajectory information

model had the lowest AIC and ABIC indices of the six models (636 and 774, respectively). The 3-class model had the lowest BIC value of the six models (932). Thus, model selection was among models with 3, 4, or 5 latent classes. Considering the fit statistics along with parsimony and interpretability, the model with 4 classes was selected as it provided enough information about the population and was easily interpretable, unlike the 5-class model.

Figure 4.3.2 shows the four adherence trajectories (n=2282) selected for HPTN 035. The first trajectory of the 4-latent trajectory model chosen for HPTN 035 was characterised by one larger group, estimated to be 59% of the trial population, which had a consistently high probability of reporting that they had used gel at the last sex act at each quarterly visit over the course of the trial ("Consistently high" group). The second trajectory was estimated to be 20% of the trial population. This trajectory was characterised by initially having a high probability of reporting "yes" to gel use at last sex act as well as the probability of reporting that they had used the gel diminishing considerably after the first year ("Later decliners" group). The third trajectory was estimated to be 5% of the trial population and was estimated to have a 62% probability of reporting at their first quarterly visit that they had used the gel at their last sex act. However, the probability of reporting gel use then diminished quite quickly and stayed very low for the remainder of the trial ("Early decliners" group). The fourth latent adherence trajectory was estimated to be 17% of the study population and the pattern of adherence reporting was somewhat variable over the course of the trial, with a range of adherence probabilities from 87%–34% throughout the trial ("Variable" group).



Latent class membership prevalences n=2282	
Consistently high	59%
Later decliners	20%
Early decliners	5%
Variable	17%

Figure 4.3.2: HPTN 035 latent class model

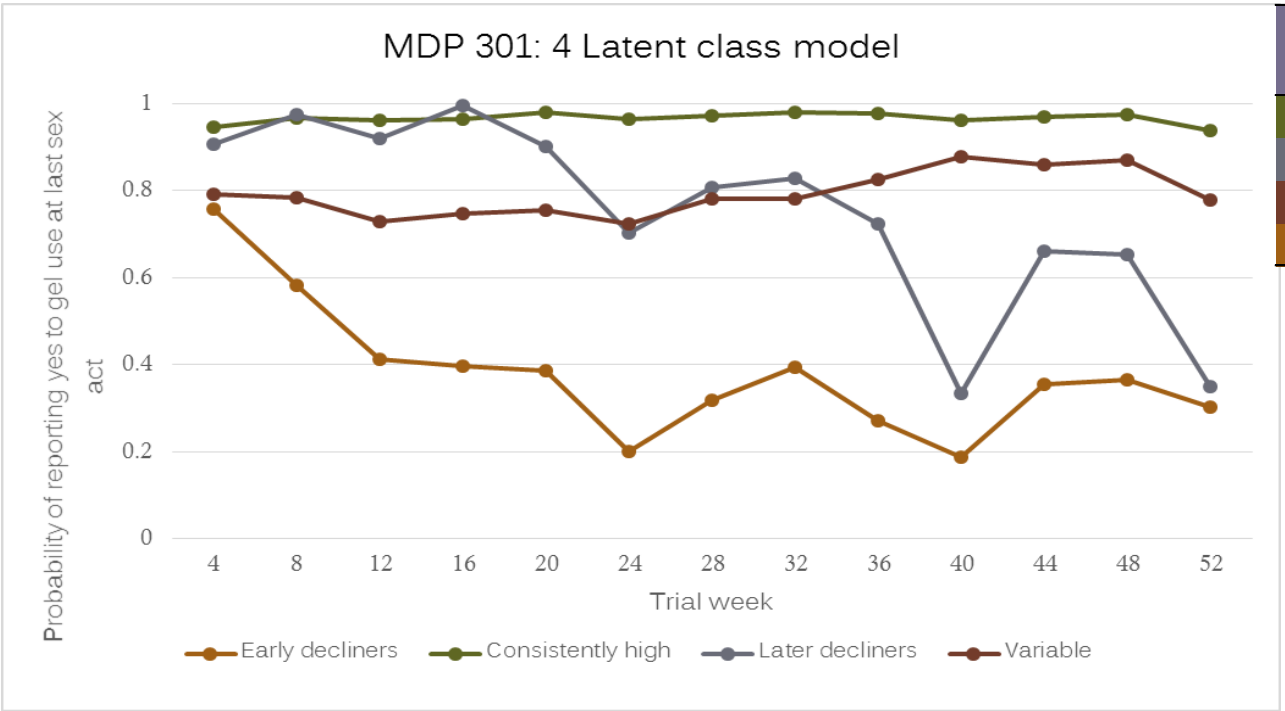
MDP 301 Latent models (n=6,238)						
Number of latent classes	Number of parameters estimated	Log likelihood	AIC	BIC	ABIC	Relative entropy
1	13	-19,787	4,426	4,514	4,473	1
2	27	-18,627	2,134	2,316	2,231	0.7
3	41	-18,536	1,980	2,256	2,126	0.74
4	55	-18,446	1,828	2,199	2,024	0.69
5	69	-18,426	1,815	2,280	2,061	0.71
6	83	-18,407	1,806	2,366	2,102	0.56

Table 4.3.2: MDP 301 latent trajectory information

4.3.2.2 MDP 301

Table 4.3.2 provides information about each of the models for MDP 301 with 1–6 latent adherence trajectories. Figure 4.3.3 shows the latent adherence trajectory chosen for MDP 301, which was the model with four trajectories. Table 4.3.2 shows that the 6-class model had the lowest AIC value (1806) whereas the 4-class model had the lowest values for both the BIC and ABIC (2199 and 2034, respectively). As the 4-class model also fit the criteria for parsimony and interpretability, the 4-class model was selected.

Figure 4.3.3 shows the four latent adherence trajectories (n=6238) selected for MDP 301. Seventy percent (70%) of the trial population was estimated to be in the class that consistently had a high probability of reporting they had used the gel at their last sex act ("Consistently high" group). Nine percent (9%) of the trial population of MDP 301 was estimated to be in a latent adherence trajectory which initially had a high probability of saying they had used the gel at last sex act and then by week 20, reported lower adherence, which continued for the rest of the trial ("Later decliners" group). The smallest subgroup in this model was estimated to be 3% of the trial population and was characterised by initially having a high probability of reporting adherence, which then dropped off at week 8 and stayed lower than any other trajectory for the remainder of the trial ("Early decliners" group). Eighteen percent (18%) of the trial population was estimated to be in a subgroup whose probability of reported adherence trajectory ranged between 72% and 87% throughout the trial (mid-high "Variable" group).



Latent class membership prevalences n=6238	
Consistently high	70%
Later decliners	9%
Variable	18%
Early decliners	3%

Figure 4.3.3: MDP 301 latent class model

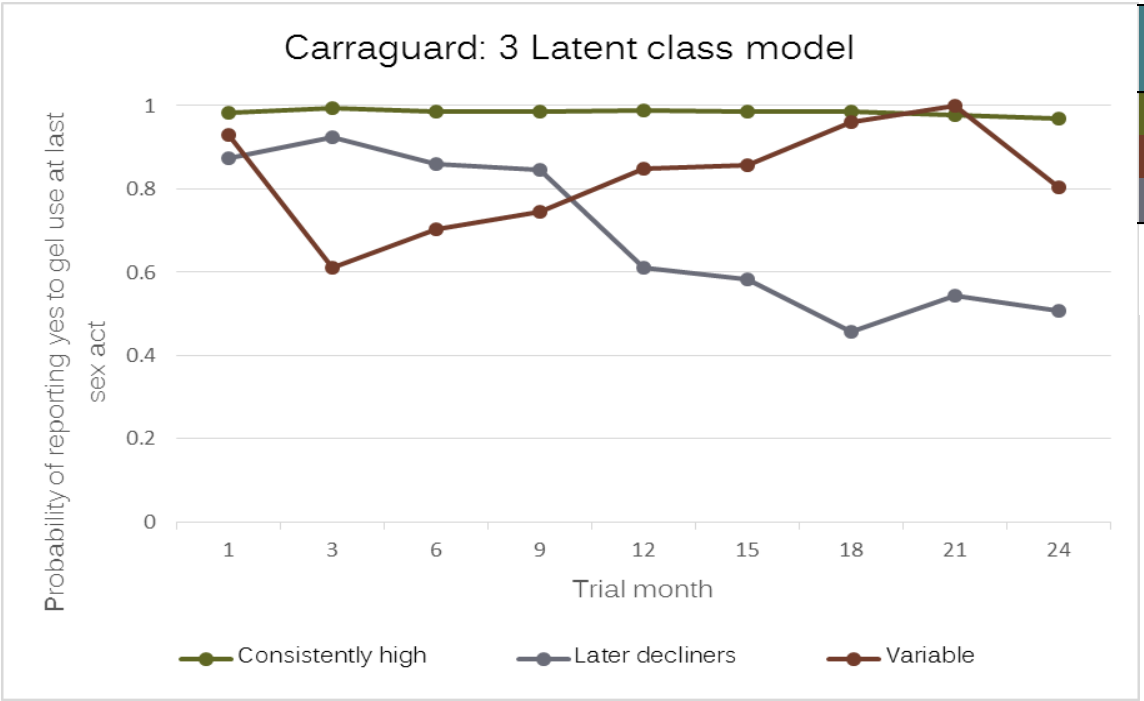
Carraguard Latent models (n=6,039)						
Number of latent classes	Number of parameters estimated	Log likelihood	AIC	BIC	ABIC	Relative entropy
1	9	-4,915	667	728	699	1
2	19	-4,681	221	349	288	0.76
3	29	-4,664	206	401	309	0.8
4	39	-4,654	207	469	345	0.74
5	49	-4,646	211	539	384	0.74
6	59	-4,641	221	617	429	0.59

Table 4.3.3: Carraguard latent trajectory information

4.3.2.3 CARRAGUARD

Table 4.3.3 provides information about each of the models for Carraguard with 1–6 latent adherence trajectories. Figure 4.3.4 shows the latent adherence trajectory chosen for Carraguard, which was the model with three trajectories. Table 4.3.3 shows the 3-class model had the lowest AIC index (206), whereas the 2-class model had the lowest BIC and ABIC indices (349 and 288, respectively). Thus, selection was between the 2-class and 3-class models. As the 3-class model was easily interpretable, provided more information than the 2-class model, and had large enough proportions of the population belonging to each class, the 3-class model was selected.

Figure 4.3.4 shows the model with three latent adherence trajectories (n=6039) selected for Carraguard. Ninety-one percent (91%) of the trial population was estimated to belong to a class whose probability of reporting "yes" to gel use at last sex act was consistently high throughout trial follow-up ("Consistently high" group). Five percent (5%) of the trial population was estimated to be in the subgroup which initially reported high adherence and then about halfway through follow-up reported lower adherence for the remainder of the trial ("Later decliners" group). Four percent (4%) of the trial population was estimated to be in a subgroup characterised by a medium-to-high probability of reporting adherence, ranging from 61% to 96% over trial follow-up ("Variable" group).



Latent class membership prevalences n=6039	
Consistently high	91%
Variable	5%
Later decliners	4%

Figure 4.3.4: Carraguard latent class model

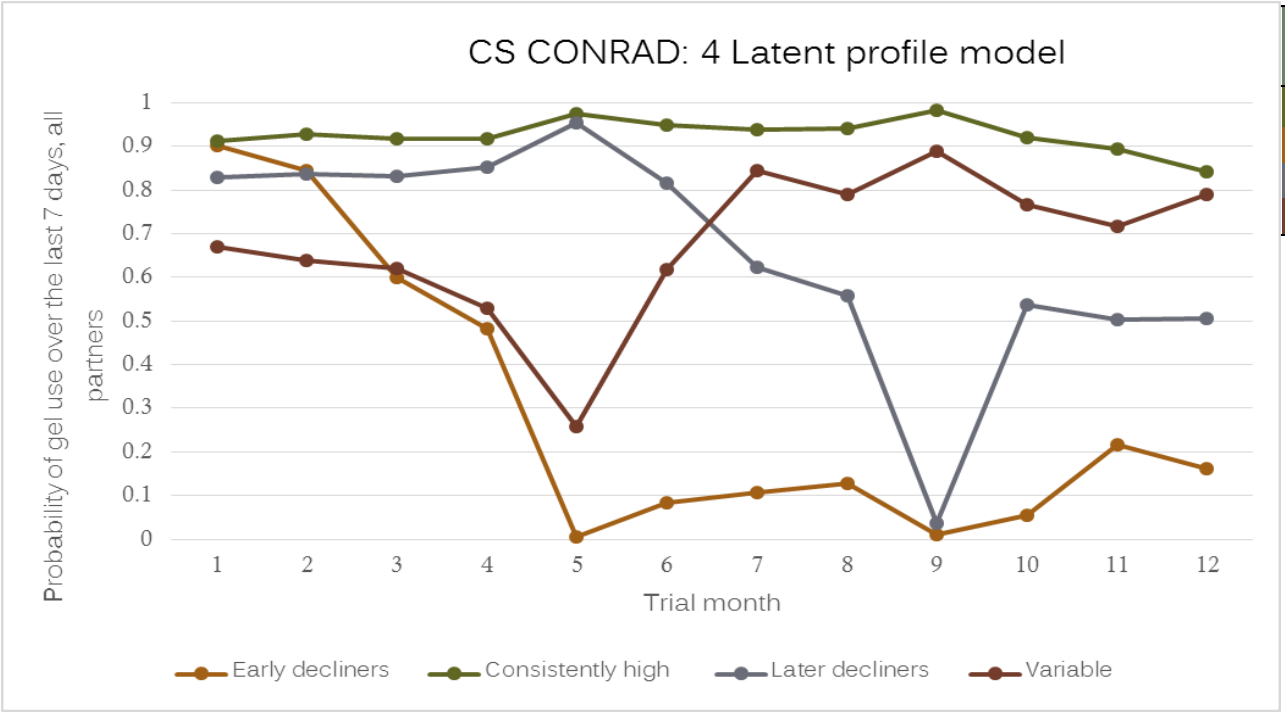
CS CONRAD Latent models (n=1,393)						
Number of latent profiles	Number of parameters estimated	Log likelihood	AIC	BIC	ABIC	Relative entropy
1	24	-2,800	5,647	5,773	5,697	1
2	37	-1,526	3,125	3,319	3,201	0.86
3	50	-1,029	2,158	2,420	2,262	0.89
4	63	-525	1,175	1,505	1,305	0.82
5	76	-23	198	596	354	0.84
6	89	289	-400	66	-217	0.83

Table 4.3.4: CS CONRAD latent trajectory information

4.3.2.4 CS CONRAD

Table 4.3.4 provides information about each of the models for CS CONRAD with 1–6 latent adherence trajectories. Figure 4.3.5 shows the latent adherence trajectory chosen for CS CONRAD, which was the model with four trajectories. Table 4.3.4 shows that fit indices for CS CONRAD did not point to a particular solution. Because the fit indices kept decreasing as the number of trajectories increased, parsimony and interpretability were used to select a model. The 4-trajectory model provided more information about the population than the 3-trajectory model, and was more interpretable than the 5-trajectory model; therefore, it was selected as the optimal model.

Figure Figure 4.3.5 shows the model with a 4-latent trajectory solution (n=1393) that was chosen for CS CONRAD. The largest subgroup was estimated to be 65% of the trial population and belonged to the trajectory that had a consistently high probability of reporting high adherence over the 12-month follow up period ("Consistently high" group). Sixteen percent (16%) of the trial population was estimated belong to the subgroup which initially had high probability of reporting gel use over the last 7 days but whose reported adherence declined after month 5 ("Later decliners" group). Nine percent (9%) of the trial population was estimated to be in a subgroup that initially had a high probability of reported adherence but whose probability of reported adherence immediately declined and stayed low for the remainder of the trial follow-up ("Early decliners" group). Ten percent (10%) of the trial population was estimated to be in a group whose reported adherence was somewhat variable over the trial, mostly ranging from medium to high reported adherence (62–89%) except for one month where reported adherence on average dropped to 26% ("Variable" group).



Latent profile membership prevalences n=1393	
Consistently high	65%
Early decliners	9%
Later decliners	16%
Variable	10%

Figure 4.3.5: CS CONRAD latent profile model

4.3.2.5 ACROSS TRIALS

For all four trials, the largest subgroup within the trial population was the group that consistently reported high adherence throughout trial follow-up ("Consistently high" group). In all four trials, this was also the subgroup that had the least variability in its adherence reporting. In all four trials, a subpopulation was identified whose initially high adherence changed about midway to lower adherence reporting ("Later decliners" group). The specific shape of the declining curves varied across the trials, although there were two consistencies: the drop in the reported adherence around midway, and that while reported adherence then remained low for the rest of the trial, adherence for this subgroup never stayed as low as adherence for those in the "Early decliners" subgroup. "Early decliners" were identified in three of the four trials (HPTN 035, MDP 301, and CS CONRAD). While the particular shape of the curve was different in each trial, a drop after the first or second visits where adherence was reported was consistent in all three trials. Also consistent was that the "Early decliners" trajectories were characterised by the probability of adherence remaining lower than any other trajectory within the trials for the remainder of follow-up. Finally, a subgroup with somewhat variable mid-high adherence ("Variable" group) was identified in each trial. In two trials (MDP 301 and Carraguard) this subgroup's pattern was more consistent than in the two other trials (HPTN 035 and CS CONRAD).

4.3.3 IDENTIFYING FACTORS ASSOCIATED WITH ADHERENCE PATTERNS

Multinomial logistic regression was used to examine which demographic, baseline sexual behavioural, and gel acceptability factors might be associated with membership of different latent adherence trajectories for each microbicide trial. In multinomial logistic regression, relative risk ratios (RRR) for each factor were estimated by comparing these factors or covariate data between one latent trajectory and a selected reference trajectory. For example, for a model with four latent trajectories, RRRs were estimated for each included variable for three of the four trajectories; the reference trajectory served as the comparison for all other trajectories. For this analysis, the latent adherence trajectory that consistently had a high probability of reporting adherence ("Consistently high" group) was selected as the reference trajectory for all trials.

4.3.3.1 HPTN 035

FACTORS INCLUDED IN MULTINOMIAL LOGISTIC REGRESSION

Table 4.3.5 provides detailed information about the factors examined in the multinomial logistic regression for HPTN 035 and the number of trial participants in each category. Table 4.3.5 also provides estimates of the numbers of participants in the various categories, by latent class. As each trial participant had a probability of belonging to each of the latent trajectories, the estimated numbers of participants in these categories are not represented by integers.

AGE ADJUSTED UNIVARIABLE MULTINOMIAL LOGISTIC REGRESSION

Table 4.3.6 provides results from the age-adjusted univariable multinomial logistic regression for HPTN 035. There was strong evidence that age was associated with latent adherence trajectory. Of the other factors, site and partner dislike of gel had the strongest evidence for being associated with latent adherence trajectory when adjusted only for age.

MULTIVARIABLE MULTINOMIAL LOGISTIC REGRESSION

Table 4.3.7 provides results from the multivariable multinomial logistic regression for HPTN 035 (n=2174). Variables at the top of the table show an association with latent adherence trajectory at the p=0.05 level based on the likelihood ratio chi-square-ratio test and are adjusted for each other. Variables at the bottom of the table did not meet the criterion for being included in the model as having been associated with the latent adherence trajectories, but are included so that they may be compared across the trials. Variables in this section are adjusted for the variables which were associated with latent adherence trajectory, but not adjusted for the other variables which did not meet the criterion of p=0.05 for the likelihood ratio chi-square test. This approach was used for all of the trials described in subsequent sections.

Factors found to have an association with latent adherence trajectory (Table 4.3.7) were age, site, and reported partner dislike of gel. Women less than 30 years of age, compared to women 30 and older, had a greater chance of being in the trajectory groups that did not consistently report high adherence compared to the group that reported consistently high adherence (Later decliners, RRR 1.64; Early decliners, RRR 2.31; Variable group, RRR 1.62). Evidence was strong that age was associated with latent adherence trajectory

	Characteristic	Total number of participants	Reference group: consistently high adherence		Early decliners		Variable		Later decliners	
			Estimated number	Estimated prevalence	Estimated number	Estimated prevalence	Estimated number	Estimated prevalence	Estimated number	Estimated prevalence
	Overall total	**n=2282**		**59%**		**5%**		**17%**		**20%**
Demographics	**Age**									
	30 and over	597	393.5	65.9%	20.7	3.5%	83.7	14.0%	99.1	16.6%
	Under 30	1685	942.1	55.9%	87.4	5.2%	293.2	17.4%	362.4	21.5%
Demographics	**Site**									
	Durban, South Africa	522	284.5	54.5%	27.0	5.2%	93.5	17.9%	116.9	22.4%
	Philadelphia, PA, US	146	82.8	56.7%	12.8	8.8%	21.9	15.0%	28.4	19.5%
	Harare, Zimbabwe	169	117.4	69.5%	3.8	2.2%	14.4	8.5%	33.4	19.8%
	Chitungwiza, Zimbabwe	193	145.6	75.5%	3.2	1.7%	11.1	5.7%	33.0	17.1%
	Hlabisa, South Africa	256	149.4	58.4%	13.0	5.1%	48.0	18.7%	45.7	17.8%
	Blantyre, Malawi	321	200.0	62.3%	11.6	3.6%	56.0	17.4%	53.4	16.6%
	Lilongwe, Malawi	439	213.2	48.6%	26.6	6.1%	99.4	22.6%	99.8	22.7%
	Lusaka, Zambia	236	142.6	60.4%	9.9	4.2%	32.7	13.8%	50.8	21.5%
Demographics	**Education**									
	Secondary and above	1437	858.1	59.7%	70.3	4.9%	213.8	14.9%	294.9	20.5%
	Primary and under	844	476.7	56.5%	37.8	4.5%	163.1	19.3%	166.4	19.7%
Baseline behavioural	**Number of sex partners at baseline**									
	1 male partner in last 3 months	2215	1302.2	58.8%	102.5	4.6%	364.6	16.5%	445.7	20.1%
	2 to 6 male partners in last 3 months	67	33.4	49.9%	5.6	8.3%	12.3	18.3%	15.8	23.5%
Baseline behavioural	**Number of sex acts at baseline**									
	0 to 4 sex acts in past week	1905	1102.8	57.9%	89.9	4.7%	318.1	16.7%	394.2	20.7%
	5 to 21 sex acts in past week	377	232.8	61.8%	18.1	4.8%	58.8	15.6%	67.3	17.8%
Baseline behavioural	**Condom use at baseline**									
	Yes used condom at last sex act	727	396.4	54.5%	37.8	5.2%	135.6	18.7%	157.2	21.6%
	No did not use condom at last sex act	1555	939.2	60.4%	70.3	4.5%	241.3	15.5%	304.2	19.6%
Baseline behavioural	**Anal sex at baseline**									
	No anal sex ever	2186	1289.5	59.0%	97.7	4.5%	361.3	16.5%	437.5	20.0%
	Yes anal sex ever	96	46.1	48.0%	10.4	10.8%	15.6	16.2%	24.0	25.0%
Baseline behavioural	**Exchanged sex for money, gifts, items, housing, etc.**									
	No did not accept last time had sex	2239	1305.6	58.3%	107.1	4.8%	373.3	16.7%	452.9	20.2%
	Yes did accept	42	29.6	70.5%	0.8	1.9%	3.4	8.2%	8.2	19.4%
Exit acceptability	**What did you not like about your study gel?**									
	Other responses	2017	1194.9	59.2%	90.4	4.5%	327.6	16.2%	404.1	20.0%
	The gel was messy	156	83.3	53.4%	9.8	6.3%	28.6	18.3%	34.4	22.0%
Exit acceptability	**What did you not like about your study gel?**									
	Other responses	2016	1189.2	59.0%	88.4	4.4%	328.5	16.3%	409.8	20.3%
	Gel was difficult to remember	157	88.9	56.6%	11.8	7.5%	27.6	17.6%	28.6	18.2%
Exit acceptability	**What did you like about the gel?**									
	It may protect against HIV	1670	985.1	59.0%	71.3	4.3%	280.5	16.8%	333.1	19.9%
	Other responses	504	293.8	58.3%	29.0	5.7%	75.6	15.0%	105.5	20.9%
Exit acceptability	**The last time you used the gel, what were your partner's reactions?**									
	He liked it	842	511.2	60.7%	35.5	4.2%	135.3	16.1%	160.0	19.0%
	Other responses	1332	767.8	57.6%	64.8	4.9%	220.8	16.6%	278.6	20.9%
Exit acceptability	**The last time you used the gel, what were your partner's reactions?**									
	Other responses	2119	1261.9	59.6%	92.8	4.4%	339.6	16.0%	424.7	20.0%
	He did not like it	55	17.1	31.1%	7.5	13.6%	16.5	30.0%	14.0	25.4%

Table 4.3.5: HPTN 035 factors for multinomial logistic regression

HPTN 035 age-adjusted univariable multinomial logistic regression				
	Reference Class: Reported consistently high adherence			
	Early decliners	Variable	Later decliners	
n=2282	Age-adjusted RRR [95% CI]	Age-adjusted RRR [95% CI]	Age-adjusted RRR [95% CI]	Likelihood ratio chi-square test
Age (crude)	1.77	1.46	1.53	p< 0.001
Under 30 vs. 30+	[1.08- 2.89]	[1.12-1.92]	[1.19-1.96]	
Site (vs. Durban)				p<0.001
Philadelphia	2.37 [1.13-5.01]	1.00 [0.59-1.73]	1.05 [0.64-1.72]	
Harare	0.37 [0.12-1.12]	0.39 [0.22-.72]	0.73 [0.47-1.14]	
Chitungwiza	0.23 [0.07-0.76]	0.23 [0.12-.45]	0.55 [0.36-.85]	
Hlabisa	0.95 [0.48-1.90]	1.00 [0.67-1.50]	0.76 [0.51-1.13]	
Blantyre	0.63 [0.31-1.28]	0.87 [0.59-1.27]	0.66 [0.46-0.96]	
Lilongwe	1.45 [0.82-2.56]	1.51 [1.08-2.11]	1.21 [.88-1.68]	
Lusaka	0.64 [0.30-1.37]	0.64 [0.41-1.00]	0.79 0.54-1.17]	
Education	1.02	1.43	1.06	p=0.028
Primary or less vs. secondary+	[0.68-1.55]	[1.13-1.81]	[0.85-1.33]	
Number of sex partners at baseline	2.34	1.4	1.48	p=0.268
2-6 vs. 1 in last 3 months	[0.93-5.90]	[0.72-2.73]	[0.80-2.74]	
Number of vaginal sex acts at baseline	0.97	0.88	0.82	p=0.556
5-21 vs. 0-4 in past week	[0.57-1.64]	[0.65-1.21]	[0.61-1.10]	
Condom use at baseline	0.766	0.74	0.8	p=0.039
No vs. yes to condom at last sex act	[0.51-1.16]	[0.58-0.94]	[0.64-1.01]	
Anal sex at baseline	3.56	1.35	1.74	p=0.0072
Yes to anal sex ever vs. no	[1.73-7.30]	[0.74-2.43]	[1.0-2.90]	
Exchanged sex for money, etc. at baseline	0.29	0.38	0.74	p=0.175
Yes vs. no	[0.03-2.79]	[0.12-1.17]	[0.37-1.62]	
Participant thought gel was messy	1.65	1.30	1.27	p=0.356
Yes vs. no	[0.82-3.31]	[0.83-2.03]	[0.84-1.93]	
Participant thought the gel was difficult to remember	1.86	1.16	0.96	p=0.310
Yes vs. no	[0.98-3.55]	[0.74-1.81]	[0.62-1.49]	
Participant liked the gel because they thought it may protect against HIV	1.34	0.90	1.05	p=0.451
No vs. yes	[0.86-2.11]	[0.67-1.19]	[0.81-1.36]	
Participant reported that their partner liked the gel the last time they used it	1.19	1.07	1.14	p=0.591
Other responses vs. yes he liked it	[0.78-1.83]	[0.84-1.37]	[0.91-1.43]	
Participant reported that their partner did not like the gel the last time they used it	6.24	3.72	2.52	p<.001
He did not like it vs. other responses	[2.56-15.20]	[1.87-7.41]	[0.19-0.30]	

Table 4.3.6: HPTN 035 age-adjusted multinomial logistic regression

HPTN 035 multivariable multinomial logistic regression					
		Reference Class: Reported consistently high adherence			
		Early decliners	Variable	Later decliners	
n=2282		Adjusted RRR [95% CI]	Adjusted RRR [95% CI]	Adjusted RRR [95% CI]	Likelihood ratio chi-quare test
Age					
	Under 30 vs. 30+	2.31 [1.34-4.00]	1.62 [1.21-2.17]	1.64 [1.25-2.15]	p<0.001
Site (vs. Durban)					p<0.001
	Philadelphia	2.15 [0.98-4.71]	0.96 [0.55-1.68]	1.01 [0.61-1.67]	
	Harare	0.39 [0.13-1.20]	0.40 [0.22-0.74]	0.74 [0.47-1.16]	
	Chitungwiza	0.24 [0.07-0.82]	0.24 [0.12-0.47]	0.55 [0.35-0.87]	
	Hlabisa	0.83 [0.39-1.73]	0.94 [0.62-1.42]	0.72 [0.48-1.09]	
	Blantyre	0.62 [0.30-1.29]	0.85 [0.58-1.26]	0.65 [0.44-0.95]	
	Lilongwe	1.46 [0.80-2.64]	1.51 [1.06-2.14]	1.22 [0.87-1.70]	
	Lusaka	0.66 [0.30-1.44]	0.63 [0.39-1.00]	0.80 [0.54-1.19]	
Partner dislike of gel		5.53	3.37	2.57	p<0.001
	He did not like it vs. other responses	[2.23-13.75]	[1.67-6.79]	[1.25-5.32]	
Education		0.87	1.17	0.95	p=0.711
	Primary or less vs. secondary+	[0.47-1.59]	[0.83-1.64]	[0.69-1.30]	
Number of sex partners at baseline		1.68	1.51	1.47	p=0.503
	2-6 vs. 1 in last 3 months	[0.60-4.71]	[0.72-3.13]	[0.75-2.87]	
Number of vaginal sex acts at baseline		1.43	1.29	0.96	p=0.308
	5-21 vs. 0-4 in past week	[0.81-2.54]	[0.92-1.82]	[0.70-1.33]	
Condom use at baseline		0.86	0.88	0.81	p=0.361
	No vs. yes to condom at last sex act	[0.55-1.34]	[0.68-1.14]	[0.64-1.04]	
Anal sex at baseline		2.52	1.36	1.82	p=0.103
	Yes to anal sex ever vs. no	[1.02-6.21]	[0.67-2.73]	[0.99-3.34]	
Exchanged sex for money, etc. at baseline		0.31	0.44	0.73	p=0.305
	Yes vs. no	[0.03-3.04]	[0.14-1.38]	[0.32-1.66]	
Participant thought gel was messy		1.07	1.17	1.19	p=0.857
	Yes vs. other responses	[0.50-2.32]	[0.72-1.89]	[0.76-1.85]	
Participant thought the gel was difficult to remember		1.26	0.90	0.83	p=0.694
	Yes vs. other responses	[0.64-2.49]	[0.57-1.42]	[0.53-1.30]	
Participant liked the gel because they thought it may protect against HIV		1.32	0.96	1.05	p=0.672
	No vs. yes	[0.82-2.14]	[0.71-1.30]	[0.80-1.37]	
Participant reported that their partner liked the gel the last time they used it		1.10	1.14	1.18	p=0.555
	Other responses vs. yes he liked it	[0.68-1.79]	[0.87-1.50]	[0.92-1.51]	

Table 4.3.7: HPTN 035 multivariable multinomial logistic regression

(likelihood ratio chi-square test $p<0.001$).

For the overall model, site was also found to be associated with belonging to latent adherence trajectory (likelihood ratio chi-square test $p<0.001$). Durban served as the reference category for site; whether there was an increased or decreased chance of being in the high-adhering group versus another trajectory depended on which site was being compared to Durban. At the individual site level, not all sites compared to Durban were found to have an association with latent adherence trajectory and the effect sizes for some sites were small.

If a participant reported that her partner did not like the gel, her chance of being in one of the latent adherence trajectories that did not report consistently high adherence was greatly increased (RRR 2.57 of being in the Later decliners group compared to the Consistently high group, RRR 5.53 of being in the Early decliners group compared to Consistently high group, and RRR 3.37 of being in the Variable group compared to the Consistently high group; likelihood ratio chi-square test $p<0.001$). Evidence for this association was strong and the effect size was large.

Factors that were not found to be associated with latent adherence trajectory for HPTN 035 in the multivariable model were education, number of sex partners at baseline, number of sex acts at baseline, condom use at baseline, anal sex at baseline, exchange of sex, participant thinking the gel was messy, participant thinking the gel was difficult to remember, participant liking the gel because she thought it may protect against HIV, and participant reporting that her partner liked the gel.

4.3.3.2 MDP 301

FACTORS INCLUDED IN MULTINOMIAL LOGISTIC REGRESSION

Table 4.3.8 provides detailed information about the factors examined in the multinomial logistic regression for MDP 301 and the number of trial participants in each category. Table 4.3.8 also provides estimates of the number of women in the various categories, by latent class. As each trial participant has a probability of membership for each of the latent trajectories, the estimated number of participants in these categories are not represented by integers.

	Characteristic	Total number of participants	Reference group: consistently high		Early decliners		Variable		Later decliners	
			Estimated number	Estimated prevalence	Estimated number	Estimated prevalence	Estimated number	Estimated prevalence	Estimated number	Estimated prevalence
	Overall total	n=6238		70%		3%		18%		9%
Demographics	**Age**									
	30 and over	2761	2101.9	76.1%	49.2	1.8%	416.2	15.1%	193.7	7.0%
	Under 30	3477	2280.3	65.6%	130.0	3.7%	694.4	20.0%	372.3	10.7%
	Site									
	Durban	1700	1213.7	71.4%	44.2	2.6%	279.3	16.4%	162.7	9.6%
	Johannesburg	1643	950.1	57.8%	89.9	5.5%	426.2	25.9%	176.8	10.8%
	Masaka	572	446.3	78.0%	6.3	1.1%	90.1	15.7%	29.3	5.1%
	Mwanza	730	546.5	74.9%	15.1	2.1%	105.0	14.4%	63.3	8.7%
	Africa Centre	779	617.3	79.2%	12.9	1.7%	90.8	11.7%	58.0	7.4%
	Mazabuka	814	608.3	74.7%	10.7	1.3%	119.1	14.6%	75.9	9.3%
	Education									
	Secondary and above	1508	914.2	60.6%	67.4	4.5%	354.6	23.5%	171.8	11.4%
	Primary and under	4730	3468.0	73.3%	111.8	2.4%	756.0	16.0%	394.3	8.3%
Baseline behavioural	**How many different people have you had sex with in the last week?**									
	1 person in the last week	5044	3491.9	69.2%	155.7	3.1%	927.2	18.4%	469.3	9.3%
	More than one partner in the last week	38	23.4	61.5%	1.8	4.7%	7.4	19.6%	5.4	14.2%
	How many times have you had sex in the past week?									
	1 to 3 sex acts past week	3599	2561.8	71.2%	100.7	2.8%	613.5	17.0%	322.9	9.0%
	4 to 77 sex acts in past week	1484	954.3	64.3%	56.7	3.8%	321.2	21.6%	151.8	10.2%
	Did you use a condom the last time you had sex?									
	No did not use condom	3261	2348.0	72.0%	82.3	2.5%	557.2	17.1%	273.5	8.4%
	Yes used condom at last sex act	2926	1999.1	68.3%	96.4	3.3%	542.5	18.5%	288.1	9.8%
	Have you had anal sex in the last 4 weeks?									
	No anal sex in the last 4 weeks	6166	4339.1	70.4%	174.7	2.8%	1092.9	17.7%	559.4	9.1%
	Yes anal sex in the last 4 weeks	69	41.4	60.1%	4.5	6.6%	17.5	25.3%	5.6	8.1%
Exit acceptability	**Would you encourage or discourage your friends to use the gel if we showed this microbicide halves women's risk of getting HIV?**									
	Encourage	4426	3171.2	71.6%	108.5	2.5%	768.7	17.4%	377.6	8.5%
	Discourage	140	99.3	71.0%	3.2	2.3%	22.8	16.3%	14.7	10.5%
	Was it easy to predict when you may need to insert the gel?									
	Yes	560	380.1	67.9%	22.7	4.1%	103.2	18.4%	53.9	9.6%
	No	4095	2948.3	72.0%	90.8	2.2%	706.3	17.2%	349.6	8.5%
	How likely do you think it is that you might get infected with HIV?									
	Very likely	1536	1118.4	72.8%	38.8	2.5%	258.7	16.8%	120.2	7.8%
	Not very likely	2249	1604.7	71.3%	53.0	2.4%	390.4	17.4%	201.0	8.9%
	Impossible	724	506.3	69.9%	18.4	2.5%	132.8	18.3%	66.4	9.2%
	What did your partner think of the gel?									
	Other responses	4503	3236.4	71.9%	106.0	2.4%	771.2	17.1%	389.5	8.6%
	Disliked it	153	94.1	61.5%	7.5	4.9%	37.7	24.6%	13.6	8.9%
	Did the gel affect how much your partner enjoyed sex?									
	Other responses	4436	3169.6	71.5%	108.7	2.4%	771.9	17.4%	385.9	8.7%
	Made sex less enjoyable	225	163.6	72.7%	4.9	2.2%	39.2	17.4%	17.3	7.7%

Table 4.3.8: MDP 301 factors for multinomial logistic regression

AGE ADJUSTED UNIVARIABLE MULTINOMIAL LOGISTIC REGRESSION

Table 4.3.9 provides results from the age-adjusted univariable multinomial logistic regression for MPD 301. There was strong evidence that age was associated with latent adherence trajectory. Site, education, number of sex acts at baseline, and partner dislike of gel had the strongest evidence for being associated with latent adherence trajectory when adjusted only for age.

MULTIVARIABLE MULTINOMIAL LOGISTIC REGRESSION

Table 4.3.10 provides results from the multivariable multinomial logistic regression for MDP 301. Factors found to be associated with latent adherence trajectory were age, site, number of sex acts at baseline, and education. Women who were less than 30 years old versus 30 or older had an increased chance of being in the three latent adherence trajectories that did not consistently report high adherence (Later decliners, RRR 1.53; Early decliners, RRR 1.80; Variable mid-high adherers, RRR 1.21). There was strong evidence of the association between age and latent adherence trajectory (likelihood ratio chi-square test $p<0.001$).

There was strong evidence that site was also associated with latent adherence trajectory (likelihood ratio chi-square $p<0.001$). Durban was used as the reference category, and the direction of the estimate depended on which site was being compared to Durban. At the individual site level, not all sites compared to Durban were found to have an association with latent adherence trajectory and the effect sizes for some sites were small.

Participants with primary education or lower versus participants with secondary or higher education had a lower chance of being in latent adherence trajectories which did not consistently report high adherence (Later decliners, RRR 0.79; Early decliners, RRR 0.79; Mid-high variable adherence reporters, RRR 0.76). There was strong evidence that education was associated with latent adherence trajectory in the multivariable multinomial logistic regression for MDP 301 (likelihood ratio chi-square test $p=0.009$).

There was also strong evidence that number of sex acts at baseline was associated with belonging to latent adherence trajectories (likelihood ratio chi-square test $p=0.017$). Four or more sex acts in the last week prior to enrolment versus 3 or fewer sex acts reported at baseline was associated with an increased chance of being in one of the trajectories which did not consistently report high adherence (Later decliners, RRR 1.16; Early decliners,

MDP 301 age-adjusted multinomial logistic regression				
	Reference Class: Reported consistently high adherence			
	Early decliners	Variable	Later decliners	
n=5083	Adjusted RRR [95% CI]	Adjusted RRR [95% CI]	Adjusted RRR [95% CI]	Likelihood ratio chi-square test
Age (crude)	2.44	1.54	1.77	p<0.001
under 30 vs. 30+	[1.75-3.40]	[1.34-1.76]	[1.47-2.13]	
Site vs. Durban				p<0.001
Joburg	2.43 [1.68-3.52]	1.89 [1.59-2.25]	1.32 [1.05-1.66]	
Masaka	0.44 [0.19-1.02]	0.93 [0.71-1.20]	0.53 [0.35-0.80]	
Mwanza	0.79 [0.44-1.43]	0.85 [0.66-1.09]	0.89 [0.65-1.21]	
Africa Centre	0.65 [0.35-1.22]	0.68 [0.52-0.87]	0.76 [0.56-1.05]	
Mazabuka	0.48 [0.24-.94]	0.85 [0.67-1.07]	0.93 [0.69-1.23]	
Education	2.11	0.61	0.69	p<.001
Primary or less vs. secondary +	[1.50]	[0.53-0.71]	[0.57-0.84]	
Number of sex partners at baseline	1.65	1.17	1.67	p=0.730
>1 partner in last week vs. 1	[0.36-7.61]	[0.51-2.69]	[0.65-4.29]	
Number of sex acts at baseline	1.47	1.39	1.24	p<0.001
4+ or more last week vs. 3 or less	[1.05-2.06]	[1.19-1.62]	[1.01-1.52]	
Condom use at baseline	1.24	1.09	1.16	p=0.176
Yes vs. no condom at last sex	[0.92-1.68]	[0.95-1.24]	[0.97-1.38]	
Anal sex at baseline	2.66	1.66	1.03	p=0.151
Yes anal sex in last 4 weeks vs. no	[0.99-7.14]	[0.94-2.91]	[0.42-2.51]	
Recommend gel to friends if halves women's risk of HIV?	0.92	0.94	1.23	p=0.881
Discourage vs. encourage	[0.29-2.87]	[0.59-1.50]	[0.70-2.15]	
Was it easy to predict when you needed to use the gel?	0.52	0.89	0.85	p=0.059
No vs. yes	[0.33-0.84]	[0.71-1.12]	[0.62-1.15]	
How likely do you think it is that you might get infected with HIV?				p=0.908
Not very likely vs. very likely	0.91 [0.59-1.38]	1.03 [0.86-1.22]	1.13 [0.89-1.43]	
Impossible vs. very likely	0.99 [0.56-1.74]	1.10 [0.87-1.39]	1.18 [0.85-1.62]	
Partner dislike of gel	2.31	1.63	1.16	p=0.036
Disliked it vs. other responses	[1.07-4.98]	[1.11-2.40]	[0.65-2.07]	
Effect of gel on partner's enjoyment of sex?	0.86	0.98	0.86	p=0.934
Less enjoyable vs. other responses	[.344-2.17]	[0.68-1.40]	[0.52-1.43]	

Table 4.3.9: MDP 301 age-adjusted multinomial logistic regression

MDP 301 multivariable multinomial logistic regression				
	Reference Class: Reported consistently high adherence			
	Early decliners	Variable	Later decliners	
n=5083	Adjusted RRR [95% CI]	Adjusted RRR [95% CI]	Adjusted RRR [95% CI]	Likelihood ratio chi-square test
Age	1.80	1.21	1.53	p<0.001
Under 30 vs.30+	[1.25-2.60]	[1.04-1.42]	[1.24-1.88]	
Site vs. Durban				p<0.001
Joburg	2.24 [1.50-3.33]	1.77 [1.47-2.14]	1.25 [0.98-1.60]	
Masaka	0.49 [0.19-1.28]	1.05 [0.77-1.43]	0.62 [0.39-0.99]	
Mwanza	1.00 [0.52-1.91]	0.92 [0.69-1.23]	0.96 [0.67-1.37]	
Africa Centre	0.77 [0.38-1.57]	0.72 [0.53-0.97]	0.79 [0.54-1.15]	
Mazabuka	0.46 [0.22-0.95]	0.88 [0.68-1.13]	0.91 [0.66-1.25]	
Number of sex acts at baseline	1.28	1.27	1.16	p=0.017
4+ or more last week vs. 3 or less	[0.91-1.81]	[1.08-1.48]	[0.94-1.44]	
Education	0.79	0.76	0.79	p=0.009
Primary or less vs. secondary +	[0.55-1.14]	[0.64-0.91]	[0.63-1.00]	
Number of sex partners at baseline	1.67	1.19	1.62	p=0.757
>1 partner in last week vs. 1	[0.35-7.98]	[0.51-2.78]	0.62-4.25]	
Condom use at baseline	0.92	0.88	1.05	p=0.329
Yes vs. no condom at last sex	[0.66-1.30]	[0.75-1.02]	[0.85-1.29]	
Anal sex at baseline	2.21	1.33	0.81	p=0.397
Yes anal sex in last 4 weeks vs. no	[0.81-6.04]	[0.72-2.45]	[0.30-2.17]	
Recommend gel to friends if halves women's risk of HIV?	0.90	0.86	1.14	p=0.900
Discourage vs. encourage	[0.27-3.01]	[0.51-1.46]	[0.62-2.10]	
Was it easy to predict when you needed to use the gel?	0.57	0.89	0.84	p=0.167
No vs. yes	[0.34-0.96]	[0.69-1.16]	[0.59-1.18]	
How likely do you think it is that you might get infected with HIV?				p=0.620
Not very likely vs. very likely	0.63 [0.39-1.02]	1.00 [0.80-1.25]	0.94 [0.71-1.27]	
Impossible vs. very likely	0.63 [0.33-1.19]	0.95 [0.72-1.24]	1.04 [0.72-1.48]	
Effect of gel on partner's enjoyment of sex?	1.08	1.00	0.92	p=0.990
Less enjoyable vs. other responses	[0.42-2.78]	[0.67-1.48]	[0.53-1.60]	
Partner dislike of gel	2.01	1.50	1.26	p=0.165
Disliked it vs. other responses	[0.87-4.64]	[0.98-2.29]	[0.68-2.33]	

Table 4.3.10: MDP 301 multivariable multinomial logistic regression

RRR 1.28; Mid-high variable adherence reporters, RRR 1.27). However, the effect sizes were not very large.

Factors that were not associated with latent adherence trajectory for MDP 301 in the multivariable model were number of sex partners at baseline, condom use at baseline, anal sex at baseline, whether the participant would recommend the gel to another person, whether the participant could predict needing the gel, whether the participant thought she might be infected by HIV, whether the participant reported the gel affected sex, and whether the participant reported that her partner did not like the gel.

4.3.3.3 CARRAGUARD

FACTORS INCLUDED IN MULTINOMIAL LOGISTIC REGRESSION

Table 4.3.11 provides detailed information about the factors examined in the multinomial logistic regression for Carraguard and the number of trial participants in each category. Table 4.3.11 also provides estimates of the number of participants in the various categories, by latent class. As each trial participant has a probability of membership for each of the latent trajectories, the estimated numbers of participants in these categories are not represented by integers.

AGE-ADJUSTED UNIVARIABLE MULTINOMIAL LOGISTIC REGRESSION

Table 4.3.12 provides results from the age-adjusted univariable multinomial logistic regression for Carraguard. There was strong evidence that age was associated with latent adherence trajectory. Site and partner refusal of gel had the strongest evidence for being associated with latent adherence trajectory when adjusted only for age.

MULTIVARIABLE MULTINOMIAL LOGISTIC REGRESSION

Table 4.3.13 provides results from the multivariable multinomial logistic regression for Carraguard. Factors found to be associated with latent adherence trajectory were age, site, number of sex partners at baseline, and partner refuse of gel use (data only available for a subsample of 1191). Participants who were less than 35 years of age versus over 35 had an increased chance of being in a latent adherence trajectory that did not consistently report high adherence (Later decliners, RRR 1.63; Variable adherence reporters, RRR 1.40).

	Characteristic	Total number of participants	Reference group: consistently high		Later decliners		Variable	
			Estimated number	Estimated prevalence	Estimated number	Estimated prevalence	Estimated number	Estimated prevalence
	Overall total	n=6039		**91%**		**4%**		**5%**
Demographics	**Age**							
	35 and over	2180	2018.5	92.6%	85.9	3.9%	75.5	3.5%
	Under 35	3859	3463.4	89.7%	229.4	5.9%	166.2	4.3%
	Site							
	UTC	2245	2030.7	90.5%	109.1	4.9%	105.1	4.7%
	Medunsa	2329	2211.0	94.9%	66.5	2.9%	51.5	2.2%
	MRC	1465	1240.2	84.7%	139.7	9.5%	85.1	5.8%
	Education							
	Secondary and above	1142	1032.9	90.4%	63.7	5.6%	45.4	4.0%
	Primary and under	455	421.2	92.6%	19.1	4.2%	14.7	3.2%
Baseline Behavioural	**Number of sex partners at baseline in past 3 months**							
	1 partner	5518	5020.5	91.0%	282.3	5.1%	215.2	3.9%
	2 or more partners	521	461.4	88.6%	33.0	6.3%	26.5	5.1%
	Number of vaginal sex acts in past two weeks							
	0 to 4 sex acts	4257	3859.8	90.7%	228.5	5.4%	168.7	4.0%
	5 to 56 sex acts	1781	1621.2	91.0%	86.8	4.9%	73.0	4.1%
	Condom use at last sex with steady partner?							
	No	3557	3228.7	90.8%	183.7	5.2%	144.7	4.1%
	Yes	1073	978.2	91.2%	54.0	5.0%	40.8	3.8%
	In the past 3 months have you had unprotected anal sex?							
	No	5908	5367.9	90.9%	306.2	5.2%	233.9	4.0%
	Yes	130	113.0	86.9%	9.2	7.1%	7.8	6.0%
	Have you ever had sex in exchange for money?							
	No	5872	5328.3	90.7%	306.7	5.2%	237.0	4.0%
	Yes	167	153.6	92.0%	8.7	5.2%	4.7	2.8%
Exit acceptability*	**What effect did the study gel have on your sexual pleasure?**							
	More pleasure	623	574.7	92.3%	28.5	4.6%	19.7	3.2%
	Less Pleasure	40	34.4	86.1%	4.9	12.2%	0.7	1.8%
	No effect	938	848.9	90.5%	49.5	5.3%	39.6	4.2%
	What effect did the gel have on your most recent partner's sexual pleasure?							
	Other responses	1431	1315.2	91.9%	66.3	4.6%	49.5	3.5%
	Made sex less pleasurable	60	54.2	90.3%	3.7	6.2%	2.1	3.5%
	What was your most recent parner's reaction to you using the study gel?							
	Other responses	1568	1435.4	91.5%	76.7	4.9%	55.9	3.6%
	He refused to allow me to use the gel	31	21.1	68.0%	5.7	18.5%	4.2	13.5%

*Subsample of 1191 participants

Table 4.3.11: Carraguard factors for multinomial logistic regression

Carraguard age-adjusted univariable multinomial logistic regression			
	Reference Class: Reported consistently high		
	Later decliners	Variable	
n=6039	Adjusted RRR [95% CI]	Adjusted RRR [95% CI]	Likelihood ratio chi-square test
Age (crude)	1.56	1.28	p<0.001
Under 35 vs. 35+	[1.21-2.01]	[0.97-1.69]	
Site vs. UTC			p<.0001
Medunsa	0.51 [0.37-0.070]	0.42 [0.30-0.059]	
MRC	1.97 [1.52-2.57]	1.27 [0.94-1.71]	
Education*	0.92	0.95	p=0.952
Primary or less vs. secondary +	[0.52-1.65]	[0.49-1.84]	
Number of sex partners at baseline	1.23	1.32	p=0.276
2 or more in past 3 months vs. 1	[0.85-1.79]	[0.87-1.99]	
Number of sex acts baseline	0.91	1.03	p=0.723
5 or more sex acts in past 2 weeks vs. 4 or less	[0.70-1.17]	[0.78-1.37]	
Condom use at baseline	1.08	1.12	p=0.742
No condom used at last sex act with steady partner vs. yes condom	[0.79-1.48]	[0.78-1.59]	
Anal sex at baseline	1.38	1.55	p=0.387
Yes unprotected anal sex in the past 3 months vs. no	[0.70-2.73]	[0.74-3.25]	
Have you ever had sex in exchange for money?	1.00	0.70	p=0.722
Yes vs. no	[0.50-2.00]	[0.28-1.76]	
What effect did the study gel have on your sexual pleasure?*			p=0.318
Less pleasure vs. more pleasure	2.73 [0.98-7.61]	0.58 [0.05-6.37]	
No effect vs. more pleasure	1.15 [0.72-1.85]	1.34 [0.77-2.32]	
What effect did the gel have on your most recent partner's sexual pleasure?*	1.36	1.02	p=0.866
Less pleasure vs. other responses	[0.46-3.99]	[0.25-4.18]	
What was your most recent partner's reaction to you using the study gel?*	4.93	4.96	p=0.002
Refused me to use gel vs. other responses	[1.90-12.80]	[1.68-14.69]	

*Subsample of 1191 participants

Table 4.3.12: Carraguard age-adjusted multinomial logistic regression

Carraguard multivariable multinomial logistic regression			
	Reference Class: Reported consistently high		
	Later decliners	Variable	
n=6039	Adjusted RRR [95% CI]	Adjusted RRR [95% CI]	Likelihood ratio chi-square test
Age	1.63	1.40	p<.001
Under 35 vs. 35+	[1.26-2.11]	[1.06-1.86]	
Site			p<.001
Medunsa (vs. UTC)	0.48 [0.34-0.66]	0.39 [0.27-0.55]	
MRC (vs. UTC)	1.94 [1.49-2.52]	1.24 [0.92-1.66]	
Number of sex partners at baseline	1.56	1.74	p=0.008
2 or more vs. 1	[1.06-2.29]	[1.13-2.67]	
What was your most recent partner's reaction to you using the study gel?*	3.26	3.98	p=0.016
Refused me to use gel vs. other responses	[1.22-8.69]	[1.30-12.17]	
Education*	0.79	0.82	p=0.621
Primary or less vs. secondary +	[0.44-1.40]	[0.42-1.60]	
Number of sex acts baseline	1.08	1.11	p=0.677
5 or more sex acts in past 2 weeks vs. 4 or less	[0.83-1.41]	[0.83-1.48]	
Condom use at baseline	0.99	0.91	p=0.882
No condom used at last sex act with steady partner vs. yes condom	[0.71-1.39]	[0.62-1.33]	
Anal sex at baseline	0.94	1.24	p=0.844
Yes unprotected anal sex in the past 3 months vs. no	[0.47-1.89]	[0.58-2.62]	
Have you ever had sex in exchange for money?	0.99	0.72	p=0.773
yes vs no	[0.48-2.06]	[0.27-1.86]	
What effect did the study gel have on your sexual pleasure?*			p=0.531
Less pleasure vs. more pleasure	2.20 [0.77-6.29]	0.44 [0.04-4.91]	
No effect vs. more pleasure	1.09 0.67-1.79	1.18 [0.67-2.09]	
What effect did the gel have on your most recent partner's sexual pleasure?*	1.38	0.99	p=0.859
Less pleasure vs. other responses	[0.46-4.10]	[0.24-4.09]	

*Subsample of 1191 participants

Table 4.3.13: Carraguard multivariable multinomial logistic regression

There was strong evidence that age in the Carraguard study was associated with latent trajectory membership (likelihood ratio chi-square test $p<0.001$).

Site was also found to be associated with latent adherence trajectory (likelihood ratio chi-square $p<0.001$). Participants from Medunsa versus UTC had a decreased risk of being in either the Later decliners group (RRR 0.48) or the Variable trajectories group (RRR 0.39) compared to the reference group, Consistently high adherence group. Participants from MRC had a greater chance of being in the Later decliners (RRR 1.94) or Variable (RRR 1.24) groups compared to the reference High adherence-reporting group.

There was strong evidence in this analysis that number of sex partners at baseline was associated with membership of the latent adherence trajectories (likelihood ratio chi-square test p=0.008). Participants who reported two or more sex partners at baseline versus participants who reported one sex partner were more likely to be in one of the adherence trajectories that did not consistently report high adherence (Later decliners, RRR 1.56; Variable adherence reporters, RRR 1.74).

Study exit data completed with a subsample of Carraguard trial participants allowed exploration of latent adherence trajectory membership with several additional factors that were not available for the whole trial population. In a subsample of 1191 trial participants, those who reported their partner refused their use of the gel had a greater chance of being in the latent adherence trajectories that did not consistently report high adherence. There was strong evidence of the association of partner refusal and latent class membership (likelihood ratio chi-square test p=0.016), and effect of partner refusal was large (Later decliners, RRR 3.26; Variable adherence reporters, RRR 3.98).

Factors that were not associated with latent adherence trajectory for Carraguard in the multivariable model were education (subsample) number of baseline sex acts, condom use at baseline, anal sex at baseline, exchanging money for sex, whether the participant reported that gel affected her pleasure during sex, and whether the participant reported that the gel affected her partner's pleasure.

4.3.3.4 CS CONRAD

FACTORS INCLUDED IN MULTINOMIAL LOGISTIC REGRESSION

Table 4.3.14 provides detailed information about the factors examined in the multinomial logistic regression for CS CONRAD and the number of trial participants in each category. Table 4.3.14 also provides estimates of the number of women in the various categories, by latent class. As each trial participant has a probability of membership for each of the latent trajectories, the estimated numbers of participants in these categories are not represented by integers.

AGE-ADJUSTED UNIVARIABLE MULTINOMIAL LOGISTIC REGRESSION

Table 4.3.15 provides results from the age-adjusted univariable multinomial logistic regression for CS CONRAD. There was strong evidence that age was associated with latent

	Characteristic	Total number of participants	Reference group: consistently high adherence		Early decliners		Later decliners		Variable	
			Estimated number	Estimated prevalence	Estimated number	Estimated prevalence	Estimated number	Estimated prevalence	Estimated number	Estimated prevalence
	Overall total	**n=1393**		**65%**		**9%**		**16%**		**10%**
Demographics	**Age**									
	30 and over	668	453.9	67.9%	45.1	6.8%	100.7	15.1%	68.3	10.2%
	Under 30	725	454.5	62.7%	84.6	11.7%	120.8	16.7%	65.2	9.0%
	Site									
	South Africa	589	385.0	65.4%	68.8	11.7%	93.9	15.9%	41.4	7.0%
	Bangalore	22	13.4	60.8%	3.8	17.2%	2.6	11.9%	2.2	10.2%
	Benin	227	158.6	69.9%	15.9	7.0%	39.2	17.3%	13.3	5.9%
	Chennai	252	145.9	57.9%	11.9	4.7%	49.2	19.5%	45.0	17.9%
	Uganda	303	205.4	67.8%	29.4	9.7%	36.6	12.1%	31.6	10.4%
	Education									
	Secondary and above	633	403.1	63.7%	77.1	12.2%	96.5	15.2%	56.3	8.9%
	Primary and under	673	453.6	67.4%	47.4	7.0%	110.0	16.3%	62.0	9.2%
Baseline behavioural	**In the last 30 days, with how many different men have you had vaginal sex?**									
	0-4	640	422.3	66.0%	69.8	10.9%	96.9	15.1%	51.0	8.0%
	5 or more	753	486.0	64.5%	59.9	8.0%	124.5	16.5%	82.5	11.0%
	How many times did you have vaginal sex in the last 7 days?									
	8 or less	1001	644.1	64.4%	92.9	9.3%	165.1	16.5%	98.9	9.9%
	9 or more	392	264.2	67.4%	36.9	9.4%	56.4	14.4%	34.6	8.8%
	The last time you had vaginal sex, did you use a condom?									
	Yes	850	561.1	66.0%	72.3	8.5%	133.8	15.7%	82.8	9.7%
	No	543	347.2	64.0%	57.4	10.6%	87.6	16.1%	50.7	9.3%
	Have you had anal sex in the past 30 days?									
	No	1341	873.0	65.1%	123.9	9.2%	212.5	15.8%	131.6	9.8%
	Yes	52	35.3	67.9%	5.8	11.2%	8.9	17.2%	2.0	3.8%
Exit acceptability	**What effect does the gel have on sexual intercourse?**									
	I enjoy sex more									
	Other responses	425	260.6	61.3%	51.2	12.1%	68.5	16.1%	44.7	10.5%
	Yes	945	638.8	67.6%	73.5	7.8%	148.9	15.8%	83.8	8.9%
	I enjoy sex less									
	Other responses	1351	888.8	65.8%	121.0	9.0%	214.8	15.9%	126.3	9.4%
	Yes	19	10.6	55.9%	3.7	19.6%	2.5	13.3%	2.1	11.3%
	Partner enjoys sex more									
	Other responses	729	450.4	61.8%	73.3	10.1%	131.0	18.0%	74.3	10.2%
	Yes	641	449.1	70.1%	51.4	8.0%	86.4	13.5%	54.2	8.4%
	Partner enjoys sex less									
	Other responses	1351	890.6	65.9%	122.7	9.1%	123.2	9.1%	214.5	15.9%
	Yes	19	8.9	46.6%	2.1	11.0%	5.2	27.6%	2.8	14.8%

Table 4.3.14: CS CONRAD factors for multinomial logistic regression

CS CONRAD age-adjusted univariable multinomial logistic regression					
		Reference Class: Reported consistently high adherence			
		Early decliners	Later decliners	Variable	
n=1393		Adjusted RRR [95% CI]	Adjusted RRR [95% CI]	Adjusted RRR [95% CI]	Likelihood ratio chi-square test
Age		1.87	1.20	0.95	p = 0.008
	Under 30 vs.30+	[1.27-2.75]	[0.89-1.61]	[0.66-1.37]	
Site vs. South Africa					p<0.001
	Bangalore	1.56 [0.48-5.09]	0.80 [0.21-3.07]	1.55 [0.36-6.64]	
	Benin	0.52 [0.29-0.93]	0.97 [0.64-1.47]	0.77 [0.40-1.46]	
	Chennai	0.54 [0.28-1.03]	1.51 [1.01-2.26]	3.00 [1.86-4.80]	
	Uganda	0.66 [0.41-1.06]	0.65 [0.42-1.00]	1.36 [0.81-2.26]	
Education		0.60	1.05	0.98	p=0.058
	Primary or less vs. Secondary +	[0.40-.88]	[0.77-1.43]	[0.67-1.45]	
Number of sex partners at baseline		0.71	1.10	1.41	p=0.049
	5 or more in the past 30 days vs. 3 or under	[0.49-1.04]	[0.82-1.48]	0.97-2.05]	
Number of sex acts at baseline		0.87	0.80	0.86	p=0.546
	9 or more in last 7 days vs. 8 or less	[0.57-1.31]	[0.57-1.13]	[0.56-1.30]	
Condom use at baseline		1.32	1.07	0.99	p=0.532
	No condom at last sex vs. yes	[0.91-1.92]	[0.79-1.44]	[0.68-1.44]	
Anal sex at baseline		1.19	1.05	0.37	p=0.414
	Yes anal sex in last 30 days vs. no	[0.48-2.9]	[0.50-2.02]	[0.09-1.56]	
I enjoy sex more		0.59	0.89	0.76	p=0.050
	Yes vs. other responses	[0.40-.88]	[0.65-1.23]	[0.52-1.13]	
I enjoy sex less		2.59	0.98	1.42	p=0.531
	Yes vs. other responses	[0.78-8.62]	[0.25-3.92]	0.32-6.24	
Partner enjoys sex more		0.66	0.65	0.73	p=0.008
	Yes vs. other responses	[0.45-0.97]	[0.48-0.88]	[0.50-1.07]	
Partner enjoys sex less		1.88	1.36	4.25	p=0.123
	Yes vs. other responses	[0.41-8.68]	[0.35-5.24]	[1.42-12.73]	

Table 4.3.15: CS CONRAD age-adjusted multinomial logistic regression

adherence trajectory. Site, number of partners at baseline, participant enjoying sex more, and partner enjoying sex more had the strongest evidence for being associated with latent adherence trajectory when adjusted only for age.

MULTIVARIABLE MULTINOMIAL LOGISTIC REGRESSION

Table 4.3.16 provides results from the multivariable multinomial logistic regression for CS CONRAD. Age and site were the only factors which were found to be associated with latent adherence trajectory for CS CONRAD. Women who were less than 30 years of age versus 30 and over had a greater chance of being in one of the latent adherence trajectories which did not consistently report high adherence (Later decliners, RRR 1.44; Early de-

cliners, RRR 1.92; Variable adherence reporters, RRR 1.44). There was strong evidence for the association between age and belonging to latent adherence trajectory (likelihood ratio chi-square test $p<0.001$). Similarly, there was strong evidence of an association between site and belonging to a latent adherence trajectory (likelihood ratio chi-square test $p<0.001$). Sites were compared to South Africa; the direction of effect varied depending on which site was being compared to South Africa. At the individual site level, not all sites compared to South Africa were found to have an association with latent adherence trajectory and the effect sizes for some sites were small.

Factors not associated with latent adherence trajectory for CS CONRAD in the multivariable model were education, number of sex partners at baseline, condom use at baseline, anal sex at baseline, participant reporting she enjoys sex more with the gel, participant reporting she enjoys sex less when using the gel, participant reporting her partner enjoys sex more, and participant reporting her partner enjoys sex less.

4.3.3.5 ACROSS TRIALS

Results from the multinomial logistic regression analyses across all four trials are summarised in Table 4.3.17. Factors are divided by tier. Tier 1 indicates factors that had consistent results across all four trials and where there was strong evidence for an association between the factor and latent trajectory membership. Tier 2 includes factors for which there was strong evidence of an association between the factor and latent trajectory membership in two out of the four trials. Tier 3 shows factors for which there was strong evidence of an association between the factor and latent trajectory membership in one of the four trials.

AGE

Across all four trials (Table 4.3.17; Tables 4.3.7, 4.3.10, 4.3.13, 4.3.16), older age was associated with belonging to the latent adherence trajectory which consistently reported high adherence. In all trials included in this study, younger women had a greater chance than older women of belonging to adherence trajectories whose adherence diminished later, whose adherence diminished earlier, or whose adherence was somewhat variable, compared to the consistently high adherence-reporting group. There was strong evidence for this association across all trials (likelihood ratio chi-square testing $p<0.001$).

CS CONRAD multivariable multinomial logistic regression					
		Reference Class: Reported consistently high adherence			
		Early decliners	Later decliners	Variable	
n=1393		Adjusted RRR [95% CI]	Adjusted RRR [95% CI]	Adjusted RRR [95% CI]	Likelihood ratio chi-square test
Age		1.92	1.44	1.19	p<0.001
	Under 30 vs.30+	[1.28-2.88]	[1.05-1.97]	[0.79-1.78]	
Site vs. South Africa					p<0.001
	Bangalore	1.56 [0.48-5.09]	0.80 [0.21-3.07]	1.55 [0.36-6.64]	
	Benin	0.52 [0.29-0.93]	0.97 [0.64-1.47]	0.77 [0.40-1.46]	
	Chennai	0.53 [0.28-1.03]	1.51 [1.00-2.26]	2.99 [1.86-4.80]	
	Uganda	0.66 [0.41-1.06]	0.65 [0.42-1.00]	1.36 [0.81-2.26]	
Education		0.67	1.11	0.81	p=0.209
	Primary or less vs. secondary +	[.43-1.05]	[0.78-1.57]	[0.53-1.25]	
Number of sex partners at baseline		2.03	2.02	0.75	p=0.086
	5 or more in the past 30 days vs. 3 or less	[0.76-5.4]	[0.95-4.28]	[0.36-1.54]	
Number of sex acts at baseline		1.33	0.97	0.87	p=0.693
	9 or more in last 7 days vs. 8 or less	[0.76-2.31]	[0.63-1.48]	[0.52-1.46]	
Condom use at baseline		1.13	1.03	1.26	p=0.718
	No condom at last sex vs. yes	[0.75-1.70]	[0.74-1.43]	[0.83-1.91]	
Anal sex at baseline		1.05	0.95	0.32	p=0.358
	Yes anal sex in last 30 days vs. no	[0.42-2.62]	[0.44-2.01]	[0.08-1.40]	
I enjoy sex more		0.65	0.96	0.67	p=.084
	Yes vs. other responses	[0.43-0.99]	[0.68-1.36]	[0.44-1.02]	
I enjoy sex less		2.36	0.93	1.39	p=0.600
	Yes vs. other responses	[0.70-7.97]	[0.23-3.73]	[0.31-6.23]	
Partner enjoys sex more		0.70	0.72	0.69	p=0.102
	Yes vs. other responses	[0.44-1.12]	[0.50-1.03]	[0.44-1.10]	
Partner enjoys sex less		2.14	1.10	2.91	p=0.310
	Yes vs. other responses	[0.45-10.22]	[0.28-4.30]	[0.94-9.03]	

Table 4.3.16: CS CONRAD multivariable multinomial logistic regression

Tier	Factor	Trial			
		HPTN 035	MDP 301	Carraguard	CS CONRAD
1: Strong evidence of association of factor and latent trajectory membership in all 4 trials	Site	↕	↕	↕	↕
	Older participants compared to younger participants	↑	↑	↑	↑
2: Strong evidence of association of factor and latent trajectory membership in 2 trials	Participant reported partner dislike or refusal of gel	↓		↓	
3: Strong evidence of association of factor and latent trajectory membership in 1 trial	Higher number of sex partners reported at baseline			↓	
	Higher number of sex acts reported at baseline		↓		
	Lower education		↑		

↑= Increased probability of membership of consistently high adherence reporting latent trajectory

↓= Decreased probability of membership of consistently high adherence reporting latent trajectory

↕ = Increased or decreased probability of membership of consistently high adherence reporting latent trajectory, dependent on which sites are compared

Table 4.3.17: Summary of effects of selected factors on reported adherence across four trials

SITE

In all trials (Table 4.3.17; Tables 4.3.7, 4.3.10, 4.3.13, 4.3.16), site was found to be associated with latent adherence trajectory membership. The direction of the association depended on which site was being compared to the reference site. In this study, model results consistently showed strong evidence across all trials that site was associated with latent adherence trajectory ($p<0.001$).

REPORTED NEGATIVE REACTION OF PARTNER TO GEL

There was strong evidence that reported partner dislike or refusal of gel was associated with an increased risk of being in a latent adherence trajectory that did not consistently report high adherence in two of the four trials (HPTN 035, Table 4.3.7; and Carraguard, Table 4.3.13) included in this study. Results from the age-adjusted univariable multinomial logistic regressions of reported partner dislike of gel in MDP 301 (Table 4.3.9) and CS CONRAD (Table 4.3.15), showed a similar pattern where partner dislike of gel was associated with belonging to trajectories that reported lower adherence, although this association did not reach statistical significance in the overall adjusted model at the $p=0.05$ level in these particular analyses.

NUMBER OF SEX PARTNERS AT BASELINE

Results from the Carraguard analysis showed (Table 4.3.13) there was strong evidence that higher number of sex partners at baseline was associated with belonging to latent trajectories that did not consistently report high adherence. While the association of a high number of sex partners and latent trajectory did not reach statistical significance for the overall models in the other three trials, age-adjusted and fully-adjusted analyses in the other trials (Tables 4.3.6, 4.3.7, 4.3.9, 4.3.10, 4.3.15, 4.3.16) showed a similar trend with all estimates except one showing an increased risk of belonging to latent trajectories that did not consistently report high adherence for participants reporting higher numbers of sex partners at baseline.

NUMBER OF SEX ACTS AT BASELINE

A higher number of sex acts reported before enrolment was associated with a decreased risk of being in the latent adherence trajectories that consistently reported high adherence in the MDP 301 trial (Table 4.3.10). Number of sex acts at baseline in relation to latent trajectory membership in the fully-adjusted models for HPTN 035, Carraguard, and CS CONRAD did not reach statistical significance. While there was a trend for a higher number of sex acts to be associated with a decreased risk of being in latent adherence trajectories which consistently reported high adherence, this was not observed in all cases and the effect sizes were small (Table 4.3.7, Table 4.3.13, Table 4.3.16).

EDUCATION

There was strong evidence in MDP 301 that lower education level was associated with an increased chance of being in the group that consistently reported high adherence (Table 4.3.10). Education in relation to latent trajectory membership in the fully adjusted models for HPTN 035, Carraguard, and CS CONRAD did not reach statistical significance. While there was a trend that lower education level was associated with belonging to the high adherence-reporting trajectories, this was not observed in all cases and the effect sizes were small (Table 4.3.7, Table 4.3.13, Table 4.3.16).

4.4 DISCUSSION

Microbicide trial teams typically report adherence in primary results manuscripts as overall averages[8] which give an impression that trial participants have one type of adherence. This study sought to investigate if self-reported data from previously completed pre-ARV microbicide gel trials could be used to provide more information about how trial participants used study products over follow-up. This study used latent class and latent profile analysis to identify latent adherence trajectories. This study also explored, through multinomial logistic regression, if individual-level factors were associated with belonging to different latent adherence trajectories and how associations of individual-level factors and belonging to latent adherence trajectories might be similar or different across the trials.

4.4.1 LIMITATIONS

There are a number of limitations to this study. All of the adherence and behavioural data are self-reported. Self-reported adherence may be higher than actual adherence as participants may have been motivated to please staff members or may have worried if they reported their actual adherence they might have been removed from the trial.[95,114,115,116,117,118] Participants may not have answered all of the sexual behaviour questions honestly for fear of how staff might perceive them. For example, they may have feared being judged by trial staff and under-reported information such as number of sex acts, number of sex partners, and stigmatised behaviours such as anal sex or exchanging sex for money. Behaviours seen as positive for HIV prevention and promoted by trial staff, such as condom use, may have been inflated.[18,71] Thus associations identified, or not identified, may be biased by how participants reported their information.

Another limitation of this study is that it only includes microbicide trials that ended most recently in 2009. Current microbicide trials focus on ARV-based products, and trials have developed new strategies for adherence counselling based on experience gained over years of conducting microbicide trials.[90,91,92] Thus, results presented in this analysis may represent reported adherence patterns resulting from earlier approaches to microbicide trial conduct. Moreover, ARV-based trials are also able to examine data about participant adherence via biological samples rather than just verbal self-report. Last, biomarker-based methods were unavailable with the earlier types of microbicides included in this study

and the DSA, used in Carraguard, was completed on batched applicators at the end of the trial.

There are less data available to inform the modelling process at the later stages of trial follow-up. Latent adherence trajectories were modelled using all of the data available from each of the trials for the selected adherence variables. There are varying levels of data that were available for any given point in time. For example, HPTN 035 followed participants for 12–30 months; Carraguard followed participants for 9–24 months; and all trials had participants who were lost to follow-up. Therefore, more data were available to model patterns from the beginning to the middle of the total trial period, compared to amount of data available for the later stages of the overall trial.

As noted in the results section, in the datasets available for this PhD research, time points for when there are no adherence measures for participants are due to a number of factors, such as the product being withheld or the participant having officially exited the study; in some cases, the adherence data were actually missing. The trials included in this study attempted to keep loss to follow-up to a minimum and had good retention overall. According to trial-specific definitions, HPTN 035 had 93.6% retention; MDP 301 had 81% retention; Carraguard had 14% loss to follow-up; and CS CONRAD had 9.9% loss to follow-up.[29,30,26,28]

For data which are truly missing (which are not identifiable as such in the particular datasets available for this PhD research), it is impossible to know whether sex acts at those time points were covered by gel. It is likely, however, that a larger proportion of missing data would correspond to non-use of gel than to use of gel. Participants who were lost to follow-up for multiple remaining months would not likely have an adequate gel supply to use during all sex acts. For participants who did complete their follow-up per protocol but missed some follow-up visits, it is possible that those missing data would also be associated with non-use of the gel because they also might not have an adequate supply of gel, although it is also possible that they did not use all of the gel issued from the previous visit and that lack of gel might not be a reason for non-use.

It may be that missing adherence data could be associated with gel non-use because a participant who misses a clinic visit might experience barriers or factors beyond her control to both using the gel and attending clinic visits. It is also possible that participants who miss visits may represent those who are less interested in using the gel or fully participating in the trial. If missing data are likely to correspond to non-use of gel, the latent adherence

trajectories may be biased in the direction of showing overall higher adherence than in reality, as in that case those who did not use the gel would not be contributing data.

Latent structure software uses full information maximum likelihood (FIML) to estimate the trajectories and uses all available data. Full information maximum likelihood assumes that data are missing completely at random or missing at random. In this PhD research, it is not possible with the available datasets to assess accurately how truly missing data are distributed across the adherence trajectories. Given the type of data (use or non-use of gel) and the outcome (latent trajectories of gel-use patterns), it would not be surprising, however, if the early declining or later declining trajectories were associated with truly missing data.

While modelling latent adherence trajectories is helpful in understanding longitudinal adherence reporting patterns in trials, it is also important to remember that the model is not representing "the truth." For the purposes of this PhD research, LCA and LPA are modelling strategies that provide useful simplifications of large amounts of data that can aid in interpreting results. The number of latent trajectories chosen is arbitrary and the model will mathematically separate the population based on the number of trajectories specified by the user. The fact that the model then separates the population into the specified number of categories does not prove the existence of those latent structures. In reality, each participant has a particular pattern of adherence and the model uses that pattern to estimate her probability of belonging to each of the imposed estimated subgroups.

4.4.2 PATTERNS OF ADHERENCE

Latent class and latent profile analysis were able to identify subpopulations of participants with different adherence patterns in all four trials included in this study. Given that the average adherence for all four trials was high, it is unsurprising that results included a substantial subpopulation for each trial that reported consistently high adherence (59% of the HPTN 035 population, 70% of the MDP 301 population, 91% of the Carraguard population, and 65% of the CS CONRAD population). Despite the high overall adherence averages reported by trial teams in primary results publications, LCA and LPA were also able to identify additional latent adherence trajectories in each of the trials.

The most surprising result of this study was that latent adherence trajectories identified across the trials were quite similar. In addition to each trial having a subgroup of partic-

ipants that consistently reported high adherence, three other adherence trajectories were identified. Subgroups characterised by "later decliners" and mid-to-high "variable" adherers were identified in all four trials as well. A subgroup characterised by "early decliners" was identified in three of the four trials in the models selected.

Identifying different adherence patterns in microbicide trials is a useful starting place for understanding adherence and adherence reporting, what might be affecting how women use these topically applied products, and how they report their use. While the models identified different types of decliners (early and later), there is likely to be a difference between the types of "decliners". Early decliners may represent a proportion of women who joined the trial without the intention of using the study gel. Alternatively, they may have found using the gel initially difficult. Later decliners are likely to be composed of participants who stop using the gel for a number of different reasons. Some may decline because of fatigue with using the gel, while others may still desire to use the gel but might be experiencing real-life barriers that make gel use around the time of sex difficult to implement.

By identifying trajectories, trial teams can attempt to understand the causes of reporting patterns of gel use by following up with participants either prospectively during the trial or retrospectively once the trial is complete. Information learned through follow-up, particularly in the form of qualitative research, can then be integrated into trial procedures during trial implementation or for future studies in order to better support adherence and adherence reporting.

4.4.3 FACTORS ASSOCIATED WITH ADHERENCE PATTERNS

4.4.3.1 SITE

There was strong evidence that site was associated with latent adherence trajectory membership in all four of the trials included in this study. It is important to note, however, that as the sample sizes are large for each trial, small p-values may not necessarily indicate large effect sizes. The magnitude and direction of the effect depended on which two sites were being compared. Site being associated with adherence has been observed in results of other studies using data from the included trials[119,120,121] as well as other HIV prevention trials such as MIRA,[122] which looked at diaphragm with gel (non-microbicidal); and FEM-PrEP,[94] which involved using oral PrEP. This finding indicates that local culture and site staff factors may have played a role in how participants reported their adherence

or may have influenced participants' actual adherence. It is likely that in some locations, underlying culture may influence participants to report higher adherence so as to "please" site staff, or participants may report gel use in order to avoid being reprimanded, removed from the trial, or showing vulnerability to site staff.[95,114,115,116,117,118]

Staff conduct is a critical factor in ensuring valid clinical trial results; it is particularly important in a trial where the investigational product is user controlled and adherence is assessed through participant self-report or means which can be manipulated by participants, such as using the product just prior to a follow-up study visit. If staff members do not adequately explain trial procedures and help participants understand why adherence is important as well as how to manage difficulties around using the gel, adherence might be lower than optimal in a specific location. It is important to note that if staff members do not build good rapport with participants, participants may be reluctant to answer behavioural questions honestly.

Together with multinomial logistic regression, LCA and LPA can be used to understand how participants are reporting adherence in comparison to various other latent adherence trajectories. During trial conduct, this method can be used to examine differences in reported adherence across trial sites within one trial. Trial sites might be identified which have consistently high reported adherence, and other trial sites might be identified as having consistently lower reported adherence. Research teams can then investigate why those data might be observed in the different trial sites and take corrective action if necessary.

If a site is identified as having consistently high adherence compared to other sites, this may be due to participants actually consistently using the study gel. That consistency of use may be due to particular circumstances of the trial populations or it might be affected by particularly effective strategies that trial staff members use to engage and support trial participants. In such cases, the effective strategies could be shared with other trial sites across the trial. Consistently high reported adherence might suggest a different situation: perhaps trial participants at that site are not comfortable reporting their adherence truthfully. Such reluctance might be due to less-than-optimal relationships between participants and certain staff members. Trial teams may want to investigate that and retrain staff to improve rapport-building techniques, or reassign certain staff members to other roles within the trial.

If low reported adherence is consistently identified at a particular site, trial teams could also investigate reasons behind those observed data. Low reported adherence could be

due to the unique challenges or culture of the particular population at that site. It might also be due to factors related to the relationship between participants and staff members. Perhaps staff members could be better trained to help support participants with the barriers they are facing. Perhaps relationships between staff and participants are not optimal and participants therefore are not as interested in using the study gel. Again, staff can be retrained or reassigned to improve the situation. From another perspective, low reported adherence—although not ideal for the clinical trial—could indicate that participants at a particular site are giving candid answers to staff members. In that case, both staff and participants at that site might be able to provide honest suggestions on how to improve adherence, if asked.

4.4.3.2 AGE

Older age, in all four trials, was found to be associated with the subpopulations of participants that consistently reported high adherence; this finding has been observed in other studies.[120,121,122,123] There are a number of reasons why older women may report higher adherence or may actually have higher adherence. Older women may be more aware of their risk of HIV because, for example, they may recognise that their partners are not faithful to them. As mothers, they may be more interested in protecting themselves and their children from HIV. They may also be living in more stable households where logistically they can better manage gel use, compared to younger participants who may be having sex outside of locations where they reside.[124] Older participants, compared to younger participants, may have more self-efficacy and be better prepared to negotiate gel use with their partners or decide to use it even without partner approval. Younger women may be less likely to be in stable relationships, have more partners, and be less able to plan sex and therefore use of the gel. Biomarker data from the most recent research results have indicated that women 21 years and younger have significantly lower adherence than older participants.[125,126] If this analysis were repeated, it would be interesting to examine the results with separate age categories for to those 21 and younger, and those 22 and older.

4.4.3.3 PARTNER DISLIKE OF GEL

It is not surprising that if a participant reports her partner did not like the gel or refused her use of the gel, her adherence to the gel would be negatively affected. In this study, the factor that had the strongest effect on membership of latent adherence trajectories was a reported negative reaction of the partner to gel (RRR 1.20–5.53); however, the association

between reported partner negative reaction to gel and decreased risk of being in the high adherence-reporting group did not reach statistical significance in two of the four trials in the fully adjusted models. A body of evidence is growing that shows partner dynamics is a critical factor that affects participants' adherence and participation in biomedical HIV prevention trials. Important factors which participants have reported as affecting their adherence and study participation are what their partners think about them participating in the trial, what their partners think of the study product, how participants think their partners will react to study participation or study products, and history of intimate partner violence.[95,116,121,127,128,127,129,130]

It is ironic that the need for vaginal microbicides came from the reality that many male partners refuse to use condoms and women need an HIV prevention strategy they can control, and yet this same dynamic continues to be a barrier for female participants to use the very product being tested to free themselves from that constraint. This speaks strongly to the real and ongoing challenges that women face in relationships with men. While the impetus of vaginal microbicides came from the important need for women to have a way to protect themselves without necessarily having their partner's knowledge or consent, and while this criterion is still critical for implementation of a licenced product, seeing that partner dislike of the gel can strongly affect participant adherence to the gel indicates the importance of integrating this critical reality into future trials. To improve adherence, trial teams can include more systematic opportunities, with the consent of female participants, to engage male partners at the beginning of trials and throughout follow-up.[121,127,131]

From a critical perspective, it is important to note that questions about partner dislike of gel in this study were asked at the end of each trial, after each participant had already reported her adherence, and that information on partner dislike of the gel is also self-reported data. It is possible that some participants were aware that their reported adherence was low and may have been motivated to provide an explanation for that, whether or not it was the true cause.

4.4.3.4 HIGHER NUMBER OF SEX PARTNERS AND HIGHER NUMBER OF SEX ACTS

Results from multivariable multinomial logistic regression showed that a higher number of sex acts reported at baseline in MDP 301 and a higher number of sex partners re-

ported at baseline in Carraguard were associated with membership of the latent trajectories that did not consistently report high adherence. These results are in agreement with trial teams' own findings in other studies.[119,120] Participants who reported more sex acts or more sex partners at baseline might be in less economically stable situations than participants who report fewer sex partners or sex acts. Those who report more sex and sex partners might be exchanging sex, living or working in less stable environments, and be more mobile, all of which may make it challenging to use the gel at each sex act. Participants with fewer sex partners and sex acts at baseline might represent a population of women who are in more stable relationships and might have home situations that are more established. If the latter is the case, they may be able to store the study gel in their home and also be more likely to be having sex in their own home, where the study gel is available.

By contrast, it might be expected that participants who have more sex partners or more sex and are likely exchanging sex might see themselves at greater risk of HIV and might be inclined to use the gel more frequently than other participants. This expectation, however, seems to be at odds with the observed results in MDP 301 and Carraguard. If it were true, the observed results might be better understood in the context of additional results in trials that compared self-reported adherence and drug levels through biomarker data. In some biomedical HIV prevention trials, it was found or suspected that participants who reported perfect or near-perfect adherence may have been less adherent than participants who reported imperfect use or slightly lower adherence.[132,133,134] In reality, it may be that the observed results are a mixture of a number of possible realities.

4.4.3.5 EDUCATION

Results from the multivariable multinomial logistic regression for MDP 301 indicated there was strong evidence that lower education level was associated with membership of the trajectory that consistently reported high adherence. Lower education being associated with better adherence was in agreement with MDP 301's own findings when looking at predictors of consistent adherence in the trial[120] in separate analyses. Results from the other trials included in this study, however, were variable. In this study, there is not clear evidence on how education may be related to latent adherence trajectories. It is possible that women with lower education levels have less economic stability and thus might be more inclined to report "good" adherence for fear of being removed from the trial and losing reimbursements. It is also possible that participants with lower education levels are more inclined to follow directions from clinic staff or report that they are following

those directions than women with more education. Women who are more highly educated could have more economic stability and might not fear reporting lower adherence because the risk of losing reimbursements might not be as severe for them.

4.4.4 LATENT CLASS AND LATENT PROFILE ANALYSIS AS A METHOD FOR UNDERSTANDING ADHERENCE IN MICROBICIDE TRIALS

Latent class analysis and latent profile analysis are methods that allow microbicide adherence data to be examined in a longitudinal fashion. A longitudinal approach provides more information than overall averages for trial populations. In this study, the use of LCA and LPA was effective at identifying subpopulations of microbicide trial participants that had not been identified previously in published analyses conducted with these datasets. Trajectory analysis, using a similar method to latent structure analysis, was used to identify patterns of adherence in the MIRA trial and to compare the utility of monthly versus quarterly adherence data collection in CS CONRAD.[122,132] This method showed that the seemingly homogeneous populations of trial participants with high adherence were actually composed of participants with different patterns of adherence. This information was obtained with the least resource-intensive form of data possible: self-reported adherence collected at routine follow-up visits. While there is much interest in using biomarker data to assess adherence in current and future microbicide trials, biomarker data are expensive to procure and results can be biased as participants can adjust their product adherence to precede follow-up visits when specimens will be collected. If reliable biomarker data are available at repeated time points, those data can also be used with a latent structure analysis approach to examine adherence trajectories within a population of microbicide trial participants. Latent structure analysis together with logistic regression could also be used to examine the association between adherence latent trajectory and HIV endpoint status.

A critical benefit of an adherence analysis strategy that relies on self-reported data is that the method does not break blinding, which is required in randomised controlled clinical trials. Thus adherence data can be collected, analysed, and fed back to participants prospectively during trial follow-up to improve adherence and adherence reporting. Results that reveal adherence patterns and factors associated with different adherence trajectories are an excellent starting place for trial teams to conduct qualitative research with different types of adherers to improve understanding of product use behaviour. The knowledge gained can then be integrated into future recruitment efforts, adherence coun-

selling, and overall trial conduct, with the aim of increasing the chance of identifying an efficacious product and correctly interpreting trial results through improved adherence and adherence reporting.

5

DESIGN YOUR OWN MICROBICIDE TRIAL

OPINIONS OF FORMER MICROBICIDE TRIAL PARTICIPANTS ON HOW TO IMPROVE ADHERENCE AND ADHERENCE REPORTING IN FUTURE MICROBICIDE TRIALS

OBJECTIVE

To use the expertise of former microbicide trial participants to understand barriers to adherence and accurate adherence reporting, and to seek their opinions about how to improve adherence and adherence reporting in future microbicide trials

INCLUDED TRIALS

MDP 301
VOICE

NOTE

This chapter is written in first person to clarify the role played by the PhD candidate in data collection.

5

DESIGN YOUR OWN MICROBICIDE TRIAL

5.1 INTRODUCTION

Condoms are currently the only coitally dependent method women can use to protect themselves from sexual transmission of HIV. Condoms, however, require the cooperation of male partners. Cultural and gender norms in some locations may make it difficult for women to suggest their use and even put women at risk for doing so.[1,135] There is a need for women to have a coitally dependent method of protecting themselves from sexual transmission of HIV which they can control and does not require the cooperation of male partners. In the 1990s, the field of vaginal microbicides was initiated to develop vaginally inserted products such as gels so that women could protect themselves from HIV infection.[7]

Products being tested in clinical trials of vaginal microbicides are user-controlled. Thus, each enrolled participant is able to use the gel in accordance with the protocol, or not. In trials of coitally-dependent products, adherence is estimated in the context of the number of sex acts covered by gel in a given time period. Most microbicide trials rely on participants to provide information about both product use and sex acts. This reality has created major challenges in the field of microbicides because low product adherence and inaccurate adherence reporting has inhibited the ability of trials to accurately assess the biological efficacy of candidate products.[11,12,8,26,136,124]

As adherence has continued to be a challenge despite many years of conducting microbicide trials, it is important to consider effective ways to adjust microbicide trial design to increase the chance of improving adherence and adherence reporting. Two key guidance documents which provide direction for ethical conduct of microbicide trials, *Ethical Considerations in Biomedical HIV Prevention Trials*[49] and *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*,[40] state the importance of stakeholder involvement in trial design to ensure ethical and scientific quality and successful imple-

mentation.

As tens of thousands of women have participated in microbicide trials to date, they can serve as a rich source of expertise about difficulties with adherence and adherence reporting and also provide insights on how to address these issues in future microbicide trials. The purpose of this qualitative study was to engage former microbicide gel trial participants in focus group discussion workshops (FGDWs) to understand barriers to adherence and accurate adherence reporting and to seek their opinions on how to improve gel adherence and gel adherence reporting in future microbicide trials.

5.2 METHODS

5.2.1 FORMAT OF STUDY AND INCLUDED TRIALS

This qualitative study engaged former gel trial participants from two completed effectiveness trials of microbicide gels in focus group discussion workshops (FGDWs) that included a combination of discussion and participatory activities to explore issues around trial participation, gel adherence, and reporting of gel adherence. This study was conducted in the fourth quarter of 2014 at two locations: Tongaat, Durban, South Africa; and Mwanza, Tanzania.

Participants included in this study were former clinical trial participants of the Microbicides Development Programme 301 (MDP 301) and the Vaginal and Oral Interventions to Control the Epidemic (VOICE) clinical trials (Table 5.2.1). MDP 301 was a randomised, double-blind, placebo-controlled phase III clinical trial of PRO 2000 vaginal gel to reduce HIV-1 transmission. MDP 301, which tested a coitally dependent regimen of PRO 2000, was conducted in South Africa, Tanzania, Uganda, and Zambia between 2006 and 2009.[30] In Tanzania, the MDP 301 study was not conducted at a single stable clinic location. Rather, guesthouses in Mwanza were rented on certain days to conduct trial procedures with participants in a particular area. VOICE was a randomised, double-blind, placebo-controlled phase IIb trial of 1% tenofovir gel (as well as oral tenofovir and oral tenofovir + emtricitabine) to reduce HIV-1 transmission. VOICE tested a daily use regimen of 1% tenofovir gel and was conducted in South Africa, Uganda, and Zimbabwe between 2009 and 2012.[136]

Trial	Product	Number of participants	Locations	Years conducted
MDP 301	0.5% PRO 2000, 2% PRO 2000	9,385	South Africa, Tanzania, Uganda, Zambia	October 2005-September 2009 (2% dropped February 2008)
VOICE	1% tenofovir gel (plus oral tenofovir disoproxil fumarate, oral tenofovir–emtricitabine)	5,029 (all regimens)	South Africa, Uganda, Zimbabwe	September 2009-August 2012

Table 5.2.1: Trials included in qualitative study

5.2.2 SITE SELECTION

The objective of site selection was to include as much diversity as possible for this small qualitative study. As multiple effectiveness microbicide trials have been conducted in Durban, South Africa, this location had the greatest potential to recruit former participants from a range of completed trials. A collaboration with the HIV Prevention Unit of the South African Medical Research Council Durban was initiated. Due to the small size of this qualitative study, one clinic, in the vicinity of Durban, was chosen to conduct the FGDWs. Tongaat was chosen as the study location because it enabled recruitment of participants from two completed microbicide trials: MDP 301 and VOICE.

Mwanza, Tanzania was chosen as the second location because culturally it is extremely different from South Africa and because my fluency in Swahili allowed me to play a leading role in conducting the FGDWs. A collaboration with the Mwanza Intervention Trials Unit (MITU) was initiated for this study.

5.2.3 STAFF TRAINING

5.2.3.1 TONGAAT

Three staff members experienced in conducting qualitative research at the HIV Prevention Research Unit were seconded to assist with the conduct of the FGDWs. One staff member was designated to take notes. Two staff members were trained to alternate between implementing the discussion and participatory activities, and providing simultaneous written translation from Zulu to English for me. Formal data processing was then carried out by individuals not involved in the FGDW implementation. Additional staff members were responsible for transcribing the audio recordings upon completion of the

FGDWs, and a translator experienced in the conduct of microbicide trials was hired to formally translate transcripts from Zulu to English.

Training of staff on objectives of the research and how to conduct research activities related to implementation of FGDWs, transcription, and translation was led by me. Training for FGDW implementation included detailed discussions of the objectives of the research, qualitative methods for conducting focus group discussions and participatory activities, objectives for each segment of the workshop, and extensive role-plays and practice as a team; the latter included detailed review of role-plays and practice sessions. Final determinations of roles and responsibilities were made based on the staff members' demonstrated competency in the above elements. As the team demonstrated a high level of skill in understanding the nuanced nature of the discussions and activities, I decided they would facilitate the FGDWs in Zulu while I received simultaneous written translations. This use of simultaneous written translation allowed me to follow the content in real time during the FGDWs, ensure quality of the conduct of the FGDWs, and intervene in case opportunities for probing or collecting important data were initially missed.

5.2.3.2 MWANZA

In Mwanza, one research assistant (RA) was hired to assist with recruitment of participants and conduct of the FGDWs; a separate individual was hired to transcribe the audio recordings; and a third individual was hired to translate the transcripts from Swahili to English. Training proceeded as had been done in Durban. The RA was responsible for physically tracing the former participants and liaising with them about FGDW scheduling. During the discussion segments of the FGDWs, I was responsible for leading discussions, conducted in Swahili, while the RA acted as note-taker. The RA was responsible for leading the participatory activities, assisted by me.

5.2.4 RECRUITMENT

The recruitment process began by acquiring official lists of all participants enrolled in MDP 301 and VOICE who were assigned to use a study gel in Tongaat and Mwanza. These lists were composed of participant identification numbers (PTIDs) and were then put in a random order using Stata SE 13. Participants would be contacted, starting at the top of each list of randomised PTIDs, until enough participants had been contacted to

participate in the FGDWs. The recruitment process was intended to provide all former gel trial participants with an equal chance of being contacted and invited to participate in the qualitative study.

5.2.4.1 TONGAAT

The lists of PTIDS placed in random order were linked to trial participant names using the trials' link logs. Name files containing participant contact information were retrieved and mobile phone numbers were accessed. Using the lists of PTIDs in random order, former MDP 301 and VOICE trial participants were called and informed about the qualitative study, according to a recruitment script, and asked if they might be interested in participating. Two FGDWs were scheduled for former MDP 301 trial participants and two FGDWs were scheduled for former VOICE participants. Those who were interested were booked for one of the FGDW dates and told they would be given a reminder call with final logistical details a day or two before the scheduled FGDW. The day before each workshop, all former participants booked were called. Not all were reachable.

5.2.4.2 MWANZA

MDP 301 locator forms were accessed from the data archives room at MITU for matching with the list of randomised PTIDs. The archived locator forms available were actual carbon copies of the original forms; some were difficult to read due to faint ink transfer. Examination of the locator forms revealed that no phone numbers were available for any former MDP 301 participants and that they were organised by geographic location. Key information available included the name of the participant, the name of the ward she lived in or worked in, and a written description of how to find her home or workplace. These descriptions included information about the type of building, any identifying features of the building, and nearby landmarks such as trees, shops, or schools. Addresses, streets, and building numbers do not exist in this setting.

Due to all former participants needing to be traced by car and then on foot over a large geographical area, for practical reasons it was not possible to recruit them based on the order of the list of randomised PTIDs. A new recruitment strategy was therefore devised to contact former participants in a manner intended to recruit a representative sample for the qualitative study. A list of all of the geographical locations was developed and a plan was made to visit a different geographical area for each day of recruitment, alternating be-

tween urban and peri-urban locations.

Each day, locator files for a particular area were reviewed and a batch of about 10–15 locator forms was selected, based on the ink transfer of the form being legible, the description of the location being understandable, and that the form itself could be photocopied successfully. The RA went to each area by car and traced each former MDP 301 participant by foot. If the former participant was found, she was informed about the new qualitative study, using the recruitment script, and asked if she would like to hear more about it. If she did, the RA explained the study in full and if the participant wanted to be called once the study was underway, the RA took her phone number and other details. In some cases, the RA came across former participants who were not in the batch of locator forms in hand. If they expressed interest in joining the study, they were told about it as well, and details were taken for contacting them again once the FGDWs were to be booked.

Prospective participants who expressed interest in joining the qualitative study were placed into four groups, by rough age categories. Several days before FGDWs were to take place, prospective participants were called and booked in for one of the four dates. The women were given another reminder call the day before their appointed FGDWs.

5.2.5 FGDW IMPLEMENTATION

5.2.5.1 IMPLEMENTATION WITH PARTICIPANTS

Eight FGDWs, four in each location, were designed to take the better part of a day, with tea breaks and lunch provided to break up blocks of data collection sessions. In the mornings, while waiting for those booked to arrive, refreshments and copies of the informed consent (IC) forms for review were provided. Once an adequate number of prospective participants arrived, or enough time had passed, the written IC form was read aloud verbatim and explained to the group. If individuals were interested in staying and participating, they sat with a staff member one-on-one to review any questions they might have about participation; if interested in participating, they signed the IC forms. Illiterate women signed with a thumbprint in front of a witness, who also signed. After each IC form had been fully signed, staff members completed a demographics form with each participant. Each participant was provided with a numbered sticker, acting as a pseudonym, to wear for the FGDW in order to protect her identity among her peers and on the audio record-

	Session name	Method	Objective
	Welcome and Introduction		Welcome participants, describe logistics for the day
1	Remembering the trial	Discussion	Help participants remember the clinical trial
2	Microbicide trial presentation with participation	Presentation with participation	Provide education about how trials answer their research questions so participants can understand why adherence is critical in microbicide trials, and will be better able to make helpful and honest suggestions during the workshop
3	Reasons for joining the trial and gel use	Discussion	What are the real reasons women join trials? How do those reasons affect adherence?
4	Feelings and Needs/Clinic atmosphere	Discussion + group activity	What really matters to participants? How do they feel? What are their needs, what is important to them?
5	Research staff and participants	Role-play activity	Understand participant views of research teams and how they believe research teams view participants.
6	Who is the trial for?	Discussion	What is the dynamic of the relationship between research teams and participants? How might these dynamics affect adherence? How can we improve trials?
7	Telling the truth	Staff role-play, discussion, group activity	Understand what factors affect if participants answer honestly, what aspects of the trial or relationship with staff can be changed to improve honest reporting.
8	Design your own microbicide trial	Group activity	Provide participants with opportunity to make suggestions for how future microbicide trials should be designed.

Table 5.2.2: Focus group discussion workshop sessions

ing.

While the overall FGDWs in some cases took the entire workday, data collection periods ranged from approximately 2 to 4 hours. The process was generally faster with Durban participants, with FGDW implementation in Mwanza taking more time. A summary of the FGDW sessions is given in Table 5.2.2

The FGDW began with an introduction to welcome and orient the participants on the objectives and logistics of the day's activities. Each participant was asked to introduce herself by saying her pseudonym (number) as practice for the session. During discussions, if a participant forgot to state her number, the staff members facilitating discussions had

been trained to state that participant's number aloud for the audio recording.

The first session began with a "Remembering the trial" discussion during which participants were invited to share what they remembered about the trial and its purpose, the gels, and their trial participation. This was an important introductory step for the day, as nearly 7 years might have passed since some of them had engaged in the past clinical trials.

The second session was an interactive educational discussion about microbicide trials that used a simple diagram (Figure 5.2.1) to explain to participants how microbicide gel trials are designed to identify potentially efficacious products. As the primary objective of the FGDWs was for participants to think critically about how to improve adherence and adherence reporting in future microbicide trials, it was essential for them to understand why adherence is fundamental in microbicide trial design and how low adherence affects interpretation of trial results. The diagram, which was provided to each participant, showed how women who are not infected with HIV are recruited at the beginning of a microbicide trial and then are randomised to receive either the placebo gel, which has no active drug, or the active gel, which contains the real drug that is being tested. Through the diagram and discussion, the participants were shown that both groups of women, those who received placebo gel and those who received the active gel, were asked to use the gel in the same way and also asked to use condoms. At the end of the trial, shown in the picture, the number of women who became infected with HIV was compared between the group who used the placebo gel and the group who used the active gel. This comparison of those infected with HIV in the two groups is used to determine if the gel is effective at reducing HIV. To check comprehension of the participants, the facilitator proposed different findings than those in the diagram and asked them what conclusions could be drawn from various scenarios of observed data.

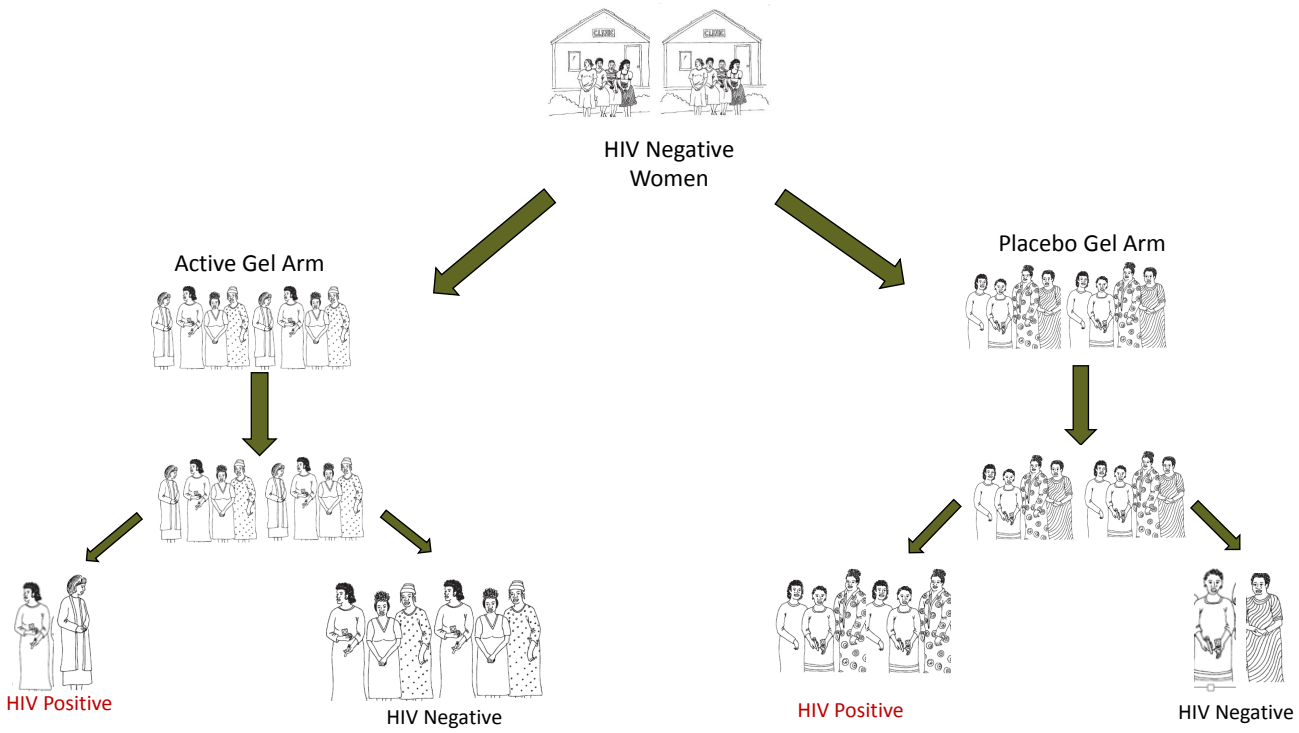


Figure 5.2.1: Diagram of how a microbicide trial answers its research question

Figure 5.2.2: Picture of results of Carraguard's dye stain assay for vaginal applicators

Once the facilitator was satisfied that the participants understood how a candidate microbicide is assessed, the educational discussion then went on to introduce what happens when trial participants do not use the gels very much. The participants were asked to explain what kind of results would be observed and what conclusions trial teams could make from the data. The participants were provided with historical information about past microbicide trials, using the Carraguard trial as an example of a trial where participants reported high adherence (96%) and no HIV reduction effect was observed in the data. The participants were each provided with a picture of gel applicators subjected to the dye stain assay (DSA) (Figure 5.2.2) and it was explained that at the end of the trial, all of the applicators were tested using this special procedure to find out if the applicators had actually been inserted vaginally. The DSA showed that, despite high reporting, adherence had been only 42%. Therefore, in actuality, trial participants' adherence was different from what they had reported in the trial and the actual biological effect of Carraguard was not clear. It was explained to the participants that once expensive trials do not show a protective effect of a candidate gel, research is not likely to continue with that product even though trial teams cannot be certain of its biological effect. A situation such as this may mean women have to wait longer for a microbicide gel that is able to prevent HIV transmission.

After it was clear the participants had a good understanding of how trials answer their research questions and why adherence and adherence reporting are important, it was pos-

sible to proceed to the rest of the discussions and participatory activities for the FGDWs.

The FGDW then continued into more focused data collection activities. The third session, which covered reasons for joining the trial and gel use, was a discussion intended to increase understanding of trial participants' true motivations for joining and staying in the trial, how much trial participants thought the gel had been used in the trial, how participant motivations for joining the trial might affect adherence, and what suggestions participants had to improve adherence in those cases. The session also sought feedback from participants about different proposed modes of HIV prevention, such as a vaginal ring or pill, and an alternative microbicide trial design that included a non-randomised, no-gel arm.

The fourth session was in two parts, with a discussion and participatory activity to explore the feelings and needs of participants, both as trial participants and as women. After discussion on what matters to them, they were broken into two groups to write down their feelings and needs on different cards. The two groups then were asked to put their cards together and to work as a group to categorise and sort them in any way they liked.

The fifth session involved a role-play game where participants were asked to act as either research staff or trial participants. The objective of the session was to gain insight into how participants viewed trial team staff and how they believed they had been viewed by trial team staff.

The sixth session was a discussion called "Who is the trial for?" which had the objective of understanding the dynamic of the relationship between trial participants and research teams, how that dynamic might affect adherence, and participants' thoughts on how trials can be improved to increase trial participant motivation to use the gel.

The seventh session included a role-play performed by staff, a discussion in reaction to the role-play, and an activity focused on telling the truth. Staff members performed two different vignettes showing two examples of trial participants using the gel during a sex act, and then showed how the two trial participants reported their behaviour differently: one honestly and one dishonestly. Present participants were invited to react to the two vignettes and then guided through a discussion about reporting behaviour at clinic visits. Questions addressed were how difficult present participants believed it was for trial participants to answer questions honestly, why some trial participants experienced difficulty in doing so, and what could be changed about trials to help trial participants feel more

comfortable answering questions honestly. Answering these questions was followed by an activity where participants worked in groups to write ideas related to these topics on different cards.

The eighth activity, which was the final activity of the day, was titled "Design your own microbicide trial." It sought to bring all of the ideas addressed during the day together and to provide an opportunity for participants to make any suggestions they liked to improve design of future microbicide trials, with a focus on how to improve adherence and adherence reporting. Participants were divided into two groups and given flip-chart paper and a set of questions to guide their discussions. The participants then presented their ideas to the whole group.

At the end of the FGDW, once data collection had ended, participants were invited to ask any questions they might have, in particular about conduct of the trials, upcoming studies, or specific health information.

The above description provides an overview of the FGDW guide. Implementation of the guide was adapted in real time to better suit the needs of each group. For example, if we noticed that a particular group was more forthcoming with information in the discussion format, but did not enjoy or disclose much information during an activity, we modified the rest of the day's sessions to focus on discussion or vice versa.

5.2.5.2 DAILY DEBRIEFING SESSION

Immediately after each FGDW, a debriefing session took place with staff members that served as the initial stage of data analysis and provided an opportunity to modify future FGDWs for optimal implementation. A debriefing guide was used to facilitate and document the sessions, which were audio recorded. Key points included reviewing what the participants said (and, in the Tongaat site, translation of key terms and written work by participants in Zulu), what was not said by participants, at what stages facilitators thought participants might not have been forthcoming with honest information, if the objectives of each session had been met, and what modifications for implementation would be appropriate to try for the next FGDW.

5.2.6 DATA PROCESSING

Standard operating procedures (SOPs) for transcription and translation were written and provided to transcribers and translators as a part of the training process.

Tongaat audio recordings were transcribed verbatim into a text document by an independent staff member not present at the FGDWs. Each individual speaker on the audio recording was identified by a unique code throughout the transcript. Unique codes for participants contained the assigned pseudonym number, the location of the FGDW, and the FGDW session attended. For example, NO8.DUR.W3 indicates that this participant was participant number eight, who attended the third FGDW in Tongaat, Durban, South Africa. Once the primary transcriber transcribed the audio recordings, they listened to the audio recording a second time to perform a quality control check of their own work and make any corrections. A second staff member also not present at the FGDWs listened to 100% of the recordings while reviewing the text transcripts, making corrections using Tracked Changes as needed. A third staff member translated transcripts from Zulu to English, and performed a quality check review of their work.

Mwanza audio recordings were transcribed verbatim by an independent staff member not present at the FGDWs. Transcripts were then translated from Swahili to English by another staff member also not present at the FGDWs. I reviewed 100% of the transcripts in both Swahili and English for problems or errors. Recordings were checked as needed and corrections were made to resolve any problems.

5.2.7 DATA ANALYSIS

All data analysis was completed by me. My familiarity with the data began with my in-person participation in the FGDWs and analysis began with my participation in the debriefing sessions and my reviews of transcripts for quality assurance. Transcripts of text containing blocks of each language (Zulu and English; Swahili and English) were managed using NVivo10 (QSR International, 2012). Information contained in demographic forms was entered into NVivo for data management purposes.

Transcripts were coded inductively for themes that were identified from the data.[137] As transcripts were read, portions of text, in both local language and English, containing

statements, thoughts, concepts, or meanings relevant to my research questions were highlighted and grouped into unique codes that represented themes. For example, a code called "More and better education" was used to group any segments of data that contained statements by participants expressing they were not provided with particular information or had unanswered questions about aspects of trial participation, or statements that contained explicit suggestions about how information provision could be improved or how it "should" be. Using the software, all data coded to a particular code (or theme) could then be reviewed together to further understand the meaning or importance of a particular theme.

As transcripts were read and reread, codes were refined through an iterative process to better organise and understand meaning in what participants said that was relevant to understanding their experiences in the trials, factors affecting adherence and adherence reporting, and participant suggestions. Themes were often broken down into sub-themes. Some structural codes (codes based on questions from the actual FGDW guides) were added to aid organisation of the data. Negative cases, examples of views or situations that were different from those more commonly expressed in the set of data, were coded as such when examples existed.

Through the software package, NVivo, data could be viewed in different ways, such as by theme or sub-theme, by each participant, or by each FGDW. During the coding process, analytic memos were written within the software package, reflecting on the meaning of what participants said, relationships between different themes identified, comparisons between different groups, and higher level or "overarching themes" relevant to the research questions. Memos were often used to document and characterise overarching themes, which synthesised and described relationships between themes in the data.

One hundred percent of the transcripts were coded a first time. After completion of coding 100% of the transcripts, all of the data coded into themes were reviewed and codes were then condensed, expanded, or harmonised to help ensure that each code described a unique concept relating to what participants said. One hundred percent of the transcripts were coded a second time for quality assurance. Memos were written to note important findings, such as questions or relationships, and to summarise findings from themes. Themes that were relevant to the research questions were then further analysed in the context of how they relate to microbicide trial design. More-refined overarching themes were described in memos, which led to creating a structure for reporting the re-

sults of this study.

5.2.8 ETHICAL REVIEW

This qualitative study of adherence was first submitted to the London School of Hygiene & Tropical Medicine Ethics Committee and received a favourable review. This study was then submitted to the South African Medical Research Council Ethics Committee, and the Tanzania Lake Zone Institutional Review Board, which both granted ethical approval. Final ethical clearance in Tanzania was then received from the Tanzanian National Institute for Medical Research.

5.3 RESULTS

Results reported here address key barriers to adherence and accurate adherence reporting and key suggestions for how to improve adherence and adherence reporting in future microbicide gel trials.

5.3.1 STUDY PARTICIPANTS

Forty-six participants (present participants) enrolled in this qualitative study. A total of 19 attended FGDWs in Durban, and 27 in Mwanza. Overall, 41 participants had participated in MDP 301 and 5 participants had participated in VOICE. One participant in Tongaat participated in two FGDWs, as she had been a participant in both trials; therefore, while the number of participants in this study is 46, the number of individual women who participated is 45. Results from the recruitment process for MDP 301 in Tongaat are shown in Figure 5.3.1; results from the recruitment process for VOICE in Tongaat are shown in Figure 5.3.2; and results from the recruitment process for MDP 301 in Mwanza are shown in Figure 5.3.3. Table 5.3.1 provides information about participant characteristics.

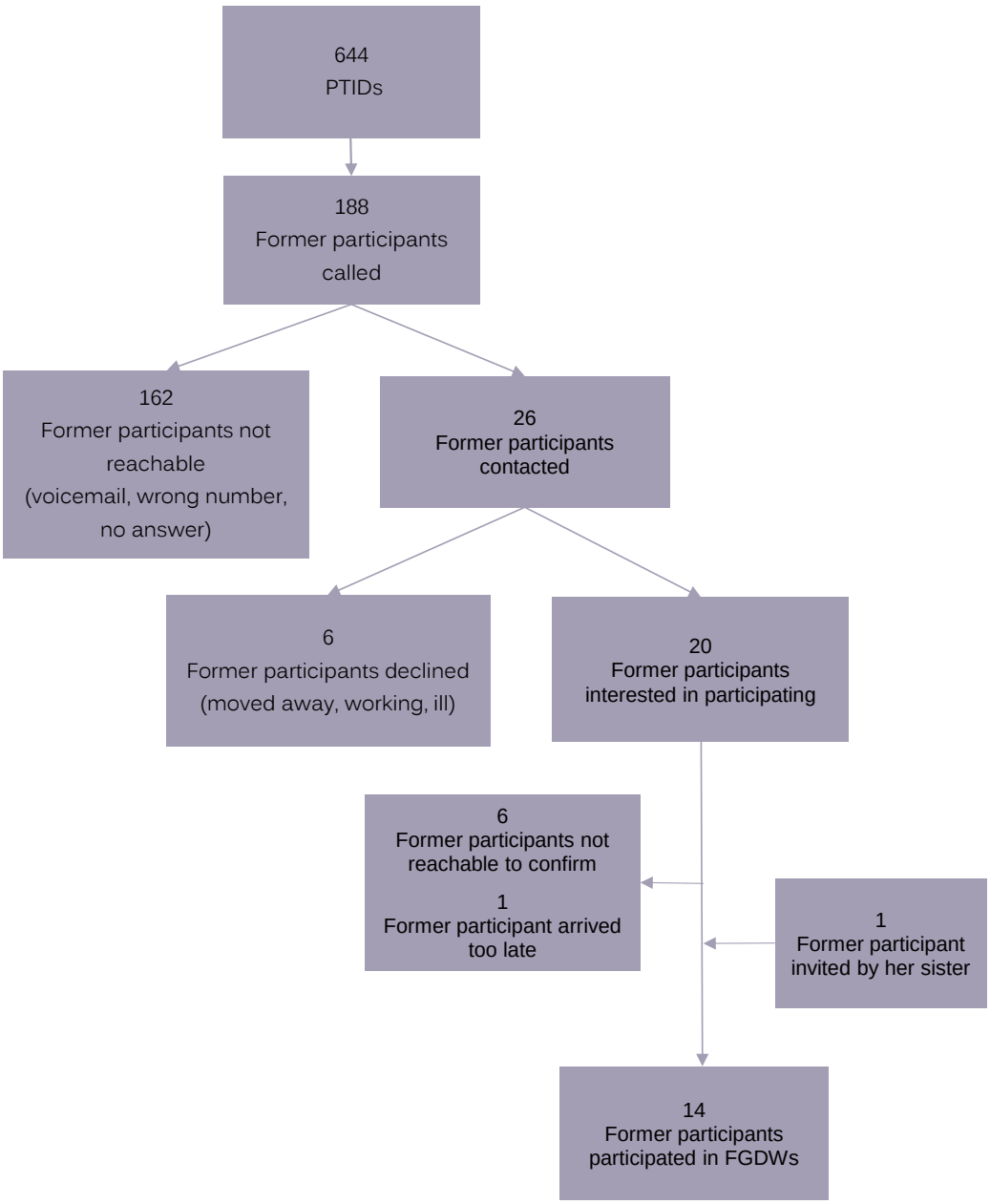


Figure 5.3.1: Recruitment results for MDP 301 at Tongaat

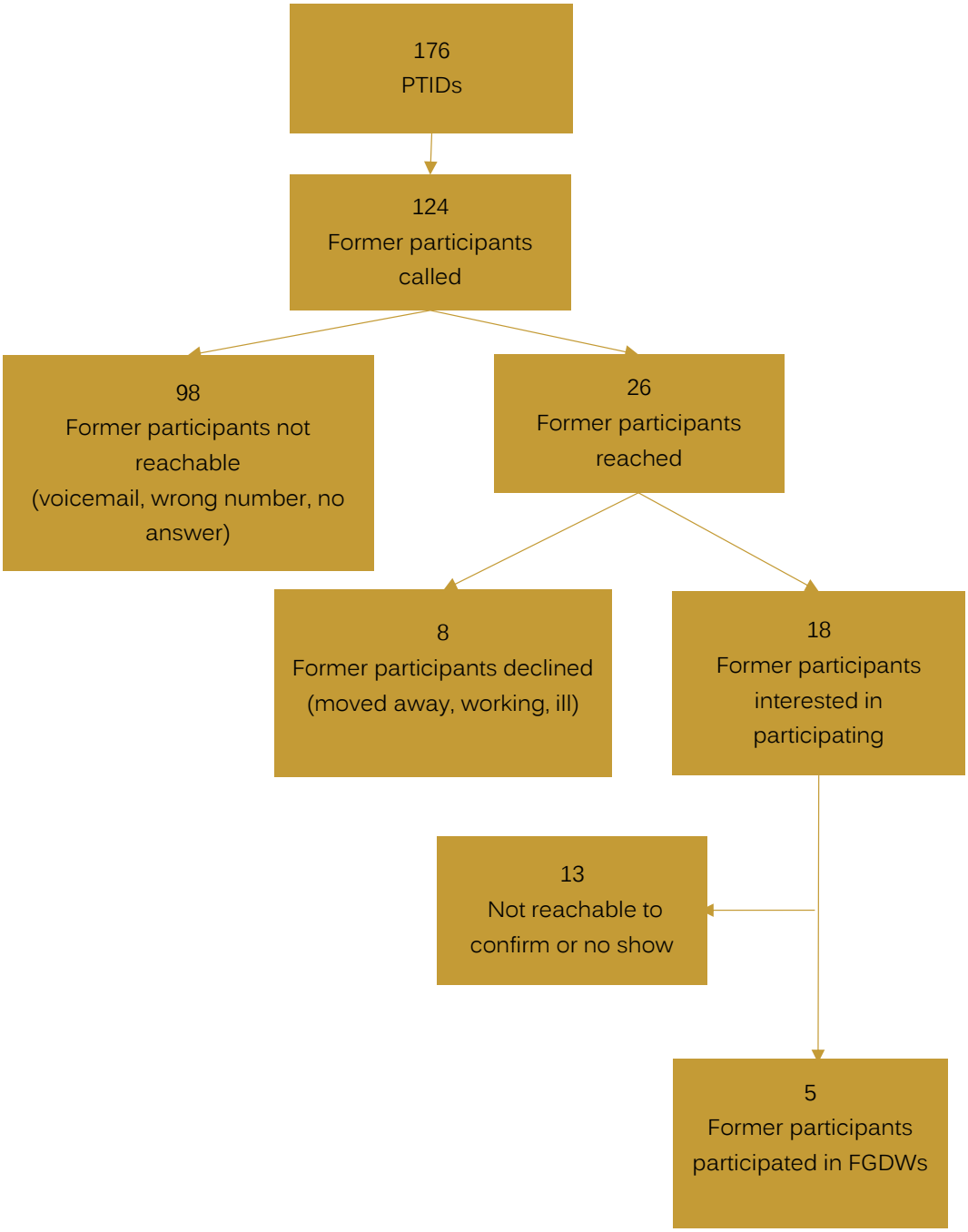


Figure 5.3.2: Recruitment results for VOICE at Tongaat

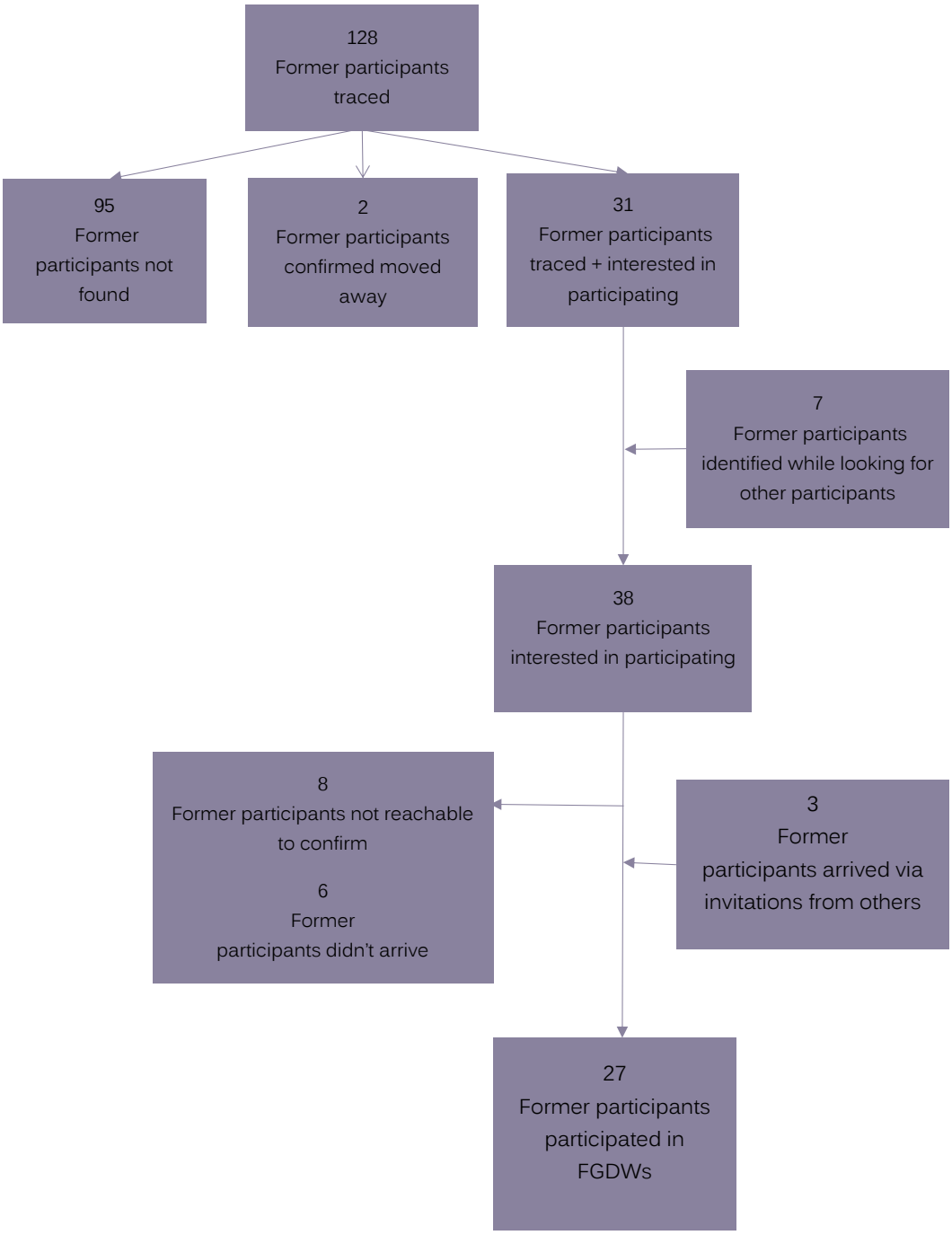


Figure 5.3.3: Recruitment results for MDP 301 in Mwanza

Participants	Tongaat	Mwanza
Number of participants (n=46)		
MDP 301 (n=41)	14	27
VOICE (n=5)	5	
Total	19	27
Current age range	27-51	24-73
Education level at time of trial participation	15 (80%) Some/completed secondary education	1 Completed secondary education
	3 Some/completed primary education	20 (74%) Some/completed primary education
	1 Illiterate	6 Illiterate
Employment at time of trial participation	16 (84%) No work	17 (63%) Informal vendor
	3 Employed	6 Bar or hotel worker
		4 No work
Relationship status at time of trial participation	18 (95%) In relationship	26 (96%) In relationship
	1 Single	1 Single

Table 5.3.1: Participant characteristics

5.3.2 REASONS FOR JOINING AND STAYING IN TRIALS

5.3.2.1 NEED FOR HIV AND STI PROTECTION

Some participants initially spoke of joining the trials to have a way to protect themselves from HIV and other sexually transmitted infections. Participants discussed how HIV has affected women more than men, how men often refuse condoms, and how they feel at risk in their relationships due to male partners having multiple sexual partners. Women who had multiple sex partners hoped the gel would protect them from HIV.

> The man may have had sex outside there with three or even four women, he will just force you to have sex with him; therefore when you get the gel, maybe a little gel, you will at least be trusting yourself.
>
> 54, Mwanza

> For me I enrolled in this study because I put in the gel, even if the husband does not want to use a condom but if I know that I had put in the gel it is

not easy to get infected with whatever disease.

49, Tongaat

...really a woman's life is always at risk he [a husband] can go somewhere for a job like [camps] and not come back. I do not know with whom he is sleeping with wherever he is, he may come back with something and infect me with it.

33, Tongaat

I had a problem that my baby's father did not want us to go there into using a condom. I did not trust him saying he does not eat a sweet in a paper.

28, Tongaat

5.3.2.2 HEALTH BENEFITS AND CARE

As discussions progressed, participants in each FGDW brought up the health benefits of trial participation. Many participants expressed appreciation for having their health checked on a regular basis, the confidential and free testing and treatment provided by the study clinics, and health education. They reported feeling happy to learn about their health status and to learn how to keep themselves healthy. That motivated them to take care of themselves.

…I felt it was right in the study…knowing my status was also encouraging…how to behave because things are bad outside. I like it most because they were checking for diseases on us…It also encouraged us not to have unplanned babies…I liked it because I found friends. Even when you came with a problem you would be able to discuss with people. You can see that, you will leave with no problem. I also liked money, money is part and parcel [laughs].

42, Tongaat

…to see the doctor needs a lot of money; you can…be told that you are suffering from this and this, definitely this will just cost you, in that case I was very happy about that project because it has facilitated many people, some people we didn't even have the ability of going to the hospital; you are sick, you just swallow Panadol until the day when you are very ill maybe they take you to the hospital, that is when you will be lucky to be checked about your health and other things but in fact you have other diseases like UTI…others

had syphilis…therefore we got cured.

43, Mwanza

Mainly this project tempted us to check our health, it attracted us to get that little income and to make us start our businesses, therefore we profited health wise and economically.

60, Mwanza

This project has helped many people because you were being tested and if you were found with a disease they treated you; if you can't and if you are at home they phone you, they come to visit you and they bring to you other needs.

30, Mwanza

It was very nice because even if you were hungry we would see ourselves eating bread and juice even when you did not bring lunch box you were able to get something too, it was nice and get money as well when you leave. It was very nice.

42, Tongaat

Some participants noted that the habit of checking their health and caring for themselves is something they learned in the trial that has stayed with them over the years. Many also discussed how they felt genuinely cared for by trial staff, found participation in the trial to have a positive impact on their lives, and hoped another project would start so they could participate again.

5.3.2.3 FINANCIAL REASONS

Money received as reimbursement for trial participation was repeatedly mentioned in the FGDWs as a reason why women join and stay in the trials. Participants spoke about how the reimbursements provided a way to purchase food and necessities and a small amount of income that they would not otherwise have had.

I liked it very much it was going to happen and according to my wish it was going to be done twice a month because after I had gotten those cents [money] they helped me, I would go to Shoprite [supermarket] and get out with a full plastic bag.

47, Tongaat

> I see the other reason which attracted them most was that of being given money whenever we went there.
>
> 43, Mwanza

Some participants, however, noted they did not attend the trial visits for money or did not think that was the reason why other trial participants joined the trials. Other participants noted that while money in some cases might not have been the primary reason for joining or staying in the trial, the money helped them and was appreciated.

5.3.3 ADHERENCE

5.3.3.1 USING THE GEL

When participants were asked to what extent they thought the gel was used, opinions varied. Some noted that they had been using the gel, or that certain groups had been using the gel, such as older trial participants, or those who saw themselves at risk for HIV, such as barmaids or trial participants who did not trust their male partners.

> ...for example for us the barmaids, we were seeing that it was helping us every time because we were having the gel, we were using the gel every time; now I mean for the others, maybe they were using it occasionally, but for us, we were working at places where there were many people; in fact it was helping us very much.
>
> 40, Mwanza

> We the older ones were using it, I think it was easy for us to use, because we had that it [gel] may really protect us...
>
> 43, Tongaat

Two participants mentioned there could be a positive effect of the gel for women who needed more lubrication during sex:

> I see that someone is using that gel because it helps the woman during sexual intercourse, you can't feel even those pains; therefore that way becomes just smooth, you don't feel bad [uncomfortable].
>
> 32, Mwanza

5.3.3.2 INVESTIGATIONAL NATURE OF STUDY GEL

While some participants spoke of themselves or select groups of trial participants using the gel, many participants spoke of low gel use in the trials. They recounted what other trial participants had told them, what was discussed in the waiting rooms, and their challenges and concerns with using an investigational product for each sex act or on a daily basis. The most significant reason given for not using the gel was the fact that the gels being tested were investigational in nature, and there was concern that the gels could harm the trial participants. This fear is founded on the fact that informed consent forms are required[44] to state risks of clinical trial participation to prospective participants, which includes known and unknown adverse effects of the investigational drug. The fears expressed by participants indicate that trial participants accurately understood the informed consent process and were aware that adverse effects were possible.

> I had fear at the beginning because they were saying they also do not know if this thing is going to work or it is not going to work…I had a fear…if it gets into my blood…in a way that is not right, and I go to them maybe having rash, maybe like this and that, and when reporting they tell me that we told you that we also do not…have a sure about it—we are testing it on you.
>
> 27, Tongaat

> Yes. They are going to check it on us fools, why are they not checking it on themselves?
>
> Tongaat participant

> One habit which prevents them from using the gel is that of having worries.
>
> 32, Mwanza

> The gel was not used in a big quantity because others were afraid that if she used the gel, it might bring her adverse effects.
>
> 44, Mwanza

> I do not think women are using the gel. When I heard about the study I heard about it from my friend...I even went to her house for her to show me that product that she takes it and put it in the toilet. She is not using it.
>
> 27, Tongaat

> I can say that some were not using it saying that they are scared that they are going to get sick, they are going to have diseases in the [womb], they do not

know what it does when stuck in there, yes only a few using it.

38, Tongaat

Participants also spoke about how community members and others not familiar with the trial played a role in promoting the idea that the study products were dangerous, would cause harm, and could cause illnesses such as cancer or HIV infection.

Yes the community was speaking badly about this gel. We were affected because they were saying how can we insert something that we do not know where it was tested. There is going to be a problem with us. That is what was discouraging us in using the gel but, because we knew what we wanted we continued using it.

42, Tongaat

And also others were telling them that you have been implanted with HIV; many were afraid and that is the reason others stopped.

44, Mwanza

...many thought that the gel it is the one that will give us the virus, there was that in my neighbourhood...

44, Tongaat

Further demonstrating the centrality of the investigational nature of the drug in preventing optimal adherence in the trials, when participants were asked for suggestions on how to improve adherence, a few participants suggested that the trial should be conducted but should not be called "research," and that trial participants should be told the products are effective at preventing HIV. Present participants with these suggestions were confident that if women were told the product does in fact prevent HIV, women would use it.

We can change the name and not say it is the study [research], we change into something that may have been licenced because people do not feel important by that... this thing is being studied, they are not sure that it is working. Maybe we can change the name and not say it is research.

Tongaat participant

Now if they are studying it now they are confusing us. This is the thing that makes a person to be reluctant.

Tongaat participant

While it is clearly not feasible in a clinical trial not to tell trial participants that the product is investigational, this suggestion poignantly highlights the most important barrier to gel use stated in the FGDWs: fear of harm, given the fact that the drug's safety and efficacy had not yet been demonstrated.

5.3.3.3 MALE PARTNERS AS A BARRIER TO ADHERENCE

The second critical barrier to adherence which emerged was the effect of trial participants' male partners. While a primary impetus for discovery of a safe and effective microbicide was to enable women to have a product they control to protect themselves from HIV, some participants explained that male partner knowledge and approval of using the gel was an important factor in their ability to adhere to the study regimen.

> It is true that you can be pressed by the man that you shouldn't use many gels, you can use it even once or once per week. Now you find many gels remaining unused and then the days to return them are ready, you find that many gels were not.
>
> 42, Mwanza

The male effect on adherence primarily manifested in two forms, as described by participants in this study. The first was related to the effects that the gel had during sexual intercourse, and culturally how those effects can be associated with infidelity. The second was related to the expressed need of participants to provide a male partner with sex when he demanded it, and not make him wait.

MALE PARTNER REACTION TO VAGINAL DIFFERENCES DURING SEX

Many participants noted that the gel, once inserted into the vagina, made a noticeable difference that could be detected by their partners. For some, this increased lubrication was not a positive attribute.

> …when he enters you it becomes open, he goes in and out, it isn't tight, it doesn't bring that heat.
>
> 36, Mwanza

> …it reduces the taste or it puts some coldness instead of being warm.
>
> 36, Mwanza

…he would also complain that you get wet quickly?…he did not like the condom and the gel as well. He did not like both.

28, Tongaat

This increased lubrication created conflict in some relationships. Male partners noticed the difference in their female partners and, in some cases, associated this increased lubrication with infidelity, at times to the point of accusing some trial participants of being unfaithful. This was in particular noted by participants in Mwanza.

That is why he was being surprised and said that 'you have been having sex with another man, you have come from having sex, why is it like this?'

60, Mwanza

...he will tell you that maybe you have had sex with other men because he will find that there is a difference.

32, Mwanza

...they were saying that it [the gel] was bringing them problems; they were using it but quarrels and problems never ended inside the house.

32, Mwanza

Some participants explained that partners disapproved of them using the gel and when they chose to use the gel, it created conflict in the relationship. Trial participants who had been in this situation had to make a choice between using the gel, which they hoped would protect them, and not using the gel, to avoid further discord with their partners.

...he would say 'why there are changes inside here?' Now he had already told you two three times, you have to stop...

42, Mwanza

...her lover said that he refused, she had to return the gel.

40, Mwanza

PROVIDING SEX AT THE MOMENT A MALE PARTNER DEMANDS IT

For some participants, the need to be ready for sex as soon as their male partners demanded it prevented them from using the gel during the trial. This was particularly the case when male partners had not been informed about the gel, when trial participants'

homes had outside latrines, and when their partners demanded sex late at night or early in the morning. Present participants who discussed this problem noted that they had to be ready when their partner "needed" sex, and that they were not in a position to make him wait, as he would not be understanding if she was not able to provide sex at the time that he wanted it. In those instances, the participants stated they were unable to use the gel, despite wanting to.

One participant noted that after going to an outside latrine for post-sex vaginal cleansing,

> ...when you return your partner wants again, and you don't have that time of evading him, he will demand. Really it was difficult.
>
> 42, Mwanza

Another participant explained a similar situation:

> When you have hidden the gel, and your husband needs you, it means you don't have time to prepare as you will be late, so you just have to go ahead, and you haven't inserted the gel.
>
> 42, Mwanza

5.3.3.4 LACK OF CLARITY AND TRANSPARENCY ABOUT THE TRIAL

THE ROLE OF ADHERENCE IN ANSWERING THE TRIAL RESEARCH QUESTION

Based on experiencing the educational session on how microbicide trials answer research questions at the beginning of the FGDW (session 2), some participants raised the concern that they thought there was a lack of clarity during the trial in which they participated about how adherence is related to answering the question of whether or not a candidate microbicide gel can prevent HIV transmission. They explained that as trial participants, they were not educated in a way to help them understand why their adherence was critical in the trial.

> Education to women should be given so that she may know in detail about the gel and the study.
>
> 60, Mwanza

> …it is that every participant is supposed to know the meaning of participation and research and as she is an important person in that research she will give correct information.
>
> 41, Mwanza

> …They should be given sufficient education like how we got education [today].
>
> 43, Mwanza

> …What is required is that…services should be given attentively…you know someone else has little understanding and another understands quickly; therefore they are supposed to go step by step, I mean slowly so that someone may understand…[if] someone understands quite well, even fear will go away.
>
> 32, Mwanza

While as trial participants were provided with required information in the informed consent forms, such as an explanation of study procedures, risks and benefits of trial participation and other details such as the concept of placebo and randomisation, present participants noted they were not told how microbicide trials answer their research questions and exactly why adherence on the part of trial participants is critical to the success of the trial and discovering a product to prevent HIV transmission.

DOUBTS

As the microbicide gels were being tested for safety and effectiveness, many trial participants had questions about what this really meant, and also had to manage comments and rumours from others in their lives and the community about the unknown effects of using such products. Lack of clarity and transparency during aspects of trial participation raised questions that may have affected trial participants' desire to use the gel or to report honestly, as noted in the examples below related to concerns about blood draws and relationships with research staff.

> …they [trial staff] were taking that other blood and they were not bringing the test results, therefore they were not open, therefore it happens that you have disbelief with that place.
>
> 43, Mwanza

> With regard to that blood for HIV we were being tested, but that blood which they were keeping in their small bottles, we didn't know for what disease it was going to be tested because that blood was being tested there [at a different location]…but that blood in those tubes…we didn't get a solution for what that blood was going to be tested.
>
> 32, Mwanza

> They [people in the community] think that as we are doing the study there is some benefit for other countries who come and take what we have done and go to do something in other places where we do not know.
>
> 43, Tongaat

> With regard to that blood, others were claiming that why are they drawing a lot of blood from us, where is this blood being taken? Others were saying that it was being taken to [another location] to be sold, I don't know if it was true, that issue of drawing blood was bringing complexity.
>
> 30, Mwanza

One participant also noted that when a trial participant feels she was not treated well by a staff member, and leaves with complaints, it may affect adherence:

> When one leaves with complaints, she thinks 'better I stop using the gels'. That brings a lot of fear for participants, what is needed is that they be given courage, courage to use the gel.
>
> 39, Mwanza

5.3.4 REASONS FOR DIFFICULTY IN ADHERENCE REPORTING

When participants discussed reporting gel use and the discrepancy between what trial participants report and actual gel use, there was wide agreement that it was difficult to be honest. Present participants did express that they, as trial participants, should try to be honest, and that being honest would be helpful to the project. They stated that they and their fellow trial participants should understand that "it isn't a crime" not to use the gel and that if they told a staff member the truth, they would not "be shouted at."

> It was difficult to say I forgot the gel just say I have used it. It is something that we were doing.
>
> 28, Tongaat

> Yes it is possible but to make yourself look like a good person and doing everything right whereas I know that when I am at home I am wrong I am not doing what I am told here in the study.
>
> 38, Tongaat

When asked why it was difficult to be truthful as trial participants, present participants gave a number of reasons. Some noted that trial participants feared being perceived as dishonest, not helpful to the project, or that they would be reprimanded.

> I think that maybe she thinks that she is going to be shouted at and asked why she did not use it.
>
> 47, Tongaat

> Yes it is going to be said I am not trustworthy. I sometimes do not use it, it is better to lie saying I am using it.
>
> 38, Tongaat

> Judging a person is what causes one to lie.
>
> 42, Tongaat

The reason most often given was that trial participants feared that if they admitted they had not used the study gel, they would be "removed" from the trial, which would mean they would no longer have access to the health care they were receiving or the reimbursement payments.

> They think they will not get the money.
>
> 44, Tongaat

> Let us say they have a fear of being withdrawn and that they want to be trusted.
>
> 44, Tongaat

> The reason that made the participants not to say the truth, she sees that if she is chased away [removed from the trial] she will miss that allowance, because there is that allowance which is being given; if she will say the truth she will be chased away and she will not get that money, therefore she tells lies.
>
> 27, Mwanza

> Someone else tells lies because maybe her husband prevents her [from using gel], then she comes there she just decides to tell lies so that she may continue with that project.
>
> 30, Mwanza

> I have seen that maybe she has a certain income [business] because we go there, there is fare [reimbursement], she has now become a businesswoman so that she may get money.
>
> 43, Mwanza

Three participants noted that inaccurate reporting of gel use might not be related to any reason in particular, except that some people are in the habit of lying and have become accustomed to lying in many aspects of their life, not just for reporting adherence in the trial.

> …I mean it is someone's habit to speak like that, it's like to tell lies is someone's habit, this one has become used to telling lies and they succeed…you can't know if this one has used [the gel] [or] this one has not used. If she will explain to you that she has used [it], you can just believe that she has used [the gel], but in fact she didn't use [it].
>
> 41, Mwanza

5.3.5 DESIGN YOUR OWN MICROBICIDE TRIAL: SUGGESTIONS FOR IMPROVING ADHERENCE AND ADHERENCE REPORTING

The following sections gather the important suggestions present participants made about how to improve adherence and adherence reporting in future microbicide trials. These suggestions range from overall trial design to the physical attributes of a vaginal microbicide gel. Tables 5.3.2 and 5.3.3 provide summaries of these suggestions.

5.3.5.1 TRIAL DESIGN WHICH INCLUDES NEEDS OF BOTH PARTICIPANTS AND RESEARCH OBJECTIVES

During the FGDWs, participants had a chance to react to the idea of different HIV prevention delivery forms and an alternative trial design that included a non-randomised arm with no gel. In this hypothetical design, women who would like to join the trial choose if they would like to use the gel or not. Those who would like to use the gel would be

	Gel suggestions
1	Less-watery consistency
2	Less volume
3	Warming sensation/lack of "cold" feeling upon insertion
4	Greater ability to use covertly, should not be obvious to a partner that a highly lubricating product is being used
5	Gel applicators and boxes should be smaller and more discreet

Table 5.3.2: Suggestions to improve microbicide gel formulation

randomised to either the placebo or active gel. Those who would not like to use the gel would remain in follow-up and would visit the research clinic regularly for HIV prevention counselling, health testing, and treatment as in the gel arms. This trial design was discussed via use of a simple diagram illustrating the design (Figure 5.3.4).

Because the workshop began with providing basic education about how a microbicide trial is able to answer its research question, participant responses indicated they now understood how incidence of HIV in the placebo and active arms is compared at the end of the trial, and that the participants in the no-gel arm would not directly contribute data to answer the question of whether the gel works or not. Some expressed a positive response to the idea of this three-arm trial, as trial participants would be able to choose if they use the gel or not, and through this method the trial would have better ability to ensure women randomised within the gel arms would actually be interested in using the gel.

> According to my opinion maybe this will be suitable because some women don't like the gel…if she is in this group, she can go to the group of those who don't like the gel.
>
> 42, Mwanza

> It is better like this than to take it [gel] and not use it. At least it is better because there is a group that will never use it…it is better not to take it than

to take and throw it away.

28, Tongaat

Several participants noted that the above approach would help the research staff separate who was joining the trial to help answer the research question or for HIV protection, and who was joining the trial just for health checks or money.

> If they divide it this way, it will be much better…here once they differentiate it, those who are coming for the purpose of testing only and those who are participating in the study will be known.
>
> 32, Mwanza

> …it is something that can help and make it better…these ones choose if they want the product, and you can have hope that because they chose it themselves it means…indeed it can happen that they are using it. Maybe if there can be a study like that with three groups.
>
> 27, Tongaat

Participants who thought such a design would not be a good solution thought so because they believed women joining the no-gel arm would not contribute to answering the research question to identify a way to prevent HIV. Others, to a lesser extent, expressed a negative reaction to this trial design because they thought many women would choose the no-gel arm; this reaction further demonstrated the view of many present participants that women join the trial for reasons other than to access the candidate microbicide gel.

> …if it will be so I think it will not be good because this is a research, if you will have two groups [gel vs no gel] this means most of the others will go to the group which doesn't use the gel; now where will that group be?
>
> 32, Mwanza

> …If you say that they should choose, most of them will go where there is no gel.
>
> 32, Mwanza

Despite participants having opinions, when asked, about which trial arm women might prefer to join, one participant remarked:

> Until you talk with them and hear which one will like to use the gel and which one will not like to use the gel…you can't know who will want or who will not want [the gel].
>
> 54, Mwanza

	Participant-initiated suggestions for improving future microbicide trial design
1	Provide participants with an explanation of how a microbicide trial answers its research question, using simple terms and easy to understand diagrams.
2	Provide participants with an explanation of why adherence is important in the context of a microbicide trial answering its research question.
3	Provide participants with a simple and clear explanation of the investigational nature of the product, where it has been tested before, and why it is necessary to test in humans in this trial.
4	Offer seminars, which can be held in waiting rooms, to revisit the above topics.
5	Engage experienced participants to be 'ambassadors' to share their experiences with other participants who may have questions about participation or experience difficulties.
6	Offer ways to engage participants' male partners to learn about the purpose of the trial, the investigational gel, blood draws, and study procedures.
7	Provide participants with clear information at each blood draw about the type of testing to be conducted and when the results will be provided.
8	Provide participants and invited guests with opportunities to visit clinic laboratories (and other areas) to learn about the trial.
9	Use a method to test applicators for vaginal insertion, and provide feedback to particpants on their adherence results over follow-up.

Table 5.3.3: Participant-initiated suggestions to improve design of future microbicide trials

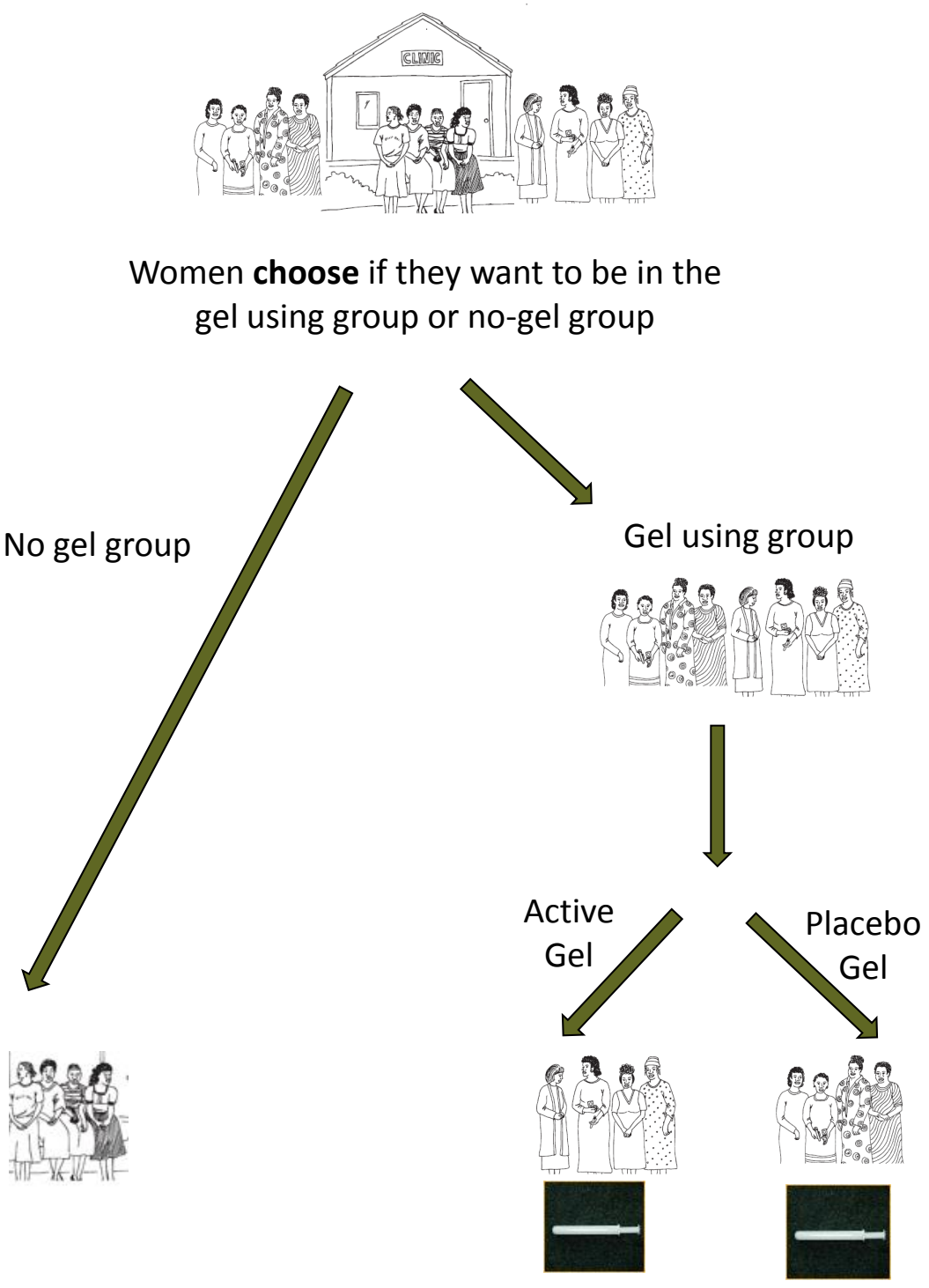


Figure 5.3.4: Diagram of a microbicide trial with a non-randomised, no-gel arm

5.3.5.2 TESTING APPLICATORS FOR VAGINAL INSERTION

While the example of Carraguard's applicator DSA to determine vaginal insertion of the applicators was used at the beginning of the workshops to help explain why low adherence can interfere with interpretation of null trial results, this technology was not brought up by study staff again and was not intended to be discussed further in the FGDWs. Interestingly, throughout the FGDWs, and during the last activity when participants were asked to work in groups to make recommendations for future trials, applicator testing was repeatedly mentioned as a viable addition to microbicide trial design. Participants stated that if trial participants can be shown results of an applicator test that demonstrates their own use in real time, it would encourage them to use the gel correctly and be honest in their reporting. Participants did not offer advice about procedures they might recommend in response to the different levels of adherence that participants report.

> In order that they may improve it I was requesting for that testing instrument...when they return those boxes they should actually test them so that they know that they have used them or not. Therefore that testing instrument is needed.
>
> 32, Mwanza

> The product has to have a mark [like DSA]...that the product has been used
>
> First Tongaat FGDW, flipchart, session 8

5.3.5.3 SUGGESTIONS TO ADDRESS ADHERENCE BARRIERS RELATED TO MALE PARTNERS

IMPROVED FORMULATION OF GEL

As noted earlier, Mwanza participants in particular had recommendations about the gel formulation. These participants recommended that it should have a less-watery consistency, less volume, not be as highly lubricating, and have a warming sensation upon application. Some thought that vaginal capsules might solve this problem or that the microbicide should be available in both formats, capsules and gel. Some acknowledged that different bodies are different, thus what works for one person might not work for another. Mwanza participants spoke of the importance of making these changes so that the microbicide could be used covertly, which was important for some, and so that microbicide use would not be surprising for the male partners who might notice a difference during sex and then accuse the trial participants of having sex with other men.

> My suggestions are...medicine should continue being improved so that it should be warm, I mean that gel should not be light [liquidy], it should be heavy [thick].
>
> 40, Mwanza

> So that when you bring it here at least it should have some certain warmth to make the man also get the desire when she inserts it inside the vagina.
>
> 39, Mwanza

> We have suggested that we should involve our partners regarding the gel so that they may be able to completely understand that we are using the gel, then that gel should be improved so that it may be attractive even to my partner.
>
> 32, Mwanza

With regard to the packaging, one participant suggested the boxes should be smaller and more discreet. Others spoke of the importance of being able to leave their appointments and not "advertise" to community members what they had been doing at the clinic. More-discreet packaging would not provide an opportunity for community members to spread rumours about trial participants carrying HIV medications.

> It should be improved, and its packaging, does it mean if you pack them in boxes...? Let it be changed, it should be even in a bag which...it shouldn't be a burden even when we go to take them; to carry that box people really...that appearance should improved.
>
> 52, Mwanza

EXPLICITLY CONSIDER HOW TO ENGAGE MALE PARTNERS IN MICROBICIDE TRIALS FOLLOWING PARTICIPANT REQUEST

Participants advocated for better inclusion of male partners in the research process. Many agreed that if there were more support in the trials to engage and educate male partners, it would be extremely helpful. They thought that male partners would likely be supportive of the gel and the research, thus improving a trial participant's ability to adhere to the study protocol and use the gel as directed.

> ...men should be given education on how to protect themselves against HIV infections, they should be educated about the gel; the participants are not

> supposed to be women only and young men too need education.
>
> 30, Mwanza

> ...when this project starts it should involve men and women and there shouldn't be something like a secret; if her partner doesn't like it, it's better she quits, if her partner will be ready then she should agree; particularly those with husbands...if you involve him, he will understand...We have said that education should be given openly to both sexes.
>
> 60, Mwanza

Participants suggested that male partners should be included from the beginning of the process and that there should be opportunities for them to receive counselling on HIV, health, the research, and the gel. Participants thought this education should be detailed and complete, so that trial participants and their partners would not be left with doubts. Present participants also noted that better education would also help the trial participants themselves to have courage and strength to tell their male partners about the details of the trial. Participants thought that once male partners were involved and understood the purpose of the study, they would be supportive. For a coitally dependent regimen, this support could translate into, for example, male partners wanting sex being willing to wait for trial participants to insert the gel, thereby increasing adherence.

5.3.5.4 TRANSPARENCY, RESPECT, LOVE

Participants experienced feelings of fear stemming from multiple aspects of trial participation. They were asked to use an investigational drug that could cause adverse effects; they heard rumours from members of the community about the gel causing health problems; and they had to negotiate trial participation and gel use with their male partners or use the gel covertly, not knowing how their partners would react. All of these elements might create an environment where a trial participant's health, safety, and well-being are at risk.

Present participants made a number of concrete suggestions on how to improve implementation of future trials that stem from the need for transparency, respect, and love. If trial staff could create relationships and a clinic environment that embody transparency about the research, show respect for the trial participants as people who need correct information, and treat them with love, participants explained that fears they had would more easily go away. They explained that knowing more details would give them strength and courage to use the investigational products and boldness to communicate accurate information to their partners, to advocate for their participation and use of the gel. By creating

an environment of transparency, where information is clear and doubts of trial participants can be addressed with honestly, and by creating an environment where participants feel respected and loved, trial participants would have more strength to be honest with trial staff about their use of the gel. Without fear of being judged and without fear of being removed from the trial and losing access to health care and reimbursement, which they had valued and needed, present participants thought there could be increased accurate reporting of gel use by trial participants.

MORE ACCURATE AND CLEARER EDUCATION

More accurate and clear information was seen as a way of demonstrating transparency, respect, and love within trial conduct. Participants noted that members of the research team must have enough education and understanding about the research and the gel to be able impart that understanding to the trial participants themselves.

> Yes, research workers should be given more education so that they may give more education to their participants.
>
> 27, Mwanza

Interestingly, this sentiment was echoed by my own RAs after I presented the "How a microbicide trial answers its research questions" lesson to them as a part of their training. The RAs who had been involved in prior microbicide trials (in non-clinical roles) noted that the scientific process of comparing HIV incidence between the randomised arms had not been explained to them clearly, and that they wished they had had that training when they worked in their previous positions.

Participants spoke of the importance of providing clear education which could then allay fears. More education meant explaining clearly and fully how the research question is answered, what is known about the gel and its known side effects, which disease each tube of blood was to be tested for, and when results would be returned.

> I would request that when we take the participants, education is just needed. I mean it is education that will help the people to rid themselves of the fear and not even to fear anything.
>
> 32, Mwanza

> ...these researchers, maybe they should be going to people and give them just little seminars that when you give your blood, not that your blood is going to be sold, that blood is going to be stored in a special place and if you want to prove that it is your blood, we have the ability to take you...we go and show you that here is your blood.
>
> 39, Mwanza

Present participants also wanted general procedures to be explained to trial participants as they were happening, so trial participants would know what to expect. When aspects of the trials were conducted in a way that was not clear to trial participants, it was confusing and raised suspicion. As noted above, blood draws were a significant source of concern for the participants at both sites. Another example, raised by one participant in Tongaat, was why, after "completing" their study visit, trial participants had to wait before they received the final approval to leave the clinic. Respecting time was highly valued by this participant and Tongaat trial participants, and being "held" for an unknown reason was a source of frustration.

> Eh maybe you have finished here, you are sitting and told to wait for the money you should get. You will stay maybe...30 minutes or more than 39 minutes you are sitting waiting for the money having finished everything. That was not good to me.
>
> 32, Tongaat

Providing transparent information about trial procedures in this case would have meant letting trial participants know that after they complete their visit procedures, their files are reviewed by a staff member in the data room while the trial participants are still in the clinic, in case there are any data issues that require correction or clarification. Once it is determined that a file is satisfactory, that trial participant is given her reimbursement.

In thinking about how to help improve education within the trials, one present participant stated that trial participants who are already experienced with using the gel and have decided that participation in the clinical trial is beneficial for them could be used to help other trial participants who have doubts, worries, or questions.

> ...we who came here should be the ambassadors of those others. My friends, we happened to use the gel and we didn't get any adverse effects, in fact even

> during that period we had doubts, but until now we haven't had any problem...
>
> 52, Mwanza

CLOSENESS OF STAFF AND PARTICIPANTS

Participants in Tongaat and Mwanza spontaneously spoke of the importance of respect, saying that research staff should respect them and that they, as trial participants, should respect the research staff. Being clear and transparent about the trial, the gel, and procedures was thought to be an important way that trial teams could demonstrate respect.

Participants at both sites also spoke about the importance of trial staff showing love, kindness, and care to trial participants. Present participants thought that trial participants and research staff should be close. Some present participants noted that when trial participants are treated with love and respect, fears and doubts are removed and participants feel encouraged to use the gel.

> So that participants are more attracted to using the gel correctly, it is together with the researchers to be more close to the participants, they should be open to them and they should be friends...It is that they should be friends in the meaning that the researcher should not fear the participant and also me the participant should not fear the researcher so that my thoughts and hers may be close so that we may help each other.
>
> 42, Mwanza

> Like how you received us here [today], we talk nicely with love; indeed this is the way of caring about the participants.
>
> 39, Mwanza

> It is to give them [participants] respect and love and to tell them how important they are.
>
> Third Tongaat FGDW, flipchart, session 8

5.4 DISCUSSION

The aim of this study was to gain insight on how to improve adherence and adherence reporting in microbicide trials from the perspective of former trial participants. Responses

from participants indicate that low adherence and inaccurate adherence reporting are driven by the reality that many women in communities where microbicide trials are conducted participate in trials for a number of important reasons which are not related to interest in the study gel. Thus, there is a fundamental difference in the objectives of many woman who agree to participate in a microbicide trial and the research objectives of trial implementers.

5.4.1 NEEDS OF PARTICIPANTS DRIVE THEIR PARTICIPATION IN MICROBICIDE TRIALS

For many participants, the trials provided free, high-quality, confidential health services. Participants spoke positively about being tested for a number of health issues, receiving treatment, knowing about their health, and gaining valuable education. The trials, through reimbursements, provided a type of income that was utilised and appreciated. Other studies have also shown access to health care and money in the form of reimbursements as an important motivating factor for trial participation.[114,115,116,95,117] When asked why they thought it was difficult for some trial participants to report gel use accurately, the most common response was that trial participants feared they would be asked to leave the trial, thus losing access to the health care and reimbursement. This fear was also cited as a reason for lack of honest adherence reporting in other trials. Negative responses to the hypothetical trial design with a non-randomised, no-gel arm highlighted that some present participants believe the gel is not the primary reason, nor a reason at all, for many women to join trials.

5.4.2 FEAR OF INVESTIGATIONAL NATURE OF CANDIDATE MICROBICIDE GELS

The most important reason why participants thought the gel was not being used by trial participants was fear of the investigational nature of the gel. This fear stemmed from two general sources: the true nature of a clinical trial, where risks are both known and unknown, and from rumours heard from the community. Participants made suggestions on how to minimise fears that were perpetuated by the community, such as providing better education, using ambassadors or peer educators, providing more male partner engagement opportunities, and better transparency overall about the procedures at each stage

of the trial. In addition to being explicitly discussed, the barrier to adherence that the investigational nature of the study products provides was evidenced indirectly by other statements participants made. When asked how to improve adherence in future trials, some suggested not calling the clinical trial "research" and telling participants that the gel "worked." When asked for reactions to the hypothetical trial design that included one non-randomised no-gel arm, some participants remarked that they thought that most women would want to join the no-gel arm.

Concerns around adverse effects and unknowns about the gel will continue to be a source of fear and cause hesitation for trial participants about using the study products. This effect has been observed in other trials of biomedical HIV prevention methods,[116,138,118] and will always be a concern for healthy participants who are asked to test a drug for efficacy and safety.

5.4.3 INNOVATIVE TRIAL DESIGN FOR PARTICIPANT NEEDS AND RESEARCH NEEDS

Acknowledging that many women join trials for reasons outside of the desire to use an investigational gel, yet participate and report high adherence, a hypothetical trial design with a non-randomised, no-gel arm intended to address this issue was proposed to FGDW participants for their feedback. As many women join trials for health checks and other means of support, this trial design would allow women to choose if they would like to use the gel, or not, when they enrol. This trial design gives women an acceptable way to participate without having to pretend they are using gel. Women who are interested in using the gel would elect to do so, and would then be randomised as participants to the placebo or active gel arm. This design seeks to improve adherence in the gel arms by eliminating the dilution effect[11] caused by participants who do not use the investigational gel.

Some participants in the FGDWs liked the idea of this trial design and thought it would be appropriate as women would have the freedom to choose if they use the gel or not, would still benefit from the trial, would not waste gel unnecessarily, and would not be preventing the research from discovering a potentially effective microbicide. While this design may improve adherence, it will certainly be more costly than a conventional trial because more women will need to be enrolled. The feasibility of such an innovative design would need to be assessed with formative research. Microbicide effectiveness trials are expensive, with estimates of phase III trials costing up to $70 million USD.[33,34] If multiple trials have null results due to low adherence, considerable funds are wasted and a potentially effica-

cious product may be eliminated from the product development pipeline. While initially expensive, investing in a trial design that could potentially meet the needs of women in high HIV incidence communities and also meet the needs of the research question might be a wise investment. This possibility is worth considering. Trial teams can work with trial populations to conduct formative research to consider various innovative trial designs[139] and their potential feasibility.

5.4.4 MALE PARTNER EFFECT ON PARTICIPANT ADHERENCE

While the microbicides field has endeavoured to discover a female-controlled product women can use to prevent sexual transmission of HIV, ironically, the field has learned through the process of conducting microbicide trials that male partners are an important factor in determining female trial participants' ability to adhere to the study regimens.[115,116,117,127,128,131,140,141,142,143] Participants reported that trial participants who desired to use the study gels as directed were sometimes not able to do so due to gender norms and factors related to their male partners. In some cases, male partners did not like the lubricating effect of the gel, or forbade their female partners to use the gel. In other cases, trial participants feared using the gel because their male partners had accused them of being unfaithful, due to the increased lubrication. In yet other cases, the need to be ready for sex exactly at the time their partner demanded it meant there was no time for insertion of the gel. The experiences of these trial participants indeed highlight the need for women to have more control over their own health and additional means to protect themselves from HIV infection.

Despite the challenges related to male partners for some trial participants, participants in the FGDWs in this study thought that better involvement of male partners in the trial process would likely result in agreement and support from male partners. Trial participants would need to determine if, and when, to inform their male partners about participation in the microbicide trial; results in this study, as well as others,[116,127,131,143,121,144,145] suggest that there is a greater need to inform longer-term or cohabitating male partners than casual partners. Trials can offer a number of mechanisms to better include male partners and support participants in informing their male partners about the microbicide trial and the gel itself. Trial sites can offer more robust provision of HIV and health information to both partners, joint orientation to the trial, and tours of the laboratory and clinic facilities.

Another important aspect of male partner influence on participant adherence was related to gel attributes. As discussed by some participants, particularly from Mwanza, the gel consistency made it difficult to use covertly, was not always liked by male partners, and put some women at risk for being accused of infidelity, thereby causing considerable discord within trial participants' intimate relationships. Previous studies have reported trial participants' positive experiences with the gel, in that it may reduce their sexual pain or improve their pleasure.[146,147,148,149,129,150,151] There were participants in this study who also mentioned positive effects of the gel; in addition, present participants were generally supportive of the idea of a gel for HIV prevention and thought that negative aspects related to its effect during sex could be addressed with improved formulation. Some amount of lubrication was seen by some as positive, but not to the point that the ability to use the gel covertly would be impossible. Vaginal suppositories or a dissolving microbicide film would provide a coitally dependent form of protection but potentially with less obvious lubrication.

5.4.5 APPLICATOR TEST FOR VAGINAL INSERTION

Another strongly supported suggested trial design element was a method to test applicators for adherence. The DSA for applicators, which was developed for the Carraguard trial, served as a pivotal moment for the microbicide field in documenting the discrepancy in microbicide trials between self-reported and actual product use. The advantage of applicator tests is they can preserve blinding and results could be reported back to participants throughout their participation, which ideally could help improve adherence prospectively. Biomarker testing used in anti-retroviral based trials, by contrast, cannot be reported at an individual level due to blinding and would thus not provide individual participants with real-time feedback. Since the development of the DSA, research has continued to progress on how to identify applicator testing methods that will be more sensitive to identifying vaginal insertion of gel under typical field conditions within microbicide trials.[152,99,153,100]

5.4.6 CLEARER AND MORE COMPLETE EDUCATION ABOUT THE GEL AND TRIAL PROCEDURES

In this study, former microbicide trial participants discussed a strong desire to have improved education about the gel, the research process, and why adherence is important. Participants stated that they and other members of the community had had many questions and concerns about the research. Improved education could allay fears, help trial participants feel comfortable, help their partners feel comfortable, and potentially improve both adherence and adherence reporting. Tools, including simple diagrams such as those used in this qualitative study to explain trial design and adherence, were effective and well received by the study participants.

Interestingly, while trial teams often expend time and resources to educate local community advisory boards (CABs) and other community entities about how research is done, that same information is often not shared with trial participants. Rather, information shared with trial participants tends to focus on the contents of the informed consent form and trial procedures, rather than on a broader understanding of how and why a clinical trial is conducted. Trial teams can ensure that these broader topics are addressed by developing materials and adding these discussions to visit checklists. As suggested by participants, short talks or seminars in group settings can be provided on a regular basis. These topics can be revisited with trial participants over their follow-up to ensure clarity around the trial and to continue to answer questions a participant might have, especially about the investigational gel. Peer educators can also be used to help in these processes. By following these suggestions, trial teams can create a trial atmosphere that is more transparent and respectful of the trial participants as humans who have fears and who have a need for correct and clear information.

5.4.7 TRANSPARENCY, RESPECT, LOVE

It is not surprising that participants in this study stressed the importance of transparency, respect, and working together with research staff as key elements for a successful trial. The history of biomedical HIV prevention research has shown that these are important elements for trial communities and are, indeed, why respect, transparency, and mutual understanding are three of the guiding principles included in the *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials* (GPP).[40] These elements of coopera-

tion and mutual understanding were lacking in some of the first PrEP trials in the field of biomedical HIV prevention trials, which resulted in negative consequences for prospective participants, investigators, and the research effort to find an additional method of HIV protection.[42,43,154] Participants in both Tongaat and Mwanza valued the positive interactions they experienced with trial staff and felt cared for. They advocated for working closely with trial staff, as friends, and thought that when trial staff members treat trial participants with love, it helps them to feel important and helps to remove doubts they might have about aspects of their trial participation.

5.4.8 LIMITATIONS AND STRENGTHS

This qualitative study endeavoured to explore former microbicide gel trial participants' opinions on how to improve adherence and adherence reporting in future microbicide trials. Given the number of women who have participated in effectiveness trials of candidate microbicides, the sample size was small (n=46). An advantage of this study is that it was conducted in two different countries, South Africa and Tanzania, that have very different cultures and histories. The most notable differences observed were that participants in Tongaat highly valued time in relation to study visits not being too long, and that in Mwanza there was more concern expressed over the physical characteristics of the gel in relation to their male partners' reactions. This study also included participants from two different microbicide gel trials, although there was much greater representation of MDP 301 as only five participants in this qualitative study represented the VOICE trial.

Recruitment methods attempted to invite a representative sample of former gel participants from MDP 301 and VOICE to join the qualitative study in the respective locations of Mwanza and Tongaat. Former participants who were contacted or able to participate on the day of the FGDW were more likely to be women who had not moved far away from the trial sites. Former participants who attended the day of the FGDW were also more likely not to be formally employed compared to those who did not attend.

A potential limitation of this study is that many years had passed since participation for some participants, particularly for those who participated in MDP 301. Therefore, specifics about trial participation may not have been fresh in present participants' minds, which could lead to recall bias. While the long amount of time that passed between trial participation and FGDW attendance may have caused some problems with recall, the fact that this study took place well after trial participation may have increased the chance that

participants were truthful in their responses and that they had time to reflect on their experiences. More truthful responses about adherence after completion of trial participation, compared to upon study exit, have been reported in other biomedical HIV prevention trials.[115,95]

An advantage of using a group-based format to explore sensitive and stigmatised behaviours is that individuals can talk about themselves and their behaviours in the guise of talking about "other people." This can result, however, in having a smaller amount of data that appears to be first-hand accounts. Another advantage to using a group-based method for this research is the benefit derived from the synergy amongst the participants to build rapport and camaraderie, which facilitates discussion, speaking freely, remembering experiences and feelings, generating ideas, and expressing opinions.

A unique aspect of this study was the format of focus group discussion workshops which included both discussion and participatory activities and sought to cover the research questions both in nuanced ways and from several angles over the course of the day. This format provided a platform for participants to help each other remember their experiences and views as trial participants from several years past, to think critically together about what factors might contribute to aspects of adherence and adherence reporting, and to generate suggestions or new ideas about conduct of future microbicide trials. Using a number of different methods to elicit information may also improve the chance of gaining useful data because participants might respond differently to different techniques. The FGDWs were longer than standard focus group discussions, which allowed participants to think about and provide input on more aspects of the research topic. A disadvantage of the long format was that some participants felt tired by the end of the FGDWs.

5.4.9 FUTURE MICROBICIDE GEL TRIAL DESIGN

Recent efforts to improve adherence for women in microbicide trials such as CAPRISA 004, VOICE, and FACTS 001[91,90] have included adopting more participant-centred approaches to adherence counselling which address barriers to adherence and tailor counselling to help participants increase gel use. While these adherence support strategies may have shown improvements in adherence, these methods have not necessarily been effective to the extent needed to demonstrate effectiveness of the candidate microbicides, as in the cases of VOICE and FACTS 001. The underlying assumption of these approaches is that participants enrol in microbicide trials with the intention of using the microbicide

gels.

Through the use of FGDWs with former participants from two microbicide trials in two countries, this study has identified that women join microbicide trials for a number of important reasons which are not related to using the study product, and that the largest barrier to using the study product for participants is fear of adverse effects from a still-investigational product. This result shows that there is a fundamental difference between the objectives and needs of participants and the research objectives of a microbicide trial. Without addressing these two different perspectives, it will be difficult to address low adherence and inaccurate reporting of adherence in future microbicide gel trials.

As participants have expertise in the local communities where microbicide trials are conducted and in trial participation, both of which trial investigators lack, former microbicide trial participants can give important feedback on how to address microbicide trial design in a way that can help harmonise the needs and objectives of participants and the needs and objectives of the research. This is the first qualitative study to engage microbicide trial participants in explicitly thinking about the design of future microbicide trials to address the challenge of suboptimal adherence and inaccurate reporting. Former microbicide gel participants gave concrete and viable suggestions on how to improve adherence and adherence reporting, and gave thoughtful reactions to an innovative trial design with a non-randomised no-gel arm, intended to address the fundamental issue that some women join and remain in microbicide trials without using or intending to use the microbicide gel according to protocol requirements.

The field of microbicides, over many years, has endeavoured to discover a product women can control to protect themselves from HIV. The field has searched for ways to address the complexities of conducting vaginal microbicide trials in communities with high HIV incidence. In addition to seeking new modes of microbicide delivery, such as rings, and looking for ways to improve adherence and adherence monitoring through improved adherence counselling and biomarker testing, it is important for research teams to examine and appropriately address the underlying dynamics within microbicide trials. For optimal results, these underlying dynamics can be addressed in the actual design of vaginal microbicide trials. Doing so may require thinking creatively to develop new and different ways of designing clinical trials. As this study has demonstrated, participants and research teams can work collaboratively to consider such designs. When participants and trial teams work together with transparency, respect, and mutual understanding,[40] difficult challenges such as low adherence and inaccurate reporting can better be addressed in

future trials.

6

DISCUSSION

"BRING US THE ONE THAT WORKS."

6

DISCUSSION

This chapter provides a review of the studies undertaken within this PhD research, a summary of the key findings, an update on trials reporting primary results since the start of this PhD research in 2012, and a discussion of the results of this research, contextualised within microbicide trial research findings that have been published through 2015.

6.1 SUMMARY OF THE PHD RESEARCH

At the time of the start of this PhD research, 12 microbicide effectiveness trials had been conducted, with only one which showed a decrease in HIV transmission. Adherence, at the time, was increasingly being recognised as the Achilles heel of microbicide trials. There was an urgent need to better understand adherence within microbicide trials and to use this information to improve microbicide trial design so that future microbicide effectiveness trials would be better positioned to answer their research questions.

The goal of this PhD research was to critically examine, from different perspectives, experiences of past vaginal microbicide effectiveness trials, in order to better understand how adherence and adherence assessment can be improved for future microbicide trial design. Adherence assessment here refers to the measurement of adherence and sexual behaviour data as well as to the analysis and reporting of those data.

This goal was accomplished by conducting three different studies, with each study looking at adherence from a different perspective and addressing a different objective. A summary of each study is provided below, followed by a brief outline of the key findings.

6.1.1 OBJECTIVE ONE

WHAT DO WE REALLY MEAN BY "ADHERENCE"? A COMPARATIVE STUDY OF MEASURING, CALCULATING, AND REPORTING ADHERENCE IN FIVE MICROBICIDE GEL EFFECTIVENESS TRIALS sought to critically examine how five completed microbicide effectiveness trials measured, calculated, and reported microbicide gel adherence.

This objective was accomplished by conducting a comparative analysis of trial methods using trial protocols, case report forms (CRFs), statistical analysis plans (SAPs), and primary results manuscripts, and by conducting a trial team survey. The comparative analysis was undertaken to identify which source data were collected to measure sexual behaviour and adherence, to identify how trial teams reported adherence estimates in primary results manuscripts, and to determine how trial teams used source data to calculate the published adherence estimates.

6.1.2 OBJECTIVE TWO

HIDDEN HETEROGENEITY: DISCOVERING ADHERENCE PATTERNS IN VAGINAL MICROBICIDE HIV PREVENTION CLINICAL TRIALS sought to examine, using self-reported adherence data from four completed effectiveness microbicide trials, if longitudinal patterns of adherence are evident and, if so, what individual-level factors were associated with observed patterns of adherence.

This objective was accomplished by conducting latent class and latent profile analysis on self-reported adherence data to identify patterns of adherence, followed by conducting multivariable multinomial logistic regression to identify factors associated with patterns of adherence.

6.1.3 OBJECTIVE THREE

DESIGN YOUR OWN MICROBICIDE TRIAL: OPINIONS OF FORMER MICROBICIDE TRIAL PARTICIPANTS ON HOW TO IMPROVE ADHERENCE AND ADHERENCE REPORTING IN FUTURE MICROBICIDE TRIALS sought the expertise of former microbicide trial participants about barriers to adherence, accurate reporting of adherence during trial participa-

tion, and how to improve adherence and adherence reporting in future microbicide trials.

This objective was accomplished by conducting focus group discussion workshops (FGDWs) that used participatory activities and discussions with former trial participants. Participants were engaged in concepts around microbicide trial design; asked to give their views on trial participation, barriers to adherence, and accurate adherence reporting; and asked to provide suggestions for future microbicide trials. Eight FGDWs in total were conducted in Tongaat, South Africa, and Mwanza, Tanzania.

6.2 KEY FINDINGS OF THE PHD RESEARCH

6.2.1 WHAT DO WE REALLY MEAN BY "ADHERENCE"? A COMPARATIVE STUDY OF MEASURING, CALCULATING, AND REPORTING ADHERENCE IN FIVE MICROBICIDE GEL EFFECTIVENESS TRIALS

- There was considerable diversity in methods used to collect adherence and sexual behaviour data among the five trials. These methods used both self-reported data and non self-reported data, different recall periods, different frequencies of data collection, and different wording of questions.
- Trials used considerably different methods to calculate adherence estimates and combined source data in unique ways.
- Two overall methods to calculate the final adherence estimates were identified: using the total number of sex acts in the trial as the denominator, with the numerator being gel use, or using the number of participants as the denominator, with the numerator being average adherence calculated from participants' adherence over follow-up.
- Unclear or ambiguous wording was present in some of the questions used to collect source data from participants.
- Trial documentation and publications lacked clarity in exact methods used to calculate adherence estimates.
- Means or medians used to characterise overall adherence in trials did not provide meaningful information about how adherence might have varied over time or in different groups of participants.

- Adherence questions which ask about non-adherence first may help participants feel more comfortable to answer questions honestly. (Finding from trial team survey)
- Inclusion of self-reported adherence by participants is essential for trial staff to know if participants understand the study regimen or are having problems with product use. (Finding from trial team survey)
- Both biomarkers and a strong social science component are important for future successful microbicide trial implementation. (Finding from trial team survey)

6.2.2 HIDDEN HETEROGENEITY: DISCOVERING ADHERENCE PATTERNS IN VAGINAL MICROBICIDE HIV PREVENTION CLINICAL TRIALS

- Using self-reported data, different trajectories or patterns of adherence to microbicide gels were observed in all four trials.
- The patterns of adherence were similar among the four trials.
- Latent class and latent profile analysis is a useful method to understand the longitudinal nature of adherence patterns in coitally dependent microbicide trials.
- Latent class and latent profile analysis can be used with inexpensive self-reported data or with other adherence data that are collected longitudinally over follow-up.
- Using multivariable multinomial logistic regression, certain individual-level factors were found to be associated with adherence patterns in all four trials.
- Older age versus younger age was associated with consistently reporting high adherence in all four trials.
- Site was associated with different patterns of adherence in all four trials; this finding indicates that culture or staff characteristics may be influencing adherence and adherence reporting.
- Participant report of male partner dislike or refusal of gel use was associated with membership of trajectories that had decreasing reported adherence. The effect size of this association was large, and evidence for this association was strong in two out of the four trials in the final adjusted analyses.

6.2.3 DESIGN YOUR OWN MICROBICIDE TRIAL: OPINIONS OF FORMER MICROBICIDE TRIAL PARTICIPANTS ON HOW TO IMPROVE ADHERENCE AND ADHERENCE REPORTING IN FUTURE MICROBICIDE TRIALS

- Women join and stay in microbicide trials for their own needs, which are not necessarily related to interest in using the investigational product.
- Access to free, high-quality health care was an important reason for joining and staying in trials.
- Access to money, through reimbursements provided by the trial, was an important reason for joining and staying in trials.
- Being cared for and valued was a reason participants stayed in trials.
- Fear of adverse effects or harm from the investigational product is the most important reason why some participants did not use the gel in accordance with instructions.
- The lubricating effect of the gel was noticeable to regular male partners during sex.
- Participants reported that male partners can act as barriers to using the gel.
- Some participants reported that the lubricating effect of the gel caused regular male partners to suspect that they were having sex with other men.
- Fear of this suspicion or direct accusation created barriers for some participants to use the gel as directed.
- Participants reported that the need to provide sex to male partners at the time it was demanded was a barrier to using the gel as directed.
- Fear of removal from the trial, and thus loss of perceived benefits such as health care and reimbursements, was the primary reason for reporting gel use when the gel had not been used.
- An innovative trial design with a non-randomised, no-gel arm was seen as a good option by some participants to address low adherence in microbicide trials because, as some reported, some women who join trials will never want to use an investigational gel.

- Participants who expressed concern about this trial design with a non-randomised, no-gel arm did so because they thought that many woman would choose the no-gel arm.
- Applicator testing, such as the DSA, and reporting of those results, was strongly recommended by participants for inclusion in future microbicide trials.
- A gel formulation that offers lubrication but is less noticeable to male partners was requested by participants in Mwanza, Tanzania.
- To improve gel adherence, trials should explicitly include methods for male partner engagement, with participant consent.
- Participants reported that they were not provided with explicit information about how trials answer their research question and the mechanism by which their adherence can affect trial results.
- A simple diagram showing the trial process, and how the number of women infected with HIV by the end of trial follow-up is compared across study arms, was a simple and effective way to teach participants how trial teams answer the question of whether an investigational gel can prevent HIV transmission for women.
- Participants reported that they were not always given clear information about trial processes while they were taking place, and this raised doubts about the research.
- For future trials, participants request an atmosphere of transparency, respect, and love between research teams and trial participants.

6.3 Summary of microbicide effectiveness trials reporting between 2013 and 2016

Prior to the start of this PhD research, 12 microbicide trials had been conducted, with only CAPRISA 004 reporting a statistically significant reduction in HIV incidence. During the period of conducting this PhD research, four microbicide trials reported results, two testing 1% tenofovir gel and two testing a vaginal ring containing dapivirine for monthly use. The two coordinated trials of the dapivirine ring reported results while writing up this thesis. The sections below provide a brief description of those four trials and their results.

6.3.1 ASPIRE TRIAL

The Microbicide Trials Network's (MTN) A Study to Prevent Infection with a Ring for Extended Use (ASPIRE, MTN 020), was a randomised, double-blind, placebo-controlled phase III trial to test the effectiveness and safety of a four-weekly vaginal ring filled with dapivirine (25 mg), used to prevent HIV infection in healthy women.[125] Dapivirine is a non-nucleoside reverse transcriptase inhibitor. The trial enrolled 2629 participants, aged 18–45 years; was conducted in Malawi, South Africa, Uganda, and Zimbabwe; and followed participants for a minimum of 1 year. The trial started in August 2012 and completed in June 2015. The dapivirine ring was found to reduce HIV-1 infection by 37% (95% CI 12–56). Adherence was measured quarterly using plasma samples. Adherence was defined as dapivirine levels of greater than 95 pg/mL, which indicated at least 8 hours of continuous use. Residual drug levels were also assessed in rings after the first year of the study. A level of less than 23.5 mg of dapivirine remaining in the used vaginal ring was defined as adherence; this amount indicated that at least 1.5 mg of dapivirine was released, which indicated some use during the month. Eighty-two percent (82%) of plasma samples detected dapivirine at concentration levels of greater than 95 pg/mL. These analyses indicated that better adherence was associated with improved HIV protection. While overall the trial found a reduction in HIV incidence, HIV protection was not observed in women aged between 18 and 21 years. Both adherence and biologic effects are believed to have contributed to this finding. The dapivirine ring was also found to be safe.[125]

6.3.2 IPM DAPIVIRINE RING STUDY

The International Partnership for Microbicides's (IPM) Ring Study[126] was a randomised, double-blind, placebo-controlled phase III trial to test the effectiveness and long-term safety of a 4-weekly vaginal ring filled with dapivirine (25 mg), used to prevent HIV infection in healthy women. A total of 1959 women were enrolled in South Africa and Uganda. The trial began in April 2012 and was scheduled to end in December 2016. Due to the HIV prevention results of the ASPIRE study, the Ring Study reported their results early. The Ring Study found the dapivirine ring was able to reduce HIV incidence by 31% (95% CI 1–52). The Ring Study also found that HIV protection was less in women aged 21 and younger. The ring was also found to be safe in this study. Adherence was measured by testing the amount of dapivirine in plasma samples collected each month, and the amount of residual dapivirine in used rings, collected every month. These analyses indicated that

better adherence was associated with improved HIV protection. Due to the beneficial findings of the ASPIRE study together with the Ring Study, all participants in the Ring Study were provided with dapivirine rings for the remainder of their participation.[126]

6.3.3 VOICE

The MTN's Vaginal and Oral Interventions to Control the Epidemic (VOICE) study was a 5-arm, randomised, placebo-controlled phase IIb trial to assess daily use of 1% tenofovir (TFV) vaginal gel, or oral tenofovir disoproxil fumarate (TDF), or oral tenofovir–emtricitabine (TDF/FTC) against HIV infection. Women in South Africa, Uganda, and Zimbabwe were enrolled. The trial began in 2009, and results were reported in February 2015. At the start of this PhD research, VOICE was an ongoing trial actively collecting data.[136]

In September 2011, the DSMB recommended that the oral TDF arm be suspended due to futility, followed by a recommendation in November 2011 that the TFV gel arm be suspended for futility. The TDF/FTC and oral placebo arms continued until trial completion in August 2012. In the final analysis, no study product was found to affect HIV incidence compared to the placebo arms (TFV gel vs placebo gel HR 0.85; 95% CI 0.61–1.21). The mean proportion of quarterly plasma samples with TFV detected was 25%, and the mean proportion of vaginal swab samples with TFV detected was 49%. Adherence assessed by FTFIs for TFV gel and placebo gel in the past week were 90% and 90%, respectively. Applicator counts conducted at the clinics indicated 83% and 84% adherence, respectively. The mean rates of adherence via ACASI for TFV gel and placebo gel were 88% and 89%, respectively. As evidenced by the biomarker data for TVF, poor adherence was identified as the cause of the inability of the trial to demonstrate an HIV prevention effect. The VOICE trial team also reported that the daily use regimen for this population was not ideal.[114] Tenofovir gel was deemed safe in this clinical trial.

6.3.4 FACTS 001

The Follow-on African Consortium for Tenofovir Studies (FACTS) 001 study was a phase III, randomised, placebo-controlled trial of peri-coital use (BAT 24 regimen) of 1% tenofovir gel against transmission of HIV. This trial was intended to confirm the results of

CAPRISA 004 and was conducted in nine sites in South Africa over 27 months, with 2059 women aged 18–30.[124] The trial was conducted between October 2011 and August 2014. The primary results of the study did not show a protective effect of before and after sex gel dosing to prevent HIV transmission (incidence rate ratio 1.0; 95% CI 0.7–1.4). The gel was found to be safe. Adherence was measured as an estimate of the percent of sex acts covered, calculated by inspected returned used applicators and self-reported number of sex acts. Adherence was estimated to be 50–60% of sex acts per month covered by gel. In a pre-specified case cohort sub-study, quarterly cervical vaginal lavage (CVL) samples were used to measure tenofovir levels and found that tenofovir was associated with a reduction in HIV incidence in those who reported sexual activity in the past 10 days (HR 0.48; 95% CI 0.23–0.97).[124]

A unique aspect of FACTS 001 was that the trial team aimed to recruit young women, with the oldest age for eligibility being 30 years old. Seventy percent (70%) of the participants were less than 25 years of age. Eighty-nine percent (89%) of the study population was single, and 61–63% were living with their parents or siblings, which may have meant that sex was occurring outside of the home and thus might have made adherence additionally challenging for this population.

6.4 THE CHANGING HIV PREVENTION LANDSCAPE

During the period of this PhD research, much progress has been made in the field of biomedical HIV prevention. In 2015, the World Health Organization (WHO) released *Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV*,[155] which recommends that oral PrEP containing TDF be offered to individuals at substantial risk of HIV infection, as a part of HIV combination approaches, and defines substantial risk as HIV incidence of greater than 3 per 100 person-years. Recommending oral PrEP adds to the combination of HIV prevention options being rolled out and scaled up globally; these include male and female condoms, voluntary medical male circumcision, HIV testing, and ARV initiation when testing HIV positive.

WHO guidelines must be adopted by individual countries and then scaled up to make prevention options, such as oral PrEP, available to residents in need. Oral PrEP may be an excellent option for women who see themselves at risk for HIV and would like to take an oral pill on a daily basis to protect themselves from HIV. Currently, research results to

support coital or "on demand" dosing of oral PrEP for women do not exist.

While new WHO recommendations are being adopted and scaled up globally, research must continue to identify more HIV prevention options which women can control themselves, and particularly ones which can be effective when used just around the time of sex. While the new WHO recommendations are milestones in biomedical HIV prevention research, they will also make the clinical trial landscape more challenging to identify novel methods.[156]

6.5 DISCUSSION OF PHD RESEARCH RESULTS IN CONTEXT OF RECOMMENDATIONS FOR FUTURE TRIALS

This section provides a discussion of the key findings in this PhD research within the context of recommendations for future microbicide trial design. This discussion is organised into sections describing trial planning, trial implementation, and results analysis and reporting. While topics are discussed within one of the three stages of the trial life-cycle, some of the topics, in reality, span more than one category. Relevant research results from biomedical HIV prevention trials, published through 2015, are included where appropriate. A summary of recommendations for future microbicide trial design is provided in Table 6.5.1.

6.5.1 TRIAL PLANNING

6.5.1.1 OVERALL DESIGN OF TRIALS NEEDS TO MARRY OBJECTIVES OF PARTICIPANTS AND OBJECTIVES OF RESEARCH TEAMS

Results from the qualitative study in this PhD research found that women join and stay in trials for a number of important reasons that may not be related to using a drug whose efficacy at preventing HIV is unproven and whose complete safety is unknown.

Participants in this qualitative study reported that it was difficult for some participants to honestly report their adherence because they thought doing so would put them at risk for being removed from the trial and thus lose the benefits and financial reimbursements they were receiving. Discrepancies in self-reported adherence data compared to biomarker or applicator data from recent biomedical HIV prevention trials for women have shown

Recommendations for improving microbicide trial design
Trial planning
•Trial design needs to consider participant objectives and perspectives
•Conduct formative research and community engagement to consider innovative trial design ideas
•Improve gel formulation: less watery consistency, warming sensation, ability to use more discretely, and more discreet packaging
•Questions about adherence should ask about non adherence first
•Include more careful wording of questions on CRFs which clearly refer to the information being asked
•Recruitment of participants should balance those likely to adhere and those in populations of higher HIV incidence
•Hire staff with excellent interpersonal skills who share trial values of respect and transparency
•Train all staff on the science of microbicide trials
•Provide clear and specific information in statistical analysis plans about how adherence will be estimated
•Conduct formative research for designing a male engagement plan
Trial implementation
•Use a simple diagram showing the microbicide trial process to teach participants how microbicide trials answer their research questions
•Create diagrams which show the chain of custody for blood samples, including bloods which are stored or used for confirmatory testing in central laboratories
•Explain trial procedures to participants while they are happening, including any reasons for delays.
•Checklists should include that staff have informed participants of the purpose of each tube of blood collected, and when results will be given.
•Provide a comprehensive male engagement programme which offers opportunities for engaging male partners throughout trial follow-up.
•Include questions in visit checklists about new male partners and whether the participant would like support disclosing trial participation.
•Offer "open days" for male partners at the study clinic to describe the purpose of the trial and to provide information about the gel and trial procedures.
•Create and use a peer educator programme to assist with adherence.
•Include a technology for applicator testing to identify applicators expelled vaginally.
•Provide applicator-testing results to participants on a regular basis.
•Provide sites with ongoing information about adherence, explore site differences in adherence, take corrective actions as necessary.
Trial results analysis and reporting
•For adherence data, use an analysis approach which shows patterns of adherence over time, such as latent class and latent profile analysis.
•Use multinomial logistic regression to look at factors associated with different patterns of adherence.
•Methods and results sections of publications should include clear information about adherence estimation, and any deviances from planned analyses.
•Adherence results in publications should include analyses which describe microbicide use over time.

Table 6.5.1: Summary of recommendations for future microbicide trial design

that participants consistently overreport their adherence. CAPRISA 004 found that adherence based on self-reported last sex act alone resulted in an estimate of 82% adherence, whereas estimates of adherence which were derived from self-report and applicator counts resulted in an estimate of adherence of 72.2%.[157] The VOICE trial also found evidence that participants overreported their own adherence. A sub-study of 158 active gel users found an estimated 65% had not used the gel in the past 7 days, according to pharmacokinetic (PK) data taken from vaginal swabs. For the same period of 7 days, self-reported adherence in FTFIs indicated non-adherence was only 2%. When ACASI was used to ask the same questions, non-adherence was estimated to be 6%.[88]

FEM-PrEP, a phase III trial of once daily oral FTC/TDF pills for women, experienced poor adherence which led to trial closure due to futility. Using self-reported data, 95% of participants reported they had usually or always taken their study pill. Using pill counts, it was estimated that participants took pills for 88% of the days on trial.[94] Plasma and intracellular drug concentrations among a sub-cohort showed that only 12% of the sub-cohort had achieved good adherence throughout their participation and 23% had rarely, if ever, taken their study pills; 60% of participants had fluctuating adherence throughout the trial.[96] In a FEM-PrEP follow-up study with 224 former trial participants, 31% stated they overreported adherence while in the trial. Sixty-nine percent (69%) of those who reported that they had overreported their adherence during trial participation said they did so because they were worried they would be terminated from the trial.[95]

PARTICIPANT OBJECTIVES

The VOICE trial team found, in two separate qualitative studies related to VOICE, that participants joined and stayed in trials for quality health services, free treatments, regular HIV testing, and reimbursements.[114,115,116] FEM-PrEP also found that participants stated they joined and stayed in trials for health care services, such as regular HIV and pregnancy testing, free check-ups, contraceptives, and treatment for common ailments, as well as reimbursements.[95,117] MDP 301 also heard reports from participants that women joined to know their HIV status, to receive physical exams, and that some joined and remained in trials for reimbursements, which in South Africa, due to a regulatory guideline, greatly exceeded the cost of travel to and from the clinic.[118]

PARTICIPANT FEAR

Critical to the improvement of microbicide trial design is to understand that many participants have concerns about using an investigational product or do not intend to use it. Results from VOICE were similar to findings in the qualitative study within this PhD research, where some participants expressed fear of experiencing side effects or harm from the experimental products. A quotation from a participant in the VOICE D study states "Why don't they do the research on themselves? They do it on us. I do not use that thing, I just put it there. I do not insert it. Why do they not use it? What if it causes a problem to us?"[116] This sentiment was expressed by participants in this PhD research. The FEM-PrEP trial found that participants were willing to be more truthful after trial completion. In a follow-up study, it was found that the investigational nature of the drug accounted for 47% of participant non-adherence. The trial team concluded that apprehension around the investigational drug and potential side effects was a substantial contributor to non-adherence in their trial.[117] They noted that "alternative study designs or procedures may be needed in future studies to provide women an opportunity to receive the benefts of a study without being enrolled, reserving enrolment and study product distribution for participants who are more likely to adhere."[117] The trial team also observed that "Improvements to adherence counselling and participant self-reports will only be benefcial if study populations enrol in such trials with some interest in taking the study product."[138]

Recent research findings suggest that when participants know the product is effective and are enrolled in open label studies of oral PrEP, their adherence is improved[158] and estimates of effectiveness are even higher than in phase III trials.[159] As microbicide research results indicate that adherence is suboptimal due to participants' concerns about the investigational nature of the products, it would be expected that open label studies with products whose effectiveness has been demonstrated would likely result in higher adherence by participants, resulting in improved rates of HIV incidence reduction.

NEED FOR INNOVATIVE DESIGN

In thinking about how microbicide trials can be designed to better answer their research questions, research teams need to consider that the way they design and run clinical trials is from a particular perspective, which is their own perspective, and to consider that their own perspective is different from the perspective of participants who are asked to join these trials in sub-Saharan Africa. Trial funders, sponsors, and implementers have been trained to see a clinical trial as a scientific study where individuals are asked to volunteer to

use an experimental product in accordance with a specific protocol; in exchange for time and inconvenience, those volunteers are provided with a type of reimbursement.

Recent research using qualitative methods has shown that trial participants in biomedical HIV prevention trials have a different perspective. Many women in these settings see a clinical trial as a way to receive health care and money to help improve their lives. While research teams are often aware that participants in trial communities would like to be provided with long term income and health care, research teams also know that provision of these is not possible within the context of clinical trials. This creates an ongoing tension between trial implementers and communities where microbicide trials are conducted. Years of research has shown that researchers continue to design microbicide trials in a similar fashion which does not fully integrate the realities of participants' perspectives into trial design, and, prior to when this PhD research commenced, sometimes misunderstood the underlying reasons why adherence may be low. Research teams need to work harder to design microbicide gel trials that will be able to answer their research questions in the context of how women being asked to participate perceive these trials. As shown in the findings of the qualitative study in this PhD research, one possibility would be to explore a trial whose design includes the option for women to join and receive the benefits they would like, and assign the gel only to women who explicitly would like to use it. While it is unlikely that trial funders would initially agree to such a trial design, the results from VOICE and FACTS 001 provide merit to the argument that innovation in trial design is warranted. The findings of this PhD research showed that trial teams can work together with former microbicide participants to brainstorm and consider different innovative options for trial design. These consultations and collaborations should take place at the formative stage of research, in accordance with the GPP guidelines.[40] Meaningful understanding and integration of the underlying reasons for low adherence and true engagement with former trial participants and communities around innovative ways to consider trial design may result in more creative solutions than what trial teams may have expected was possible.

6.5.1.2 GEL FORMULATION

Overall, results from microbicide studies provide good evidence that the gels have been received well by participants. Participants have reported that the gel has made sex more pleasurable, decreased pain from sex, increased libido, and, in the context of trial participation, has increased intimacy and dialog with male partners. Results have also shown

that gel use fits into vaginal practices in some areas.[160,161,146,147,148,149,129,150,151]

The qualitative study in this PhD research focused on understanding barriers to adherence and barriers to accurate reporting of adherence. Results from this study indicate that negative male partner response or fear of negative male partner response had a negative effect on some participants' ability to use the gel in accordance with the protocol. This issue was brought up as a factor by participants in Mwanza, Tanzania. Participants in Mwanza noted that the increased lubrication was noticeable to their regular male partners, and that some male partners who were not informed in advance about the gel or trial participation perceived the increased lubrication to mean their partners were having sex with other men. Participants reported that this led to conflict in some relationships, some participants dropping out of the trial, and some participants not being able to adhere to gel use in accordance with the protocol. These experiences caused some participants in Mwanza to suggest that the gel formulation be modified so that it was not as easily detectable to male partners. They suggested the consistency of the gel be thicker, less runny, and have a warming sensation rather than a coldness. Even with these reported problems with the gel, participants in the qualitative study within this PhD research expressed interest in and hope for a gel that could prevent HIV transmission. Some participants also acknowledged that the lubricating effects of the gel could help reduce pain during sex, and that different people have different needs and preferences.

Results found in this PhD study do not contradict the findings of other studies where results reported dominant themes around increased pleasure and benefits from the lubricating effects of the gel. Rather, the findings in this PhD research, which included 46 former microbicide trial participants, add to the body of data about women's experiences with investigational microbicide gels in clinical trial settings. This PhD study focused on barriers to adherence, and thus the discussions were focused on problem-solving. As women were no longer enrolled in the trials, they also may have been more willing to disclose problems with adherence. While the VOICE team found that participants were not more willing to disclose non-adherence at study exit compared to during regular follow-up visits,[162] they did find that participants presented with their own PK results in a follow-up study were able to acknowledge product non-use and provide reasons for lack of adherence.[114]

Remembering the context of the evolution of the microbicide field is important in examining the breadth of reactions to microbicide gels. Initially in the microbicide field, there was concern that a lubricating gel might not be acceptable in parts of Africa, especially in locations where "dry sex" had been reported as preferred.[148] Questions around

the feasibility of a vaginal microbicide for HIV prevention in African settings were focused on whether such a product would be acceptable to users. The field was surprised when a considerable amount of data, particularly from MDP 301, indicated that the gel was not only acceptable but also appreciated and perceived as highly beneficial by trial participants. These results were unexpected, and exciting for the feasibility of vaginal microbicide development.

While participants who experienced relationship conflicts around gel use would be more likely to withdraw or be lost to follow-up, results from studies have not been universally positive. An analysis of qualitative data from MDP 301 participants in Johannesburg found that 51% of cases of intimate partner violence (IPV) reported due to trial participation were attributed to partner dissatisfaction with the gel,[141] for reasons similar to those reported by participants in Mwanza. Results from the pilot study of MDP 301 recruiting 320 women in South Africa, Tanzania, Uganda, and Zambia found that male partners in Tanzania liked the gel less than in other locations due to the increased lubrication.[163] VOICE and CAPRISA 004 also found that participants reported fear that the extra lubrication might cause suspicion or complaints by male partners,[116,164] and reports of male resistance to gel use were documented in the Carraguard trial.[140]

The combined experiences of microbicide gel use by different participants provides further evidence that a single HIV prevention technology or strategy will not be appropriate for the diverse population of humans. Individuals have different needs, and the needs of each individual change as their circumstances change through life. A range of HIV prevention options and a range of female-controlled HIV prevention options are an appropriate public health response to the HIV epidemic. A vaginal ring might be an appropriate solution for some women. Those who benefit from additional lubrication might prefer a vaginal gel. Others who want a product they can use covertly and only around the time of sex might prefer a less-lubricating formulation such as a vaginal film or capsule.

Overall, evidence from the body of microbicide gel trials is strong that women liked the gels tested and would like to have HIV prevention methods available to them that they can control and that are effective and safe. The vaginal ring is likely to be the first method approved by regulatory agencies and rolled out to communities. While the availability of any effective female-controlled HIV prevention method will be a major benefit for women globally, this method does not address a number of important needs for some women. A ring will not meet the needs of women who would like a coitally dependent regimen, a ring will not meet the needs of women who would like an HIV prevention

method which has the added effect of lubrication, reducing pain during sex and making sex more pleasurable, and a ring will not meet the needs of women who would not like to expose their bodies to an anti-retroviral drug on a continuous basis. These are all reasons why the biomedical HIV prevention community must continue to work to identify a coitally dependent vaginal gel for HIV prevention.

6.5.1.3 DESIGN OF QUESTIONS ON CRFS

Results from the comparative study in this PhD research showed that the wording of some questions designed to gather data on sexual behaviour and adherence were ambiguous, and this ambiguity may have led to different interpretations by different participants. Results from the trial team survey indicated that, in order to reduce social desirability bias, questions on product use should be asked in a way that begins with the assumption that some non-use will occur.

Including clear language such as the number of days, 7 or 30, rather than ambiguous terms like "week" and "month" are recommended. Adherence questions introduced with permissive statements acknowledging that it is not possible for everyone to have perfect adherence are also recommended. These questions can be followed by questions on the number of times in a particular period of time when product use was not possible. Questions that ask about product use over a series of sex acts or days may be more easily answered by asking participants about their last sex act, followed by asking about the sex act prior to that one, and so on. Terms and their translations should be validated before being used in forms. For example, vaginal sex can be clarified by statements such as "when a man puts his penis in your vagina." Trial teams can also consider using triangulation forms that can help reconcile data from different adherence collection methods. Trial teams should conduct formative research and pilot questions to verify questions are understood in the way trial teams intended.

6.5.1.4 RECRUITMENT OF PARTICIPANTS

The latent structure analysis in this PhD research has shown that older participants report higher adherence. This has been observed in other studies as well.[120,121,122,123] Data from multiple studies also suggest that younger participants, who may have lower adherence, may also be more at risk for HIV infection.[123,1] The reality of biomedical HIV prevention trials is that groups who typically have lower adherence to study products are also

the same groups who have the highest rates of HIV incidence, and are therefore essential to include in trials in order to meet their research objectives. Trial teams can use the body of data about participant attributes, and their relation to both HIV risk and adherence, to recruit prospective participants so the overall composition includes a balance of participants who may be more likely to use the gel and who are also likely to have a higher incidence of HIV infection.

6.5.1.5 RECRUITMENT AND TRAINING OF STAFF

Participants in the qualitative study of this PhD research spoke of the importance of friendly, transparent relationships between participants and staff. The MDP 301 trial team, in its analysis of data from using mixed methods to capture adherence data, acknowledged the importance of interpersonal skills of staff members, as well as their training, in obtaining accurate results.[70] The importance of staff selection, training, and supervision is critical to successful clinical trial implementation. Its importance, however, is often overlooked and not discussed thoroughly in the literature.

Future trials should invest the time and resources it takes to ensure that staff being hired have excellent interpersonal skills and have values that align with treating participants with respect and making them feel welcome, comfortable to answer sensitive questions, and happy to discuss trial procedures candidly to improve trial transparency.

6.5.1.6 STATISTICAL ANALYSIS PLANS

Results from the comparative study in this PhD research showed that there was a lack of clarity in trial materials about analysis of adherence data. Given the central importance of adherence to microbicide trial interpretation, trial teams should take care to define plans for adherence analysis and clearly describe those in the statistical analysis plans before trial data are analysed, in order to avoid selective reporting of data.

6.5.2 TRIAL IMPLEMENTATION

6.5.2.1 MALE PARTNER ENGAGEMENT

Both the qualitative and the latent structure studies in this PhD research found that male partners have an effect on participants' abilities to use the gel in accordance with the protocol. A large body of data including both qualitative and quantitative data now shows that successful participation in microbicide trials by women can be affected by male partners.[127] Findings from studies have shown that participants overwhelmingly prefer to tell their partners about gel use during microbicide trial participation. Results have also shown that adherence can be improved when male partners are aware of gel use or provide support, and that negative reactions by male partners can lead to suboptimal adherence, conflict, and intimate partner violence. These results are discussed below.

The VOICE trial, through a qualitative study with participants in Johannesburg,[115,116,128] found that male partners directly and indirectly affected participant trial participation and gel use, and that this was true for both gel users and tablet users. Some participants were afraid of male partner reactions to trial participation, expecting they would refuse or react negatively. Other participants found that they were eventually able to gain approval after telling their partners about the study and the benefits of participation. Male partner discontent influenced participants' willingness to use products, in some cases made use difficult for participants, and in other cases promoted clandestine use.[116] Women who reported living in a supportive or understanding environment reported fewer problems with using their products.[116] The site in Kampala, Uganda, found that partners who came to the study clinic played a supportive role in product use.[131]

The Carraguard trial, in examining qualitative data from two sub-studies[140] during the phase III trial, found that participants largely preferred to communicate involvement in the trial to their male partners. The timing and nature of discussions, however, depended on the motivation for disclosure. Some participants chose to disclose trial participation to promote positive trust-building aspects of the relationships, while others disclosed to avoid negative consequences within the relationship if they did not disclose. A minority of participants chose not to disclose, and this was more common in relationships with non-regular partners. Based on experiences reported by participants, male partner engagement fell into three broad categories: active support, non-interference, and active resistance.[140]

MDP 301 results from South Africa also found that male partners were a factor for women enrolled in the trial.[141,142] In Johannesburg, a qualitative study of 150 participants found that 129 decided to tell their partners about their trial participation, either for reasons of trust and respect or out of fear of negative repercussions in the relationship or to avoid conflict. This study also found that 52% of IPV reported by participants was attributed to trial participation, due either to gel use or aspects of trial requirements and participation.[141] In KwaZulu-Natal, participants preferred to tell their partners about gel use: 60% had discussed microbicides with their male partners within 4 weeks of participating in the trial, and 84% had done so after 52 weeks of participation. The MDP 301 trial team found a significant association between younger age and discussing gel use with male partners after 4 weeks of trial participation.[142]

FEM-PrEP, looking at ARV pill use in women rather than gel use, found similar results to vaginal gel trials with regard to the influence of male partners on trial participants' use of study products. In this trial, participants' pill-taking behaviour was negatively affected by both perceived and actual discouragement by male partners, and some participants chose to hide their trial pills due to fear of a negative response.[117] In looking at factors that facilitated adherence in the trial, the trial team found that partners who were aware of trial participation could play a role in facilitating participant adherence to pills.[165]

CAPRISA 004, the only microbicide gel trial to find a significant reduction in HIV transmission, found a modest but significant relationship between adherence and disclosure of gel use to male partners, with participants who disclosed gel use having 4.2% ($p=0.03$) increased adherence.[143] A total of 67.3% (569) of participants who completed a partner disclosure questionnaire at study exit reported that they had disclosed gel use to their last sex partner. While women in both the disclosing and non-disclosing groups were similar in age, marital status, and income, women who disclosed were more likely to be living with their regular partner. Trial results indicated a trend that participants who disclosed had lower incidence of HIV infection.[143]

Using a special questionnaire at study exit about partner change,[121] HPTN 035 found that self-reported gel use at last sex act was more likely to be reported by participants with ongoing partners as opposed to participants with new partners. In addition to lower self-reported adherence, this study found that participants with new partners had higher HIV incidence. The HPTN 035 trial team concluded that specific counselling should be offered to participants for when they change partners.[121]

An older HIV prevention trial, the Methods for Improving Reproductive Health in Africa (MIRA) trial, tested a diaphragm used with a lubricating (non-microbicidal) gel for HIV prevention and was one of the first HIV prevention trials to report data about the relationships between product adherence and male partners.[144,72] In an ancillary study looking at male partner influence on trial participation, the trial team found that most participants (96.3%) stated they asked permission from their male partners to join the trial. Of those women, 70% were concerned that if they did not ask permission they would face conflict in their relationship. Women who reported telling their partner about study product use every time they had sex were more than twice as likely to consistently use study products (AOR 2.28, 95% CI 1.55–3.35). The trial team found that participants who stated they would "face problems at home" by not first asking permission to join the study were less likely to be consistent users (AOR 0.70, 95% CI 0.51–0.96). The study also found that a participant's perception of her partner's view of study products affected adherence: participants who reported that their partner strongly liked the diaphragm were more than twice as likely to be consistent diaphragm and gel users (AOR 2.27, 95% CI 1.64–3.15).[144] A separate analysis looking at predictors of product use in the trial found that consistent use of diaphragm was associated with being less likely to have experienced IPV (AOR, 0.38; 95% CI 0.15–0.95). This analysis also showed that participants whose partners always knew when they used the diaphragm were 2.18 times (95% CI 1.06–4.49) more likely to be consistent users compared to sometimes users.[145]

In the past different trial teams have tried various partner engagement strategies and have found this issue difficult to tackle. The types of strategies and whether they were implemented comprehensively as a programme have not been well documented in the literature; nor has evaluation of such strategies. It is clear from a wide range of research results that male partner influence is a critical factor in participant adherence. Future trials will need to do more than include a number of male partner engagement strategies. Rather, they will need to create robust, comprehensive programmes for male partner engagement from the start of the trial and continuing through follow-up, as participants can have multiple partners and change partners over time. The plan can be designed during the formative research process. Trial procedures can include informing participants at the start of the trial about partner involvement support mechanisms, in case they would like to inform a partner and receive support in that process. Participants can be informed of experiences of past microbicide gel trial participants, for example that most found their regular partner was able to notice a difference when having sex with the gel, that most participants eventually chose to inform their regular male partners about the gel, and that telling partners has helped some participants receive support from partners for us-

ing the gel. Participants can then be informed about a range of support mechanisms to help participants tell their male partners about the study. These can include provision of study information materials targeted at partners and provision of invitations for partners to come to the trial clinic to meet with a trial team member, with or without the participant. The trial team could host special seminars or "open days" at the clinic, during nights or on weekends, that would explain the purpose of the trial and what the gel is, and include a tour of the clinic and laboratory while explaining trial procedures. In particular, tours should offer detailed explanations about blood tests and blood processing. For participants who have partners who are too busy to visit the clinic, trial teams could offer to visit participant homes to speak directly with partners, upon invitation from participants.

Visit checklists can include specific questions about whether the participant would like support around disclosing to male partners, or if she would like support on how to use the gel without disclosing. As participants may have different needs and different partners over time, it is important that visit checklists, used at regular intervals, include questions about whether participants would like support in informing partners. If couples who use and like the gel are identified over time, they could be asked to be peer educators and receive special training on how to support other participants who would like to disclose to male partners. A critical component of a comprehensive support programme is to ensure that participants understand disclosure is their decision, and that the trial team will support them in whatever choice they make.

6.5.2.2 CLARITY AND TRANSPARENCY IN TRIAL CONDUCT

HOW TRIALS ANSWER THEIR RESEARCH QUESTIONS

Results from the qualitative study in this PhD research identified that, from the perspective of participants, there was a lack of clarity about how microbicide trials answer their research questions and the mechanism by which participant adherence affects trial results. Due to the complicated nature of microbicide trials and their required procedures, trials over the years have increasingly invested resources in providing easy to understand materials for participants. Ethical requirements of clinical trials state that informed consent (IC) forms must provide information about the trial purpose, benefits, risks, and required procedures (among other information).[44] There is no requirement to tell participants how trials answer research questions. Before the microbicide field understood the extent to which low adherence was affecting trial results, providing this additional information would not have been a priority. As participants in the qualitative study reported that un-

derstanding how the trials work and how their own adherence can affect trial outcomes, this section examines the information they did receive, and provides recommendations for information that can be included in future trials.

Microbicide trial teams have found that that additional supportive materials are helpful to ensure that participants correctly understand what participation means. More recently, trial teams have begun to typically prepare materials in the form of booklets or table-top flipcharts with culturally appropriate illustrations and simple language. In addition, trial teams may include questionnaires to test the comprehension of prospective participants to ensure that the contents of the IC forms have been correctly understood and that participation is voluntary.

Upon examination of the IC forms for MDP 301 and VOICE, and results of the qualitative study in this PhD research, it is indeed evident that participant materials are focused on trial procedures but do not explain the mechanism of how a trial answers its research question. The IC materials for MDP 301 screening state that the purpose of the trial is to find a new way to prevent sexual transmission of HIV, and that PRO 2000 is being tested for both effectiveness at prevention HIV and safety. It explains that PRO 2000 is an experimental drug and that it is not known if the drug prevents HIV transmission. The form states, "Another gel which has been specifically matched is a dummy gel known as a 'placebo'. This dummy gel has no activity against HIV." The form explains that the gels look alike and that chance will determine if the participant receives the PRO 2000 gel or the dummy gel. The form then states, "You will receive the same type of gel throughout the trial. NO-ONE KNOWS WHICH GEL THEY ARE ON, including the study staff. This is the best and only way to test the gels to see if they prevent HIV infection." The form then continues to explain the specific procedures of trial participation and other required information. At the end of the form, a section entitled "What will happen to the results?' explains that "After the study has been completed the results will be analysed." The form then states that participants will be informed of which gel they used. The enrolment IC form has a section called "A reminder about the purpose of this trial" which states, "The question we are trying to answer is 'does 0.5% or 2% PRO 2000/5 gel prevent HIV?"' The form then states, "The best way to answer this question is in a clinical trial, where women are allocated by chance to 0.5%, 2% or placebo (dummy gel with no activity against HIV). This way, the risk factors that are linked to HIV, such as not using condoms, are evenly balanced across the three groups."

The accompanying animated booklet provides clear explanations of study procedures from the perspective of the participant. Based on these materials, which are centrally provided by the trial and can be tailored at local sites, it would not be possible for a participant to understand how the trial answers its research question or why product use at each sex act would be important. While concepts of randomisation and placebo are mentioned, there is no statement that tells participants that the way trial teams learn if PRO 2000 is effective or not at HIV prevention is to compare, at the end of the trial, the number of women who get HIV in the group that used PRO 2000 with the number of women who get HIV in the trial that used the placebo gel. Unless this is stated explicitly, it is not possible for a lay person to understand how a clinical trial is able to know if an investigational gel prevents HIV transmission. Participants, therefore, would also not understand why their adherence was critical.

The VOICE IC materials, compared to the MDP 301 materials, provide more detailed explanations of the trial and trial procedures, using clear language. The enrolment IC form, under "Purpose of the study," explains that the trial is testing three products for effectiveness at preventing HIV as well as testing the safety of the products. It explains that the trial drugs are experimental and what is already known about the drugs. The IC form states it is not known if the drugs prevent HIV. Under "Study groups," the form explains that there are five groups in the trial and that women will be allocated by chance. It explains that two types of placebo exist for the trial (oral and gel), and that these products look like the actual product but do not have any ingredients that prevent HIV. The form explains that all groups are important to the study and then provides more detailed information about expected use of products and study procedures. At the very end of the form, in the "New information" section, there are two statements about what is known about the study gel from the CAPRISA 004 and from TDF/FTC from the iPrEx trial. The statement about the gel says, "The results of CAPRISA 004 showed that women who received tenofovir gel had a lower risk of getting HIV during the trial, compared to women who received the placebo gel." This is the only statement in the document that could help a woman understand what results at the end of a trial would look like, but does not explain how the VOICE trial will answer its research question. This statement also comes near the end of the form, on page 11, while discussing results of a different trial and not the trial the participant is providing consent to join. The animated booklet/flip chart provides clear and helpful information for participants about trial participation. When discussing "study groups," the booklet explains what placebos are and states that "you may wonder why" some participants are given the actual drugs while others are given placebos. The booklet then states, "the placebo gel and placebo tablets are needed to help researchers

understand the effects of Tenofovir and Truvada. No one will know which women are using Tenofovir or Truvada, and which are using placebo, until the study is finished. The researchers will then compare the women who used Tenofovir or Truvada to the women who used the placebo to find out if the Tenofovir or Truvada prevented women from getting HIV." This explanation also does not state exactly what is being compared and how, although it provides somewhat more information than what is provided in any of the other documents.

Because the purpose of the qualitative research in this PhD research was to seek suggestions from former microbicide trial participants on how to improve adherence and adherence reporting, it was essential that they understood why adherence is important in microbicide trials. Participants were first provided with a clear explanation of how microbicide trials answer their research questions. This explanation was clear enough that participants could answer for themselves what would happen if adherence was low in the trial. Participants in the qualitative study found this explanation helpful, and it was recommended that such explanations be included in future microbicide trials so that participants are more empowered to understand how their behaviour affects trial outcomes.

How a trial answers its research question is most easily explained and understood using a diagram that illustrates the trial process. The following description provides a list of key elements that should be included in such a diagram so the trial process is transparent to those who volunteer to participate. The diagram is read from the top of the page to the bottom of the page. A group of women at the top of the diagram is labelled "HIV negative women." This illustration shows participants the starting point. The diagram is then divided into two equal groups by arrows; half of the women are going to one side and half to the other side. One group is labelled "Active gel" and the other group of women, on the other side, is labelled "Placebo gel." Here, the concepts of placebo and randomisation can be explained, as well as the prevention package that goes along with each type of gel. After being assigned to use a particular gel, participants will continue with their normal lives, using the gel as directed and attending study visits.

The picture also shows that participants are followed up over time; at the bottom of the diagram, the group of participants on the active gel arm is divided into two groups that have different numbers of participants. One group is labelled "HIV positive" and the other group is labelled "HIV negative." The number of HIV positive women is noticeably lower than the number of HIV negative women. On the other side of the diagram, the placebo arm is divided into two groups: those who are HIV positive, and those who

are HIV negative. For illustration purposes, the HIV positive group should clearly include more women than the number of HIV positive women on the active gel side. What can then be explained to participants is that the number of women who become positive in the two groups is compared; thus, participants can see for themselves that because everything else was the same, the difference in HIV infection must have been due to the special ingredients in the active gel, which in turn shows that the active gel was effective at preventing HIV transmission. The diagram can then be used as the basis for discussion of different outcomes in HIV results and what the interpretations could be. The concept of adherence can then be introduced, and participants can be asked what HIV results would look like if no one used the gel.

CLARITY IN PROCEDURES AT EACH STAGE OF TRIAL PARTICIPATION

Trial teams over the years have increasingly included culturally sensitive materials to help participants understand the purpose of blood draws, how much blood will be taken, and how blood specimens will be handled. Both MDP 301 and VOICE developed and used such carefully created materials. Participants from both trials in the qualitative study within this PhD research raised concerns about not knowing why certain test tubes of blood were drawn, not always knowing where the blood was taken to, and sometimes not receiving the test results. These circumstances raised doubts in the participants' minds about the research; moreover, such doubts can easily be exacerbated by rumours in the community. While some trial teams have been careful to be clear about these procedures due to the sensitive nature of blood draws in Africa, it is also important to remember that most of this information is provided to participants at screening and enrolment and may not necessarily be repeated or reinforced throughout the trial. Participants are provided with a substantial amount of information at the beginning of the trial, and they may forget some of those details as time passes. Also, as time passes, participants may start to have doubts or questions which they did not have at the start of the trial. Trial teams can mitigate negative consequences of participant doubt by creating a structure of communication that helps procedures appear transparent to participants throughout the trial process.

Results from this research indicate that participants would like to know about each procedure as it is happening. This updating can create an atmosphere of greater transparency and trust. Visit checklists can include a section for informing participants about what each test tube of blood will be tested for and when the results will be ready. Trial teams

can create simple diagrams that show the local chain of custody for blood, where each tube of blood is tested, and where it is stored. Tubes of blood which are sent to a central laboratory for confirmatory testing or for blood storage do not necessarily give rise to a test result being reported back to participants, which can be confusing for participants. Therefore, it is important for trial teams to create explanatory materials and diagrams to explain confirmatory testing and blood storage.

6.5.2.3 INCLUSION OF APPLICATOR TESTING AND FEEDBACK TO PARTICIPANTS

Different approaches to applicator assessment have been used in trials and continue to be under development. As discussed earlier in this thesis, Carraguard developed a special DSA to detect vaginally inserted applicators. HPTN 035 and VOICE did not ask participants to return used applicators. MDP 301 did ask participants to return used applicators.

Participants in the qualitative study in this PhD research strongly suggested the use of a system in which used applicators could be distinguished from unused applicators, and suggested that those results be provided to participants on an ongoing basis over follow-up. Participants felt these procedures would help microbicide trial participants both to have improved adherence and to be more likely to report their gel use accurately. These results are echoed by findings in other biomedical HIV prevention trials for women. For example, the VOICE trial team found that providing participants with their PK results in the follow-up study, VOICE D, was acceptable and elicited more honest responses from participants. In addition, the VOICE D study participants suggested that participants should be provided with real-time adherence feedback.[114,162] The FEM-PrEP trial also concluded that real-time adherence feedback which preserves blinding could prevent social desirability bias and should be included in future trials.[95,138] While provision of individual drug levels to participants can only be implemented after study exit in a blinded trial, the advantage of systems to assess applicators is that results can be provided to participants over follow-up, as they do not break blinding.

CAPRISA 004 asked participants to return used applicators. Fifteen months into trial implementation, the trial team initiated a standardised protocol to differentiate empty applicators from vaginally inserted empty applicators. The protocol, Visual Inspection of Returned Empty Applicators (VIREA), was then used until trial completion.[166] Results of implementing the protocol showed that more-accurate assessment of applicator use

was possible. Participants self-reported that 93.4% of returned applicators had been used; however, using VIREA, the research team found that only 77.5% of the empty applicators had been used. An increased risk of HIV (HR 1.9; 95% CI 1.1–3.5) was found among participants who had fewer than half of the empty returned applicators determined to be used by VIREA. While this method requires visual inspection which is subjective, has a learning curve, and requires training and quality assurance monitoring, it is inexpensive and can be completed in trial clinics in real time, which in turn enables research teams to provide participants with adherence feedback in a prospective manner. The trial team also found that asking participants not to wipe or wash used applicators and return them to the clinic in provided strip-lock bags was feasible.[166]

More sophisticated methods of measurement are in development, such as viewing used applicators under ultraviolet light (UVL)[152,99] and swabbing used applicators to detect DNA and protein biomarkers for vaginal insertion and semen exposure.[153] A study comparing UVL reading, visual inspection, and the DNA and protein biomarkers found that the DNA and protein biomarker method had better sensitivity and specificity than UVL or visual inspection, which were both found to be subjective and to have a learning curve for readers.[100] While testing for DNA and protein biomarkers for vaginal insertion performed better according to sensitivity and specificity, they are labour-intensive processes that require expensive equipment and supplies. Technological progress in developing improved ways to test applicators, as well as other ways to assess adherence,[167,168,114,166,169] are exciting steps towards improved adherence measurement. Advantages of new technologies will have to be balanced with feasibility and cost—factors which will likely change over time.

6.5.2.4 FEEDBACK ADHERENCE DATA TO PARTICIPANTS AND SITES OVER FOLLOW-UP

To facilitate improving adherence prospectively, trial teams can analyse real-time adherence data. These results can be reported back to participants as a platform to discuss adherence and trial participation. This can be integrated into a comprehensive adherence program, which also asks participants at selected points in time if they have any questions about blood draws, problems with partners, influence from other individuals or community members, or procedures that are not clear. Individual participant adherence can be provided to participants, or results of analyses such as latent structure analysis can be used to describe adherence. Analyses can be conducted with data, such as looking at differences

in adherence by site; these differences can be explored to understand potential reasons for differences, and corrective actions taken.

6.5.3 TRIAL RESULTS ANALYSIS AND REPORTING

6.5.3.1 ANALYSIS

The results of this PhD research have shown that trial results are typically reported as overall averages, which do not appropriately convey the reality of adherence of trial participants, as this changes over time. The latent structure analysis in this PhD research showed that adherence data analysed over time reveals different patterns of adherence in the trial population, which conveys more information than reporting averages alone, even with self-reported data. This research has also shown that multinomial logistic regression can help identify which factors are associated with different patterns of adherence. Both of these methods are inexpensive and can be used with self-reported or biomarker data.

6.5.3.2 RESULTS REPORTING IN PUBLICATIONS

Due to the benefit of understanding adherence patterns gained through latent structure analysis, it is recommended that trials use this method to report adherence information, in addition to providing averages or static estimates. If space limitations restrict full descriptions of adherence analyses in primary results publications, trial teams can use the option of supplemental online information that many publications now offer. Methods and results sections of publications should be clear and transparent about how adherence calculations were made. If adherence calculations deviate from SAPs, this should be stated and the reasons given.

6.6 LIMITATIONS AND STRENGTHS

The research chapters of this thesis (Chapters 3, 4, and 5) describe in detail the limitations of the particular studies. This section provides a summary of key limitations of this PhD research and discusses the strengths of the research.

6.6.1 LIMITATIONS

Overall, the main limitation of this research is that the trials and data included largely draw from second generation microbicide trials, whereas the field has moved on to test microbicides with ARVs, which allows greater ability to use biomarkers for adherence estimation. Third generation microbicide trials have been designed in the context of knowing that adherence in microbicide trials may be low while self-reported adherence may be high. Third generation trials have more carefully considered adherence counselling, measurement, and estimation. While CAPRISA 004 was included in the comparative study of this PhD research, the other five trials were second-generation microbicide trials.

The main limitation of the latent structure analysis is that all of the adherence and behavioural data used in the analysis were self-reported. Results of the study are therefore subject to both recall bias and social desirability bias. It is likely that estimates of adherence are inflated compared to actual adherence. Another limitation of the latent structure analysis is that participants who missed study visits or were lost to follow-up did not contribute adherence data to the models. Those participants may represent a group of women who are more likely to have lower adherence than participants who attended regularly and completed the trials. These limitations may have resulted in latent structures that are biased in the direction of showing more adherence at each of the time points.

The qualitative study within this PhD research was small, with only 46 participants, and was conducted in two locations. For the majority of participants, a long time had elapsed between microbicide trial participation and participation in this study, and the participants who did participate in the qualitative study represented individuals who were still living in the vicinity of the trial sites. These women may be different in a number of ways from those who are no longer living in the same areas or not able to attend on the days of the FGDWs.

6.6.2 STRENGTHS

A strength of this PhD project is that it critically examined adherence in vaginal microbicide gel trials as a trial design issue from three perspectives, using three different types of data and three different analytical approaches. This project used data sources that included trial implementation and reporting materials, quantitative adherence data from

microbicide trials, and qualitative data from former microbicide trial participants, in order to understand ways to improve the design of future microbicide trials for improved adherence, improved estimation of adherence, and improved reporting of adherence.

The comparative study was the first study to compare exactly how a selection of microbicide trials calculated and reported adherence and to link this process to statistical analysis plans and source questions on CRFs. This study identified issues with wording of questions used to collect data from participants and gaps in explanations about analysis methods in SAPs and publications. This study found that trials described adherence in primary results manuscripts as means or medians, despite adherence data being collected throughout follow-up. This study, which was comprehensive in that five microbicide trials were included in its analysis, found that there was considerable variability in how trial teams collected adherence data and estimated and reported adherence.

The latent structure study was the first study to use latent class analysis and latent profile analysis to identify patterns of adherence across four different microbicide trials using self-reported adherence data that, on average, appeared consistently high. This study demonstrated that latent structure analysis is a feasible method to analyse and characterise the longitudinal nature of adherence data in microbicide trials. This study showed that patterns of adherence appear to be similar across four different microbicide trials, and that age and site are associated with different patterns of adherence. This study also found that male partner disapproval of the gel was associated with trajectories of adherence that decreased over trial follow-up.

The qualitative study included in this PhD research was the first study to engage former microbicide trial participants in participatory activities to think explicitly about future microbicide trial design with respect to improving adherence and adherence reporting. This study created and used a novel approach, called focus group discussion workshops, to combine methods such as focus group discussions, participatory activities, and small group work to engage former microbicide trial participants with limited education in thinking about how to design future microbicide trials so adherence and adherence reporting can be improved. This study, which was designed from the perspective of microbicide trial participants, developed materials so participants could understand the science behind clinical trials and low adherence, and thereby make constructive contributions to the clinical trial design process. This study revealed that participants have their own objectives for joining microbicide trials that may not be related to using an investigational product. Successful microbicide trial implementation will benefit from trial designs that

consider and include the reasons why women join and stay in trials. This study showed that trial teams can work with former trial participants and other stakeholders to consider the feasibility of creative trial designs to improve future implementation of microbicide trials.

6.7 CONCLUSION: IDENTIFYING A MICROBICIDE GEL

The microbicide field was born out the need for women to protect themselves from HIV without having to rely on male cooperation to use condoms. HIV disproportionally affects women, who often do not have choice about how and when they have sex. Structural factors perpetuate environments where women have less autonomy than men. A range of methods for HIV prevention which women can use themselves is urgently needed.

Multiple effectiveness clinical trials have tested coitally dependent candidate microbicide gels, with disappointing results. Low adherence has likely played an important role in many of these trials being unable to accurately characterise the biological efficacy of the candidate products. This PhD research has examined the complex nature of adherence and adherence assessment in microbicide trials from three different perspectives, with the goal of making concrete recommendations for future microbicide trial design to increase the chance of demonstrating effectiveness of candidate products. This PhD research has shown there are improvements to be made in how trialists plan, conduct, analyse, and report results of microbicide trials.

Results of this PhD research have shown that the imbalance of power in intimate relationships affects even the ability of trials to identify an effective microbicide, as trial participants' adherence can be affected by male sexual partners. Results of this research have also shown that women in the settings where effectiveness microbicide trials are conducted join trials for their own reasons, and not necessarily for the reasons that microbicide trialists initially assumed. Trial participants may have doubts about using an investigational product whose effectiveness and safety are not yet proven, and the presence of these doubts has affected adherence in past microbicide trials. Identifying an effective product for HIV prevention for women requires better understanding of the lives and perspectives of the women being asked to join the trials, as well as incorporating that understanding in future clinical trial design.

It is important that donors and sponsors of microbicide trials understand the reality of microbicide trials, which involve the complicated nature of sex and intimate relationships, within the context of a world that provides fewer freedoms and opportunities for women than it does for men. Rather than continuing to use standard clinical trial design approaches, innovative trial design ideas should be considered. While this consideration requires investing time and resources into formative research and stakeholder engagement, it will increase the chance of obtaining scientifically valid research results which can then be used to improve the health of populations. The results of this research show that participants and research staff can work together to develop and consider innovative trial designs which better include women's perspectives and increase the chance of identifying an effective HIV prevention microbicide for coital use.

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