IRBNET# 1035709: A randomized controlled trial of safety and effectiveness of Depo Provera intramuscular and subcutaneous administration comparing lay Lady Health Workers with clinically-trained Lady Health Visitors in Pakistan

STATISTICAL ANALYSIS PLAN

This statistical analysis plan gives a detailed explanation of the data analysis summary included in the study protocol.

I. Study Objectives

The goal of this evaluation is to assess whether the community health worker cadre, Lady Health Workers (LHWs) in Pakistan can screen and initiate women on intramuscular (IM) and subcutaneous Depo Provera injections as safely and effectively as their clinically-trained counterparts, Lady Health Visitors (LHVs). Although LHWs are already allowed to provide follow-up doses in the community, this RCT will focus on the comparison of safety and effectiveness of screening, counseling and administration of DMPA IM and the subcutaneous injection, Sayana Press® (SP).

The study's primary outcomes are:

- Proportion of Lady Health Workers and Lady Health Visitors that appropriately screen women for DMPA use;
- Proportion of Lady Health Worker and Lady Health Visitor clients that report discussion with their respective providers on side effects, danger signs, advantages and disadvantages of DMPA use;
- Proportion of Lady Health Workers and Lady Health Visitors that demonstrate appropriate injection technique
- Proportion of Lady Health Workers and Lady Health Visitors that report needle stick injuries;
- Proportion of Lady Health Workers that properly maintains a client (re)injection log.

A secondary objective is to assess whether the clients of LHWs and LHVs are equally satisfied with their respective providers and the family planning services they provide.

The study's secondary outcomes are:

- Satisfaction with the method;
- Satisfaction with the services received from the provider;
- Reports of client ability to speak freely and ask questions of provider;
- Friendly and respectful behavior toward client.

II. Study Design

This study is a randomized controlled trial conducted in urban and rural health facilities in Sindh Province, Pakistan, using quantitative methods. The study is limited to participating LHWs, LHVs and to their clients who voluntarily and independently accept DMPA as their contraceptive method before study recruitment is initiated. Clients will be randomized to receive treatment from either an LHW or an LHV and will also be randomized to receive DMPA IM or SP to prevent selection biases between these

groups. However, comparisons between these injection techniques will only be considered exploratory, focusing instead on acceptability of and satisfaction with the method as reported by clients as well as provider knowledge and the latter's comparisons of SP and DMPA IM.

III. Target Population & Eligibility

The target population for this study is Lady Health Workers and Lady Health Visitors trained to initiate intramuscular and subcutaneous Depo Provera use, as well as DMPA clients of trained Lady Health Workers and Lady Health Visitors.

Eligibility criteria for the study populations are described in table 1. All participants must be at least 18 years of age and consent to being observed and interviewed by study staff.

Table 1: Eligibility criteria

Lady Health Worker Criteria (n=30)	Lady Health Visitor Criteria (n=10)	DMPA acceptors (n=442)
• Already trained to provide follow-up DMPA IM injections in their community; • Currently providing services in their community • Willingness and ability to participate in the trial	• Assigned to health facilities that correspond to the catchment areas of the LHWs • Willingness and ability to participate in the trial	• Women who select DMPA as their contraceptive method for the first time or after more than a six-month hiatus • Age 18 to 49 and able to legally consent to participate • Consent to provision of DMPA services from an LHV or a trained LHW. • Willingness and ability to participate in the trial

IV. Sampling Design

We require a minimum of 342 DMPA clients randomized to receive care from either the LHV or an LHW (1:1 allocation) for 90% power and 5% significance level to test the non-inferiority hypothesis that LHWs can screen potential DMPA clients for method initiation just as adequately as LHVs with a non-inferiority margin of 7.5%, assuming that both LHVs and LHWs perform at a 95% success rate. In Pakistan, there is usually at least one LHV assigned to a health facility and many more LHWs affiliated with and under the supervision of resident LHVs. Therefore, we will use a 3 to 1 ratio of LHWs to LHVs at each health facility in the trial.

For logistical reasons, we plan to obtain the full target sample size of 342 DMPA initiators from the 5 urban health facilities in Karachi to ensure that adequate analyses can be done with this group. We will recruit additional participants (~100) from 5 rural facilities in Thatta to help assess possible differences in performance between LHVs and LHWs in rural and urban areas, but the expectation is that there will be no difference. LHWs undergo standardized training in Pakistan. If we can be comfortable that providers in rural and urban areas perform in similar manner, the overall sample size for the analysis may be pooled for an increase in power. The decision whether to pool the data or not will be made during the blind review of the data as described below.

Given the relationship between LHWs and LHVs within clinics, we plan to account for the correlations of participant outcomes within providers and providers within clinics in the analysis. We expect that some of these correlations would lead to decreases in power and others to lead to increases in power for within clinic comparisons. Power calculations were not adjusted for these potential correlations as the net effect on power may be offset with each other.

V. General Analytic Considerations

A. Data Sources

A.1 Client exit interview

Client exit interviews measure the study's secondary outcomes of client satisfaction with the method and provider. The exit interview also provides additional information related to appropriate screening such as discussion of side effects, warning/danger signs, advantages and disadvantages of DMPA use with clients. The client exit interview includes questions on the following domains:

1. Sociodemographic characteristics
2. Experiences using contraceptive methods
3. Factors in her decision to use DMPA
4. Interaction with and information provided by LHW/LHV about DMPA
5. Satisfaction with her choice of DMPA as a contraceptive method (IM or SP)
6. Satisfaction with LHW/LHV

A.2 LHW/LHV interview

Questionnaire items in the LHW/LHV interview instrument include:

- Sociodemographic characteristics
- Knowledge of DMPA use and provision
- Comparisons between the properties/characteristics of SP and DMPA IM injections
- General experiences and satisfaction with providing DMPA services
- Reports of needlestick injuries
- Observations of LHW (re)-injection logs

A.3 Observation Checklists

Three checklists adapted from existing instruments will be used to capture information on LHW and LHV services from the point of view of the observer. These are the source of the study's primary outcome measures for appropriate screening and counseling as well as appropriate injection technique.

The first checklist will adapt the 15 screening items from FHI 360's "Checklist for Screening Clients Who Want to Initiate DMPA" (Figure 1). In addition, items that capture the presence or absence of counseling on DMPA use will be incorporated as a second part of this checklist instrument, such as:

- Discussion of advantages and disadvantages of DMPA use
- Warning or danger signs of DMPA use
- Side effects and management of DMPA

The remaining two checklists separately assess LHW and LHV injection technique for DMPA IM and SP. The content of the checklists was adapted from instruments developed for previous task sharing studies of injectable contraception and from PATH's Sayana Press® training materials.

B. Data Management

A trained RA will be posted at each study site to conduct observations of the screening and counseling interaction between the LHW/LHV and client, and to conduct a brief interview with the client before she leaves the health facility (i.e., the client exit interview). Nurses at each health facility will serve as the gold standard to which LHW and LHV screening will be compared. That is, screening outcomes are considered accurate and appropriate if they agree with the gold standard nurse's assessment immediately following the LHV's or LHW's screening of DMPA acceptors. About four to six months after trial initiation, all participating LHWs and LHVs will be asked for their permission (via informed consent) to be interviewed by an RA at their assigned study sites. All data will be recorded via pen and paper and later entered into an electronic database.

Data Cleaning

The Department of Community Health Sciences, Aga Khan University (AKU), Pakistan, the local research agency, will create database shells. FHI 360 will review database structures and documentation prior to data entry. AKU will use a system of double data entry and frequency checks to minimize data entry errors for all interview instruments. A study coordinator at AKU will oversee day-to-day management of the trial. Clean databases will be sent to FHI 360's data manager for verification according to the timeline for those deliverables. FHI 360's data manager will provide access to the blinded data to the analysis team for blind review of the data and unblinded data for final analyses when the data analysis team is ready (see details below).

No imputation of missing data will be performed. However, to decrease the number of cases when composite measures for observations of injection technique may be missing, where less than 15% of the items are missing among variables needed for deriving composite variables, we may decide to impute the mean of the non-missing items. Missing data will be noted in Table or Figure footnotes. Proportions and mean/median values will be calculated with missing data excluded from the denominator.

During all phases of data collection, entry, cleaning and verification, access to hard copy and electronic data will only be granted to research staff at AKU and FHI 360. Hard copies of interviews, observation checklists and other materials containing study data will be stored in a locked file cabinet at AKU. Informed consent forms will be stored in a separate locked drawer or cabinet. Electronic data will be

stored in password-protected files. Only staff working on the study will have access to the cabinets and electronic files. Upon completion of the trial, all stored materials will be destroyed at AKU. However, no records will be destroyed without permission from the FHI 360 project leader.

C. Definition of Variables

Key primary outcomes will be calculated as follows.

Screening for DMPA use

There are 15 screening questions on the job aid that providers use to determine if a client is or is not a good candidate for DMPA or needs further evaluation before initiating DMPA. The provider makes a global decision of eligibility or ineligibility based on the job aid items and whether or not she would subsequently initiate the client on DMPA. The observer notes the provider's decision whether to start the client on DMPA. This global decision (and not agreement on every screening item), is compared with the gold-standard nurse's assessment of client eligibility to generate the outcome variable for appropriate screening. Thus, the gold standard nurse's overall assessment of eligibility is made after the provider's as verification, and s/he is the final arbiter of eligibility. Thus, if the gold standard nurse determines that the client is eligible to use DMPA, the latter will receive the injectable regardless of the provider's assessment. To avoid bias, the gold standard nurse is blinded to the type of provider who assessed the client beforehand. Whether or not they are deemed eligible to use DMPA as their chosen method, all clients will receive counseling appropriate to their circumstance.

Counseling for DMPA use

Appropriate counseling is a composite binary variable that will be calculated from observations of the discussion between the provider and client. If the provider spoke to the client about side effects, warning or danger signs, advantages, and disadvantages of DMPA, then the conditions are met for appropriate counseling (all conditions must be met for considering the counseling appropriate). If any is missing, the counseling is deemed inappropriate. These variables will also be presented separately in the descriptive analyses by type of provider (and urban/rural setting if the data are not pooled).

Appropriate injection technique

Appropriate injection technique is assessed using checklists for DMPA-IM and DMPA-SC previously developed and validated for this purpose. To meet the criteria for appropriate administration of the injection, the provider must complete 80% of the items on the checklist (i.e., at least 18 out of 22 for SP and at least 14 out of 17 for IM).

D. Blind Data Review

Even though the study is open labeled, the randomization was prepared by an independent randomization manager and data management is separated from the analysis team. Thus, the analysis team will initially be blinded to the group assignments. Unblinding of the analysis team will follow a three-step process: First, key decisions regarding the primary and secondary outcomes listed above will

be made blinded to study group assignment. These outcome variables will be constructed, checked for missing data, distributional anomalies or other problems, finalized and verified. Decisions about re-categorization, transformation, missing data, and final variable definition will be completed after initial descriptive analysis and prior to further analysis for the specific objectives. Descriptive analysis of the outcomes will be done by facility and rural/urban designation. This check will also include a check of protocol violations, such as randomization errors (this review will be coordinated between the data manager and the randomization manager to maintain blinding of the analysis team) to decide if any data should be excluded from the analysis. Primary analysis will be conducted based on the intent to treat (ITT) approach where all participants randomized will be analyzed in the study group to which they were randomized. During blind review, decisions will be made regarding any modification to the ITT principle for primary analysis and whether a per protocol analysis will be conducted as secondary or sensitivity analysis. Second, once these key decisions have been made, the randomization manager will provide a participant list with blinded study arm assignments to the analysis team. A descriptive bivariate analysis will be done using blinded treatment assignments stratified by rural/urban designation to assess whether pooling the data will be appropriate. A decision whether further analysis will be pooled or not will be done at this time. Partial blinding will be maintained until statistical conclusions regarding the primary outcome (screening outcome) and primary analysis have been made and verified. This will be based on the pooled data or on the urban data only depending on the decision made in the prior step. The analysis team will be fully unblinded for all remaining analysis.

E. Test Size and Confidence Levels

The type I error for the non-inferiority test and other performance outcomes will be set at the two-sided α=0.05 significance level.

VI. Analysis of Fieldwork Data

An analysis of fieldwork data will be presented. This will include the number of DMPA acceptors approached, included, and randomized to LHW or LHV care.

VII. Analysis of participant characteristics

A descriptive summary of DMPA user, LHV, and LHW characteristics will be presented by urban and rural setting. DMPA client characteristics will include age, marital status, education, number of children, desire for more children, and birth spacing plans. Provider characteristics will include age, marital status, education, years of service, and years of DMPA experience.

VIII. Analysis of Study Objectives

We plan to compare a series of indicators of the performance of LHWs compared to LHVs in the provision of injectable contraception services. Our primary outcome, appropriate screening, is a binary variable comprised of the gold standard nurse's assessment of client eligibility for DMPA compared with the LHV's or LHW's assessment of client eligibility. If the LHV's or LHW's assessment agrees with the gold standard nurse's assessment, the screening is deemed appropriate.

Analytical model

We will test the non-inferiority hypothesis that LHWs can screen potential DMPA clients for method initiation just as adequately as LHVs with a non-inferiority margin of 7.5%. Given the relationship between LHWs and LHVs within clinics, we will employ a generalized mixed model using a logit link to account for the correlations of participant outcomes within providers and providers within clinics. Random effects will be included for clinics and providers within clinic. The non-inferiority test will be conducted at a 5% significance level. A similar approach will be used to compare appropriate counseling. No covariate adjustments are planned for the primary analyses. However, exploratory analyses will include the following covariates: LHV/LHW age, marital status, education level, years of service, years of experience with DMPA, and average DMPA-IM injections given per month prior to the trial. Years of service, years of experience with DMPA, and average injections per month will be analyzed either as categorical or continuous variables based on exploratory analyses; either odds ratios or beta coefficients will be reported.

As part of the blind analysis review, we will ascertain whether or not study outcomes differ for rural and urban sites. If they do not differ, as anticipated, we will combine the data from the five sites in Karachi with the five sites in Thatta. If differences are detected via descriptive analyses, we will present stratified results, but will be unable to test for significant differences as the trial was not powered for that purpose. In that event, the focus will be on the urban sites only, whose sample size (n=342) was powered to test the non-inferiority hypothesis.

Other comparisons between groups will be primarily descriptive to explore the differences in the provision of DMPA services and client satisfaction measures by each cadre of provider, by DMPA type and urban/rural setting if those data are not pooled. Similarly, objective and provider-perceived comparisons between injection techniques and injection characteristics, respectively, will be primarily descriptive and exploratory.

Analyses by Objective

Objective 1: *To assess whether LHWs can screen and initiate women on DMPA injections as safely and effectively as LHVs.*

To answer this objective, the analysis will report the odds ratio of appropriate screening and counseling by LHWs compared with LHVs using multi-level generalized mixed models as described above. The generalized linear mixed model accounts for the multilevel structure of the data (i.e., clinics and providers).

Objective 2: *Assess whether DMPA clients of Lady Health Workers and Lady Health Visitors are equally satisfied with their respective providers and the family planning services they provide.*

Descriptive analysis will be completed using indicators of client satisfaction and client-provider interactions for LHW and LHV clients.

Table 2: Summary of analysis approach and data sources for the primary and secondary outcomes

Outcome	Analysis	Stratified by	Source
Objective 1 Outcomes			
Screening for DMPA use	GLMM and descriptive	Cadre, urban/rural	Observation checklist of screening and gold-standard nurse's assessment
Counseling/Discussion of DMPA side effects, danger/warning signs, advantages and disadvantages	GLMM and descriptive	Cadre, urban/rural	Observation checklist of screening
*Appropriate injection technique**	Descriptive	Cadre, urban/rural	Observation checklist for DMPA-IM, q1-q17; Observation checklist for DMPA-SP, q1-q22
*Needle stick injuries**	Descriptive	Cadre, urban/rural	LHW/LHV questionnaire
*Use of client (re)injection log**	Descriptive	urban/rural	LHW/LHV questionnaire, qLHW6
Objective 2 Outcomes			
Client satisfaction with DMPA*	Descriptive	Cadre, DMPA type	Client exit interview, q313
Client satisfaction with service delivery*	Descriptive	Cadre, DMPA type	Client exit interview, q318
Client comfort asking provider questions*	Descriptive	Cadre, DMPA type	Client exit interview, q303
Friendly and respectful behavior by provider*	Descriptive	Cadre, DMPA type	Client exit interview, q301

* If the data are pooled, there will be no urban/rural stratification

Objective 1 Table Shells: Screening and counseling for DMPA

Table 1: Odds of appropriate screening and counseling for DMPA initiation by Lady Health Workers compared with Lady Health Visitors in Pakistan

	OR	90%CI	p-value
Appropriate screening			
Appropriate counseling			

Appropriate screening defined as agreement between the provider and independent assessment by a gold standard nurse
Appropriate counseling defined as having discussed side effects, warning/danger signs, advantages, and disadvantages of DMPA
95% CI and p-value reported for test of non-inferiority

Table 2: Exploratory analysis of factors affecting appropriate screening for DMPA initiation by Lady Health Workers compared with Lady Health Visitors in Pakistan

	N (%)	OR (or β)	95%CI	p-value
Age				
Age cat 1				
Age cat 2				
Etc.				
Marital status				
Marital status 1				
Marital status 2				
Etc.				
Education level				
Education level 1				
Education level 2				
Etc.				
Years of service				
Categorical or continuous TBD				
Years of DMPA experience				
Categorical or continuous TBD				
Avg. DMPA injections/month				
Categorical or continuous TBD				

Appropriate screening defined as agreement between the provider and independent assessment by a gold standard nurse

Table 3: Exploratory analysis of factors affecting appropriate counseling for DMPA initiation by Lady Health Workers compared with Lady Health Visitors in Pakistan

	N (%)	OR (or β)	95%CI	p-value
Age				
Age cat 1				
Age cat 2				
Etc.				
Marital status				
Marital status 1				
Marital status 2				
Etc.				
Education level				
Education level 1				
Education level 2				
Etc.				
Years of service				
Categorical or continuous TBD				
Years of DMPA experience				
Categorical or continuous TBD				
Avg. DMPA injections/month				
Categorical or continuous TBD				

Appropriate counseling defined as having discussed side effects, warning/danger signs, advantages, and disadvantages of DMPA

Table 4: Comparison of Lady Health Workers and Lady Health Visitors on DMPA service delivery indicators (n, %)

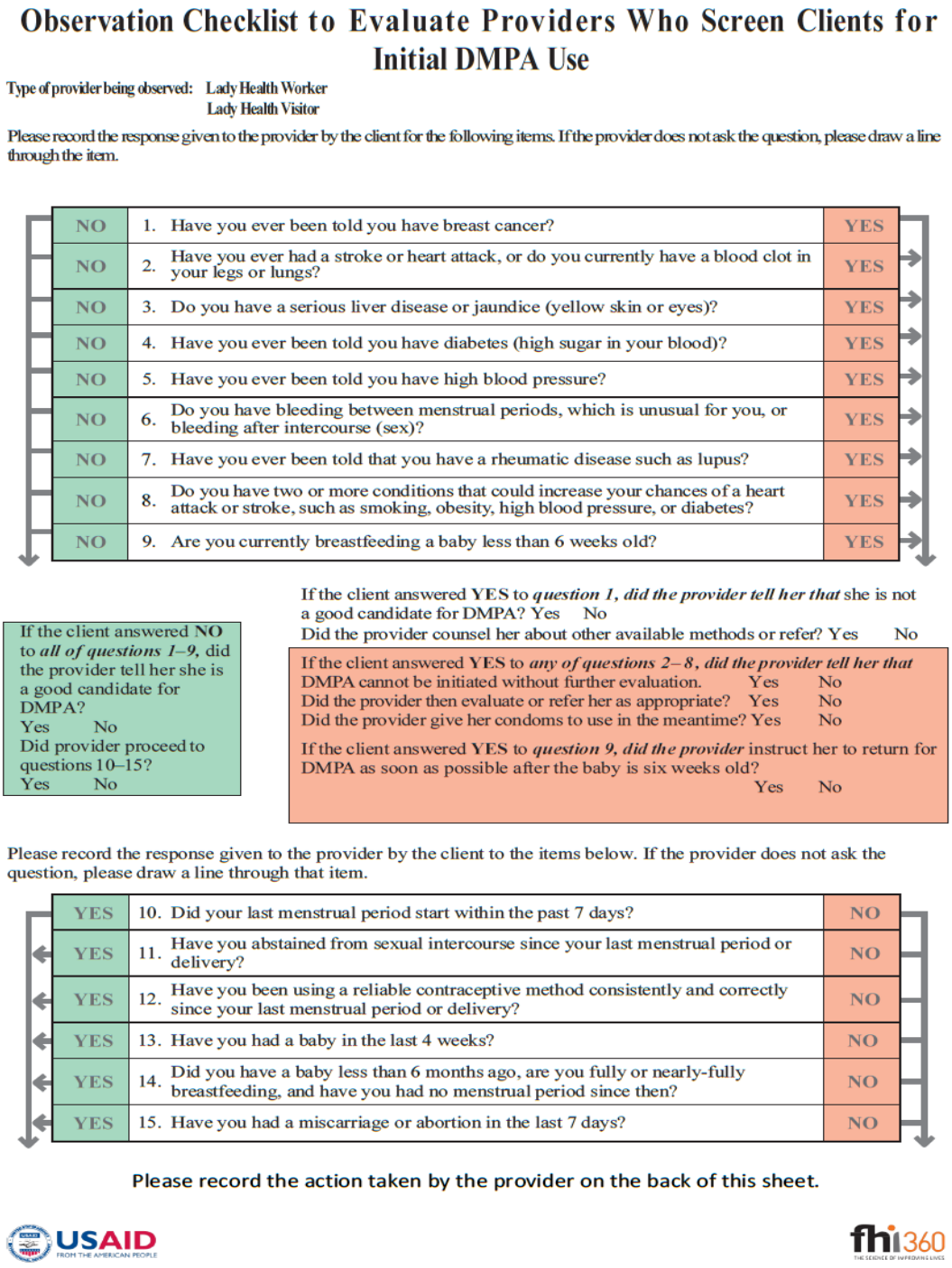
	Urban		Rural	
	LHW	LHV	LHW	LHV
Appropriate screening				
Appropriate counseling				
side effects				
danger signs				
advantages/disadvantages				
Appropriate injection technique				
Needle stick injuries				
Client log maintained		[redacted]		[redacted]

Objective 2: Client Satisfaction and Client-Provider Interaction

Table 5: Exemplar of Client Satisfaction and Client-Provider Interaction items (n, %)

	LHW		LHV	
	SP	IM	SP	IM
Satisfaction with method				
very satisfied				
somewhat satisfied				
not satisfied				
Satisfaction with services				
very satisfied				
somewhat satisfied				
not satisfied				
Satisfaction with provider				
very satisfied				
somewhat satisfied				
not satisfied				
Comfort asking questions				
yes				
no				

Figure 1: Graphic presentation of observation checklist for screening



Observation Checklist to Evaluate Providers Who Screen Clients for Initial DMPA Use

Type of provider being observed: Lady Health Worker
Lady Health Visitor

Please record the response given to the provider by the client for the following items. If the provider does not ask the question, please draw a line through the item.

NO	1. Have you ever been told you have breast cancer?	YES
NO	2. Have you ever had a stroke or heart attack, or do you currently have a blood clot in your legs or lungs?	YES
NO	3. Do you have a serious liver disease or jaundice (yellow skin or eyes)?	YES
NO	4. Have you ever been told you have diabetes (high sugar in your blood)?	YES
NO	5. Have you ever been told you have high blood pressure?	YES
NO	6. Do you have bleeding between menstrual periods, which is unusual for you, or bleeding after intercourse (sex)?	YES
NO	7. Have you ever been told that you have a rheumatic disease such as lupus?	YES
NO	8. Do you have two or more conditions that could increase your chances of a heart attack or stroke, such as smoking, obesity, high blood pressure, or diabetes?	YES
NO	9. Are you currently breastfeeding a baby less than 6 weeks old?	YES

If the client answered **NO** to ***all of questions 1–9,*** did the provider tell her she is a good candidate for DMPA?
Yes No
Did provider proceed to questions 10–15?
Yes No

If the client answered **YES** to ***question 1, did the provider tell her that*** she is not a good candidate for DMPA? Yes No
Did the provider counsel her about other available methods or refer? Yes No

If the client answered **YES** to ***any of questions 2–8, did the provider tell her that*** DMPA cannot be initiated without further evaluation. Yes No
Did the provider then evaluate or refer her as appropriate? Yes No
Did the provider give her condoms to use in the meantime? Yes No

If the client answered **YES** to ***question 9, did the provider*** instruct her to return for DMPA as soon as possible after the baby is six weeks old?
Yes No

Please record the response given to the provider by the client to the items below. If the provider does not ask the question, please draw a line through that item.

YES	10. Did your last menstrual period start within the past 7 days?	NO
YES	11. Have you abstained from sexual intercourse since your last menstrual period or delivery?	NO
YES	12. Have you been using a reliable contraceptive method consistently and correctly since your last menstrual period or delivery?	NO
YES	13. Have you had a baby in the last 4 weeks?	NO
YES	14. Did you have a baby less than 6 months ago, are you fully or nearly-fully breastfeeding, and have you had no menstrual period since then?	NO
YES	15. Have you had a miscarriage or abortion in the last 7 days?	NO

Please record the action taken by the provider on the back of this sheet.

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