

# Effect of self-administration versus provider-administered injection of subcutaneous depot medroxyprogesterone acetate on continuation rates in Malawi: a randomised controlled trial



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## Summary

**Background** Injectable contraceptives are popular in sub-Saharan Africa but have high discontinuation rates due partly to the need for provider-administered re-injection. We compared continuation rates of women who self-injected subcutaneous depot medroxyprogesterone acetate (DMPA-SC) and women who received DMPA-SC from a health-care provider, including community health workers (CHWs).

**Methods** We did an open-label randomised controlled trial based at six Ministry of Health clinics in rural Mangochi District, Malawi. Health-care providers recruited adult women who presented at the six clinics or to CHWs in rural communities in the clinic catchment areas. Participants received DMPA-SC and were randomised (1:1) to receive provider-administered injections or training in how to self-inject DMPA-SC. Randomisation was done via a computer-generated block randomisation schedule with block sizes of four, six, and eight and stratified by study site, generated by an independent statistician. Self-injectors administered the first injection under observation and were sent home with three doses, written instructions, and a calendar. The provider-administered group received a DMPA-SC injection and a calendar, and were asked to return for subsequent injections. Data collectors contacted participants after the 14-week re-injection window at 3, 6, and 9 months to collect continuation data. At 12 months after enrolment or early discontinuation, women had their final interview, which included pregnancy testing. The primary outcome was discontinuation of DMPA-SC, as assessed in the intention-to-treat population. We used Kaplan-Meier methods to estimate the probabilities of continuation and a log-rank test to compare groups. Safety was assessed in the as-treated population, which consisted only of participants who successfully received at least one DMPA-SC injection after randomisation. This trial is registered with ClinicalTrials.gov, number NCT02293694.

**Findings** This study lasted from Sept 17, 2015, to Feb 21, 2017. 731 women underwent randomisation, with 364 assigned to the self-administered group and 367 to the provider-administered group. One woman in the self-injection group withdrew at month 0. Treatment was discontinued by 99 women in the self-administered group and 199 women in the provider-administered group. The 12 month continuation rate was 73% in the self-injection group and 45% in the provider-administered group, giving an incidence rate ratio of 0.40 (95% CI 0.31–0.51;  $p < 0.0001$ ). Adverse events deemed to potentially be treatment-related were reported by ten women (20 events) in the self-administered group and 17 women (28 events) in the provider-administered group. Five serious adverse events were reported during the trial by four women; two events related to DMPA-SC (menorrhagia and anaemia requiring hospital admission) were reported by the same woman in the provider-administered group and resolved without sequelae. The other serious adverse events, including one death, were deemed to be unrelated to DMPA-SC.

**Interpretation** Women who self-injected DMPA-SC had significantly higher rates of continuation than those receiving provider-injected DMPA-SC. Community-based provision of injectable contraception for self-injection in low-resource settings seems to be safe and feasible. Self-administration of DMPA-SC should be made widely available.

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## Introduction

Injectable contraceptives are the most popular modern contraceptive method in sub-Saharan Africa because of their effectiveness, long-acting nature, potential for discrete use, and reversibility.<sup>1</sup> Of the options available, a formulation of depot medroxyprogesterone acetate (DMPA) that is delivered subcutaneously (DMPA-SC) in

a prefilled, auto-disabled Uniject injection system known as Sayana Press (Pfizer, New York, NY, USA)<sup>2</sup> is gaining recognition as an easy-to-use injectable contraceptive that is suitable for administration by community health workers (CHWs), and potentially by women themselves. In studies in Uganda and Senegal,<sup>3,4</sup> most women and health-care providers ( $\geq 80\%$ ) preferred DMPA-SC over

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### Research in context

#### Evidence before this study

We conducted a literature search, and found that evidence to date suggests that, although side-effects are the most commonly reported reason for discontinuation of depot medroxyprogesterone acetate (DMPA) among women still in need of family planning, access to services is also an important factor in low-income and middle-income countries (LMICs) in sub-Saharan Africa. Subcutaneous DMPA (DMPA-SC) offers a potential solution to the access issue because its simplified delivery system and subcutaneous administration route enable DMPA to be delivered by health workers with less training and potentially by women themselves. Existing evidence shows that self-administration of DMPA-SC is safe, acceptable, and feasible, and in high-income countries is associated with continuation rates similar to those of provider-administered DMPA. However, the potential for self-injection to increase DMPA continuation rates had never been assessed in LMIC settings, and the safety and feasibility of self-injection had never been assessed in the context of community-based distribution of injectable contraceptives, which is the current standard practice in Malawi and many other countries in sub-Saharan Africa.

#### Added value of this study

Our study is, to our knowledge, the first to provide evidence on the important global public health question of whether self-injection improves DMPA continuation rates in an LMIC setting and we used the gold-standard design (a randomised controlled trial) to do so. We noted a strong effect of self-administration of DMPA-SC on continuation rates compared with administration by a provider. The effect was robust to a more lenient definition of continuation in a sensitivity analysis, increasing our

confidence in the findings. Moreover, since the study took place in a real-world setting, with Ministry of Health providers and community health workers, this study will contribute to the growing body of knowledge around community-based access to injectable contraceptives. It is also the first study to provide evidence on the safety and feasibility of community-based provision of injectable contraceptives for home and self-injection.

#### Implications of all the available evidence

Other studies have found self-administration of DMPA-SC to be safe, acceptable, and feasible in LMIC settings. Our findings contribute by showing that self-administration can improve continuation rates compared with provider-administered DMPA-SC and provide evidence that community health workers can safely and effectively train women to self-inject DMPA-SC in LMIC settings. A barrier to the rapid programmatic uptake of DMPA-SC is its anticipated higher cost relative to intramuscular DMPA; however, costs might be substantially reduced if DMPA-SC is self-administered. Self-administration might attract new users of family planning, including through the private sector, pharmacies, and drug shops and could reduce the cost of serving existing DMPA users by decreasing operational costs and more efficiently using resources such as the providers' time. Moreover, the opportunity costs for women would be reduced through the removal of the need to travel as often to receive re-injections from health-care providers. Given the advantages we and others have found, DMPA-SC self-administration could be adopted by a substantial number of users which, in turn, might drive down the cost, a key factor in adoption of any contraception in LMICs.

the usual DMPA intramuscular (DMPA-IM) injection, suggesting that the introduction of DMPA-SC into family planning programmes—including administration by trained CHWs—could expand contraceptive options and access.

Although many women start to use them, discontinuation rates are high, placing women at risk of unintended pregnancy and adverse maternal health outcomes. In a study of discontinuation rates in 19 countries, including five in sub-Saharan Africa, injectables had the shortest duration of use compared with other modern methods.<sup>5</sup> In two prospective studies, the 12-month discontinuation rates among injectable users were 25% in Kenya,<sup>6</sup> 24% in Zimbabwe,<sup>7</sup> and 27% in Uganda.<sup>7</sup> The findings of a retrospective study of Demographic and Health Survey data from 21 countries showed a 12 month discontinuation rate of 32% for injectable users overall<sup>1</sup> and a 2015–16 discontinuation rate of 41% in Malawi.<sup>8</sup>

Malawi has made great strides in increasing the prevalence of modern contraceptive use, from 7% in 1992 to 58% in 2015–16, primarily through increased

use of injectable contraceptives.<sup>8</sup> Injectables are the most widely used modern method in Malawi: nearly a third of currently married women (30%) who practised modern family planning in 2015–16 used injectables. However, according to findings from a study in rural Malawi,<sup>9</sup> only half of new users received their first follow-up injection within 13 weeks, and method switching is not common among women who discontinue for method-related reasons.<sup>5</sup> In a study from 2012, 38% of women in Malawi who did not switch to another method after discontinuing for method-related reasons became pregnant and more than half of those pregnancies were either mistimed or unwanted.<sup>10</sup> Many women in Malawi would benefit from innovations to increase the continuation rate of injectables.

Although method-related concerns, such as side-effects, are the most commonly reported reasons for discontinuation of modern contraceptives among women still in need of family planning, access to services is also an important factor in low-income and middle-income countries (LMICs) in sub-Saharan Africa.<sup>5</sup> In Malawi, discontinuation was more likely among users of

injectables than of other modern methods because of poor access to re-injection.<sup>8</sup> Furthermore, women in rural areas with better access—defined by distance and supply reliability—were significantly more likely to use injectables than were women with worse access.<sup>11</sup> This finding suggests that injectables are failing to meet the contraceptive needs of women, especially those with poor access who would otherwise like to use them. Specifically, the need for quarterly clinic visits, which increases the cost of and time spent on contraceptive use, might contribute to discontinuation of injectables. Furthermore, although community-based provision of injectables by CHWs is a safe, acceptable, and effective way to increase access to family planning in LMICs, studies of such interventions in Kenya and Zambia found relatively high 12 month discontinuation rates of 32% and 37%, respectively.<sup>12–14</sup>

A 2013 Cochrane review of interventions to increase continuation rates of hormonal methods of contraception<sup>15</sup> identified only one study with a positive effect on continuation; however, the evidence for this intensive counselling intervention, which provided women with audiovisual messaging at each follow-up visit, was categorised as “low grade”.<sup>15</sup> Another study identified in that review examining the role of counselling on oral contraceptive continuation found an effect only when counselling was coupled with phone calls. Even if intensive counselling interventions were found to be effective, they would require highly trained staff and increased resources—conditions that are rarely feasible in most LMICs.

To overcome challenges to accessibility that result in discontinuation of injectables, there has been an increase in efforts to explore the feasibility of self-injection of DMPA-SC in the form of both Sayana Press and depo-subQ provera 104 (medroxyprogesterone acetate injectable suspension 104 mg in 0.65 mL in a prefilled glass syringe; Pfizer). As of August, 2017, Sayana Press was registered for self-injection in 18 countries, including seven in sub-Saharan Africa (Radola A, Pfizer, personal communication). Proponents of self-injection cite the potential for improved contraceptive use due to increased timeliness of re-injection;<sup>16</sup> self-injection would also eliminate the barrier of having to visit the clinic or CHW. Indeed, previous research in high-income countries has shown that self-injection of DMPA-SC is feasible and safe. In a trial in New York (NY, USA),<sup>17</sup> in which women were randomly assigned to self-administration or clinic administration of DMPA-SC, the continuation rates and MPA serum concentrations were similar between the self-administered (71%) and clinic-administered (63%) groups. Similarly, results from a non-comparative study at Planned Parenthood clinics in Florida (USA) showed high continuation (74%) of self-injected DMPA-SC at the fourth injection.<sup>18</sup> In a study done at a large family planning clinic in Edinburgh (UK), self-administration of DMPA-SC was feasible and associated with similar

continuation rates and satisfaction as clinician-administered DMPA-IM, and all self-injections were given within the appropriate interval.<sup>19</sup> Studies in sub-Saharan Africa are yielding similarly promising results: findings from studies assessing the feasibility of self-injection showed that 87% of Senegalese participants<sup>20</sup> and 88% of Ugandan participants<sup>21</sup> could competently self-inject DMPA-SC 3 months after being trained.

We did the first study in an LMIC setting to investigate whether self-administration of DMPA-SC could improve continuation rates and whether community-based provision of injectable contraceptives for self-injection is safe and feasible. Our primary objective was to compare continuation rates between women who self-inject DMPA-SC and women who receive DMPA-SC from a provider, including CHWs, within the context of family planning in Malawi's public sector.

## Methods

### Study design and participants

We did an open-label, randomised controlled trial at six Ministry of Health clinics in rural Mangochi District, Malawi, that offer family planning services and have established community-based distribution programmes in which CHWs provide DMPA-IM. In addition to family planning, the CHWs (also called health surveillance assistants) provide child immunisations and counselling on childhood illnesses, malaria, and HIV in community settings. They provide health services to catchment areas of approximately 1000 people each and are the lowest level of paid government worker. They must complete secondary school and are trained for 12 weeks, the first 8 of which are classroom-based, followed by 4 weeks of practical training.<sup>22</sup>

The protocol was reviewed and approved by the Protection of Human Subjects Committee at FHI 360 (Durham, NC, USA) and the College of Medicine Research and Ethics Committee at the University of Malawi (Blantyre, Malawi). All study staff completed training on research ethics, the protocol, and informed consent administration.

Women were recruited into the study during routine family planning visits at participating clinics or while receiving family planning services from participating CHWs. Eligible participants were aged 18–40 years, in self-reported good general health, able to understand and willing to sign an informed consent document, willing to give contact information for follow-up, willing to have follow-up visits or interviews, willing to be assigned to the self-injection group or the provider-administered injection group, not pregnant according to WHO guidelines, and able to meet eligibility criteria for receiving DMPA as per WHO medical eligibility criteria.<sup>23–25</sup> During the informed consent process, potential participants were told that the DMPA-SC injections would not protect them from becoming infected with HIV or other sexually transmitted

infections or infecting others and that it was unknown whether women who use injectable contraceptives are more likely to get HIV.<sup>26</sup> Potential participants were also instructed that they should not join the study if the possibility existed that they could be harmed if someone found the study product or learned about their participation. Potential participants were deemed ineligible if they planned to become pregnant or relocate outside the study area in the next 12 months, or had any condition (social or medical) that the investigator considered would make study participation unsafe, interfere with adherence to study requirements, or complicate data interpretation.

### Randomisation and masking

Participants were randomly assigned (1:1) to receive DMPA-SC administered by a family planning provider or be trained to self-inject DMPA-SC in accordance with a computer-generated block randomisation schedule with block sizes of four, six, and eight and stratification by study site. Allocation concealment was achieved with sequentially numbered opaque envelopes. The randomisation schedule and envelopes were prepared by an independent statistician who was not otherwise involved in the study. Once assigned to a group, crossover was not permitted. Neither participants nor study staff were masked after randomisation. However, the statistical team remained masked until key decisions for the primary analysis were made.

### Procedures

All women received DMPA-SC injections in the form of Sayana Press 104 mg in a 0.65 mL suspension. Providers instructed women that DMPA-SC injections should be given every 13 weeks, but could be given up to 1 week early and 1 week late (12–14 weeks). Women in the self-injection group who successfully self-injected at enrolment were given three doses of DMPA-SC to take home for subsequent self-injections and written instructions to remind them of the injection procedures. Participants in the self-injection group could also ask the provider to train a trusted person to give them DMPA-SC at home. For women in the provider-administered group, providers administered the DMPA-SC injection at the enrolment visit and participants were asked to return to the provider for injections at 3, 6, and 9 months post-enrolment. To mimic normal service delivery procedures, participants in both groups were not reminded of scheduled re-injections. However, at enrolment, women were provided with a written note showing their future injection dates (every 13 weeks) and a calendar to assist them in remembering when to re-inject or return for re-injection.

Data collectors (who were separate from the providers) contacted participants in both groups for a follow-up interview within 2 weeks after the DMPA-SC re-injection window had elapsed (ie, weeks 15 and 16). Follow-up interviews were done in a private setting at a study clinic

or a private location of the woman's preference. In both groups, data collectors asked women about continuation status, acceptability, adverse events, and experiences with side-effects. If a participant suspected pregnancy or reported a health problem at any time during the study, she was referred to a study clinic for diagnosis and care. If, during a follow-up interview, a participant reported that she had missed her scheduled injection, her injections were discontinued and she was instructed to return any remaining study product (if in the self-injection group) and referred for family planning counselling.

About 12 months after the enrolment visit or when participants discontinued DMPA-SC, data collectors contacted participants for their final interview to record any medical problems experienced since their last visit and asked participants to do a urine pregnancy test. If a participant was pregnant, the study staff recorded the pregnancy event, and the participant was referred to a study clinic for diagnosis and care. Participants were compensated approximately US\$2.50 for each interview.

### Outcomes

The primary outcome for this study was discontinuation of DMPA-SC. Women were deemed to have discontinued if they reported not receiving an injection within the allowable window, as per the Sayana Press label (12–14 weeks after the last injection). Given that re-injection provides 3 months of protection, a participant who did not have a DMPA-SC injection within the re-injection window or was lost to follow-up was considered to have discontinued 3 months after the previous injection. Those who had not discontinued by 12 months were censored at 12 months, when DMPA-SC was no longer offered. The secondary outcomes were pregnancy, adverse events, and reported side-effects. During analysis, we compared the estimated date of conception to the participant's enrolment date to determine whether a pregnancy was due to method failure or screening failure. Adverse events could be reported at any time during the study. Additionally, we began each follow-up visit (3, 6, 9, and 12 months) by asking women the open-ended question, "Have you had any new or worsening health problems since your last visit?" If they answered yes to this question, we collected information about each adverse event. After asking about adverse events at the 3, 6, and 9 month follow-up visits, we asked women about specific side-effects they might have experienced using DMPA-SC over the previous 3 months. Providers' experiences and recommendations were also prespecified as a secondary outcome and will be reported elsewhere.<sup>27</sup>

### Statistical analysis

We planned to enrol 734 eligible women attending family planning clinics or seeking family planning services from CHWs: 734 participants (with 367 women in each group) would provide approximately 80% power to detect

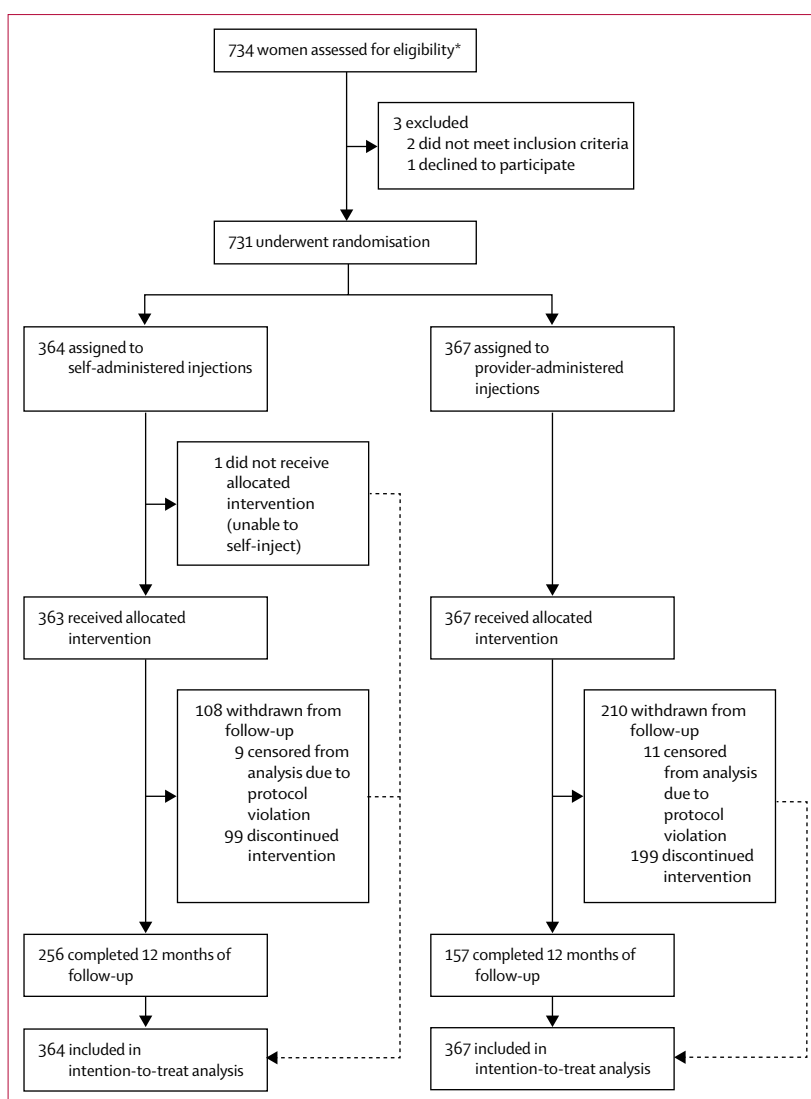
a 50% increased risk of discontinuation between groups with a two-sided log-rank test, assuming 25% early discontinuation in the provider group based on a review of the literature.

For the primary intention-to-treat analysis, a participant was deemed to be continuing DMPA-SC if she reported receiving an injection within the allowable window. Missing this window resulted in discontinuation, whereas failure to provide the dates of the injection resulted in censoring. Study staff were instructed to discontinue women if they reported having an injection outside the injection window. However, during the analysis, we checked the timing of each re-injection and identified additional women whose reported injection dates fell outside the allowable window, despite being continued by study staff. We also reviewed cases in which study staff contacted women before the re-injection window had elapsed and censored any cases where women had not received a re-injection by that time. Women who missed a follow-up interview could provide re-injection data for missed interviews at a later follow-up visit.

We did a sensitivity analysis, which was specified before unblinding occurred, to explore an alternative, more lenient definition of continuation in which women were considered to be continuing the intervention if they reported receiving an injection irrespective of whether the date of re-injection fell outside the allowable window. Any women who were discontinued by study staff because they missed the injection window were censored for this alternative definition. The lenient definition of continuation more closely reflects normal service delivery contexts.

Estimates of cumulative continuation probabilities were tabulated with Kaplan-Meier methods and Greenwood's formula for standard errors (with 95% CIs at 3, 6, and 9 months) and plotted for each treatment group. Given that an injection provides 3 months of contraceptive protection, the 9 month continuation probabilities extend throughout 12 months of use. The primary comparison between the groups was done with a log-rank test stratified by site. We also calculated crude incidence of discontinuation (ratio of the number of discontinuations to the amount of person-time based on the number of 3 month injection cycles contributed) and 95% CIs by treatment group and provided an estimate of the incidence rate ratio (IRR) and 95% CIs to compare the groups. We categorised the reasons for discontinuation and compared their distributions between groups using Fisher's exact test.

The overall proportions of detected pregnancies in each group were compared with Fisher's exact test. We also compared frequency and tolerability of side-effects reported by the two groups during the 3, 6, and 9 month re-injection window interviews. Frequencies and percentages of women experiencing different levels of pain, irritation, and soreness during the most recent



**Figure 1: Participant flow diagram**

\*N=738 participants were screened for eligibility, but all data from four participants were excluded due to issues with informed consent.

injection were likewise tabulated by study group for each re-injection interview, with differences in proportions assessed with Fisher's exact tests.

The analysis of safety data was based on the as-treated population, which consisted only of participants who successfully received a DMPA-SC injection after randomisation. Adverse events were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA version 19.1) and summarised descriptively by group. The proportion of participants experiencing adverse events within each system organ class was compared between groups with Fisher's exact tests.

All statistical tests were done at a significance level of 0.05 for two-sided comparisons with SAS version 9.4. This trial is registered with ClinicalTrials.gov, number NCT02293694.

	Provider-administered (n=367)	Self-administered (n=364)
<b>Provider type at enrolment</b>		
Clinic-based	108 (29%)	97 (27%)
Community health worker	259 (71%)	267 (73%)
<b>Age (years)</b>		
18–24	142 (39%)	122 (34%)
25–29	119 (32%)	119 (33%)
30–35	85 (23%)	99 (27%)
>35	21 (6%)	24 (7%)
Mean (SD)	26.5 (5.20)	27.2 (5.21)
<b>Education</b>		
No school or less than primary school	275 (75%)	270 (74%)
Completed primary school or higher	92 (25%)	93 (26%)
No response	0	1 (<1%)
<b>Religion</b>		
Christian	149 (41%)	161 (44%)
Muslim	217 (59%)	201 (55%)
None	0	1 (<1%)
No response	1 (<1%)	1 (<1%)
<b>Married or has regular sexual partner</b>		
Not married and no regular sexual partner	11 (3%)	14 (4%)
Married or regular sexual partner	356 (97%)	349 (96%)
No response	0	1 (<1%)
<b>Husband or partner knows respondent is receiving family planning today (among those with partner)*</b>		
No	70/343 (20%)	67/337 (20%)
Yes	263/343 (77%)	259/337 (77%)
Don't know	7/343 (2%)	6/337 (2%)
No response	3/343 (1%)	5/337 (1%)

(Table 1 continues in next column)

### Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

This study lasted from Sept 17, 2015, to Feb 21, 2017. Staff screened 738 women for eligibility (figure 1), of whom three were excluded. At the end of the study, documentation of informed consent for four further participants was determined to be inadequate (three in the self-administered group and one in the provider-administered group). Thus, data from these four cases were excluded from all analyses. 731 women were enrolled into the study, with 364 in the self-administered group and 367 in the provider-administered group. One woman in the self-injection group was not able to self-inject at enrolment after being trained by the provider and was discontinued at month 0. The other 730 women received DMPA-SC at enrolment.

	Provider-administered (n=367)	Self-administered (n=364)
(Continued from previous column)		
<b>Ever given birth</b>		
No	3 (1%)	2 (1%)
Yes	364 (99%)	361 (99%)
No response	0	1 (<1%)
<b>Number of living children (among those who gave birth)</b>		
<3 living children	171/364 (47%)	150/361 (42%)
≥3 living children	193/364 (53%)	211/361 (58%)
Mean (SD)	3 (1.57)	3.2 (1.69)
<b>Would like to have a child/another child</b>		
No	90 (25%)	92 (25%)
Yes	264 (72%)	265 (73%)
Don't know	11 (3%)	6 (2%)
No response	2 (1%)	1 (<1%)
<b>Ever used contraception</b>		
No	27 (7%)	20 (5%)
Yes	338 (92%)	341 (94%)
No response	2 (1%)	3 (1%)
<b>Ever used injectables (among those who ever used contraception)</b>		
No	8/338 (2%)	13/341 (4%)
Yes	329/338 (97%)	328/341 (96%)
No response	1/338 (<1%)	0

Data are n (%) or n/N (%) unless specified otherwise. \*This question purposefully excludes 25 women who were married but were not living with their husband and had no other regular sexual partner (13 women in the provider-administered group and 12 in the self-administered group).

**Table 1: Baseline sociodemographic characteristics by group**

Women in both groups were similar in terms of demographic characteristics (table 1). 526 (72%) of 731 women were enrolled by a CHW and the mean age was 26.9 years (SD 5.21). 545 (75%) had no school or less than primary school education. 418 (57%) were of Muslim faith. Almost all participants were married or had a regular sexual partner (705 [96%] women), but 137 (20%) of 680 respondents (excluding 25 women who were married but not living with the husband and had no other sexual partner) said their husband or partner did not know about their appointment to receive a family planning method. Almost all (725 [99%]) women had previously given birth and had an average of 3.0 (SD 1.64) living children. 679 (93%) women had ever used contraception, with most (657 [97%] of 679 women) having previously used injectables. 182 (25%) women did not want any more children.

Cumulative probabilities of continuation are shown in figure 2 and reported with 95% CIs for each quarter in table 2. 99 women in the self-administered group and 199 in the provider-administered group had discontinued the intervention by the end of the study. The continuation rate through 12 months of contraceptive use was significantly higher for women in the self-injection

group (73%) than for those in the provider-administered group (45%; log-rank  $p < 0.0001$ ). The incidence of discontinuation in the self-administered group was 8.2 per 100 injection cycles (6.7–10.0) compared with 20.6 per 100 injection cycles (17.9–23.7) in the provider-administered group (IRR 0.40, 0.31–0.51). Results were consistent across clinics (data not shown).

Discontinuation in the provider-administered group tended to occur earlier in the follow-up period (ie, within 3 months), whereas discontinuation in the self-administered group occurred more gradually. However, both groups struggled with missing re-injection windows throughout the entire study period (table 3). At least 83 (47%) of 178 women who discontinued because of missing the window said they still wanted to continue using DMPA, whereas 23 (13%) said they wanted to stop. Whether or not they desired to continue using DMPA was unknown for 72 (40%) women. This large proportion of unknown responses resulted from the application of our primary definition of continuation whereby, during the analysis phase, women were discontinued if they missed their re-injection window even if study staff allowed them to continue during the trial. This definition meant that, for those discontinuations, we did not ask the women about their desire to continue using DMPA, although we suspect that they would have preferred to continue using DMPA since they received another injection, albeit outside the window. Other reasons for discontinuing (in order of decreasing frequency) included loss to follow-up, the woman's request (mostly related to side-effects of DMPA-SC), and less commonly, provider request for medical reasons. Despite the higher rate of discontinuation in the provider group, the distribution of reasons for discontinuation did not differ significantly between the two groups ( $p = 0.56$ ).

Data from pregnancy tests were incomplete because of refusals, loss to follow-up, and data collectors neglecting to administer a pregnancy test as planned (pregnancy status was unknown for 42 (12%) of 364 women in the self-administered group and 77 (21%) of 367 women in the provider-administered groups). Among 612 women who were tested, eight pregnancies were identified, one with a conception date before enrolment and seven during follow-up. Of the seven pregnancies that occurred during the follow-up period three were in the self-injection group and four were in the provider-administered group. This difference was not significant ( $p = 0.71$ ).

The proportions of women who continued the intervention who had side-effects decreased with time in both groups (table 4). Differences in the proportions of women reporting side-effects were not significant between the self-administered and provider-administered group ( $p = 0.066$  at 3 months,  $p = 0.14$  at 6 months; and  $p = 0.17$  at 9 months; table 4). Among the women who reported side-effects, most reported little to no effect on daily life (71 [78%] of 91 women in the self-administered group vs 92 [84%] of 110 women in the provider-

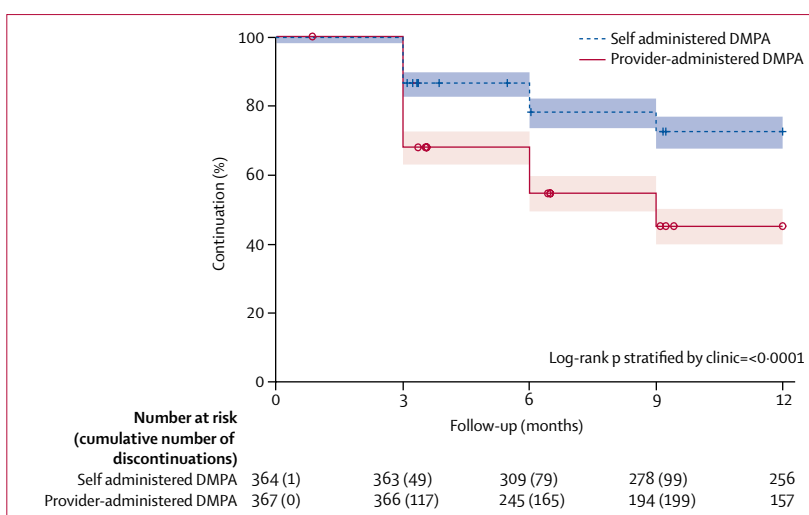


Figure 2: Cumulative probability of continuation of DMPA

DMPA=depot medroxyprogesterone acetate. Discontinuation events were not measured at 12 months.

	Provider-administered		Self-administered	
	Number at Risk	Probability (95% CI)	Number at Risk	Probability (95% CI)
<b>Primary analysis</b>				
First quarter	367	1.00	364	1.00
Second quarter	366	0.68 (0.63–0.73)	363	0.87 (0.83–0.90)
Third quarter	245	0.55 (0.49–0.60)	309	0.78 (0.74–0.82)
Fourth quarter	194	0.45 (0.40–0.50)	278	0.73 (0.68–0.77)
<b>Sensitivity analysis (lenient)</b>				
First quarter	367	1.00	364	1.00
Second quarter	366	0.74 (0.69–0.78)	363	0.93 (0.90–0.96)
Third quarter	267	0.62 (0.57–0.67)	336	0.88 (0.84–0.91)
Fourth quarter	220	0.53 (0.48–0.58)	314	0.84 (0.80–0.88)

Table 2: Cumulative probability of continuation by study group

	Provider-administered (n=199)	Self-administered (n=99)	Overall (n=298)
Missed DMPA-SC re-injection window	122 (61%)	56 (57%)	178 (60%)
Participant request (unable or unwilling to continue using DMPA-SC)	30 (15%)	13 (13%)	43 (14%)
Provider request (medical reason)	3 (2%)	3 (3%)	6 (2%)
Lost to follow-up, missed visit, or moved	44 (22%)	27 (27%)	71 (24%)

Data are n (%). DMPA-SC=subcutaneous depot medroxyprogesterone acetate.

Table 3: Reasons for discontinuation

administered group at 3 months; 49 [89%] of 55 vs 49 [88%] of 56 at 6 months; and 40 [98%] of 41 vs 33 [87%] of 38 at 9 months). Across the full range of responses, there were no significant differences between groups in the effect of side-effects on daily life ( $p = 0.40$  at 3 months,  $p = 0.65$  at 6 months,  $p = 0.20$  at 9 months).

At 3 months, among women reporting side-effects (n=110 in the provider-administered group and n=91 in the self-administered group), the most commonly

	3 month follow-up			6 month follow-up			9 month follow-up		
	Provider-administered	Self-administered	Overall	Provider-administered	Self-administered	Overall	Provider-administered	Self-administered	Overall
<b>Any side-effects?</b>									
No	232 (68%)	264 (74%)	496 (71%)	198 (78%)	269 (83%)	467 (81%)	175 (82%)	265 (87%)	440 (85%)
Yes	110 (32%)	91 (26%)	201 (29%)	56 (22%)	55 (17%)	111 (19%)	38 (18%)	41 (13%)	79 (15%)
Total	342	355	697	254	324	578	213	306	519
<b>Type of side-effects (among women reporting side-effects)</b>									
Abdominal pain, nausea, or vomiting	54 (49%)	40 (44%)	94 (47%)	25 (45%)	27 (49%)	52 (47%)	12 (32%)	19 (46%)	31 (39%)
Irregular or heavy bleeding	48 (44%)	33 (36%)	81 (40%)	14 (25%)	9 (16%)	23 (21%)	12 (32%)	7 (17%)	19 (24%)
Headaches	48 (44%)	29 (32%)	77 (38%)	19 (34%)	17 (31%)	36 (32%)	14 (37%)	13 (32%)	27 (34%)
Injection-site pain or irritation	27 (25%)	38 (42%)	65 (32%)	13 (23%)	19 (35%)	32 (29%)	5 (13%)	16 (39%)	21 (27%)
Amenorrhoea	32 (29%)	32 (35%)	64 (32%)	22 (39%)	28 (51%)	50 (45%)	14 (37%)	24 (59%)	38 (48%)
Backaches	33 (30%)	27 (30%)	60 (30%)	21 (38%)	20 (36%)	41 (37%)	17 (45%)	16 (39%)	33 (42%)
Other aches or pains	20 (18%)	26 (29%)	46 (23%)	16 (29%)	13 (24%)	29 (26%)	8 (21%)	8 (20%)	16 (20%)
Decreased libido	15 (14%)	15 (16%)	30 (15%)	9 (16%)	9 (16%)	18 (16%)	11 (29%)	5 (12%)	16 (20%)
Weight changes	9 (8%)	5 (5%)	14 (7%)	8 (14%)	7 (13%)	15 (14%)	11 (29%)	1 (2%)	12 (15%)
Total	110	91	201	56	55	111	38	41	79
<b>How much did these side-effects interfere with daily activities?</b>									
Not at all	71 (65%)	57 (63%)	128 (64%)	42 (75%)	46 (84%)	88 (79%)	30 (79%)	38 (93%)	68 (86%)
Very little	13 (12%)	5 (5%)	18 (9%)	5 (9%)	2 (4%)	7 (6%)	2 (5%)	0	2 (3%)
Little	8 (7%)	9 (10%)	17 (8%)	2 (4%)	1 (2%)	3 (3%)	1 (3%)	2 (5%)	3 (4%)
Moderate	7 (6%)	5 (5%)	12 (6%)	4 (7%)	2 (4%)	6 (5%)	2 (5%)	0	2 (3%)
Very much	11 (10%)	14 (15%)	25 (12%)	3 (5%)	4 (7%)	7 (6%)	3 (8%)	1 (2%)	4 (5%)
Don't know	0	1 (1%)	1 (<1%)	0	0	0	0	0	0
Total	110	91	201	56	55	111	38	41	79

Data are n (%) or n. Side-effects were assessed in the as-treated population. For the type of side-effects, participants could choose more than one response.

**Table 4: Side-effects in previous 3 months**

reported effects in both groups were abdominal pain, nausea, or vomiting, followed by irregular or heavy bleeding, headaches, injection-site pain or irritation, amenorrhoea, backaches, other aches or pains, decreased libido, and weight changes (table 4). Of these side-effects, only injection-site pain or irritation significantly differed between women in the self-administered and provider-administered groups, with more occurring in the self-administered group ( $p=0.010$ ). At 6 and 9 months, abdominal pain, nausea, or vomiting, amenorrhoea, backaches, and headaches remained the most commonly reported side-effects. At 9 months, we again observed that the proportion of women in the self-administration group who reported injection site pain or irritation was greater than that in the provider-administered ( $p=0.011$ ). In general, discomfort at the injection site was more prevalent at the 3 month injection than at later times (data not shown). Except for the proportion of women reporting some pain after the injection at 3 months, the proportions of women reporting pain at later times and soreness and irritation at any timepoints were less than 12% in both groups when we specifically asked about the injection site.

Overall, 50 adverse events were reported by 22 women in the self-administration group, and 54 adverse events

were reported by 24 women in the provider-administration group. Among these adverse events, 20 that were related or possibly related to the intervention were reported by ten women in the self-administration group and 28 such events were reported by 17 women in the provider-administered group ( $p=0.24$  for the difference in proportions of women reporting events). Among the related or possibly related adverse events, only one severe event was reported: a case of back pain in the provider-administered group. Only one unrelated severe event was reported: the serious adverse event classified as menorrhagia described subsequently. 17 at least possibly related adverse events (seven in self-administered group and ten in provider-administered group) were considered moderate with most of these events (six self-administered and seven provider-administered) classified as reproductive system and breast disorders. 30 at least possibly related adverse events (13 self-administered and 17 provider-administered) were considered mild, with 11 (five self-administered and six provider-administered) classified as reproductive system and breast disorders, seven classified as general disorders and administration site conditions (three self-administered, four provider-administered), and the remaining types having two or fewer events per group. All adverse events reported were

resolved without sequelae except one unrelated event still present at the end of follow-up (a snake bite). The types of adverse events did not differ significantly between the groups. During the trial, five serious adverse events were reported by four women. Two events related to DMPA-SC (menorrhagia and anaemia requiring hospitalisation) were reported by the same woman in the provider-administered group and resolved without sequelae. The other serious adverse events were unrelated to DMPA-SC and consisted of a snakebite in the self-administered group, menorrhagia (possibly due to a miscarriage) in the provider-administered group, and a death due to an unrelated illness in the self-administered group, possibly liver failure.

In a sensitivity analysis of the primary outcome that used a more lenient definition of continuation, the 12 month continuation rate was 84% in the self-injection group and 53% in the provider-administered group (table 2;  $p < 0.0001$ ). The incidence of discontinuation in the self-administered group was 4.3 per 100 injection cycles (95% CI 3.3–5.6) compared with 16.2 per 100 injection cycles (13.9–18.9) in the provider-administered group (IRR 0.27, 0.19–0.36).

## Discussion

In this study, we found a clinically significant improvement in the rate of DMPA-SC continuation among women assigned to self-administered DMPA-SC compared with those who received DMPA-SC from a provider, including CHWs. Moreover, the difference remained significant in a sensitivity analysis using a more lenient definition of continuation. Notably, we found this increase in the context of an established community-based injectable contraception distribution programme, which is currently a standard of practice for the delivery of contraception in public health systems in LMIC settings.

Although self-administration greatly increased continuation rates in our trial, more than a quarter of women in this group still discontinued early. Discontinuation rates in the provider-administered group were also higher than those reported in previous studies.<sup>1,5–8</sup> Comparing discontinuation rates across different studies is challenging as the contexts, study designs, definitions of discontinuation events, and analysis methods often differ. No consensus exists about how to define certain outcomes when modelling contraceptive discontinuation; for example, some researchers censor loss to follow-up in their analyses, whereas others, including ourselves, consider it discontinuation. The apparent high discontinuation rates in our study's provider-administered group might result from our strict rules for defining continuation with respect to missed re-injection windows. For example, in a prospective longitudinal study that used patient-held records, researchers found an 85% discontinuation rate among users of injectable contraception in rural northern Malawi.<sup>9</sup> However, the

point estimate of the prevalence of modern contraceptive use that these researchers calculated using their longitudinal data was lower than modern contraceptive use estimates reported from other cross-sectional surveys for this population. This suggests that conventional estimates of contraceptive use might be overestimates if, when responding to survey questions about past use, women consider themselves to be contraceptive users even if they were late for re-injection.

Given that some women might mistime their injections, we should consider the consequences of DMPA-SC self-administration—ie, the risk of pregnancy. We followed the product label's re-injection window (12–14 weeks) because DMPA-SC was not available in Malawi at the time the protocol was initiated, but it is well known that injectable contraceptive protection does not drop so sharply and that safety concerns are minimal when re-injections are somewhat mistimed (WHO guidelines state that repeat DMPA injections can be given up to 4 weeks late without requiring additional contraceptive protection).<sup>25</sup> However, as women get accustomed to self-injection, they might become better at timing their injections. Also, interventions and tools to help women improve adherence to re-injection timing, possibly through use of mobile technology, might be warranted.

Women in both groups had side-effects from DMPA-SC during the trial. Although most reported little to no effect of these side-effects on their daily lives, there is clearly a need to develop new, effective methods with fewer side-effects. Furthermore, a quarter of enrolled women were seeking injectable contraception (an enrolment criterion) but did not want any more children; these women, in particular, should be offered longer-acting or permanent methods, which might have fewer side-effects.

We deemed women who were lost to follow-up to be true discontinuations. However, these women might have received or administered their re-injection on time but missed the study follow-up interviews, which were done by data collectors with all women within 2 weeks after the 14 week re-injection window. We could speculate that a study loss to follow-up in this context is more likely to be a continuation in the self-injection group compared with the provider group because self-injectors had DMPA-SC with them and DMPA-SC was not available elsewhere in Malawi at the time. There were cases in which women reported being away and missing study interviews but having continued their re-injection schedule. We believe this factor makes our estimates of continuation rates and comparative analyses conservative.

One limitation of our trial, which was possibly exacerbated by the open-label design, might be that women over-reported continuation—ie, it is possible that data on discontinuation might have been affected by staff and participant knowledge of their study group. However, the scarcity of pregnancies at intervention discontinuation visits is consistent with continued use of DMPA-SC in the

periods that women reported adhering to DMPA-SC. In a randomised study of Depo-subQ Provera 104 in New York,<sup>17</sup> all women who reported continuation had MPA concentrations in the contraceptive range, although the investigators did not find a difference in continuation rates between self-administration and clinic-administration groups. This absence of a difference was possibly because women had to return to the clinic to provide blood specimens, thus hindering one of the anticipated benefits of self-administration.<sup>17</sup> The requirement for pregnancy tests might have encouraged women to report their continuation status more accurately during our trial. Another possibility is that women in the provider-administered group might be less likely to over-report continuation than those in the self-injection group if they thought that we could follow up with the providers to confirm re-injection—something that we could not do for women in the self-injection group. We attempted to minimise reporting bias by having data collectors (not providers) do the follow-up interviews with all participants and by training these data collectors to develop rapport with participants. Furthermore, during the informed consent process, we explicitly told all potential participants that we would only be collecting continuation information from the participant and that we would not ask the provider or anyone else to tell us whether the participant had had the injection.

It should be noted that the reasons for discontinuation might underestimate the role of side-effects during the trial because, after women discontinued the intervention, they were no longer counted in the estimates of side-effect occurrence as the trial moved forward. If the reasons for discontinuation had been related to the risk of side-effects, these risks would be underestimated at later timepoints and our comparisons of those risks could be biased between groups. Another challenge we faced was missing data, especially for the pregnancy outcome. Given this limitation, our pregnancy data should not be used to estimate the DMPA-SC failure rate.

In addition to the randomised design, other strengths of our trial include the use of time-to-event methods to handle incomplete follow-up data in the estimation of continuation rates and use of sensitivity analyses to check the robustness of the findings, as well as the implementation of the trial under real-world conditions in a rural district in Malawi. We strengthened the external validity of our findings by having public-sector health-care providers and CHWs train women to self-inject within their normal service delivery contexts in public-sector family planning clinics and in rural communities in Malawi. We also did a blind review of the data and made all decisions regarding discontinuation and censoring without knowledge of the study groups to help to avert potential biases during the analysis phase.

Injectables are the most popular contraception method in sub-Saharan Africa, but they also have high discontinuation rates within the first year of use—rates

that are not reflected in static measures such as prevalence of modern contraceptive use. Injectables work only if used correctly over time, so understanding of the factors that affect the dynamics of contraceptive use is important to help countries meet their development goals.

This is, to our knowledge, the first study to provide evidence of the effect of the self-administration of DMPA-SC on contraceptive continuation and the safety and feasibility of community-based provision of injectables for self-injection in LMIC settings. Given the large effect we found, and building on previous studies showing safety and feasibility, policy makers and donors should make self-administration of DMPA-SC widely available as another contraceptive option for women. Future research is needed to identify the steps to implement this practice efficiently at scale and to investigate whether self-administration of other medications could increase adherence and improve the health of people living in LMICs.

#### Contributors

HMB and MC conceived and designed the study. BN, MB, LV, and SW collected the data. RF, MC, LDS, and HMB analysed the data. HMB and MC wrote the first draft of the article. HMB, MC, MB, RF, SW, LV, LDS, and BN made substantial intellectual contributions to the Article.

#### Declaration of interests

We declare no competing interests.

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