“Health Technology Assessment of Long Acting Reversible Contraceptives in India”

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INDIAN COUNCIL OF MEDICAL RESEARCH

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"Health Technology Assessment of Long Acting Reversible Contraceptives in India"

Health Technology Assessment (HTA) Resource Hub
National Institute for Research in Reproductive Health
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LIST OF ABBREVIATIONS

ASM	Age Specific Model
CPR	Couple protection rate
Cu-IUD	Copper-Intra Uterine Device
DALY	Disability Adjusted Life Years
DCGI	Drug Controller General of India
DH	District Hospital
DHR	Department of Health Research
DMPA	Depo-Medroxyprogesterone Acetate
FP2020	Family Planning2020
FS	Female Sterilization
GOI	Government of India
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ICMR	Indian council of Medical Research
ICUR	Incremental cost-utility ratio
IUD	Intra Uterine Device
INR	Indian Rupee
IPD	In Patient Department
LARCs	Long Acting Reversible Contraceptives
LNG-IUS	Levonorgestrel Intra Uterine system
MTP	Medical Termination of Pregnancy
MeSh	Medical Subject Heading
mCPR	Modern method couple protection rate
NASM	Non-Age Specific Model
NU	Non-user (of any form of contraception)
NIRRH	National Institute for Research in Reproductive Health
NSV	Non-Scalpel Vasectomy
OCP	Oral Contraceptive Pills
OOP	Out of Pocket (expenditures)
OPD	Out Patient Department
OT	Operation Theatre

PICOS	Population - intervention - comparator - outcomes - study design
PHC	Primary Health Care
PPIUCD	Post-Partum Intra Uterine Contraceptive Device
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomized Controlled Trial
SARCs	Short Acting Reversible Contraceptives
SC	Sub Center
SC/ST	Scheduled Caste and Scheduled Tribes
SRS	Sample Registration System
TL	Tubal Ligation
USD	United States Dollar
WHO	World Health Organization

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EXECUTIVE SUMMARY

Currently India's National family planning program has two Long Acting Reversible Contraceptives (LARCs) method: Intra-uterine copper device and Depot Medroxy progesterone acetate (DMPA) three-monthly injections. The policy question of whether another LARC (Nexplanon, a sub-dermal contraceptive implant OR Levonorgestrel Intra uterine system) should be added to the 'contraceptive basket' is addressed in this report. Health technology assessment has been the chosen approach to explore this question.

A step-wise methodology has been followed to conduct this HTA. The integral elements of an HTA: Primary data methods, integrative methods (decision analytical modelling), economic and equity analysis were carried out over a period of 10 months.

On systematic review, Nexplanon was found to be highly clinically effective (Pearl index ranged from 0 to 0.4). The utility score of Nexplanon (used to calculate Quality adjusted life years - QALYs) is 0.703, the lowest among all LARC. This is due to the high rates of menstruation related side-effects, esp. amenorrhea and prolonged bleeding (>30%). LNG-IUS also had a pearl index of <1 and a utility score of 0.756. The product price of Nexplanon and LNG-IUS was INR 800 and INR 2424 respectively. A primary health system costing study was done at a sub-center, a primary health center, a Sub district hospital and a district hospital tertiary hospital in the state of Maharashtra. The unit cost of Nexplanon and LNG-IUS to be made available to one woman at tertiary, secondary and primary care levels up to PHC level is INR 5349 and INR 4902 respectively (societal perspective).

To assess cost-effectiveness of the LARC methods, a decision analytical Markov Model was constructed. The model was made to simulate the real-world scenario to a large extent. Transition probabilities, i.e. probabilities of transitioning from one health state in the model to another were considered and included parameters like discontinuation, failure and switching between contraceptives. These were derived by analyzing secondary data from National Family Health Survey-4 and DHS of Nepal (2016).

The decision model aided in arriving at the incremental cost-effectiveness ratio and the results of the model are as follows

- Incremental cost-utility ratio of adding Nexplanon to the current choice of contraceptives in the public health system is INR 17,716 (This is lower than the current GDP per capita of India, rendering Nexplanon as a cost-effective option)
- Incremental cost-utility ratio of adding LNG-IUS to the current choice of contraceptives in the public health system was INR 3,89,542 (This is more than the current GDP per capita of India, rendering LNG-IUS to not be cost-effective)
- Probabilistic sensitivity analysis for Nexplanon, shows that 80% of the 1000 simulations of the ICUR value lie below the threshold of one-time GDP per capita.
- About 10.48 lakh pregnancies and 1.17 lakh maternal deaths (among a cohort of 15-year old for 31 years i.e. until age of menopause) could be averted by adding Nexplanon to the current scenario; and 9.26 lakh pregnancies and 1.15 lakh maternal deaths could be averted by adding LNG-IUS into the current scenario

Limitations

- The World health organization has listed benefits of contraceptive methods as follows: a) Preventing pregnancy-related health risks in women b) By reducing rates of unintended pregnancies c) Reducing infant mortality d) Helping to prevent HIV/AIDS and other STIs e) Empowering people and enhancing education f) Reducing adolescent pregnancies and g) Slowing population growth. Our model accounts for a few benefits listed above and not all, due to the complex nature of analysis that may have been required for including all possible benefits. Hence a complete valuation of costs has been done, but a complete valuation of benefits has not been done, underestimating the benefits of the interventions.
- Utility weights used in our model are from studies done in western settings. Indian utility weights would have been more appropriate. The probable differences in the utility weights of western and local settings has been addressed in the sensitivity analysis to some extent.
- Out-of-pocket expenditure for availing contraceptive services was not collected as a part of the primary health system costing study but was derived from the data of the National Sample Survey Organization.
- Primary health system costing study was done in a selected few public health centers in the state of Maharashtra. The costs may not be applicable across the different states of India.

Recommendations

- Addition of Nexplanon to current Family planning scenario in the public health sector of India is found to be cost-effective. It could be considered for program introduction to improve the contraceptive basket of choice in a phased manner

  The model shows that larger the proportion of method users, the higher is the cost-effectiveness.
- The pre-requisites recommended for Nexplanon introduction into the public health sector of India are recommended to be
  - Conducting feasibility and acceptability studies before introducing Nexplanon
  - Creating awareness regarding Nexplanon among all stakeholders
  - Program introduction could be top-down from medical colleges to 24X7 PHC level manned by Medical Officers (MBBS), as Nexplanon requires surgical removal
  - Effective pre-insertion counselling and preparedness for management of side-effects by trained health personnel
  - Efficient follow-up and tracking mechanism for users of Nexplanon

CHAPTER 1: INTRODUCTION

India has been a signatory to the Family planning-2020 program, a partnership that encourages country-level progress on family planning goals. FP2020 has prioritized 69 focus countries to speed-up progress. India is one of the 36 commitment-making countries which are working to expand access to family planning commodities and services(1). India's target is to reach out to 48 million new eligible couples by 2020 and to be able to raise the modern method Couple protection rate (mCPR) to 63.7% i.e. 16% increase from where it stands today. In this light, one of the policy questions to be addressed is whether a new spacing method, a Long Acting Reversible method should be added to the existing scenario.

Currently in the National program in India, two Long Acting Reversible Contraceptives (LARCs) are available: The Copper IUD 380A (that can be used for 8-10 years) and the three-monthly injectable contraceptives. The newer LARCs that could be considered for program introduction are subdermal contraceptive implants and Levonorgestrel IUS. Some of our neighboring countries that have introduced subdermal contraceptive implants in their national programs are Sri Lanka, Bangladesh, Thailand, Vietnam and Indonesia. Most countries have an acceptance of subdermal implants below 1% except Indonesia where acceptance is nearly 5% (2).

Nexplanon/Implanon-NXT is a Long Acting Reversible Contraceptive method that contains 68 milligrams of Etonorgestrel, effective up to 3 years to prevent pregnancy. It is a small, thin, and flexible contraceptive subdermal arm implant that is placed discreetly under the skin of the inner, upper arm by a trained health care provider. Removal needs a small surgical incision. The earlier version of Implanon-NXT/Nexplanon called as "Implanon" is registered in five out of eight South Asian countries and nine out eleven South East Asian countries as of March 2014. Nexplanon is the improved version of the same device with similar drug composition but with a radiopaque substance to enable tracing the device after insertion. This revised version is registered in only one out of eight South Asian countries and nine out of eleven South East Asian countries. The older version "Implanon" is being phased out. The product has been approved for marketing by Drug Controller General of India (DCGI) and will soon be launched in India for use in private sector(3). In this report, the terms Implanon and Nexplanon have been used interchangeably as literature shows that they are bioequivalent(4).

Indian council of Medical Research (ICMR) had conducted a phase-3 clinical trial on Implanon during 2004-2008 enrolling 3119 women across India. Implanon-R was offered along with other existing contraceptive methods available in the National family welfare program. The relative acceptability of the subdermal contraceptive implant Implanon-R was observed to be 2.1 % among all contraceptive methods and 3.4% among spacing methods.

1.1 RESEARCH QUESTION

What is the health and economic impact of introducing Nexplanon (subdermal contraceptive implant containing Etonorgestrel 68mg) into the national health program in India?

1.2 AIMS AND OBJECTIVES

Aim

- To conduct a Health Technology Assessment of LARC i.e. Nexplanon to aid the policy decision of its program introduction in India

Objectives

- To assess clinical efficacy of Nexplanon and LNG IUS and their impact on Health-related Quality of life in comparison to the LARC existing in the current national program (i.e. IUD and DMPA) and female sterilization
- To evaluate the cost effectiveness of LARCs in terms of cost per unintended pregnancy averted and cost per QALY gained

CHAPTER 2: METHODOLOGY

The present study was a decision analytic model-based cost-utility analysis for estimating the costs and consequences of adding Nexplanon to the current public health sector in India. It constituted a hypothetical cohort of 15-year-old women who experience events like contraceptive use, contraceptive method failure resulting in unintended pregnancy and related outcomes (like abortion, ectopic pregnancy, vaginal or cesarean section) throughout their reproductive life span until menopause. The outcomes are measured in terms of unintended pregnancies averted (which could result in either childbirth, ectopic pregnancy or abortion), QALYS gained and maternal deaths averted. A disaggregated societal perspective was used for the model.

Ethical Clearance was obtained from the institute's Ethics Committee for Clinical Research (via letter no: D/IEC/Sci-28/30/2018 dated April 17th, 2018 and amendment letter no: D/IEC/Sci-120/127/2018 dated 26th September 2018). Informed consent was obtained for primary data collection.

2.1 Conceptualization of the Model

A Markov-transition state model was conceptualized by reviewing existing literature, consultation with experts and considering the ground reality of contraceptive use in India. The model was constructed to derive cost-effectiveness of adding Nexplanon (the sub-dermal Etonorgestrel contraceptive implant) and Levonorgestrel Intra uterine System (LNG-IUS) to the currently available basket of contraceptive methods via the public health system in India. As depicted in Figure 2.1, health states included women (in reproductive age-group: 15-49 years) who belong to any one of the following transition states during one cycle of the model

a) Non-users of any modern method of contraception
b) Users of Long Acting Reversible Contraceptives
c) Users of Short Acting Reversible Contraceptives and Female sterilization
d) Unintended pregnancy
e) Death as an absorptive state

For the model, Contraceptive methods have been grouped as shown in Table 2.1:

Table 2.1: Grouping of Contraceptive methods for the model

Group	Constituents
Long Acting Reversible Contraceptives (LARCs)	Three-monthly injectable contraceptive (Depot Medroxy progesterone acetate-DMPA) AND Copper Intrauterine device IUD-380A
Short Acting Reversible Contraceptives (SARCs) and Female Sterilization	Low dose Combined Oral contraceptive pills (OCPs), Condoms and Female sterilization which is the permanent method

2.1.a Model characteristics

We begin with a cohort of 15-year-olds (from the Indian census 2011) using various methods of contraception. The model followed these adolescents through their reproductive life span, till menopause. Hence, time horizon was chosen to be 31 years. During this phase they may fall into any of the 5 defined health states and also may move through any of these health states (i) No contraceptive Use (ii) Long Acting Reversible Contraceptive methods (iii) Short Acting Reversible Contraceptive Methods or Female Sterilization (iv) Unintended pregnancy (v) Death which is an absorbing state of the model (includes death due to age-specific all-cause mortality, maternal mortality and method- related mortality). The cycle length was one year, assuming duration of pregnancy to be 9 months, plus 3 months of lactation amenorrhea.

The probability of switching between contraceptive groups included all reasons like discontinuation/failure/desire for pregnancy. Discontinuation from exiting methods, acceptance of a different method, was incorporated into the transition matrix. The model accounts for unintended pregnancies resulting in either abortion or childbirth/ turning out as an unintended ectopic pregnancy. These possibilities are depicted as health-events in the model. Adverse events and/or side-effects attributed to method use are also considered as transient health events in the model.

Future costs and consequences were discounted at 3%, keeping in view existing HTAIn reference-case guidelines. Study findings are presented as incremental cost per QALY gained, life years saved, and pregnancies averted with addition of Nexplanon and LNG-IUS (separately).

2.1.b Model assumptions

1) Only use of modern contraceptives is considered

2) Any woman in the model is using only one contraceptive method at a time

3) The probability of switching between contraceptive groups includes different reasons like discontinuation/failure/desire for pregnancy

4) Death is an absorptive state and can happen when a woman is in any health state

5) Vasectomy being a very negligible number in Indian context, was not considered as a method in SARC+ FS health state (5)

2.1.c Two Models were developed separately

(i) Non-Age-specific model: Considering transition probabilities of contraceptive use and switching to be uniform across the age group of 15-49 years and

(ii) Age-specific model: Considering transition probabilities of contraceptive use and switching to vary with age

For example, the first age group 15-19 years will have lower probability of using LARC and permanent method compared to subsequent age groups.

2.1.d Given below are the three alternatives considered in the model

1) Current scenario (CS): Current basket of Long Acting Reversible Contraceptive methods available in the family planning program comprising of the following methods: Three-monthly injectable contraceptive (Depot Medroxy progesterone acetate-DMPA), Copper IUD-380A, Oral contraceptive pills (OCPs), Condoms and Female sterilization as it is the most commonly accepted method in India

2) Intervention 1: Nexplanon (A single rod, sub-dermal contraceptive implant containing Etonorgestrel 68 mg) added to the current basket of contraceptive methods available in the family planning program. This has been referred to as a 'Nexplanon trace' in the results section.

3) Intervention 2: Levonorgestrel Intrauterine system (LNG-IUS) added to the current basket of contraceptive methods available in the family planning program. This has been referred to as a 'LNG_IUS trace' in the results section.

2.1.e Quality check of the Markov model

The validation of model was done for concept, data flow and computerized structure by investigators other than those who worked on the model.

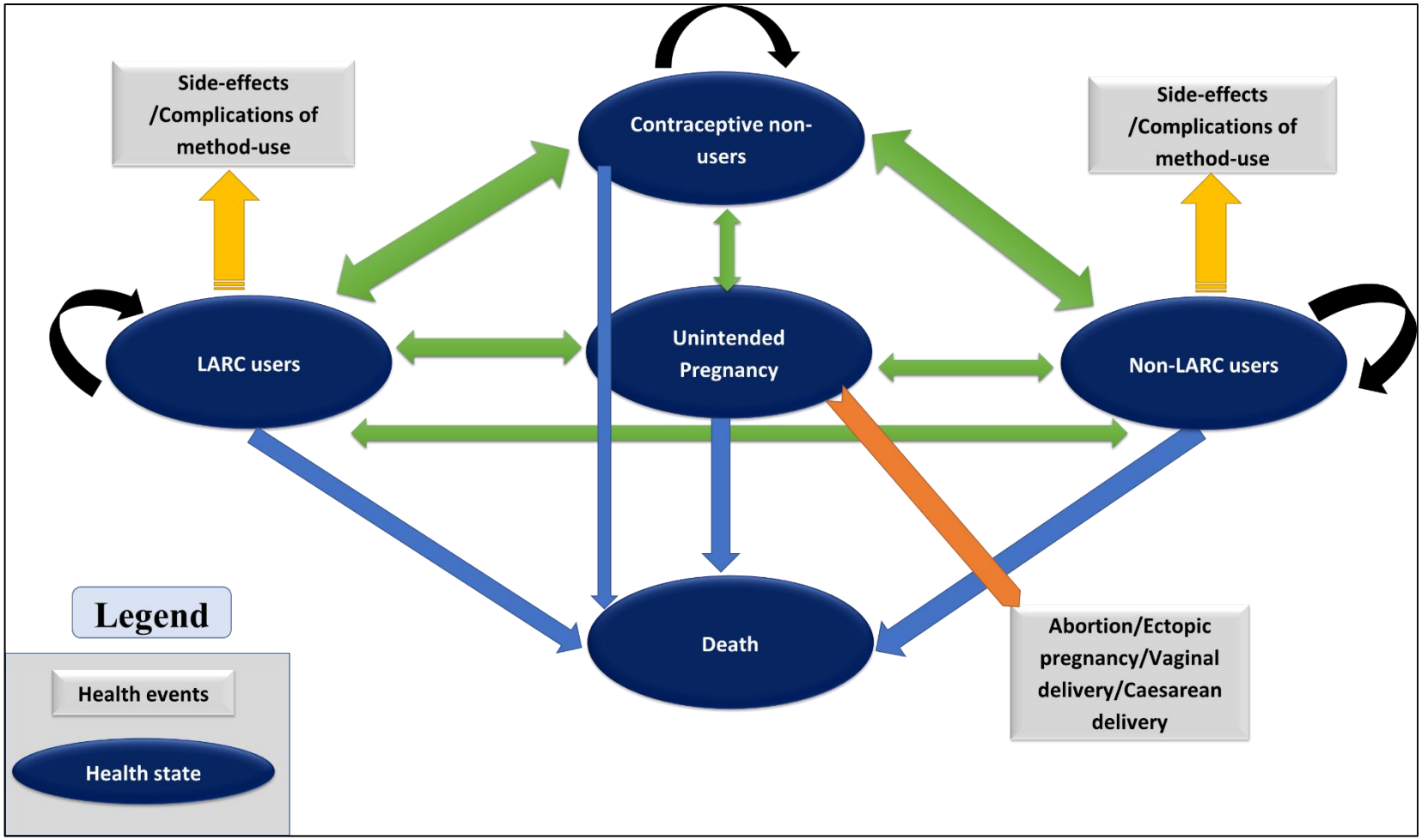

Figure 2.1: Markov Model for cost-effectiveness of adding Nexplanon/LNG IUS to the currently available basket of contraceptive methods via the public health system in India

2.2 Model Parameters

Appropriate parameters for the model were researched using the following steps. The list of model parameters is listed in Table No.2.2

2.2.1 Systematic Review to assess Clinical effectiveness of Implanon/Nexplanon compared to other LARC and female sterilization (Registered with PROSPERO: Registration number is: CRD42018116580). The systematic review was done as per standard protocol. The study included studies that compared Implanon to other LARC and female sterilization; done in the last decade. Three databases were used for the search, done independently by two researchers.

Figure 2.2 shows the PRISMA flowchart, which shows the three databases searched and the final number of studies reviewed to be seven.

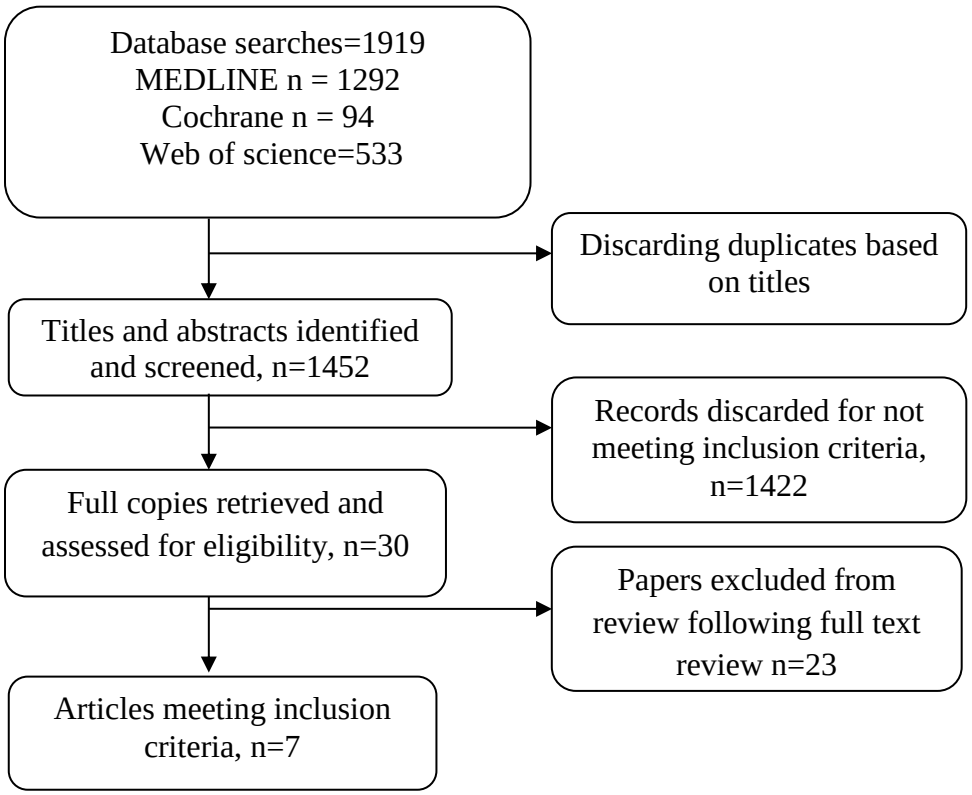

Figure 2.2: Flowchart of systematic search

2.2.1.a Summary findings of the systematic review

The review showed that Nexplanon had good clinical effectiveness. Studies reported Pearl index (contraception failures per 100-woman years (HWY) of exposure) of 0 or less than 1. Continuation rates were in a range of 69% to 86% and premature discontinuation (within 3 years of insertion) was found to be between 11- 47% at the end of 12 months of follow-up. The main side-effects were frequent bleeding (47%) and prolonged bleeding (37%).

2.2.2 Targeted literature search for the following topics:

- An unpublished ICMR multi-center study done on Implanon in India, without any comparator was considered for context-specific parameters
- Clinical effectiveness of other LARC, SARC methods and female sterilization (failure rates, side effects and adverse events, discontinuation)
- Cost effectiveness of contraceptive methods
- Health related Quality of Life (Utility scores) for all contraceptives under consideration, unintended pregnancies and their outcomes such as ectopic pregnancy, abortion, vaginal or cesarean delivery
- Equity issues for the use of contraceptives in India
- The unpublished ICMR study on Implanon done in India in 2004-08 has a similar side-effect profile as compared to western countries (41). But other side effects like headache, weight gain and acne were very minimal (<1%) unlike in international studies that reported a high incidence (>5%) of these side-effects. However, discontinuation rates due to other side effects were much lower than that reported in literature. We may be safe to say that given the similar side-effect profile, the utility weight in our setting may not be too different.

Table 2.2 shows the parameters used in the model from different sources.

Table 2.2: Model parameters used in the Markov model

Category	Input parameter		Value	Range lower limit	Range upper limit	Source
Epidemiological parameters and clinical effectiveness	Age at Menopause		46.2 years	36.4	56	(6)
	Percentage of women not using /using different modern contraceptive in India	Female sterilization	36%			(5)
		Male sterilization	0.30%			
		IUD	1.50%			
		Injectable	0.20%			
		Condom	5.60%			
		Pill	4.10%			
		Not using	47%			
		Traditional methods	5.30%			
	Clinical effectiveness of methods (Pearl index)	Pill	0.3			(7)
		Male condom	2			
		Injection	0.2			
		Implant	0.05			
		IUD	0.6			
		LNG IUS	0.2			
	Incidence of ectopic pregnancy in India (%)		0.91	0.25	2	(8)
	Incidence of abortion in India (per 1000 women in 15-49 age group)		47	42.2	52.1	(9)
	Proportion of deliveries that are vaginal in India		0.8078	0.7578	0.8578	(5)

	Proportion of deliveries that are Caesarean section in India		0.1922	0.1422	0.2422	(6)
	Implanon acceptance rate		2.10%	-0.029	0.071	(10)
	Implanon switching to other reversible methods		4.30%	-0.007	0.093	(11)
	Deaths related to female sterilization		0.0194	-0.0306	0.0694	(12)
	Deaths related to second generation Oral contraceptive pills		1 in 10,000 woman-years	-0.049	0.050	(13)
	Maternal mortality rate		8.8 per 1000	-0.041	0.058	(13)
	All cause- female mortality		6.40%	0.014	0.114	(14)
Utility scores	Utility of DMPA		0.7	0.65	0.75	(15)
	Utility of Nexplanon		0.703	0.653	0.753	(16)
	Utility of LNG-IUS		0.756	0.706	0.806	(17)
	Utility of Copper-IUD		0.715	0.665	0.765	(16)
	Utility of Female sterilization		0.95	0.9	1	(18)
	Utility of vaginal delivery		0.879	0.829	0.929	(7)

	Utility of Caesarean section		0.847	0.797	0.897	
	Disutility of amenorrhea		0.0385	-0.0115	0.0885	
	Disutility of bleeding		0.0385	-0.0115	0.0885	
	Disutility of VTE		0.0833	0.0333	0.1333	
	Utility of abortion		0.942	0.892	0.992	
	Utility of ectopic pregnancy		0.9167	0.8667	0.9667	
Probability of events following failure of contraception	Probability of Ectopic pregnancy in Copper IUD users		0.03	-0.02	0.08	
	Probability of Ectopic pregnancy in Implant users		0.01	-0.04	0.06	
	Probability of Ectopic pregnancy in LNG-IUS users		0.5	0.45	0.55	(7)
	Probability of Ectopic pregnancy in DMPA users		0.01	-0.04	0.06	
	Probability of Induced abortion in Copper IUD users		0.28	0.23	0.33	

	Probability of Induced abortion in Implant users		0.29	0.24	0.34	
	Probability of Induced abortion in LNG-IUS users		0.15	0.1	0.2	
	Probability of Induced abortion in DMPA users		0.29	0.24	0.34	
	Probability of Spontaneous abortion in Copper IUD users		0.13	0.08	0.18	
	Probability of Spontaneous abortion in Implant users		0.13	0.08	0.18	
	Probability of Spontaneous abortion in LNG-IUS users		0.07	0.02	0.12	
	Probability of Spontaneous abortion in DMPA users		0.13	0.08	0.18	
Side-effects of Contraceptive methods	Amenorrhea in Implanon		32.2	32.15	32.25	(10)
	Infrequent and prolonged bleeding in Implanon		9.1	9.05	9.15	

	Amenorrhea in LNG-IUS		27.5	27.45	27.55	(19)
	Amenorrhea in DMPA		46	45.95	46.05	(20)
	Lower abdominal pain in DMPA		10.8	10.75	10.85	(21)
	Weight gain in DMPA		8.1	8.05	8.15	
	Prolonged bleeding in Copper-IUD		5.4	5.35	5.45	
	Expulsion in Copper-IUD		5.3	5.25	5.35	

Note that, where lower and upper limits were not available, 5% standard deviation was used in the sensitivity analysis

All studies that report health utility values for contraceptive related health states are from high income countries.

2.2.3 Estimation of transition probabilities of various methods using NFHS 4 data

The calendar data for contraceptive use was extracted from NFHS-4 in which month by month data on type of contraceptive use, switching, and discontinuation are available for past 5 years preceding the survey among women aged 15-49 years. Women were excluded from the data set if they were found to be using contraceptive method at the starting of calendar year. Women who were non-users initially were considered for the following analysis.

Types of contraceptive users were divided into four groups i.e.

1) Non-users of modern contraceptive methods
2) Users of Long-Acting Reversible Contraceptives (LARCs) method includes copper intrauterine device and injectables
3) Users of Short Acting Reversible Contraceptives (SARCs) method includes OCPs and condoms
4) Female sterilization (FS)

We examined the first-time users of contraceptive methods (N=471,777) and followed up the cohort for 12 consecutive months to observe switching to another group or discontinuation of method or reporting of an unintended pregnancy

Some relevant definitions used in this analysis:

- Contraceptive continuation: When a woman reported having used same methods in consecutive months till end of follow up period.
- Contraceptive discontinuation: When a woman reported not having used any method in consecutive months of prior contraceptive use during follow up period.
- Contraceptive switching: When a woman reported having used different methods in consecutive months during follow up period.

Step 1: The probability of adopting contraceptive methods from 'non-user' state was estimated as follows: $p_i=n_i/N$, where i=type of contraceptive method and varies from 0,1,2,3, where 0 is non-user of contraceptive, 1= LARC user, 2= SARC+FS, 3=Unintended pregnancy; N=total number of eligible women and n= number of women who adopt the contraceptive method 'i'.

Step 2: Continuation, switching and discontinuation from the adopted method (from step 1) was coded as j=1, 2, 3 respectively.

Step 3: Probability of continuing, switching and discontinuing over one year were then calculated as $pij=n_{ij}/n_i$

The probability of discontinuation was calculated as the number of users, who discontinued the method over 12 months period divided by a cohort of users. Stopping the adopted method includes method failure, side-effects or any other reasons were categorized as discontinuation of contraceptive method). Similarly, the probabilities of continuing and switching were calculated. Age-specific death rates from all causes mortality for women in India were obtained from country-specific life tables published by Sample Registration System (SRS) and are shown in table 3. These were adjusted in markov trace for the percentage of deaths due to maternal causes which is 8.8% (13).

2.2.3.1 Results

Table 2.3: Transition probabilities for health states in Current Scenario model for NASM

	Non-users	LARC users	SARC + FS users	UIP	Death	Total
Non-users	0.811455	0.000257	0.084909	0.039379	0.064000	1
LARC users	0.298204	0.673453	0.022954	0.005389	0.000000	1
SARC + FS users	0.274478	0.002105	0.695151	0.008865	0.019401	1
UIP	0.579628	0.039861	0.371750	0.000000	0.008760	1
Death	0.000000	0.000000	0.000000	0.000000	1.000000	1

Note: LARC- Long Acting Reversible Contraceptives (Injectables -DMPA, Cu-IUD), SARC- Short Acting Reversible Contraceptives (Condom, Pill), FS- Female Sterilization, UIP- Unintended Pregnancy

Table 2.3 shows the transition probabilities from one health state to another for current scenario. Transition from one state to other shown in Table 2.3 is assumed to be constant for all ages (hence used for Non-Age specific model). The Non-age-specific model will be referred to as NASM in the report. The transition probabilities were derived method-wise. But, as the health states involved grouping of methods, the probabilities were combined mathematically.

Table 2.4 shows the transition matrix by adding Nexplanon to existing LARC methods. Nepal DHS (2016) report was used for transition from LARC to switch to other methods, and matrix was adjusted accordingly.

Table 2.4: Transition probabilities for health states in NXT+ Current Scenario model for NASM

	Non-users	LARC users	SARC + FS users	UIP	Death	Total
Non-users	0.800031	0.011681	0.084909	0.039379	0.064000	1
LARC users	0.189474	0.777549	0.032977	0.000000	0.000000	1
SARC + FS users	0.264902	0.011681	0.695151	0.008865	0.019401	1
UIP	0.581490	0.038000	0.371750	0.000000	0.008760	1
Death	0.000000	0.000000	0.000000	0.000000	1.000000	1

Note: LARC- Long Acting Reversible Contraceptives (Injectables -DMPA, Cu-IUD), SARC- Short Acting Reversible Contraceptives (Condom, Pill), FS- Female Sterilization, UIP- Unintended Pregnancy

Table 2.5: Transition probabilities for health states in LNG-IUS+ Current Scenario model for NASM

	Non-users	LARC users	SARC + FS users	UIP	Death	Total
Non-users	0.804211	0.007500	0.084910	0.039379	0.064000	1
LARC users	0.253125	0.713887	0.032977	0.000011	0.000000	1
SARC + FS users	0.269083	0.007500	0.695151	0.008865	0.019401	1
UIP	0.499240	0.032000	0.460000	0.000000	0.008760	1
Death	0.000000	0.000000	0.000000	0.000000	1.000000	1

Note: LARC- Long Acting Reversible Contraceptives (Injectables -DMPA, Cu-IUD), SARC- Short Acting Reversible Contraceptives (Condom, Pill), FS- Female Sterilization, UIP- Unintended Pregnancy

The discontinuation rate of LARC methods was derived from NFHS-4. But Nexplanon and LNG-IUS discontinuation rates were taken from literature(22) and brought down to a single probability by using weighted average, based on the acceptance of the two LARC methods. Since LNG IUS data on switching was not available, we assumed a probability like Copper IUD from NFHS-4. The transition matrix used for LNG-IUS addition to current scenario (uniform across ages) is shown in table 2.5

For the above tables, probabilities were uniform across all age groups. Table 2.6 shows age-related transition probabilities of current scenario while table 2.7 and table 2.8 shows transition probabilities of two interventions respectively. These were used in the **Age-specific model, henceforth referred to in the report as ASM.**

Table 2.6: Transition probabilities for health states in Current Scenario model for ASM

Transition States (CS)	Age Groups						
	15-19	20-24	25-29	30-34	35-39	40-44	45-49
NU--> LARC	0.0000	0.0002	0.0006	0.0005	0.0005	0.0005	0.0005
NU--> SARC + FS	0.0021	0.0472	0.1939	0.2514	0.2514	0.2514	0.2514
NU--> UIP	0.0076	0.0491	0.0671	0.0726	0.0451	0.0210	0.0082
NU--> Death	0.0049	0.0064	0.0067	0.0074	0.0098	0.0138	0.0188
LARC-->NU	0.5667	0.3815	0.2954	0.2605	0.2609	0.2616	0.2620
LARC--> SARC + FS	0.0333	0.0332	0.0231	0.0230	0.0231	0.0231	0.0232
LARC --> UIP	0.0000	0.0012	0.0073	0.0056	0.0040	0.0016	0.0000

LARC --> Death	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
SARC + FS -->NU	0.6207	0.4168	0.2542	0.1972	0.1981	0.1986	0.1987
SARC + FS --> LARC	0.0013	0.0021	0.0024	0.0016	0.0016	0.0016	0.0016
SARC + FS --> UIP	0.0158	0.0159	0.0096	0.0073	0.0031	0.0007	0.0003
SARC + FS --> Death	0.0194	0.0194	0.0194	0.0194	0.0194	0.0194	0.0194
UIP--> NU	0.9652	0.4728	0.1741	0.5691	0.8406	0.9279	0.9889
UIP--> LARC	0.0109	0.2609	0.4022	0.2065	0.0761	0.0435	0.0000
UIP --> SARC + FS	0.0152	0.2576	0.4149	0.2156	0.0746	0.0198	0.0023
UIP --> Death	0.0088	0.0088	0.0088	0.0088	0.0088	0.0088	0.0088

Note: NU- non-users, LARC- Long Acting Reversible Contraceptives (Injectables -DMPA, Cu-IUD), SARC- Short Acting Reversible Contraceptives (Condom, Pill), FS- Female Sterilization, UIP- Unintended Pregnancy

Table 2.7: Transition probabilities for health states in NXT+ Current Scenario model for ASM

Transition States (NXT)	**Age Groups**						
	15-19	**20-24**	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**
NU--> LARC	0.0114	0.0116	0.0121	0.0119	0.0119	0.0119	0.0119
NU--> SARC + FS	0.0021	0.0472	0.1939	0.2514	0.2514	0.2514	0.2514
NU--> UIP	0.0076	0.0491	0.0671	0.0726	0.0451	0.0210	0.0082
NU--> Death	0.0049	0.0064	0.0067	0.0074	0.0098	0.0138	0.0188
LARC-->NU	0.3093	0.1242	0.0381	0.0032	0.0036	0.0042	0.0046
LARC--> SARC + FS	0.0330	0.0328	0.0227	0.0227	0.0227	0.0228	0.0228
LARC --> UIP	0.0000	0.0012	0.0073	0.0056	0.0040	0.0016	0.0000
LARC --> Death	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
SARC + FS -->NU	0.6111	0.4073	0.2446	0.1876	0.1885	0.1890	0.1891
SARC + FS --> LARC	0.0109	0.0116	0.0120	0.0112	0.0112	0.0112	0.0112
SARC + FS --> UIP	0.0158	0.0159	0.0096	0.0073	0.0031	0.0007	0.0003
SARC + FS --> Death	0.0194	0.0194	0.0194	0.0194	0.0194	0.0194	0.0194
UIP--> NU	0.9381	0.4457	0.1470	0.5420	0.8134	0.9008	0.9618
UIP--> LARC	0.0380	0.2880	0.4293	0.2337	0.1032	0.0706	0.0271
UIP --> SARC + FS	0.0152	0.2576	0.4149	0.2156	0.0746	0.0198	0.0023
UIP --> Death	0.0088	0.0088	0.0088	0.0088	0.0088	0.0088	0.0088

Note: NU- non-users, LARC- Long Acting Reversible Contraceptives (Injectables -DMPA, Cu-IUD), SARC- Short Acting Reversible Contraceptives (Condom, Pill), FS- Female Sterilization, UIP- Unintended Pregnancy

Table 2.8: Transition probabilities for health states in LNG-IUS + Current Scenario model for ASM

Transition States (LNG-IUS)	Age Groups						
	15-19	**20-24**	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**
NU--> LARC	0.0075	0.0077	0.0081	0.0080	0.0080	0.0080	0.0080
NU--> SARC + FS	0.0021	0.0472	0.1939	0.2514	0.2514	0.2514	0.2514
NU--> UIP	0.0076	0.0491	0.0671	0.0726	0.0451	0.0210	0.0082
NU--> Death	0.0049	0.0064	0.0067	0.0074	0.0098	0.0138	0.0188
LARC-->NU	0.3948	0.2096	0.1236	0.0886	0.0891	0.0897	0.0901
LARC--> SARC + FS	0.0330	0.0328	0.0227	0.0227	0.0227	0.0228	0.0228
LARC --> UIP	0.0000	0.0012	0.0073	0.0056	0.0040	0.0016	0.0000
LARC --> Death	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
SARC + FS -->NU	0.6145	0.4106	0.2480	0.1910	0.1919	0.1924	0.1925
SARC + FS --> LARC	0.0075	0.0083	0.0086	0.0078	0.0078	0.0078	0.0078
SARC + FS --> UIP	0.0158	0.0159	0.0096	0.0073	0.0031	0.0007	0.0003
SARC + FS --> Death	0.0194	0.0194	0.0194	0.0194	0.0194	0.0194	0.0194
UIP--> NU	0.9441	0.4517	0.1530	0.5480	0.8194	0.9068	0.9678
UIP--> LARC	0.0320	0.2820	0.4233	0.2277	0.0972	0.0646	0.0211
UIP --> SARC + FS	0.0152	0.2576	0.4149	0.2156	0.0746	0.0198	0.0023
UIP --> Death	0.0088	0.0088	0.0088	0.0088	0.0088	0.0088	0.0088

Note: NU- non-users, LARC- Long Acting Reversible Contraceptives (Injectables -DMPA, Cu-IUD), SARC- Short Acting Reversible Contraceptives (Condom, Pill), FS- Female Sterilization, UIP- Unintended Pregnancy

2.2.4 Health System Costing – Primary Study

2.2.4.a Methods

An economic costing study was employed to estimate costs of various input parameters of family planning program which included both the direct and indirect costs. Written permissions were obtained from all relevant officials prior to conducting the study. The participants in the study were employees of the health centers. Patients were not interviewed. Out-of-pocket expenditures were not collected.

2.2.4.b Study Setting

The study was conducted in Maharashtra state, in one tertiary hospital, district hospital, one Sub-district Hospital, one PHC and one sub-center. These centers were chosen based on convenience sampling. The SDH was located about 120 Km from the state capital. The SC and PHC were in

the same block as the SDH, maintaining the referral chain. The district hospital was about 25 KM from the state capital. The tertiary hospital was a state-funded teaching hospital (Medical College).

2.2.4.c Data collection for the primary costing study

The bottom-up approach of costing, from health system perspective was used, which meant that prices of various components like non-consumables, consumables, transport, capital, overheads, Human resource information etc. were collected. Data for the above resources was collected for the financial year 2017-2018. Sources of data for the above-mentioned categories were as follows:

a) Written and Electronic Hospital records

b) Health Management information system: HMIS

c) Building plans of the health facility etc. maintained by the health facilities.

Apart from this, staff interviews were conducted to assess the time spent by the staff doing different activities. Activities were classified as routine/ fixed and their frequency was noted. Time spent on each patient in OPD, IPD, time taken to do a surgery was asked, to the senior-most specialist/ doctor. Also, a survey of the health facility was done to measure area, observe and count medical and non-medical equipment. This was double checked with the records provided by the facility. Laboratory: The time taken to do separate group of tests like hematological, biochemical, serological, immunological tests etc. were collected. The number of patients who received various services like OPD consultations, Inpatient admissions, vaginal and caesarean deliveries, abortions, sterilizations, contraceptive provision and related statistics in the financial year 2017-18 were collected from the HMIS in each facility. Total numbers and break-up of the above were collected. Expenditure on IEC, Training and ASHA incentives and incentives to beneficiaries and surgeons for the whole state was received from the Maharashtra state government for the financial year of 2017-18. Supplementary data from NFHS-4 and NSSO 71st round was collected to account for out-of-pocket-expenditure.

2.2.4.d Data analysis for the economic costing study

Economic costing analysis was adopted. The following were the key steps used in analysis:

1) For each of the facilities, annualization of capital costs was done. Annual factor was calculated using a discount factor of 3% and the life of the item. A maintenance rate of 10% was applied.
2) Apportioning of joint/shared costs (Personnel, Space or equipment that are being used for more than one activity) was done for each of the health facilities using standard published protocols.

3) For each health facility a unit cost was derived for OBGYN OPD consultation, IPD admission per day, OT per day and institutional delivery by using appropriate beneficiaries as denominator.
4) To derive combined health system costs for the model, percentages of health care seeking at different public health levels from NFHS-4 was used for people seeking family planning services. These percentages were applied to the different categories of OPD, IPD, OT and Institutional delivery of the health facilities that belonged to the respective levels of healthcare
5) Using these combined health system costs for OPD, IPD, OT and Institutional delivery; cost for providing Contraceptive methods, Conducting Vaginal delivery, caesarean section, abortion, ectopic pregnancy and treating side-effects of Contraceptive methods was derived.
6) Package costs are reported for each of the required unit costs, based on clinical expert opinion for number of visits and average hospitalization days. To these unit costs, unit cost of IEC, training and Incentives (method specific) was added.
7) Out-of-pocket expenditure was added to the above costs to derive societal perspective costs. NSSO was the source for these OPD and IPD, OOP costs.

2.2.4.e Results

Unit cost of delivering family planning services at various levels of health care facilities: Primary, Secondary and Tertiary level in Maharashtra

The survey was conducted at three different levels of health care facilities viz. Primary level, Secondary level and Tertiary level at the facilities located in and around the districts and places in Mumbai such as Dahanu, Ashagadh, Thane and Mumbai. In this study the cost of family planning services such as providing Long Acting Reversible Contraceptives (LARCs) and the cost of contraceptive failure and side effects are calculated. The direct and indirect costs associated with provision of various LARC methods such Nexplanon, LNG-IUS etc. were calculated separately to feed into the Markov model. Given the difference in the flow of patients across health care facilities which is observed in table 2.9, the cost of various LARC methods were calculated using the 'Weighted Average', considering the relative share from each of the health care facilities viz. primary, secondary and tertiary facilities.

Table 2.9: Family planning service provision at different healthcare levels

Healthcare level	Family planning service provision (%)
Primary level	21.77
Secondary level	30.97
Tertiary care level	47.26

Family Planning services sought at the Tertiary care level is highest at 47.26 per cent followed by Secondary level at 30.97 per cent and Primary level facility 21.77 per cent. This was used for women seeking family planning services and used to calculate weighted average.

The average cost of providing various contraceptive methods across the various service levels are projected in table 10. The calculations are done based on the outcomes of the primary, secondary and the tertiary public health care provider using the method of 'Weighted Average'. The unit costs are calculated for the contraceptive methods such as the Nexplanon, LNG-IUD, Copper IUD/Injectable, OC Pills, Condoms and Tubal ligation. An example of calculating Average Unit cost for out-patient consultation will be:

Average Unit Cost of Out-patient consultation *= FP service provision at tertiary level* unit cost of out-patient in tertiary level + FP service provision at Sub-district hospital* unit cost of out-patient in Sub-district hospital + FP service provision at PHC* unit cost of out-patient in PHC.*

Unit cost of providing various contraceptive methods:

Here, using the methodology discussed in the illustration section, an attempt is made to calculate the average weighted cost of providing various contraceptive methods in the Family Planning Programme in Maharashtra. The product cost of the LNG-IUS was highest at 2424 INR followed by Nexplanon which was 800 INR. As the survey is conducted in the Primary, Secondary and the Tertiary level public health care providers in Maharashtra alone, the costs derived in this study does not represent other states or all of India. Table 2.10 provides cost estimates of both the LARC methods and the other methods.

Table 2.10: Average unit cost of various contraceptive methods (all in INR)

	Health System Cost	Out-of-pocket expenses*	Total Cost (Societal perspective)
Nexplanon	4067.70	1281.08	5348.78
LNG-IUS	3621.32	1281.08	4902.40
Copper IUD	1406.61	1281.08	2687.69
DMPA/Injectables	769.70	1281.10	2050.80
OCPs	1717.49	1281.08	2998.57
Condoms	934.82	1281.08	2215.90
Female Sterilization	11068.58	2027.77	13096.35

**Out-of-pocket expenses are not derived from the primary health system costing study. They are derived from the National sample survey organization's study*(23)*. The OOPE are same for all the contraceptives that involve 'out-patient' visits to the health system. For tubal ligation, the 'out-patient' and in-patient' expenses are added up.*

The overall unit cost at facility level includes the component of OPD, IPD, OT and Lab costs. To this training, incentives and IEC were added (program costs). The program costs included sub-centre level activities in the community, related to reproductive health. The overall unit cost at the health system level (facility plus program) level was highest for Tubal ligation at 13096 INR.

Unit cost associated with contraceptive failure:

In this section, the same methodology is adopted as above, i.e., the weighted average of costs is calculated using the primary, secondary and the tertiary level costs associated with Unintended Pregnancy. This is shown in table 2.11.

Table 2.11: Average unit cost of Unintended Pregnancy outcomes (all in INR)

Unintended pregnancy outcomes	Health system Cost	Out-of-pocket expenses	Total Cost (Societal perspective)
Vaginal delivery	9941.1	2027.77	11968.8
Caesarean delivery	20488.5	2027.77	22516.3
Ectopic pregnancy	11087.3	2027.77	13115.1
Abortion (Spontaneous or Induced)	9035.6	2027.77	11063.4

Table 2.11 shows the costs of unintended pregnancy. It is observed that the cost of Unintended Pregnancy is highest for those who undergo Caesarean delivery which is 22516 INR whereas it is lowest for abortion at 11063 INR.

2.2.5 Markov Decision Model analysis

The model was constructed in Microsoft excel, using logical commands and linking worksheets. Life tables from SRS-2016 were used for age-specific all-cause mortality for females. An additional mortality attributed to contraceptive- method related deaths and maternal mortality were incorporated.

The model was run with a cohort size of females aged 15 years from census 2011. We calculated pregnancies, maternal deaths, childbirths and abortions in the three alternatives.

Sensitivity analysis was done to test the robustness of the ICUR estimates to account for presence of any structural, model and parameter uncertainties in our model. Effect of joint parameter uncertainty was analyzed performing a probabilistic sensitivity analysis (PSA). Appropriate distributions like Beta/Gamma/Log-normal were used to run the PSA. For percentages, probabilities and proportions, beta distribution was used. Gamma distribution was used for costs. Monte Carlo method was used to simulate the results 1000 times. Median ICUR estimate along with 2.5^{th} and 97.5^{th} percentile (as 95% confidence interval) was reported as outcome of this analysis.

CHAPTER 3: RESULTS

3.1 MARKOV MODEL

The cohort that contributed to the transition probabilities was drawn from the National family health survey-4. Table 3.1 shows the baseline characteristics of this cohort from non-user to first time using contraception.

Table 3.1: Baseline characteristics of the one-year cohort from NFHS-4 calendar data for use of contraception

Residence	**Total**	**Non-user**	**Pill**	**IUD**	**Injectable**	**condom**	**FS**
Urban	1,39,635	86.57	2.43	1.3	0.15	5.61	3.94
Rural	3,37,142	88.2	3.02	0.67	0.11	3.3	4.7
Wealth*							
Poorest	94,842	90.09	2.87	0.3	0.08	1.74	4.92
Poorer	1,03,017	88.31	3.65	0.47	0.12	2.63	4.82
Middle	99,511	87.74	2.89	0.7	0.08	3.53	5.06
Richer	93,046	86.82	2.59	1.22	0.15	4.88	4.34
Richest	86,361	85.44	2.11	1.68	0.17	7.47	3.13
Education Status							
No education	1,09,379	87.81	2.44	0.46	0.12	2.55	6.62
Primary	52,180	84.36	4.5	0.79	0.13	3.42	6.8
Secondary	2,49,963	88.08	2.99	0.95	0.11	4.11	3.76
Higher	65,255	88.2	1.64	1.33	0.16	6.68	1.99
Occupation							
Professional	2,518	86.51	2.03	2.47	0.15	6.71	2.13
Clerical/Sales	1,551	88.87	2.69	1.08	0.09	2.42	4.85
Skilled Worker	17,457	85.91	2.44	0.68	0.31	3.25	7.41
Unemployed	61,209	87.41	3.07	0.86	0.12	4.7	3.85

*Wealth quintiles from NFHS-4

The contraceptive non-user percentage is higher than that reported in NFHS-4 report, as the data taken for analysis from NFHS-4 was only for the first year of the five years of contraceptive-calendar data available. The table 3.1 shows that condom use is higher in urban areas as compared to rural areas. Acceptance of female sterilization is higher in rural areas. There is an increase in use of condoms and a decreasing acceptance of female sterilization as the wealth quintile increases (poor to rich) and as education status increases. Condom use is highest among professionals. IUD use was higher in more educated women

3.1.1 Health Outcomes

As per the model, a real-world cohort of 1,21,59,708 eligible women from age of 15 years (as per census 2011) was considered and followed up to 31 years (until they reached menopause).

Table 3.2 shows pregnancy and related outcomes and maternal deaths in the current scenario and the interventions for NASM and Table 3.3 for ASM.

Table 3.2: Health Outcomes of the three alternatives in our model (NASM)

Outcome Indicators	Current Scenario	Addition of Nexplanon	Addition of LNG-IUS
Maternal Deaths	400561.87	390473.86	394825.90
Child Births	10454469.71	10034593.32	10180245.89
Pregnancies	11491439.98	11144402.01	11314372.48
Abortions	4511818.20	4334416.90	4400361.09
Maternal Deaths Averted	-	10088.00*	5735.97**
Child Births Averted	-	419876.39	274223.82
Pregnancies Averted	-	347037.96	177067.50
Abortions Averted	-	177401.30	111457.12

**Event averted by Nexplanon= events in Nexplanon-events in Current scenario*
***Events averted by LNG-IUS= events in LNG-IUS- events in Current scenario*

About 3.47 lakh pregnancies and 10088 maternal deaths (among a cohort of 15-year old for 31 years i.e. until age of menopause) were averted by adding Nexplanon to the current scenario; and 1.77 lakh pregnancies and 5735 maternal deaths were averted by adding LNG-IUS into the current scenario (NASM).

Table 3.3: Health Outcomes of the three alternatives in our model (ASM)

Outcome Indicators	Current Scenario	Addition of Nexplanon	Addition of LNG-IUS
Maternal Deaths	231653.56	114540.97	105894.22
Child Births	9355390.42	8333246.09	8228242.24
Pregnancies	9498566.57	8450369.75	8411931.28
Abortions	4103614.87	3647668.06	3601151.59
Maternal Deaths Averted		117112.59*	125759.34**
Child Births Averted		1022144.33	1127148.18
Pregnancies Averted		1048196.82	1086635.28
Abortions Averted		455946.81	502463.28

**Event averted by Nexplanon= events in Nexplanon-events in Current scenario*
***Events averted by LNG-IUS= events in LNG-IUS- events in Current scenario*

About 10.48 lakh pregnancies and 1.17 lakh maternal deaths (among a cohort of 15-year old for 31 years i.e. until age of menopause) were averted by adding Nexplanon to the current scenario; and 9.26 lakh pregnancies and 1.15 lakh maternal deaths were averted by adding LNG-IUS to the current scenario(ASM).

3.1.2 Cost and Cost effectiveness:

Table 3.4 and 3.5 show the costs, life years and QALYs in the NASM and ASM respectively.

Table 3.4: Outcome indicators of NASM

		Current Scenario	Addition of Nexplanon	Incremental (Nexplanon trace-CS)	Addition of LNG-IUS	Incremental (LNG-IUS trace-CS)
Costs in INR (Health system+ OOP)	**UD**	82892.37	143460.02	60567.65	149055.80	66163.43
	D	55969.92	96713.06	40743.14	100422.22	44452.30
Life Years	**UD**	27.94	28.19	0.25	28.11	0.17
	D	18.92	19.04	0.12	19.00	0.08
QALY	**UD**	26.53	31.52	4.99	26.95	0.43
	D	17.97	19.38	1.42	18.22	0.25

Note: UD=Undiscounted D=Discounted

There is a gain in life years and QALYs in both the scenarios of adding Nexplanon and LNG-IUS in the NASM. There is also an incremental cost associated with adding the interventions to the public health system.

Table 3.5: Outcome indicators of ASM

		Current Scenario	Addition of Nexplanon	Incremental (Nexplanon trace-CS)	Addition of LNG-IUS	Incremental (LNG-IUS trace-CS)
Costs (Health system + OOP)	**UD**	102786.40	164015.66	61229.26	161909.02	59122.62
	D	62340.82	100179.86	37839.04	99743.01	37402.19
Life Years	**UD**	28.13	28.37	0.25	28.56	0.44
	D	19.10	19.23	0.12	19.32	0.22
QALY	**UD**	26.46	34.67	8.22	26.65	0.19
	D	18.05	20.18	2.14	18.14	0.10

Note: UD=Undiscounted D=Discounted

There is a gain in life years and QALYs in both the scenarios of adding Nexplanon and LNG-IUS in the ASM. There is also an incremental cost associated with adding the interventions to the public health system.

Incremental cost-effectiveness and Incremental cost-utility analysis

The ICER and ICUR have been calculated by using the formula:

$$\textbf{ICER/ICUR} = \frac{Cost\ of\ Intervention\ 1 - Cost\ of\ Current\ scenario}{Outcome\ in\ intervention\ 1 - Outcome\ in\ current\ scenario}$$

Three outcomes have been considered: QALYs, Unintended pregnancies averted and Life years to calculate ICUR and ICER. Table 3.6 shows outcomes, ICER and ICUR for NASM and table 3.7 shows ICER and ICUR for ASM.

Table 3.6: Incremental cost per unit gain in various health outcomes due to the interventions compared to current scenario (CS) in NASM

		Addition of Nexplanon	Addition of LNG-IUS
ICER (LY)	**UD**	165757.06	266460.46
	D	334199.74	565113.42
ICUR	**UD**	8160.90	104198.98
	D	28713.01	177662.93

Note: LY: Life year UD=Undiscounted D=Discounted

Table 3.7: Incremental cost per unit gain in various health outcomes due to the interventions compared to current scenario (CS) in ASM

		Addition of Nexplanon	Addition of LNG-IUS
ICER (LY)	**UD**	152448.35	85238.76
	D	308150.74	170977.34
ICUR	**UD**	4605.88	197422.81
	D	17716.39	389542.32

Note: LY: Life year UD=Undiscounted D=Discounted

As per NASM, Discounted ICUR of adding Nexplanon to current scenario is 28713 INR, which means that to gain one QALY, an additional 28713 INR will have to be spent (table 3.6). As per ASM, Discounted ICUR of adding Nexplanon to current scenario is 17716 INR, which means that to gain one QALY, an additional 17716 INR will have to be spent (table 3.7).

The ICUR planes are presented in figures 3.1 & 3.2 Incremental cost on Y axis and incremental QALY on X axis have been plotted on these planes.

Figure 3.1 shows NASM and ASM ICUR for Nexplanon Intervention plotted on the plane.

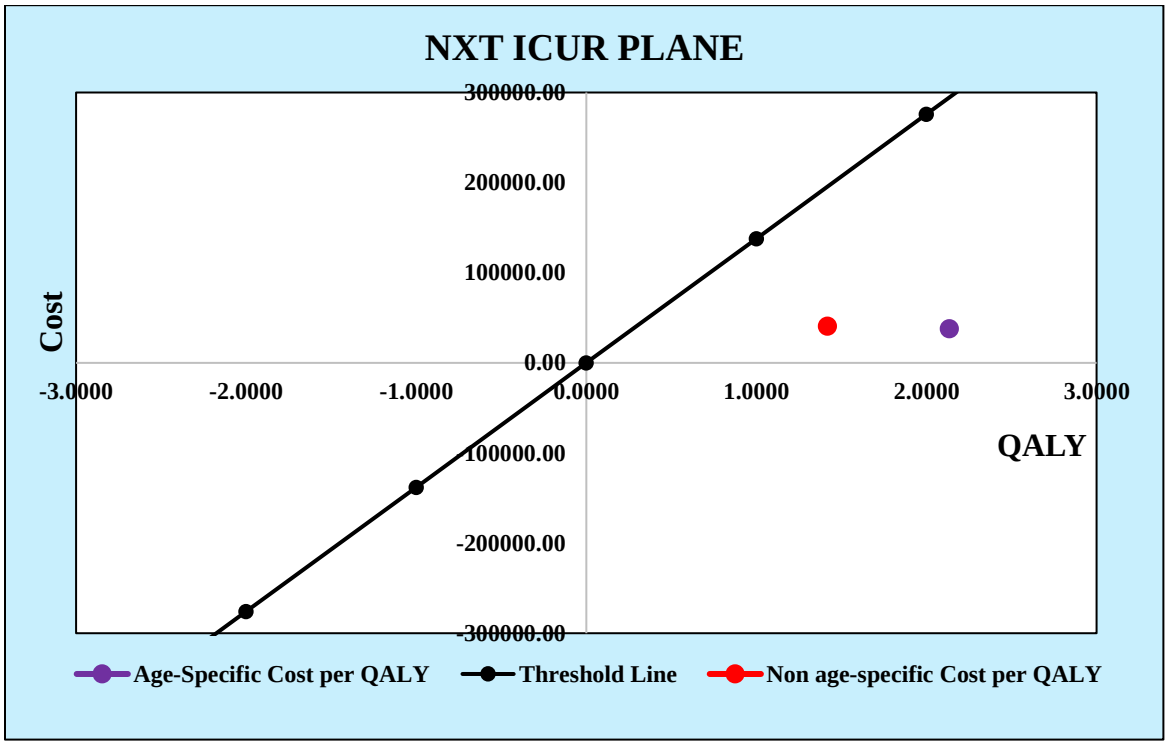

Figure 3.1: Incremental cost utility ratio of Nexplanon Vs Current scenario in the NASM and ASM

Interpretation of Cost-utility planes: The black diagonal line in Figures 3.1 & 3.2 represents the threshold, below which the intervention is cost effective. The threshold has been calculated based on the current Indian GDP per capita (137945 INR) Ref: World Bank. In figure 3.1, both the NASM and the ASM points lie below the threshold, rendering addition of Nexplanon cost-effective in both scenarios.

Figure 3.2 shows Incremental cost utility ratio of LNG IUS Vs Current scenario in NASM and ASM

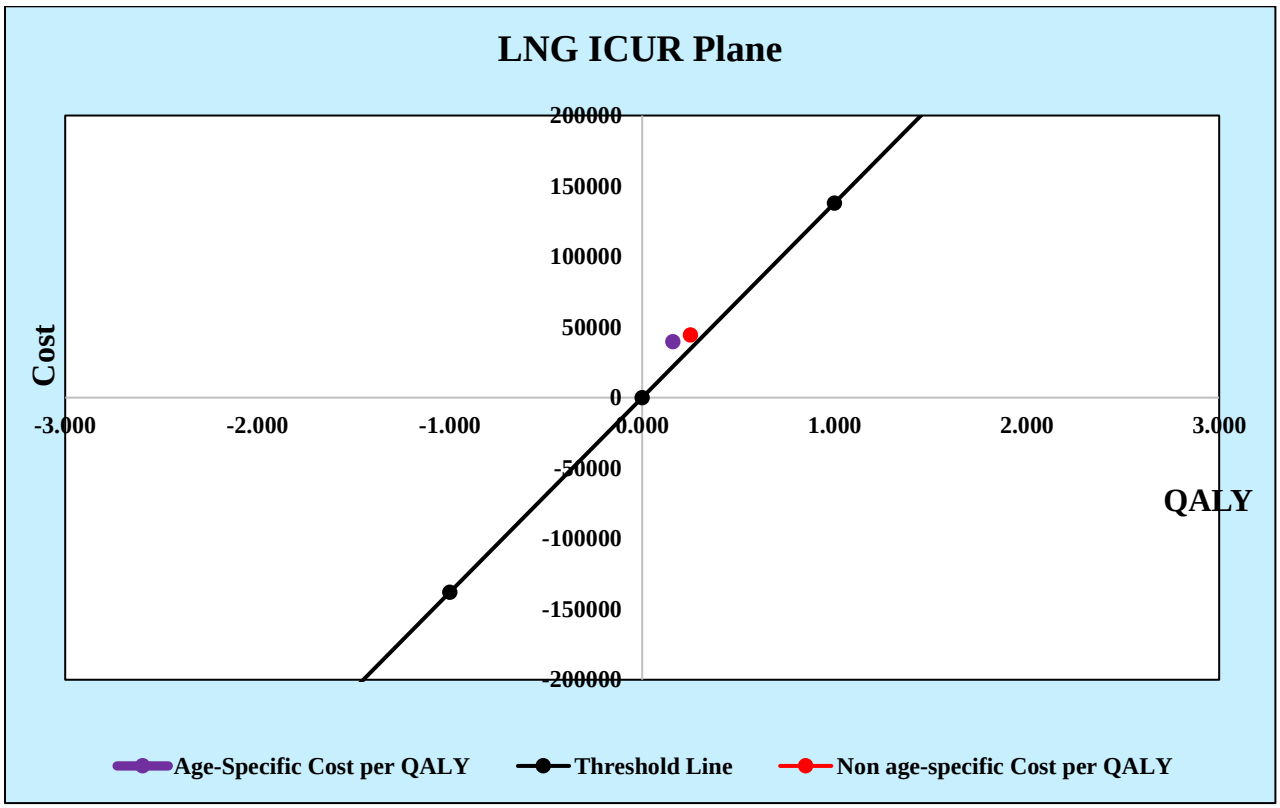

Figure 3.2: Incremental cost effectiveness ratio of LNG IUS Vs Current scenario in NASM and ASM

In figure 4, both the NASM and the ASM points lie above the threshold, rendering addition of LNG-IUS cost-ineffective in both scenarios.

3.1.3 Sensitivity analysis

3.1.3.a One-Way Sensitivity Analysis (OWSA): The standard deviation of input parameters was taken as ±5% and varied to check which parameters effected the ICUR value the most. This is depicted in the Tornado Diagram in Figure number 3.4 and 3.4 for NASM and ASM respectively.

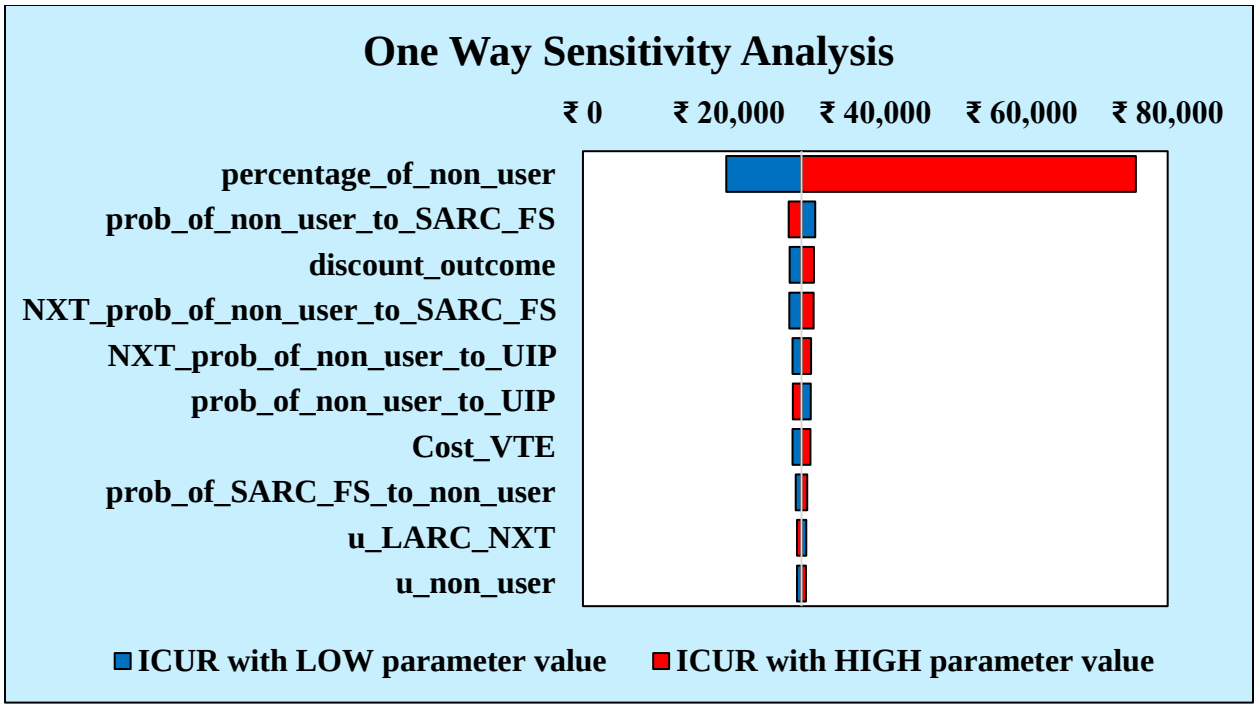

Figure 3.3: Tornado Diagram depicting input parameters that affected the model outcomes maximally in NASM

Abbreviations used in figure 3.3:

Percentage_of_non_user= Percentage of nonusers of any contraceptive methods in the Markov model.

Prob_of_non_user_to_SARC_FS= Probability of switching from non-user state to Short Acting Reversible Contraceptives or Female sterilization

Discount outcome: Discount rate used for outcome

NXT_prob_of_non_user_to_SAEC_FS= Probability of switching from Non user state to SARC+FS state in the Nexplanon trace

NXT_prob_of_non_user_to_UIP= Probability of unintended pregnancy from Non user state in Nexplanon trace

Cost_VTE= Cost of treating Venous thromboembolism

Prob_of_SARC_FS_to_non_user= Probability of discontinuing from SARC+FS state

U_LARC_NXT= Utility score of Long Acting Reversible Contraceptive in Nexplanon trace

U_non_user= Utility score of Non-users of contraceptive

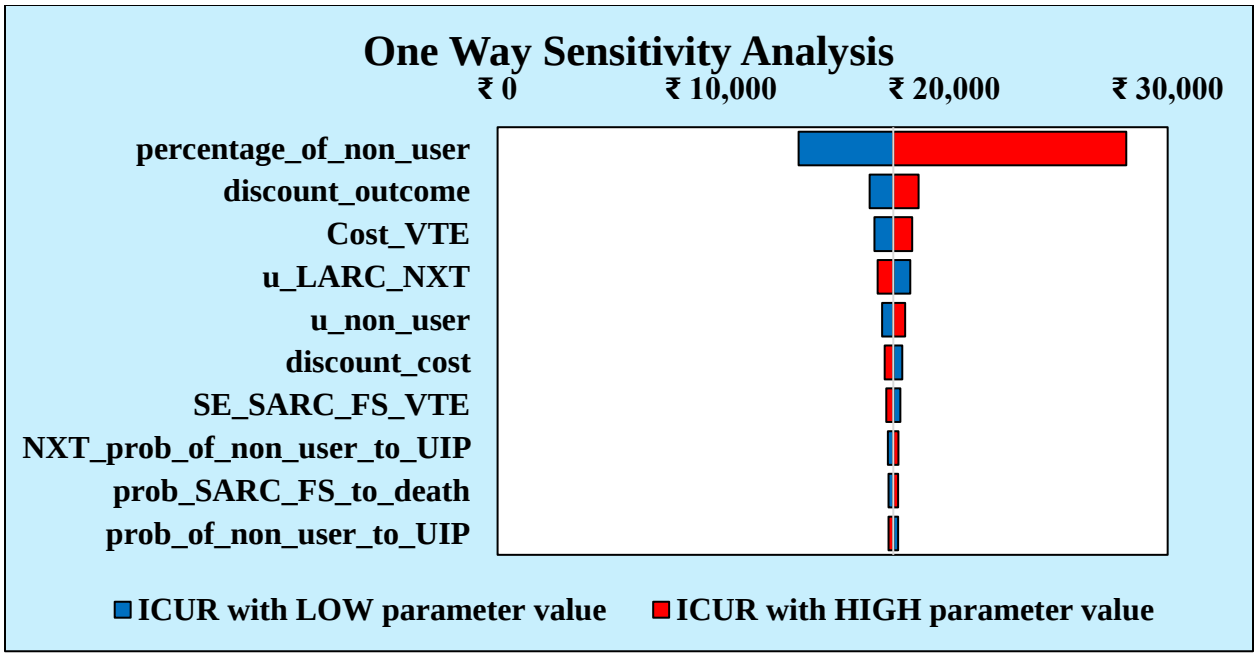

Figure 3.4: Tornado Diagram depicting input parameters that affected the model outcomes maximally in ASM

Abbreviations used in figure 3.4:

percentage_of_non_user= Percentage of nonusers of any contraceptive methods in the Markov model.

discount_outcome= Discount rate used for outcome

Cost_VTE= Cost of treating Venous thromboembolism

u_LARC_NXT= Utility score of LARC in Nexplanon trace

u_non_user= Utility score of Non-users of contraceptive

discount_cost= Discount rate used for costs

SE_SARC_FS_VTE= Side effect of venous thromboembolism in SARC+FS health state

NXT_prob_of_non_user_to_UIP= Probability of unintended pregnancy from Non user state in Nexplanon trace

prob_SARC_FS_to_death=Probability of death in the SARC+FS state

prob_of_non_user_to_UIP= Probability of unintended pregnancy from Non user state in the current scenario

Interpretation of figures 3.3 & 3.4 The tornado diagram shows the parameters that most effect the ICUR. The color of the bar represents whether the parameter has been increased or decreased. For example, in both figures, red represents that the parameter has been increased by a certain

degree. Once the parameter increases, the ICUR changes. If the ICUR increases, the red bar falls on the right of the central line and vice versa. If percentage of nonusers of contraception increases, the ICUR increases (figure 3.4)

3.1.3.b Probabilistic sensitivity analysis (PSA)

Probabilistic sensitivity analysis (PSA) was done to quantify the level of confidence in the output of the analysis, in relation to uncertainty in the model inputs. The probabilistic analysis represented parameters as distributions around the point estimate. Different distributions were used as appropriate for different types of variables and 1000 simulations were run. The figures 3.5 and 3.6 show the corresponding ICUR points of the PSA.

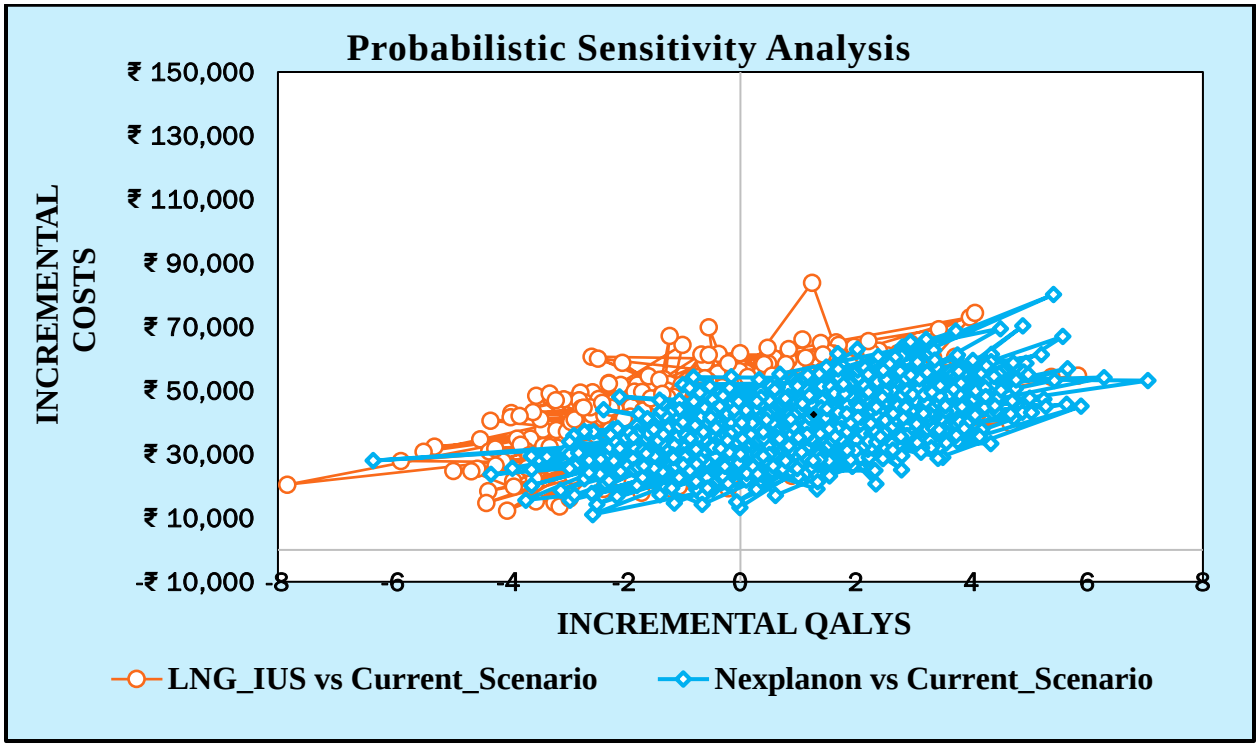

Figure 3.5: Cost-effectiveness plane showing the 1000 ICUR values obtained from the PSA in NASM

The above scatter plot, for NASM, shows the 1000 ICURs each, for Nexplanon and LNG-IUS, that have resulted from the PSA. Blue dots represent PSA of Intervention 1 (Current scenario+ Nexplanon) and orange dots represent PSA of Intervention 2 (Current scenario + LNG-IUS). The scatter plot shows that about 60 % of the times Nexplanon is cost-effective (fall below threshold of one-time GDP per capita) in the upper right quadrant and the simulations are around the base

case value (black dot). About 20% of the times LNG-IUS, ICUR values fall below the threshold line.

Figure 3.6 shows ASM results for Nexplanon alone

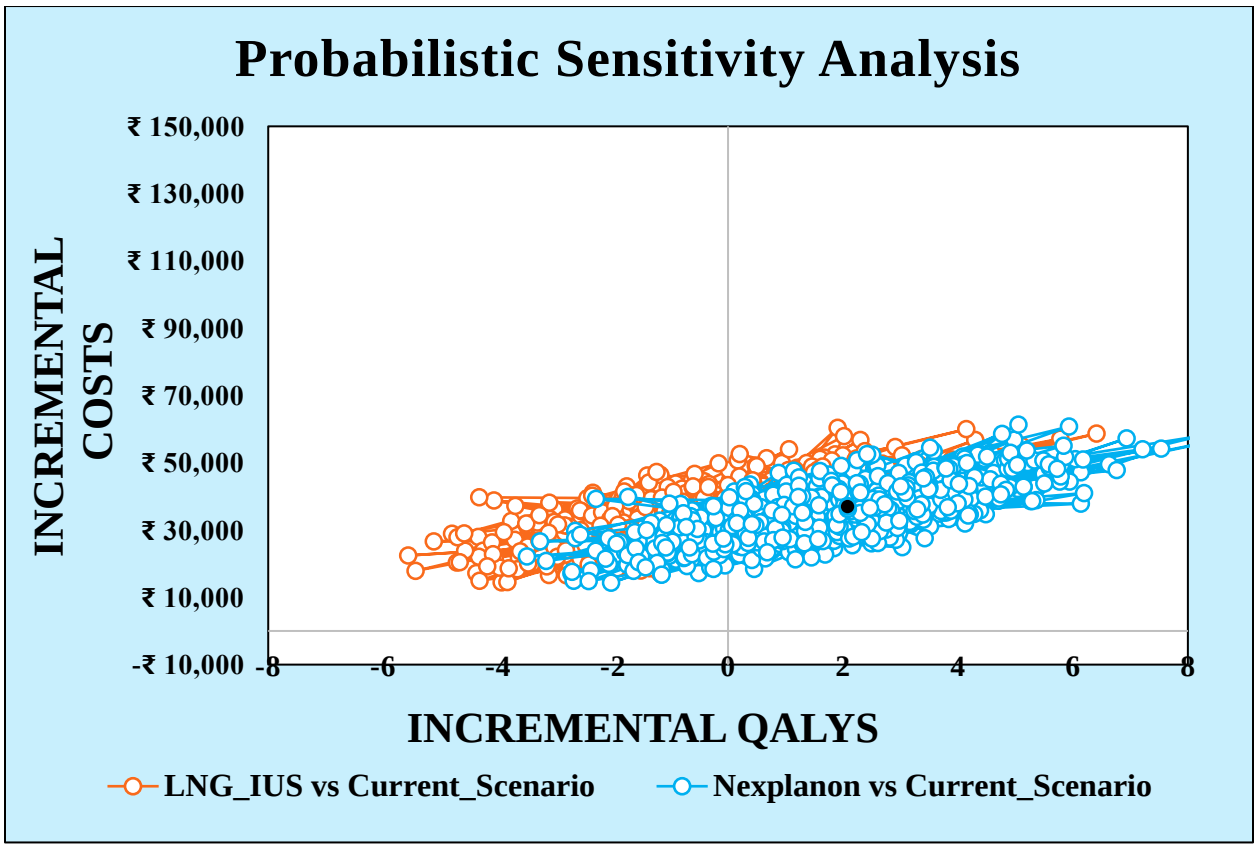

Figure 3.6: Cost-effectiveness plane showing the 1000 ICUR values obtained from the PSA in ASM

This scatter plot in figure 3.6, for ASM shows the PSA of Nexplanon's 1000 simulations; the blue dots representing the ICUR values for Nexplanon and the orange dots represent ICUR values of LNG-IUS. The plot in ASM showed about 85% of ICUR values for Nexplanon lie below the threshold line and around the base case value (black dot).

3.1.3.c Cost effectiveness analysis curve

The probability of the interventions being cost effective is plotted on the Y axis and the willingness to pay per QALY on the X axis.

Figures 3.7 & 3.8 show CEAC for NASM and ASM of Nexplanon addition to CS.

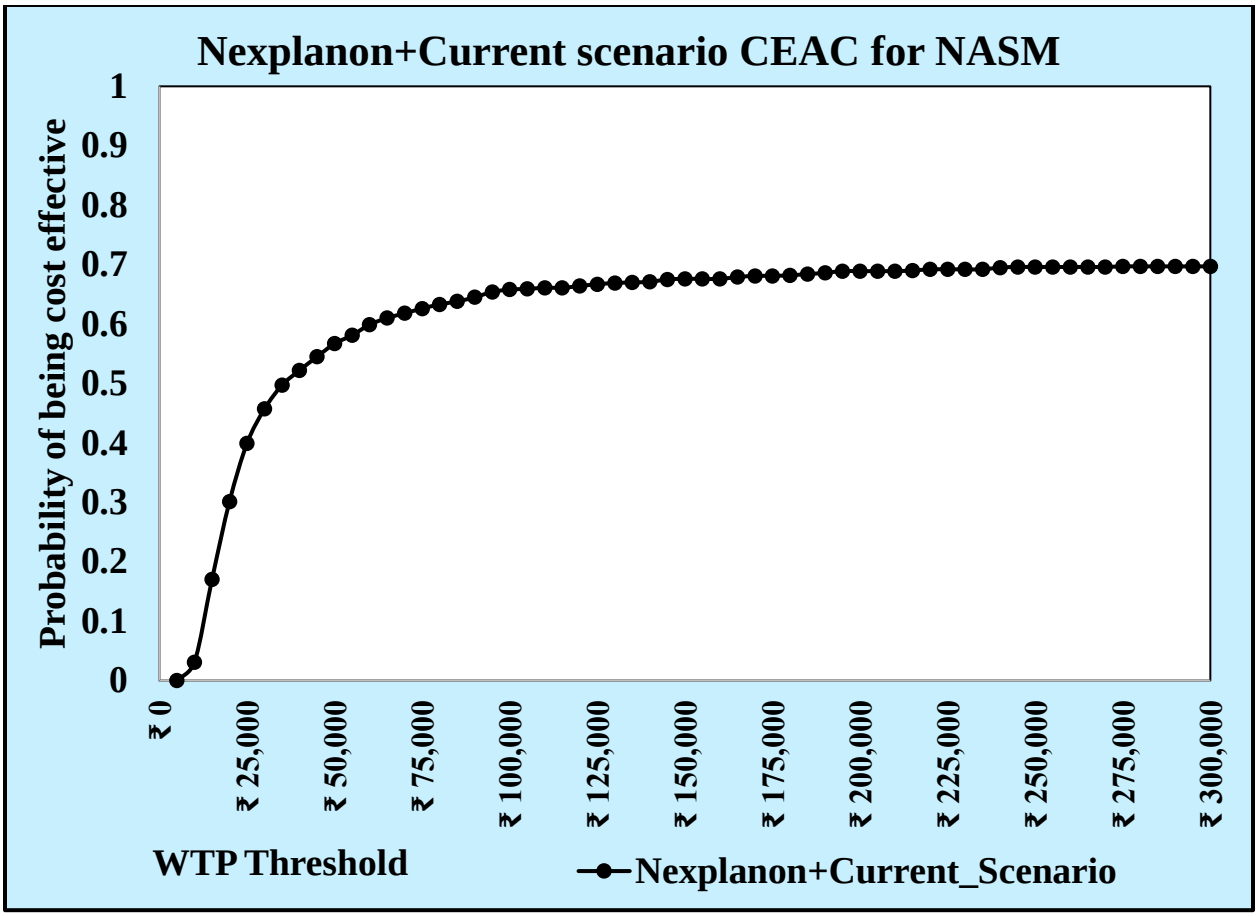

Figure 3.7: Cost-effectiveness acceptability curve (CEAC) for adding the Nexplanon intervention to the Current scenario for NASM

Interpretation: This CEAC shows the probability of Cost-effectiveness of adding Nexplanon to current scenario at different willingness to pay thresholds in NASM. At a willingness to pay threshold of about 30000 INR, the probability is 50% and at about 50000 INR/QALY and above it is 60% in the NASM.

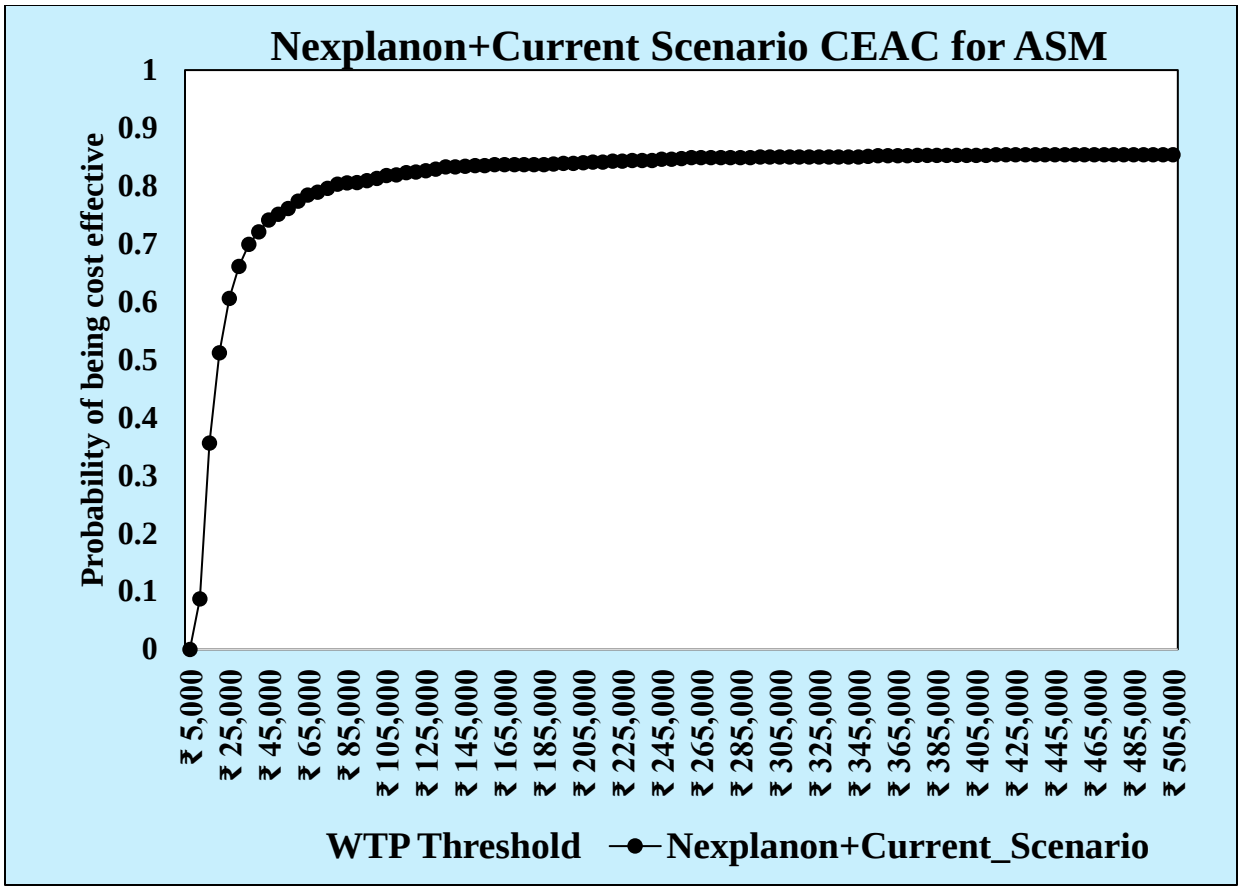

Figure 3.8: Cost-effectiveness acceptability curve (CEAC) for adding Nexplanon to the Current scenario for ASM

Interpretation: This CEAC shows the probability of Cost-effectiveness of adding Nexplanon to current scenario at different willingness to pay thresholds in ASM. At a willingness to pay threshold of about 20000 INR/QALY, the probability is 45% and at about 50000 INR/QALY and above it is 80% in the ASM.

Figure 3.9 shows CEAC for NASM of LNG-IUS addition to CS.

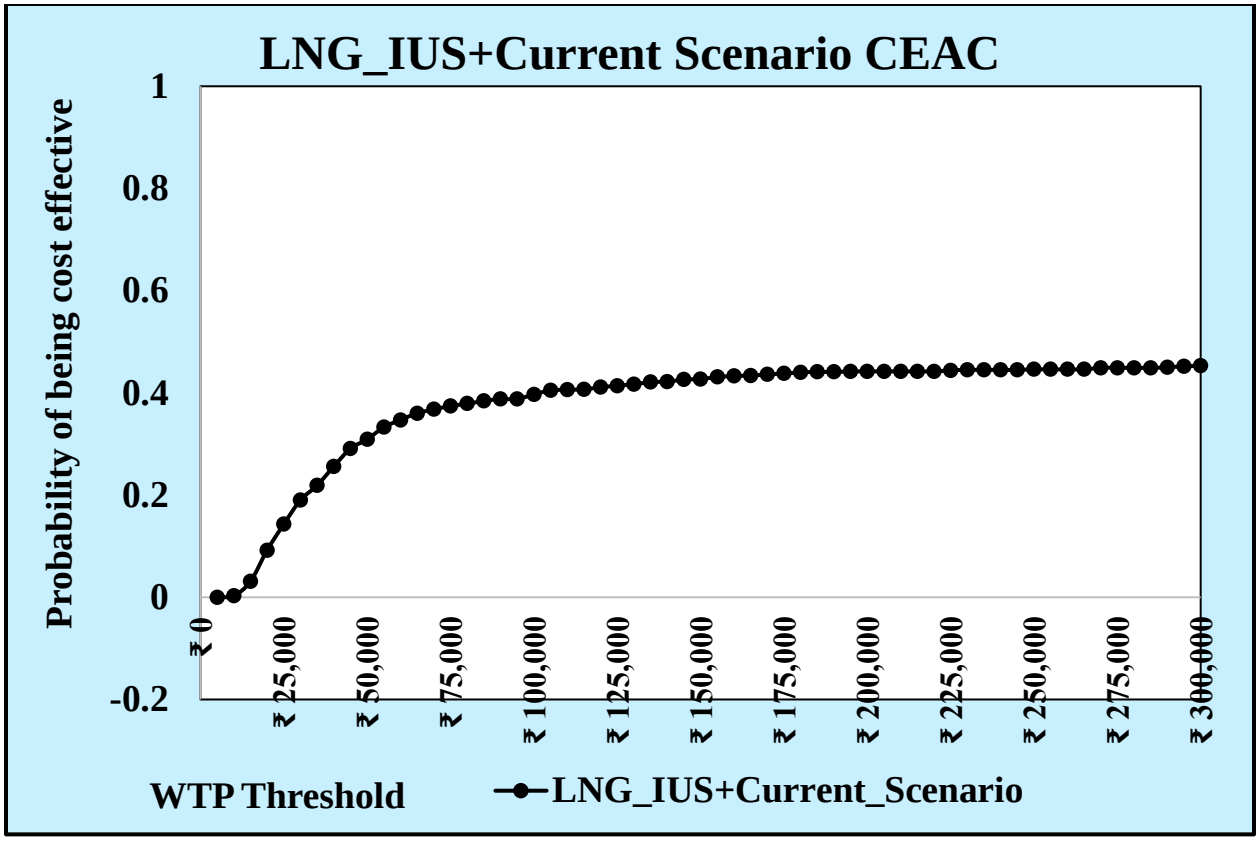

Figure 3.9: Cost-effectiveness acceptability curve (CEAC) for adding LNG-IUS to the Current scenario for NASM

Interpretation: This CEAC shows the probability of Cost-effectiveness of adding LNG-IUS to current scenario at different willingness to pay thresholds in NASM. At a willingness to pay threshold of about 50000 INR/QALY, the probability is 30% and at about 100000 INR/QALY and above it is 40% in the NASM.

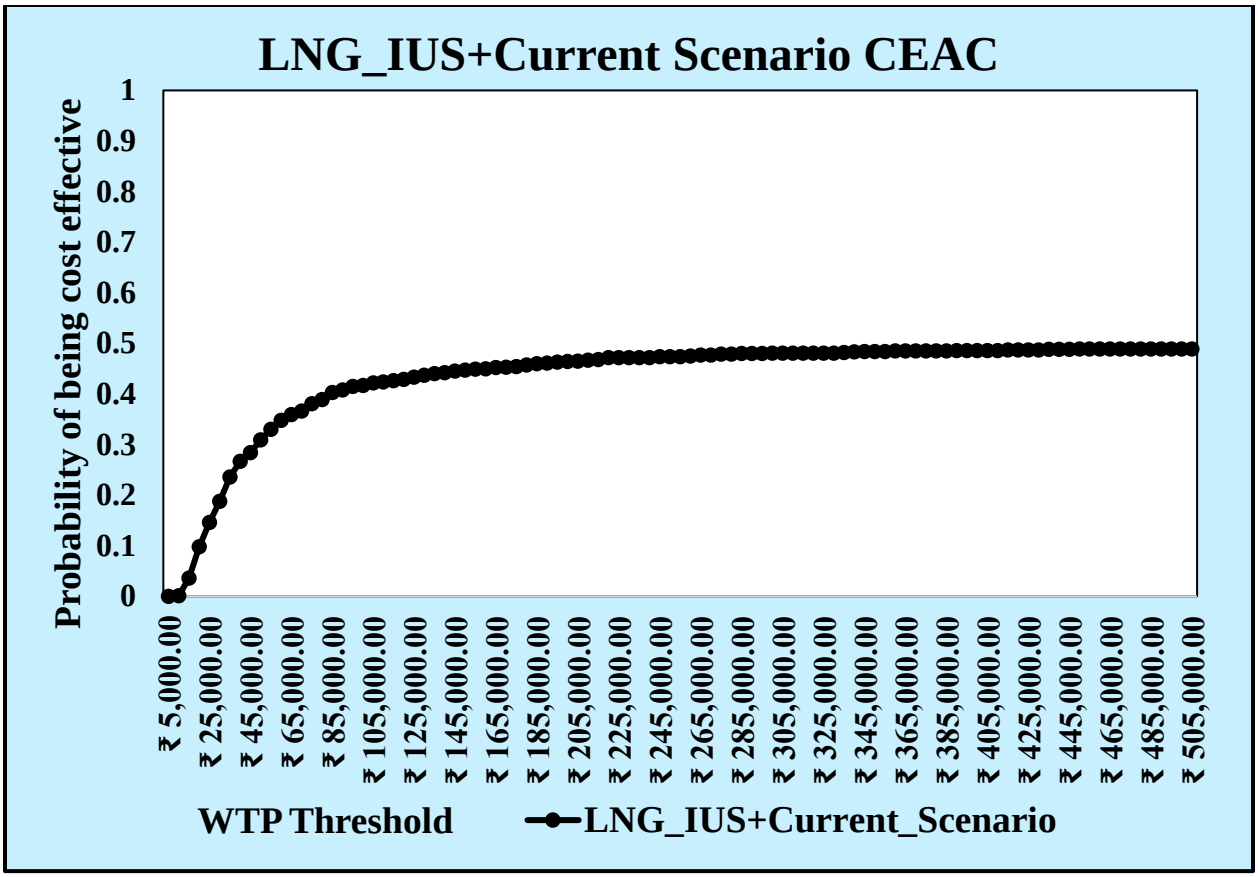

Figure 3.10: Cost-effectiveness acceptability curve (CEAC) for adding LNG-IUS to the Current scenario for ASM

Interpretation: This CEAC shows the probability of Cost-effectiveness of adding LNG-IUS to current scenario at different willingness to pay thresholds in ASM. At a willingness to pay threshold of about 45000 INR/QALY, the probability is 25% and at about 100000 INR/QALY and above it is 40% in the ASM.

CHAPTER 4: EQUITY ISSUES

An HTA is incomplete without considering equity issues. Table 4.1 lists a few key studies that highlight equity issues in the context of contraceptive use. A few select studies on Implanon acceptance from countries that are already using the implant has been included.

Table 4.1: Studies assessing equity issues

Equity issue	*Brief excerpt*	*Source*
Barriers to using modern contraceptives in developing countries	Use of hormonal methods was limited by lack of knowledge, obstacles to access and concern over side effects, especially fear of infertility. Although often more accessible, and sometimes more attractive than hormonal methods, condom use was limited by association with disease and promiscuity, together with greater male control. As a result, young women often relied on traditional methods or abortion.	(24)
Unmet need, and demand for family planning for 29 states and union territories in India	The demand for family planning among the states and union territories in India is highly diverse. Greatest attention is needed in Uttar Pradesh, Manipur, and Meghalaya to meet UN targets	(25)
Impact and equity of Family planning (FP) advice	Significant inequality among social groups (SC/ST population) in receiving advice on FP during ANC/PNC visits. Poor women are less likely to receive FP advice Findings support the need for "effective FP advice" interventions to reduce unintended births and unmet need.	(26)
Contraception use by tribal women in India	Knowledge and use of temporary contraceptive methods are considerably lower among tribal women compared to their non-tribal counterparts in the three states under study. Number of surviving boys, role of women, husbands' education, age of women were the factors affecting the use of any modern method of contraception Low acceptance due to phobia of adverse health consequences, accessibility to and lack of sound knowledge of contraception are the leading reasons for, not using contraceptive.	(11)

Contraceptive preferences of young women	A considerable number of females in the age group 25–28-years opting for sterilization and the unique preference for female sterilization when the family size is complete show the predominant reliance on female sterilization among young women. Female sterilization was significantly lower among, women with higher levels of education than in women with an education level of plus two or, below (5.8% vs 19%, p=0.006). Women were mostly in favor of female sterilization (91%), and a significantly lower proportion of highly educated women preferred female sterilization than women with an education of 12 years or below (85% vs 95.7%, p=0.008).	(27)
Priorities in Indian FP programme	The need for collaboration between scientists developing contraceptive technologies and those implementing family planning services is underscored. If contraceptive technologies are developed with an understanding of the contexts in which they will be delivered and an appreciation of end-user's needs and perspectives, they are more likely to be accepted by service providers and used by clients.	(28)
Gender equity in family planning services	The three National Family Health Surveys (NFHS) show that female sterilization is on the rise and male sterilization is declining. Gender inequalities favor men and sexual and reproductive health decisions are usually made by them. In a study of women in the slums and villages in Maharashtra, male dependent methods accounted for less than 10% of total contraceptive prevalence. The choice to adopt a contraceptive though is 'cafeteria approach' in family planning lexicon; it is the choice of the husband that is ultimately practiced.	(29)
Contraception among urban poor	The acceptance rate of contraceptives was higher among women aged ≥30 years and high literacy status of women, while non-acceptance rate of contraceptives was found much higher among women who had a low socioeconomic status and a greater number of children.	(30)

Gender based violence and contraception	The report demonstrates that equitable gender norms are positively associated with modern contraceptive use. Employment, education, increased mobility, improved roles in household decision-making and increased partner communication were critical attitudes that influenced Gender based violence	(31)
Sociocultural factors and contraception	The greatest obstacles to family planning service use for Indian women are the psychosocial barriers; which include the opposition of religion, husband or personal opposition to family planning. Social taboos such as son preference also played a strong barrier to use of contraception in India. Women's autonomy, female participation in decision making, poverty and poor physical access to services were other factors	(32)
Family planning use: factors in urban Indian women	92.2% had negative opinion towards male sterilization and 57.4% gave reason for negative opinion as weakness will develop in males following male sterilization. 10.48% as against religion misconception about contraception 0.80% as mother-in-law opposition, lack of information and fear of side effects	(33)
	Implanon acceptance and Use in African settings	
Predictors of Implanon acceptance	Women's employment (AOR: 2.73, 95% CI: 1.20-6.21), the number of modern contraceptive methods known (AOR: 2.24, 95% CI: 1.09-4.62), and the number of contraceptive methods ever used (AOR: 11.0, 95% CI: 5.06-23.90) were positively associated with Implanon use.	(34)
Implanon utilization factors	Husband approval (AOR 3.07, 95% CI 1.64-5.74), joint decision (AOR 5.65, 95% CI 2.78-11.51), married women who have income (AOR 2.74, 95% CI 1.26-5.95), joint discussion (AOR 6.53, 95% CI 3.10-13.77). Similarly, age, discussed with health workers were significantly associated with the use of implant contraceptives	(35)

Implanon discontinuation factors	Having pre-insertion counseling (AOR: 0.36, 95% CI: 0.20–0.64), having follow-up appointment (AOR: 0.35, 95% CI: 0.2–0.62), age at insertion <20 years (AOR: 3, 95% CI: 1.16–7.8), women who had no formal education (AOR: 2.8, 95% CI: 1.31–6.11), women who had ≤4 children (AOR: 1.8, 95% CI: 1.01–3.21), and women who had previous abortion history (AOR: 2.3, 95% CI: 1.10–4.63) were determinants of Implanon discontinuation.	(36)
Implanon use and discontinuation	Accepting Implanon was influenced by the educational attainment and religion of the women in our unit. The desire for another pregnancy was the commonest reason for discontinuation. However, menstrual irregularity was the commonest side effect of the implant that led to its removal especially in the first six months after insertion.	(37)

Equity issues about contraception are highly prevalent in Indian settings. Geographic access to services and sociocultural barriers stands out. With a contraceptive like Nexplanon we need to consider the following issues:

- Need for quality counseling prior to insertion and beyond
- Nexplanon is inserted in the arm and may be visible/felt sub dermally. The privacy and confidentiality of using a contraceptive may be hampered
- With evidence that providers refuse to remove IUD when women do not wish to continue using it; one could expect similar fears with Nexplanon; where the user is dependent on a trained health provider to remove it

CHAPTER 5: DISCUSSION

Both the NASM and the ASM models show that there is gain in Life Years and in QALYs on adding Nexplanon to current scenario. Apart from gain in QALYs, even the number of pregnancies, live births, abortions and deaths averted are significant in the Nexplanon and LNG-IUS intervention. The Markov model shows that introduction of Nexplanon into the Public health system in India is very cost-effective. It is imperative to compare our results and model approach with other economic evaluations done on Nexplanon.

Mavranezouli et al in 2008 compared LARC with OCP and Female sterilization. The incremental cost-effectiveness ratio of implant (most effective LARC method) versus IUD (cheapest LARC method) was £13 206 per unintended pregnancy averted for 1 year of use and decreased until implant dominated IUD in 15 years. The model considers an 'initial contraceptive method' and a subsequent 'average contraceptive method'. Outcome considered was unintended pregnancies averted(38).

Varney SJ et al in 2004, conducted a comparison between three LARC methods LNG-IUS, Implant and DMPA. Starting long-term contraception with Levonorgestrel intrauterine system or Etonorgestrel subdermal implant instead of medroxyprogesterone acetate injection was found to be a dominant strategy from the UK-NHS perspective. Outcome is unintended pregnancies averted(39).

A Lafuma et al in 2015 compared Nexplanon, OCP, LNG-IUS and Copper IUD. According to this economic evaluation, at a threshold of 10,000€ per unintended pregnancy avoided, Monte Carlo simulations demonstrated an 82.0% probability for Nexplanon® to be the most cost-effective method. Nexplanon® allowed to avoid 1.6 ‰ pregnancy per year over hormonal IUD(40).

The research question we have for our current study is different from those in the above-mentioned studies. We are considering a programmatic situation of adding Nexplanon to existing LARC methods unlike most research questions that have looked at comparing Nexplanon with other modern methods stand alone. Also, we have calculated cost per QALY gained as our primary outcome, in addition to life years saved and pregnancies averted as is cited in most of the studies. To the best of our knowledge there is no Indian study that has looked at cost-effectiveness of LARC in Indian context. Despite our method mix of contraceptive being different (While Indian

majority use permanent method of tubal ligation, in European countries, majority women use oral contraceptive pills), our results align with literature, showing Nexplanon to be cost-effective.

Several equity issues have been reported to contraceptive use in India eight from psychosocial, sociocultural, women's autonomy, privacy, confidentiality, decision making ability and socioeconomic status along with access to quality services, discrimination and awareness and knowledge of all modern methods and experience of having used any method. All these will have a role to play in the program introduction of Nexplanon.

Projections and opinions from 100 experts in Long Acting Reversible Contraceptive met in USA and concluded that efforts to increase LARC use will be more successful if providers and women feel confident that LARC policies and practices meet the dual goals of increasing access to LARC methods and protecting women's reproductive autonomy. The promise of LARC methods will be realized when they are available for free and presented as options alongside other contraceptive methods, allowing women to choose the method that best meets their individual needs(41).

Evidence exists that by adding one more method to the basket of choices increases mCPR over time. Each additional contraceptive method that is accessible to at least half of the population can increase contraceptive use by as much as eight percentage points. This increase in turn reduces unintended pregnancies, helps women and couples achieve their desired family size and spacing, and improves health and economic opportunities for women and families. Expanding method choice is, therefore, an effective investment for countries and programs to meet the Sustainable Development Goals (SDGs) and their Family Planning 2020 (FP2020) commitments while upholding and advancing individuals' rights and quality of care (42).

Globally, maternal death is the second leading cause of mortality for women of reproductive age(43). It is estimated that if unmet need for contraception were fulfilled, an additional 104,000 maternal deaths could be prevented— a 29% reduction in global maternal mortality(44). Unintended pregnancies would drop by 70%, from 74 million to 22 million per year, and unsafe abortions would decline by 74%, from 20 million to 5.1 million(45). If all birth-to-pregnancy intervals were increased to three years, an additional 1.6 million under-five deaths could be averted on an annual basis(46).

Each year, publicly funded family planning providers enable a number woman to achieve their childbearing goals and avoid unplanned pregnancies. These services have numerous benefits, including health benefits for women and infants due to better birth spacing, personal benefits for

individuals who have a greater chance of realizing their educational and career goals, and economic benefits for both families and society due to personal and public cost savings associated with fewer unplanned children. Moreover, publicly funded family planning care typically involves much more than just contraceptive services, including giving low-income women access to such preventative services as screening for cervical and breast cancers and sexually transmitted infections and referrals to a variety of health and social services that they might otherwise forgo(47).

Public expenditures for the US family planning program not only prevented unintended pregnancies but also reduced the incidence and impact of preterm and LBW births, STIs, infertility, and cervical cancer. This investment saved the government billions of public dollars, equivalent to an estimated taxpayer savings of $7.09 for every public dollar spent(48).

CHAPTER 6: STRENGTHS AND LIMITATIONS OF THE STUDY

6.1 Strengths

- Use of primary data for costs
- Comprehensive decision analytical model simulating reality
- Validation of the model by experts in the field

6.2 Limitations

- Our model accounts for a few of the benefits listed above and not all, due to the complex nature of analysis that may have been required for including all possible benefits. Hence a complete valuation of costs has been done, but a complete valuation of benefits has not been done, underestimating the benefits of the interventions.
- Utility weights used in our model are from studies done in western settings. Indian utility weights would have been more appropriate. The probable differences in the utility weights of western and local settings has been addressed in the sensitivity analysis to some extent.
- Out-of-pocket expenditure for availing contraceptive services was not collected as a part of the primary health system costing study, but was derived from the data of the National Sample Survey Organization
- Primary health system costing study was done in a few public health centers in the state of Maharashtra. The costs may not be applicable across the different states of India.

CHAPTER 7: RECOMMENDATIONS

One size does not fit all. Contraceptive choices vary due to factors such as medical conditions, sociocultural acceptance and autonomy, access, and ease of use. In this light, adding a new LARC that may suit the needs of certain eligible couples, will increase choice and use.

Nexplanon requires surgical removal; hence training of medical officers (preferably only MBBS) working in facilities which are open 24X 7 will be essential for Nexplanon delivery into the program up to PHC level. It will be very essential to ensure that adequate and timely health information is relayed to users via appropriate trained health personnel. Current data on DMPA after introduction into the program needs to be reviewed to consider implementation and acceptance challenges before Nexplanon is considered for introduction. In this context, the HTA team at NIRRH, suggests deliberation whether Nexplanon should be introduced based on the following:

- Addition of Nexplanon to current Family planning scenario in the public health sector of India is found to be cost-effective. It could be considered for program introduction to improve the contraceptive basket of choice in a phased manner

  The model shows that the larger the proportion of method users, the higher is the cost-effectiveness.
- The pre-requisites for Nexplanon introduction into the public health sector of India are recommended to be
  - To conduct feasibility and acceptability studies before introducing Nexplanon
  - Creating awareness regarding Nexplanon among all stakeholders
  - Program introduction above downwards from medical colleges to 24X7 PHC level manned by Medical Officers (MBBS), as Nexplanon requires surgical removal
  - Effective pre-insertion counselling and management of side-effects by trained health personnel
  - Efficient follow-up and tracking mechanism for users of Nexplanon

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Health Technology Assessment in India (HTAIn)

सर्वे सन्तु निरामयाः।

You have to squint really hard to make much of the movement (in the unintended pregnancy rate) over the last 20 years until now, this is an extremely welcome decline.

- James Trussell

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