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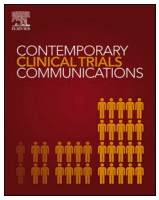

Overcoming COVID-19 disruptions: Innovations in product provision in a multi-national clinical trial among cisgender men, transgender men and transgender women in five countries

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ABSTRACT

Clinical trials often depend on participants receiving study product to meet objectives of the protocol. Vitally important are considerations for how sites receive and dispense study product during a study while ensuring appropriate handling, accountability and compliance. The process for provision of study product is detailed in Standard Operating Procedures (SOPs) which are adhered to by the research site throughout the trial. The COVID-19 pandemic unexpectedly affected the ability of study participants to receive study product. We report on the various methods implemented by trial sites to ensure timely provision of study product to participants during this unprecedented pandemic. In MTN-035, participants received 3 potential rectal microbicide formulations in randomized sequences to understand user preferences. Trial sites were permitted to revise dispensing methods to enable participants to continue to receive study product during COVID-19 restrictions. These actions mitigated disruption of study product administration and preserved the integrity of the trial. Out of the 78 participants expecting to receive study products on or after the onset of restrictions due to COVID-19, only four participants (5%) did not receive all three products. Adopting alternative methods to provide product to study participants in extraordinary circumstances was key to successful study completion and maintaining study integrity.

1. Introduction

Unprotected receptive anal intercourse (RAI) is the sexual behavior with the highest per act risk of HIV acquisition, conferring approximately 10–20 times more risk than unprotected receptive vaginal intercourse (RVI) [1,2]. There has recently been a reported increase in condomless sex [3–6] which has offset the reduction in HIV incidence due to earlier diagnosis and ART among MSM [7]. Currently there are only two medications approved for daily use as pre-exposure prophylaxis (PrEP), Truvada® and Descovy ®. Despite the efficacy of oral PrEP, usage is low with barriers such as cost, lack of awareness, lack of knowledge and prescribing by health care workers and unwillingness or stigma associated with taking a daily tablet [8,9].

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Abbreviations

SOPs	Standard Operating Procedures
RAI	Receptive Anal Intercourse
ARV	Antiretroviral
ART	Antiretroviral Therapy
MSM	Men who have Sex with Men
PrEP	Pre-exposure Prophylaxis
STIs	Sexually Transmitted Infections
ICH	International Council for Harmonization
GCP	Good Clinical Practice
PTID	Participant Identification

Microbicides are products that are designed to be applied to the vaginal or rectal mucosa with the intent of preventing the acquisition of sexually transmitted infections (STIs) including the human immunodeficiency virus (HIV) [10]. MSM have expressed a preference for topical gel microbicides because of similarities to personal lubricants which could potentially be incorporated into their usual sexual practices [11–13]. Rectal gels require administration with an applicator presenting adherence challenges for long-term use.

2. Method

The MTN-035 study was conducted to evaluate three potential rectal microbicide formulations including a placebo insert, suppository, and a douche. The primary objective was to evaluate the acceptability, adherence, safety and tolerability of each study product when applied rectally prior to RAI over a 4-week period. This was a global multi-site, randomized-sequence, three-period, open label crossover study that included 217 cisgender men and transgender men and transgender women at seven sites in five countries: Malawi, Peru, South Africa, Thailand, and the United States (3 sites). Participants were between the ages 18–35, living without HIV and reported engaging in receptive anal sex were enrolled. On average, participants were 25 years old and identified as cisgender men who have sex with men (80%), transgender women (9%), transgender men who have sex with men (1%), or another category (10%). Participants were randomized (1:1:1:1:1:1) to one of 6 study product sequences (Fig. 1). Study product was provided to participants at the start of each 4-week period. The douche involved spraying water from the nozzle of a bottle into the rectum. The suppository is a small, cone-shaped object inserted into the rectum and dissolves quickly. An insert is a small, bullet-shaped object inserted into the rectum and dissolves quickly.

Pharmacists received an MTN-035 Pharmacy Study Product Management and Procedures Manual which outlined processes and required documentation for study product including product procurement, storage, dispensing and accountability. They were required to develop and adhere to SOPs based on the guidelines of the manual. Upon receipt of a prescription for the first visit of each product use period, product dispensed was sufficient for the entire product use period. Dispensation was documented indicating which study product(s) were issued.

2.1. Pandemic onset

In March 2020, the COVID-19 pandemic affected study implementation. Restrictions hindered the ability of pharmacists to provide study product to participants as outlined in their SOPs. Sites were encouraged to determine a safe process for continuing the trial with product provision. SOPs were amended at sites to adopt new revised processes tailored to safely meet the individual needs of participants and clinic staff.

At the onset of the pandemic, targeted accrual for the study had been reached at all 7 sites; one of the sites completed prior to the onset of the COVID-19 epidemic. Six sites (referred to as Site 1, Site 2, etc.) were actively following a total of 108 study participants needing to complete enrollment and product administration. Participants in follow-up by the end of March 2020, were potentially impacted by clinic closures in effort to protect the safety and well-being of research staff and participants. To adhere to safety precautions and sustain study integrity, study leadership and the study management team developed a contingency plan which modified study implementation guidelines and procedures (e.g., safety monitoring, study product provision and other visit procedures), effective as of March 16th, 2020. Participants were offered the opportunity to engage in study visits virtually or remotely.

There were 210 participants enrolled before March 16th, 2020 of which 131 (62%) received all three products. Among the rest of the 79 (38%) participants, eight exited the study before March 16th, 2020 and were not affected by the alternative dispensing methods. Seven participants were enrolled on or after March 16th, leaving 78 participants expecting to receive product.

Good clinical practice guidelines (ICH GCP) outline the standards for involving human subjects, including the investigators responsibility for investigational drug management and accountability, which can be delegated to an appropriately qualified and trained pharmacist [14]. Although there are no universal standards for the dispensing of investigational products, each of the clinical trial sites established a plan detailed in a SOP. This document is adhered to throughout the trial, however, the COVID-19 pandemic required modification of dispensing procedures using creativity and flexibility in order to continue to provide investigational product to the participants.

In order to complete the remaining visits for the MTN-035

Sequence	N	Period 1 (4 weeks)	Washout period (~1 week)	Period 2 (4 weeks)	Washout period (~1 week)	Period 3 (4 weeks)
A	35	Rectal insert	--	Rectal douche	--	Rectal suppository
B	35	Rectal douche	--	Rectal suppository	--	Rectal insert
C	35	Rectal suppository	--	Rectal insert	--	Rectal douche
D	35	Rectal insert	--	Rectal suppository	--	Rectal douche
E	35	Rectal douche	--	Rectal insert	--	Rectal suppository
F	35	Rectal suppository	--	Rectal douche	--	Rectal insert

Fig. 1. Study product sequences.

participants currently enrolled, pharmacists developed new or modified dispensing processes to mitigate disruptions to the study related to COVID-19. They were given the flexibility to work with the clinic staff to determine the best process for their participants which often included dispensing more than one product at a time. This was in contrast to most site original dispensing procedures, which specified only the product for that study period would be dispensed. Once the site pharmacist developed a process it was documented to ensure that accountability and chain of custody were maintained. Processes ranged from minimal changes required to completely new methods of product dispensing and are summarized below for each of the six study sites.

All but one of the sites developed a policy to allow all of the remaining MTN-035 study products for each participant to be dispensed at one time. Product was packaged and labeled to include the participant identifier (PTID), product sequence (if more than one product dispensed) and the order products should be administered. The one site that did not provide all of the remaining products at once sent each product via courier at the time it was scheduled. Clinic staff communicated with participants to remind them when it was time to switch to the next product and counselling was provided regarding instructions for product administration.

Sites determined the best way to get product to participants resulting in a variety of methods. One site established "curb side pickup". Nurses contacted participants to coordinate a day and time (with a 1-h window) for retrieval of product from the clinic. Participants were instructed to follow COVID-19 protection guidelines including wearing a mask, remaining in their vehicle, and calling the clinic once in the parking lot. Nurses delivered product to participants waiting in their vehicles and reviewed the use schedule, instructions and answered questions.

Two sites provided all remaining products to participants on site at the clinic. Two other sites delivered product to participants by certified mail or express courier on the same day it was dispensed with tracking and verification of receipt by the participant. Of the two sites shipped that product to the participants, one shipped the remaining product at once and the other site sent each product at the time it was to be used. Each participant was required to provide consent to this method before product could be sent. Shipping documents were retained in the participant pharmacy file.

One site delivered all outstanding products to study participants in advance but did not use a courier. For many participants clinical staff delivered study product parcels participants at their homes (see Table 1).

3. Results

Of the 78 participants expecting to receive product on or after March 16, 2020, 74 (95%) participants received all three study products, however, four participants (5%) did not receive all three products (Table 2). Among the four participants who did not receive all three products, two exited the study after receiving their second study product due to being unwilling or unable to comply with required study procedures, one participant was lost to follow-up after receiving one study product, and the other participant didn't receive two study of the products due to travel out of the province. It was not possible to extend the duration of the trial due to product expiration. And thus, there is only one participant who did not receive all three of the study products during COVID-19.

Table 1
Number of study products received before March 16, 2020.

Site#	1	2	3	4	5	6	7	All Sites
Number of participants Enrolled	**33**	**31**	**30**	**30**	**30**	**33**	**30**	**217**
Number of Study Products Received Before March 16th, 2020								
Placebo Rectal Inserts	**27**	**11**	**24**	**15**	**29**	**27**	**30**	**163**
Placebo Rectal Suppositories	**27**	**10**	**24**	**18**	**28**	**28**	**30**	**165**
Placebo Rectal Douche	**28**	**10**	**24**	**19**	**27**	**28**	**30**	**166**

4. Discussion/Conclusion

It is essential that clinical trial sites establish clear and documented process for dispensing study product to participants. However, it is important to keep in mind that extraordinary circumstances may require thinking "out of the box" in order to support study completion. It is possible to do this while adhering to ICH GCP. One consideration not factored in the process was the readiness of study pharmacists to respond and adjust to such emergent situations that was caused by COVID-19. Having each pharmacist mitigate the dispensation process, facilitate communications with the local IRB/EC to have alternative procedures approved urgently as to not delay receipt and initiation and while ensuring the appropriate documentation was in place, was an unexpected interruption into their routine processes. The scalability of this approach could not be formally measured given the limited number of study participants affected and the inability to extend study operations. Feedback and lessons learned were also not formally captured as a part of this process. This report, however demonstrates that encouraging each site to determine an alternative method to provide investigational product to participants during a pandemic can successfully allow participants to safely continue in the trial while maintaining the integrity of the data. Of the four participants who did not receive all 3 products, one participant was from the site with "curbside pick-up", one from the site that provided all remaining product in advance and were delivered to the participants by study staff, and two participants were from the site that provided all of the products but required participants to return to the clinic. There were 3 sites that provided all 3 products to the remaining 47 participants during the pandemic. Two of the sites sent product to 17 participants via courier and the third clinic scheduled appointments for the 30 participants to return to the clinic (with a 1 h window of time) and provided all remaining product. Using a courier to get product directly to the participant or scheduled clinic visits convenient for the participants were both effective methods for providing study product. Although it is not known how many participants would have completed the trial without adopting alternative methods to provide product, it is clear that only 5% of the remaining 78 participants was relatively small and the success of the trial prevailed.

Participant access to study product is critical when conducting clinical trials and if circumstances result in participants unable to receive product, the trial may come to a halt. It is possible to allow sites flexibility to determine study product dispensing method alterations that are GCP compliant to allow the study to proceed without disruption. Although this should not be a routine practice, it is an option when a critical event such as a pandemic occurs.

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Table 2
Number of participants affected by COVID-19 and received all 3 products.

Site#	1	2	3	4	5	6	All Affected Sites
Number of participants expecting to receive study product on or after March 16, 2020	6	30	12	20	5	5	78
Number of participants received all three products	5 (83%)	30 (100%)	12 (100%)	19 (95%)	3 (60%)	5 (100%)	74 (95%)
Number of participants did not receive all three products	1 (17%)	0 (0%)	0 (0%)	1 (5%)	2 (40%)	0 (0%)	4 (5%)

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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