Strategies implemented for accurate dispensing of an investigational new drug in a multi-site HIV prevention clinical trial

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A R T I C L E I N F O

Keywords:
Pharmacy
Investigational product
Dispensing errors
Quality checks

A B S T R A C T

Safe practices for dispensing investigational product (IP) during clinical trials are not standardized and information in this regard is often limited. ASPIRE was a Phase 3 safety and effectiveness trial of a vaginal matrix ring containing 25 mg of dapivirine for the prevention of HIV-1 in women. The study enrolled 2629 women at 15 clinical research sites in Malawi, Uganda, South Africa and Zimbabwe who were randomized in a 1:1 ratio to receive either a vaginal ring containing 25 mg of dapivirine or a matching placebo vaginal ring. The vaginal rings and packaging were identical in appearance in order to maintain the study blind. A real-time, documented second check of the dispensing process was conducted by a second pharmacy staff. Frequent inventory counts and real time accountability audits were also useful for rapidly identifying a dispensing error. A total of 52,625 vaginal rings were dispensed with only three documented pharmacy dispensing errors. There were zero dispensing errors at 13 of the 15 sites with an overall rate of <1.0 per 10,000 rings dispensed. Our study findings support the implementation of a double check dispensing process and real time accountability audits as standard practice in clinical trials.

1. Introduction

Medication errors can occur in routine healthcare settings when dispensing commercial medication. These errors could happen at any stage during storing, prescribing, dispensing, preparation or administration of medication and can potentially lead to harm [1]. Such errors may impact patient morbidity, mortality and even result in litigation with economic consequences. Commercial medication utilizes strategies to reduce dispensing errors such as designing products in different shapes, sizes, colors and with imprinted codes to assist with identification. The packaging of these medication may also vary in appearance, size or be labeled with different font types [2].

Abbreviations: IP, Investigational Product; ICH, International Council for Harmonisation; GCP, Good Clinical Practice; SOPs, Standard Operating Procedures; NCR, No-carbon required; PTID, Participant Identification.

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https://doi.org/10.1016/j.conctc.2021.100859
Received 12 February 2021; Received in revised form 18 October 2021; Accepted 9 November 2021
Available online 12 November 2021

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It is acknowledged that dispensing errors may also occur during a clinical trial, although the incidence is not readily available. Such errors in a clinical trial have the potential to unblind study staff and participants, impact participant safety, data integrity and study outcomes. It is challenging to implement similar risk mitigation strategies to investigational product (IP) compared to commercial medication, due to the need to conceal allocation to the different treatment arms in blinded clinical trials. The product characteristics of IP must be similar in appearance and be labeled with a unique identifier instead of the drug name [2].

It is often difficult to identify a dispensing error that has occurred at the clinical trial site without having the proper checks and balances as well as tracking procedures [3]. Good clinical practice guidelines (ICH GCP E6) provide the standards for the design, conduct, recording and reporting of clinical trials involving human subjects [4]. These guidelines further describe the investigators responsibility for all aspects of IP management and accountability, which can be delegated to an appropriately qualified and trained pharmacist. Currently there are no universal standards for the dispensing of IP. Strategies and potentially beneficial practices should be implemented to minimize dispensing errors as a part of good clinical practice.

Here we describe the strategies implemented to minimize IP dispensing errors within the ASPIRE (MTN-020) trial.

2. Method

ASPIRE was a multicenter, randomized, double-blind, placebo-controlled Phase 3 safety and effectiveness trial of a vaginal matrix ring containing 25 mg of dapivirine for the prevention of HIV-1 in women. The study was conducted across 15 clinical research sites in South Africa, Zimbabwe, Uganda and Malawi. Details of the ASPIRE study methods, including the eligibility criteria and main study results have been described elsewhere [5]. The 2,629 women enrolled into the study between 2012 and 2014 were between 18 and 45 years of age (median age 26 years), healthy, HIV uninfected, not pregnant, and sexually active. Women needed to meet the eligibility criteria and provide written informed consent to participate in the study. They were randomized in a 1:1 ratio to receive either a vaginal ring containing 25 mg of dapivirine or a matching placebo vaginal ring. The rings were inserted into the vagina, remained in place for a minimum of 28 days to a maximum of 35 days and replaced with a new ring monthly for 12 months. The study received full ethical and regulatory approval by local and national regulatory bodies prior to implementation.

2.1. Pharmacy procedures

The pharmacy staff received protocol training and pharmacy specific training, to ensure that they were familiar with IP management processes before they commenced work on the study. The process of quality checks was documented in the ASPIRE Pharmacist Study Product Management Procedures Manual. As part of the Study Activation Checklist the pharmacists were required to develop pharmacy Standard Operating Procedures (SOPs) that described the processes utilized in each pharmacy to manage IP.

Dispensing errors in clinical research is defined as a discrepancy between the IP prescribed for the participant and the IP dispensed. Dispensing errors can be further classified as the pharmacist a) dispensed the incorrect IP; b) dispensed expired or incorrectly stored IP; c) incorrectly assigned IP; d) clinic staff collected the incorrect IP from the pharmacy. These errors can negatively impact participant safety and data integrity.

To minimize errors during the trial, the protocol pharmacist developed a system of multiple checks that were included in the design of the dispensing process. Each site pharmacist developed a quality management SOP that described how these quality control and quality assurance checks would be performed at their site.

To maintain the study blind the IP was packaged with 40 vaginal rings per carton containing either dapivirine 25 mg or placebo and was identical in terms of packaging, color, size and labelling. The outer carton was labeled with a unique bin code, which was used for the storage of the vaginal rings. Each individual vaginal ring was further packaged into a sealed pouch, with a 2-part tear off label which contained the sublot codes of the products.

The randomization and IP assignment was conducted using a manual system to allocate the assigned IP. Pharmacists were responsible for maintaining the integrity of the study’s blinded design. The IP was assigned to a participant based on the randomization number on the prescription (Fig. 1).

Each clinical research site received a binder with a set of 2-part no-carbon required (NCR) prescriptions with sequential randomization numbers. The prescription was pre-printed with the site name, location, DAIDS site ID, and a randomization number. The clinics assigned the prescriptions in ascending sequential order and sent the completed “top” form to the pharmacy. The “bottom” copy remained in the participant’s binder in the clinic. Pharmacy staff were delegated the responsibility to provide the correct coded vaginal ring to the participants using the randomization assignment. Each site pharmacy received a binder with a set of the ASPIRE Participant-Specific Dispensing Records. This was used to document all dispensations per participant and the sublot code of the vaginal rings dispensed. The pharmacist had to link the prescription, using the randomization number, to the corresponding Participant-Specific Dispensing Record located in the pharmacy. This pharmacy dispensing record had the same randomization number as printed on the prescription. The dispensing record indicated which bin code the IP should be retrieved from and listed all possible sublot codes assigned to that specific randomization number (Fig. 2).

The use of the unique numeric (sublot) codes was used to blind participants, study and pharmacy staff, and the Protocol team to the vaginal product assigned to participants. This also allowed the identification of a product to a particular manufacturing lot. The sublot codes assigned to each IP were determined by the statistician and were only shared with the labeling/distribution vendor.

Pharmacy staff obtained a ring by matching the sublot code on the vaginal ring label with one of the possible codes on the dispensing record. The ring over-wrap label contained a tear-off portion with the ring sublot code which the pharmacist placed in the designated space on the dispensing record as verification of the sublot dispensed (Fig. 3). A real-time, documented second check of the dispensing process was conducted by another pharmacy staff. At this point, the 2nd pharmacy staff verified the Participant Identification (PTID), randomization number, the bin code and sublot codes on the participant specific dispensing record. Pharmacy staff also matched the tear off label over with the sublot code, and signed off the dispensing record. The pharmacist also checked the accountability log and chain of custody at this point, so there was a complete second check of the entire dispensing process. Due to staffing issues at a few of our sites, if another pharmacist was not available to do the verification, a technician/pharmacist assistant working in the pharmacy was permitted to provide the check. If there was no other individual available in pharmacy at the time of dispensing, then the process was reviewed retrospectively as per the site pharmacy SOP. This documented double check system was implemented from the onset of the trial to reduce the probability of dispensing errors and provide an audit trail of the dispensing process [6].

In addition to completing the Participant-Specific Dispensing Record, the pharmacist also completed an Accountability Record for each sublot (Fig. 4). This document included the balance of IP remaining after each dispensing which should always have matched the physical stock on hand at all times. A check was done at each dispensing to verify that the quantities of the sublot were correct. If a discrepancy was noted, an investigation was immediately conducted to determine the cause. If an error had occurred by dispensing an incorrect sublot it would have likely been identified at this point. In addition, a documented inventory check
of all IP was conducted at a minimum of every 28–31 days. More frequent inventory checks were encouraged and were often completed weekly.

Chain of Custody documentation also served as a check to be sure the correct IP was collected for a participant from the pharmacy. This information was captured on the Record of Receipt of Vaginal Rings (Fig. 5) which was completed to document dispensing of a vaginal ring to clinic staff. Pharmacy staff completed the top section (site name, clinic name) and the first four columns on the Record of Receipt. When receiving study vaginal rings from the pharmacy, the clinic staff or runner verified the PTIDs and completed the remaining three columns on the Record of Receipt for each PTID.

### 3. Results

Of the 2,629 enrolled participants, there were 1313 and 1316 women in the dapivirine ring and placebo ring arms, respectively. A total of 52,625 rings were dispensed with only three documented pharmacy dispensing errors. The study noted zero dispensing errors at 13 of the 15 sites with an overall rate of < 1.0 per 10,000 rings dispensed. There was one dispensing error documented at one site (rate 3.0 per 10,000) and a further two dispensing errors documented at a different site (rate 4.3 per 10,000).

At the site with the single dispensing error, the pharmacist dispensed the incorrect IP to a participant and the discrepancy was realized the day
after dispensing. Another pharmacist conducted an accountability check and noted that the inventory count for IP was not tallying. Upon further investigation, it was determined that the incorrect ring had been dispensed. The cause of the error was attributed to the pharmacy dispensing double check and accountability check that were not completed at the time of dispensing. The participant was notified and received the correct ring in the clinic. Retraining of pharmacy staff was conducted to reinforce that the double-check is done in real time and to ensure adherence to all pharmacy quality checks.

At the site with two dispensing errors, the first error occurred when the pharmacist dispensed the incorrect IP to the participant and the second check was not done in real time. The next day during a routine physical inventory check the discrepancy was noted. All of the participant dispensing records for those who had attended clinic that week were reviewed. It was noted the tear-off label affixed to one of the participant-specific dispensing records did not match the sublot codes listed. This error occurred at a time when six prescriptions were received within a short period of time at the end of the day. The second incident at this site was due to the clinic staff collecting the incorrect IP from the pharmacy. This was as a result of multiple dispensed IP awaiting collection from the pharmacy. Despite the nurse signing for the product, it was not realized that the incorrect participant’s IP was received. The error was realized while the participant was still at the research site but the ring had already been inserted and was subsequently removed. Two factors that contributed to this error were a power failure resulting in less than optimal lighting and the perceived need for a speedy collection after a long clinic day. Retraining was conducted on pharmacy workflow as well as second checks done in real time. As part of the corrective

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**Fig. 3.** Sample vaginal ring label.

**Fig. 4.** Example of an accountability record.

**Fig. 5.** MTN-020 record of receipts of participant specific study product.
action, the pharmacist was retrained to ensure that the collection of the vaginal ring occurs at a dispensing area with adequate lighting and will confirm verbally with the nurse to verify the participant identification on the label as IP is collected. In all three cases of dispensing errors, the participants were immediately contacted and notified about the errors. Participants were instructed to remove the incorrect vaginal rings and return to the clinic for resupply of a new vaginal ring as soon as possible. New vaginal rings were dispensed for all three participants. The incorrect rings were collected and set aside for destruction.

The IP dispensing errors all occurred at follow-up visits and were detected and corrected within 24 h. These errors did not impact the integrity of the study due to the brief duration that the participants had the incorrect ring inserted and there was no breech in study blind. These errors were a result of not performing a second check in real time or failure to provide the IP to the correct participant. Although the participant’s safety and integrity of the data was never compromised, retraining on procedures and documentation was conducted. The checks in place may have contributed to there being very few dispensing errors despite over 50,000 IP dispensations during the trial. The checks in place also resulted in promptly and accurately determining that an error had taken place and timely institution of corrective and preventative action and subsequent resolution.

4. Discussion/conclusion

Safe practices for dispensing in a clinical trial using a manual pharmacy system is critical for success. In a clinical trial, IP packaging and labelling is identical across both the active and placebo arms due to the lack of distinguishing features may result in dispensing errors especially in a busy pharmacy environment. We have noted that a system to have an independent double check of the dispensing process and entries by a second pharmacist is an effective approach to minimize errors of dispensing incorrect IP. It is understood that staffing may not always allow for a real-time double check system. In this case, a retrospective review of IP dispensing should be done as soon as possible.

There is a paucity of published literature evaluating specific processes to ensure the accurate dispensing of product, particularly in a double-blind trial. In 2016, the Hematology/Oncology Pharmacy Association issued their own guidance for investigational drug service best practices, representing the most comprehensive outline of safe practices [7]. One of the recommendations is the use of double checks that are noted as vital in the preparation and dispensing process. They suggest that for safety and accuracy, each institution should have a policy that identifies medications that require verification by a second pharmacist prior to dispensing. For the ASPIRE trial, the protocol pharmacist determined that every dispensing required documented verification. The process of checks was documented in the ASPIRE Pharmacist Study Product Management Procedures Manual.

The low rate of dispensing errors in our study supports implementing this type of system. Frequent (weekly) inventory counts and real time accountability audits were also useful for rapidly identifying a dispensing error. Pharmacists reported that counting the remaining vaginal rings in an open carton at the time of dispensing was also useful to determine any discrepancies and prevent potential dispensing errors. However, additional studies are needed to support a double check dispensing process and real time accountability audits as standard practice in clinical trials.

Study team leadership

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Data management was provided by The Statistical Center for HIV/AIDS Research & Prevention (Fred Hutchinson Cancer Research Center, Seattle, WA) and site laboratory oversight was provided by the Microbicide Trials Network Laboratory Center (Pittsburgh, PA).

Funding

The ASPIRE study was designed and implemented by the Microbicide Trials Network (MTN) and funded by the National Institute of Allergy and Infectious Diseases (UM1AI068633, UM1AI068615, UM1AI06707), with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health (NIH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The vaginal rings used in this study were developed and supplied by the International Partnership for Microbicides (IPM).

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.

Data availability

The authors do not have permission to share data.

Acknowledgements

We are grateful to the ASPIRE site pharmacists and pharmacy teams who conducted the study with the highest level of study product management accuracy. We thank the women who participated in this study for their motivation and dedication and the communities that supported this work.

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