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DATES:

Received: 21 Apr. 2022

Revised: 09 Oct. 2022

Accepted: 15 Mar. 2023

Published: 08 Aug. 2023

HOW TO CITE:

Ahmed K, Malahleha M, Mbatsane TE, Thindisa D, Bailey VC, Seocharan I, et al. Addressing missed visits to improve retention of young South African women in clinical trials. *S Afr J Sci.* 2023;119(7/8), Art. #13809. <https://doi.org/10.17159/sajs.2023/13809>

ARTICLE INCLUDES:

Peer review
 Supplementary material

DATA AVAILABILITY:

Open data set
 All data included
 On request from author(s)
 Not available
 Not applicable

EDITOR:

Pascal Bessong

KEYWORDS:

clinical trials, retention, protocol adherence, missed visits

FUNDING:

Bill and Melinda Gates Foundation (OPP1032115), US Agency for International Development (AID-OAA-A-15-00045), Swedish International Development Cooperation Agency (2017/762965-0), South Africa Medical Research Council, United Nations Population Fund

Addressing missed visits to improve retention of young South African women in clinical trials

In clinical trials, a vital protocol requirement for participants is adherence to scheduled visits. A substantial number of missed visits and the resultant missing data could affect generalisability of the findings and undermine the scientific conclusions. We aimed to investigate the extent of and reasons for missed visits in the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial in order to optimise recruitment and retention practices. Despite being a multi-country study, we investigated missed visits only at Setshaba Research Centre in Soshanguve, Tshwane, South Africa. Of 810 participants enrolled at Setshaba Research Centre, 94 (11.6%) participants missed visits and 231 missed visits were recorded. Of the 94 participants who missed visits, 53 (56.4%) missed at least two visits; 37 (39.4%) missed three or more visits, and of these, 32 (86.5%) missed at least two visits for the same reason. Overall, the main reasons for missed visits were: participant had to work (60; 26.0%), unable to contact participant (60; 26.0%), participant relocated (32; 13.9%), and participant travelled out of area (23; 10%). The large proportion of participants who missed two or more visits indicates that participants who miss a single visit are likely to miss even more, often for the same reason. Site staff need to be vigilant to detect any trends in missed visits early and innovative in developing personalised strategies to minimise missed visits and retain participants until completion of their scheduled visits.

Significance:

- Despite trial site staff developing strategies to minimise missed visits, they will not be able to anticipate all scenarios.
- Participants' work commitments, loss of contact with participants, and participants' travel/relocation to distant areas were the main reasons for missing visits, and site staff need to consider the potential for these to arise during the course of the study when assessing potential participants at enrolment and at each follow-up visit.
- Case report forms designed for multi-country studies should be adapted to reflect the most likely reasons for missed visits for the local situation, so that trends in missed visits can be identified and addressed early.

Introduction

High participant retention is a critical element of clinical trials which can only be achieved by ensuring that participants comply with protocol requirements. A vital protocol requirement for participants is adherence to their scheduled visits. Retention of enrolled subjects is essential for both scientific and economic reasons. Missed visits can not only compromise the safety of participants but also impact on the study data and trial outcomes. Substantial instances of missed visits and the resultant missing data are serious problems and can affect generalisability of the results, significantly bias the results, reduce study power and undermine the scientific trustworthiness of causal conclusions from clinical trials.^{1,2} Keeping participants in a trial ultimately helps keep a study on track, saving time, money and resources in the process.³

Missed visits are frequently unintentional and could be due to factors outside a participant's control. Women, in particular, perform multiple social roles such as being members of kinship networks, wives, girlfriends, caregivers, income earners, and scholars. Fulfilling these roles often compromises their ability to attend clinic visits.⁴ Other reasons provided by participants for missing visits were being out of the study area, being "busy" or unavailable because of work, adverse events, not wanting to undergo HIV testing at each quarterly visit, long waiting periods at the clinics, negative rumours in the community regarding the study, disapproval of the study by partners and/or parents, relocation for employment, financial constraints, forgetting visits, incarceration, and unstable housing.^{3,5-8} However, most of the studies in which these reasons were given were conducted over a decade ago and were outside of South Africa. Reasons for missing visits are not universal and differ from place to place and over time. Therefore, there is a need to conduct such a study in South Africa.

An opportunity to investigate reasons for missed visits at a South African research site arose in the Evidence for Contraceptive Options and HIV Outcomes (ECHO) study – a randomised clinical trial which compared HIV incidence and contraceptive benefits in women using depot medroxyprogesterone acetate, levonorgestrel implant, and copper intrauterine devices.⁹ The study site, Setshaba Research Centre, was one of 12 sites across eastern and southern Africa that participated in this study. Setshaba Research Centre is situated in Soshanguve, which is about 100 km from Johannesburg in the district of Tshwane and province of Gauteng, South Africa. The catchment area is made up of peri-urban and informal settlements and is densely populated with a total population of close to a million people. The centre is located in an area of high disease burden, especially HIV/TB, with the incidence of HIV in studies among women conducted at Setshaba Research Centre ranging from 3–6 per 100 person

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years. The community has a high proportion of residents who have not completed secondary schooling, a high unemployment rate, and is poorly resourced, which influence the social, economic and structural factors that contribute to the high disease burden.^{10,11} It is against this backdrop of demographic and socio-economic factors that we aimed to investigate the extent of missed visits and the reasons thereof in the ECHO trial, in order to revise and optimise recruitment and retention practices for future studies.

Methods

This study involved a secondary analysis of data from the ECHO study. The 12 sites in the ECHO study were from across South Africa, Kenya, Eswatini, and Zambia. A total of 7830 HIV-uninfected women between 16 and 35 years of age were enrolled in the study. Despite this being a multi-country study, the aspect on missed visits was investigated only at Setshaba Research Centre, Soshanguve, in Tshwane, South Africa. Setshaba Research Centre's site-specific data for screening, enrolment and missed visits were obtained via the ECHO Research Manager, International Clinical Research Center, Department of Global Health, University of Washington, USA. Setshaba Research Centre enrolled 810 participants in 2016–2017 and they were followed up at 1, 3, 6, 9, 12, 15 and 18 months.

During the ECHO trial, Setshaba Research Centre implemented standard retention practices developed from experience in previous trials to minimise missed visits and maximise retention efforts. Relevant processes were outlined to participants prior to enrolment and reinforced during the course of the study. These included, but were not limited to, use of appointment cards, reminder calls, visit trackers and short message services (SMSs) sent to the participants, after-hour and weekend clinic visits based on participants' needs, home visits, clinic waiting area adherence discussions and collection of locator information during screening, verified and updated, if required, at each subsequent visit. Retention efforts were supplemented with an innovative strategy of quarterly informal social participant events, called 'chilling sessions', for participants to engage with staff and other participants in a relaxed setting, which provided a platform for education and information sharing as well as for addressing participant concerns, myths and fears.

When a participant missed a scheduled visit according to the visit window, the Missed Visit case report form (CRF) was used to document the relevant details. This form was sent to the data centre only once the visit window had closed and it was confirmed that the participant had missed the visit. The Missed Visit study-specific CRF contained the following information: (1) reason for missed visit (specified as follows: Unable to contact participant; Unable to schedule appointment within allowable window; Participant refused visit; Participant incarcerated; Participant admitted to a healthcare facility; Participant travelled out of area; Participant forgot; Participant did not have money; and Other (Specify)); (2) steps taken to address the missed visit (corrective action plan); and (3) additional comments.

For this sub-study, the data were analysed using descriptive statistics. The information provided by the data centre was analysed using Microsoft Excel for Office 365 and Epi Info 7. Data from the Missed Visit study-specific CRF for all those who missed visits were analysed to determine the proportion of participants who missed visits and the frequency and reasons for missing visits. Data from the screening and enrolment visit CRFs were used to report on the demographics of participants. The results are reported as frequencies and percentages.

With respect to the specified reasons 'Unable to contact participant' and 'Unable to schedule appointments within allowable window', several of these were changed in the analyses to the actual reason why participants missed their visits where staff eventually managed to contact the participant or their alternative contact person, or by conducting home visits as part of their corrective action. 'Phone only rings' as stated under 'Other (Specify)' was recoded and combined in the analyses with the specified reason 'Unable to contact participant'. If an entry recorded under 'Other (Specify)' suggested that the participant could not come to the site because of issues related to work, this was recoded as 'Work commitments'. Staff would attempt to verify the inability of the participant

to come to the site because of work commitments by following up with the alternative contact person, if this information had been provided by the participant, or by conducting home visits.

Sociodemographic comparisons were made between those who missed visits and those who did not; a significance level of 0.05 was used. The ECHO study was approved by the South African Health Products Regulatory Authority and ethical clearance was provided by the University of the Witwatersrand Human Research Ethics Committee (FHI 360 Study number 523201; Ethics reference number: 141112). Informed consent was obtained from participants at screening and enrolment.

Results

Of the 810 participants enrolled at Setshaba Research Centre, missed visits were reported for 94 (11.6%) participants over the course of the study. The mean age (\pm standard deviation) of the 94 participants was 23.5 (\pm 3.7) years; 40 (42.6%) did not complete secondary school, 42 (44.6%) completed secondary school and 12 (12.8%) attended a post-secondary institution; 92 (97.9%) were never married and only 15 (16%) were living with a partner; however, 69 (73.4%) had partner support.

Throughout study participation, 231 missed visits were recorded for the 94 participants. Thus, some participants had multiple missed visits. Of the 94 participants who missed visits, 53 (56.4%) missed at least two visits and 37 (39.4%) missed three or more visits. Of those who missed three or more visits, 32 (86.5%) missed at least two visits for the same reason. The majority (74.9%) of missed visits occurred in the second half of the study. The reasons for the missed visits are presented in Table 1.

Of the 231 missed visits, 93 (40.3%) were for specified reasons and 138 (59.7%) were for 'Other' reasons. The main reasons for missing visits were work commitments (60/231; 26.0%) and being unable to contact participants (60/231; 26%), which together accounted for just over half of all missed visits (Table 1). Additional frequently stated reasons were: 'Relocated' (32/231; 13.9%), 'Travelled out of area' (23/231; 10%), 'Unable to honour visit as promised' (20/231; 8.7%) and 'School commitments' (16/231; 6.9%).

There were no missed visits recorded for some of the specified reasons listed on the CRF, namely: Participant incarcerated, Participant admitted to a healthcare facility, Participant forgot, and Participant did not have money.

Table 1: Reasons for missed visits in the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial at the Setshaba Research Centre trial site, Soshanguve, South Africa ($N = 231$)

Reason for missed visit	<i>n</i>	%
Unable to attend because of work	60	26.0
Unable to contact the participant	60	26.0
Participant relocated	32	13.9
Travelled out of the area	23	10.0
Unable to honour visit as promised	20	8.7
School commitments	16	6.9
Participants wanting to withdraw from study participation	5	2.1
Other commitments	4	1.7
Participants wanting to have a baby	3	1.3
Participants experiencing side effects	3	1.3
Unable to schedule appointments within the allowable window	2	0.9
Other	3	1.3



The majority (63/94; 67.0%) of participants who missed visits were younger than 25 years old. There were no significant differences between those who missed visits and those who did not with respect to receiving financial support from partners, earning an income, education (completed secondary education or more versus primary education or less) or marital status (all $p > 0.05$).

Discussion

The large proportion of participants who missed two or more visits indicates that participants who miss a visit are likely to miss even more visits. Furthermore, most participants who missed multiple visits missed more than once for the same reason. It is therefore important to identify those participants and their missed visit trends early in the trial so that personalised strategies to minimise missed visits can be devised and implemented. Corrective action to get participants to adhere to their visit schedule was taken as deemed appropriate for the reason of the missed visit. Some of the actions taken were: (1) study staff performed home visits; (2) transport to the research site was arranged; (3) some participants who had relocated but were still interested in continuing with the study were offered extra reimbursement to enable them to fulfil their visit; and (4) letters to confirm study visit attendance were also issued, if requested by the participant.

Despite strategies in place to minimise missed visits at the time of this study, site staff nevertheless faced some challenges. The main reason given for over a quarter of missed visits was that participants were unable to take time off from work, including over weekends. In the VOICE Study conducted in Johannesburg, South Africa, a random sub-sample of 102 female trial participants, 18 to 40 years of age, were interviewed to explore factors that shaped trial participation and adherence to study protocols. It was found that clinic visits interfered with household responsibilities as well as work or school, and trial participants encountered difficulties when trying to balance their commitment to these different activities.⁴ Therefore, study staff need to be thorough at screening in establishing whether work commitments may make it difficult for participants to adhere to their visit schedule. Even then participants can become employed only after screening or enrolment or might change jobs, which can subsequently impact on their ability to adhere to the visit schedule. Moreover, we found that some of the participants who relocated did so because their place of employment was far from the trial site and this could not be anticipated at enrolment. Soshanguve is largely a residential area with little opportunity for employment. Thus, many local residents seek employment outside the catchment area in the cities of Johannesburg and Tshwane or in neighbouring provinces. It is therefore not surprising that a large proportion of missed visits were due to participants relocating or travelling out of the area, which could have been to seek employment or for personal reasons. Therefore, participants need to be informed at the outset and reminded during the course of the study to notify study staff of any change in their employment status so that staff can proactively assess the impact thereof on adhering to study visits and plan accordingly. In addition, if an enrolled participant relocates, it is important that the site staff are notified and arrangements can be made to accommodate their visits with extra reimbursement for travel costs and/or weekend visits.

The development and implementation of retention strategies is an ongoing and dynamic process. Yet despite site staff implementing retention measures, certain circumstances beyond their immediate control can derail plans. This was clearly illustrated by the COVID-19 pandemic which highlighted the potential for missed visits due to lockdown measures such as restricted inter-provincial travel, or reluctance by participants to use public transport to come to the research site because of the fear of exposure to the coronavirus from other symptomatic or asymptomatic passengers, particularly during each wave of the pandemic. Thus, site staff had to develop innovative means in a short time to minimise missed visits and maintain high retention to keep trials on track. Clinical trial implementation has been rigid in requiring lengthy in-person visits, which have both cost and inconvenience implications for participants and the research team alike. As a result of the COVID-19 pandemic, sponsors and researchers were forced to become more adaptable and to consider

collecting data through other mechanisms, such as telephonically and online, e.g. if no specimens need to be collected, technology can be employed for virtual visits.

Inability to make contact with participants was the other major reason for missed visits. A study team member would generally attempt to contact participants to remind them of their upcoming visit; however, participants would sometimes fail to respond to the call, leading them to not honour their visit. A subsequent study conducted at this site suggested that this could partly be due to participants experiencing physical, financial and technological challenges with their cell phones, such as the battery running flat frequently, their cell phones being unreliable, or lack of data due to high data costs, poor network signal at home and use of applications.¹² Additional strategies implemented by site staff included sending SMSs alerting them of their visit and calling after hours. It was also perceived that some participants may not have answered their phones for fear of the site's number being recognised by an unsupportive partner/family member or employer. Therefore, site staff would sometimes call participants from a number other than the site contact number stated in the consent form, such as a staff member's personal phone or another site office number.

This study also highlights the need for greater reflection on the design of CRFs. It is noteworthy that an inability to honour the visit due to work was recorded under 'Other reasons', as this circumstance accounted for over a quarter of all missed visits. Work commitments should have been anticipated as a potential reason for being unable to honour a scheduled visit. Therefore, this should be listed as a specified reason for missing a visit, particularly if the study population includes employed people. It is more difficult to keep track of reasons for missed visits if these are recorded under 'Other reasons'. Nonetheless, in the absence of regular reports on missed visits from the data management centre, it remains the responsibility of the site research team to discuss each missed visit when this becomes known and to take corrective action. CRFs also need to be modified for the local situation by removing those specified reasons for which no entries were made, as these could be recorded under 'Other reasons' if they do occur in future. This highlights the need for experienced site research staff to be consulted during protocol and CRF design in multi-site trials.

Interestingly, a higher proportion of younger participants missed visits. This could possibly be due to the schoolchildren missing visits and skewing the data towards younger age. It is understandable that participants who are attending school would find it difficult to honour their visit at certain times, particularly during examinations, as this would be their priority. From experience with previous studies, site staff were aware of the difficulty that scholars faced to honour their visit during examinations. Bearing this in mind, the recruitment team was informed that school-going potential participants should not be included in the study. In addition, while this was not a protocol-exclusion criterion, study staff responsible for screening and enrolment tried to exclude participants who were attending school by asking them if they were attending high school before the informed consent form was signed. If participants did not disclose this information, they were then enrolled in the study. Therefore, despite school attendance not being an exclusion criterion, young participants need to be scrutinised further to confirm that they are not attending school to avoid the potential problems of missed visits due to schooling priorities.

The finding that three-quarters of the missed visits occurred in the second half of the trial could indicate participation fatigue, as participants were required to be in the study for 18 months. Other factors, such as side effects and personal commitments, played a minor role in missed visits. The method of contraception did not impact upon retention; at 18 months of follow-up, retention was similar in the three arms of the trial (91.3%, 94.3% and 94.7%).⁹

Our research site conducts other clinical trials with female participants of similar demographic and socio-economic status. Furthermore, other research centres in South Africa conduct clinical trials in peri-urban areas that are similar to Soshanguve. Thus, the findings of this study are relevant to other clinical trials and to research centres in South Africa



as a whole, as well as to clinical trials in other low-to-middle-income countries.

Limitations of the study

The information on missed visits, more especially that due to unspecified 'Other reasons', was not recorded systematically. Each case required careful analysis to determine the reason for the missed visit. Depending on the completeness of information and the interpretation of the study staff, there could have been misclassification of the reason. For example, many participants could not be contacted, and these missed visits were recorded under the specified reason of 'Unable to contact participant'; however, for a substantial number of participants, 'phone only rings' was the reason recorded under 'Other (Specify)'. Furthermore, for some participants for whom initial reasons for missed visits were recorded as 'Unable to contact participant' or 'Phone only rings' or 'Unable to honour visit as promised', the reasons were changed to 'Participant relocated' or 'Unable to attend because of work' or 'School commitments' when staff eventually managed to contact the participant or their alternative contact person, or conducted home visits as part of their corrective action. Therefore, it is likely that for more participants who could not be contacted, the actual reasons for missed visits could be relocation, work or school commitments. The need for recoding of some reasons for missed visits captured on CRFs in the 'Other' field/option could have been detected during earlier site quality-control activities and staff could have been trained/retrained appropriately on CRF completion to avoid having to address this issue during analysis.

Another limitation of the study is that information on the corrective actions taken based on the information gained about non-attendance was not captured systematically, making it difficult to quantify the extent of the improvement in retention. However, the retention rate at the end of the study was 92%, which was above the standard of 90%.

Conclusions

Retention of participants in clinical trials is largely dependent upon recruitment of participants who will follow protocol requirements, with adherence to scheduled visits being one such requirement. Work commitments, inability to make contact with participants, and travel or relocation to areas distant from the research site were the main reasons for missing visits. Furthermore, we found that participants who missed a visit were likely to miss even more visits, often for the same reason. Therefore, site staff should be vigilant to detect any trends in missed visits early and develop personalised strategies to minimise missed visits and retain participants until completion of their scheduled visits. Despite trial site staff developing strategies to minimise missed visits, they will not be able to anticipate all scenarios and may still face some challenges. This has been highlighted most recently by the COVID-19 pandemic – an unprecedented event that caused chaos and immense hardship at local, national and global levels, simultaneously placing clinical trials and participants' safety at risk. Thus, sponsors and researchers must move away from rigid in-person study visits and be more flexible in collecting data, such as through virtual or telephonic means, to ensure that study visits are not compromised. In addition, research staff should investigate the different types of technological tools used by participants and the extent of their use to determine which alternative options of data collection would best suit the participants in their catchment area.

Longer duration studies require more innovative approaches and need more individualised retention strategies. Furthermore, case report forms designed for multi-country studies should be adapted to reflect the most likely reasons for missed visits for the local situation, and this may help in identifying trends in missed visits early.

Acknowledgements

This work and the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Study were made possible by the combined generous support of the Bill & Melinda Gates Foundation (grant OPP1032115), the American people through the US Agency for International Development (grant AID-OAA-A-15-00045), the Swedish International Development Cooperation

Agency (grant 2017/762965-0), the South African Medical Research Council, and the United Nations Population Fund. Contraceptive supplies were donated by the Government of South Africa and US Agency for International Development. The contents of this paper are solely the responsibility of the authors and do not necessarily reflect the views, decisions, or policies of the institutions with which they are affiliated, the ECHO trial funders, or the supporting governments.

Data availability

Access to the data from this ancillary study of the ECHO Study may be requested through submission of a research concept to the principal author: KAhmed@setshaba.org.za. The concept must include the research question, data requested, analytic methods, and steps taken to ensure ethical use of the data. Access will be granted if the concept is evaluated and found to have scientific merit and if sufficient data protections are in place. As of the time of publication, data access applications are in process with the governing institutional review boards of the ECHO Study to make de-identified data from the primary ECHO data set publicly available.

Competing interests

We have no competing interests to declare.

Authors' contributions

K.A.: Conceptualisation, study design, oversight and leadership, writing – revisions. M.M.: Conceptualisation, study design, project leadership, writing – revisions. T.E.M., D.T.: Data collection, writing – revisions. V.C.B.: Management and coordination of research activities, writing – revisions. I.S.: Data analysis, writing – revisions. A.D.: Conceptualisation, study design, data analysis, writing – initial draft, coordinated revisions and finalised the manuscript. All authors reviewed and approved the final manuscript.

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