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Essential Medicines List Committee

Levonorgestrel Intra-uterine System (LNG-IUS)

Health Economics and Budget Impact Analysis

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Contents

Tables and Figures

Glossary and Table of Abbreviations

AUB	Abnormal Uterine Bleeding
AN	Anaemia
CO	Conjugated estrogen
COC	Combined oral contraceptive
EC	Emergency contraception
EST	Estradiol
Fe	Ferrous Sulfate
HM	Hormonal treatment management
HMB	Heavy menstrual bleeding
HRT	Hormone replacement therapy
HYS	Hysterectomy
LNG-IUS	Levonorgestrel-releasing Intrauterine System
LMIC	Low Middle Income Countries
MM	Medical management
MPA	Medroxyprogresterone acetate
NOR	Norethisterone
NSD	Non-steroidal anti-inflammatory
NoTx	No treatment
OC	Oral contraception
PRG	Progestin
R-LNG	Remove LNG-IUS
TA	Tranexamic acid

1. Introduction and Background

Abnormal Uterine Bleeding (AUB) is defined by the FIGO PALM COEIN classification as heavy menstrual bleeding (HMB) that lasts more than 8 days or results in greater than 80ml blood loss per cycle. The aetiology of AUB can be due to underlying pathology such as cancer, endometrial polyps or hyperplasia, fibroids or other cervical disorders. It can also occur without any discernible cause, otherwise known as idiopathic abnormal uterine bleeding (Health Quality Ontario, 2016). AUB can occur in women from adolescence throughout adulthood until menopause, although it is more likely to occur in women older than 30 years of age. AUB has a significant negative impact on quality of life resulting from excessive, prolonged blood loss, particularly when combined with menstrual pain. This can affect a woman's physical, emotional, social and material quality of life (NICE, 2018, Weisberg et al, 2016)

For the purposes of this evaluation, it is assumed that any underlying pathology such as malignancy or structural abnormalities have been ruled out. There are a number of treatment options available for AUB including medical management such as non-steroidal anti-inflammatories, tranexamic acid, hormonal therapy (e.g. oral contraceptives), levonorgestrel intrauterine system (LNG-IUS) or surgery (hysterectomy or endometrial ablation) (NICE 2018). In South Africa the treatment of AUB varies although generally the first line is pharmacotherapy.

Although the LNG-IUS was first introduced to the market as a contraceptive device in the 1990's, it was only subsequent to this that the impact on reducing certain types of abnormal uterine bleeding led to its use as a treatment for menorrhagia. In recent years the adoption of the LNG-IUS as a first-line treatment for AUB in Europe and the US has been widespread, however its availability and accessibility has been limited in developing countries, largely due to concerns around price and affordability (Rademacher et al, 2016).

Increasingly evidence has shown that the LNG-IUS is as effective, if not more effective, in treating AUB compared to medical management or surgery (Lethaby et al, 2015). Furthermore, a number of cost-effectiveness analyses have indicated that, in developed countries, the LNG-IUS is more cost-effective or dominant (costs less with better benefits) compared to medical management (Ganz et al, 2013; Sanghera et al, 2014; Spencer et al, 2017).

In the National Essential Medicines List Committee, a medicines review was conducted in 2015 to determine whether the LNG-IUS should be included in the Standard Treatment Guidelines and Essential Medicines List for the treatment of Heavy Menstrual Bleeding. The conclusion of the review was to *not recommend* the inclusion of the LNG-IUS due to uncertainty around affordability and potential for scope creep. Subsequent to this a health economics and budget impact analysis was requested.

2. South African Guidelines

There are no formal clinical guidelines published in South Africa for the treatment of AUB at this time.

The South Africa Adult Hospital level Standard Treatment Guideline describes treatment options for Uterine Bleeding, Abnormal (Gynaecology - Chapter 5, section 5.2). These include combined oral contraceptives (for restoring cyclicity in women of reproductive years), progestin only (as an alternative to COCs), conjugated oestrogens (in peri-menopausal women), non-steroidal anti-inflammatories or tranexamic acid (Adult Hospital Level STGs and EML 2015)).

3. Aims and Objectives

The aim of this analysis was to determine the cost-effectiveness and budget impact of the LNG-IUS in a public sector setting in South Africa in order to inform whether the LNG-IUS should be included on the Essential Medicines List for the treatment of heavy menstrual bleeding.

The objectives were to;

1. Determine the clinical treatment pathway for AUB in the public sector
2. Conduct a cost-effectiveness analysis comparing LNG-IUS to current treatment options available in the public sector
3. Conduct a budget impact analysis on the introduction of the LNG-IUS to the Essential Medicines List

4. Clinical Pathway

A clinical pathway of the general practice of treatment of heavy menstrual bleeding in South Africa in a public sector setting was determined from the STG recommendations and discussions with the Directorate of Affordable Medicines and Prof Gebhardt (member of the Adult Hospital Level Expert Review Committee EML).

The clinical pathway was developed for 2 populations; women who were in their fertile years (either requiring contraception or wanting to fall pregnant) and older women who were pre- or peri-menopausal.

In the clinical pathway it was assumed that each treatment step was 3 months (ie first line with pharmacotherapy for 3 months), if the patient did not respond to treatment then they would move to the next line of treatment for 3 months before progressing on. The option for introducing the LNG-IUS was following treatment failure of 2nd-line medical management.

An option to continue with medical management or to stop treatment was considered in patients who had failed all available treatments. Surgery was included in the clinical pathway, although only as a last resort and only hysterectomy was considered.

The clinical pathway does not represent all the available treatment options or steps that a patient may take in their treatment journey. The main purpose of the pathway was to determine a structure for the health economics model.

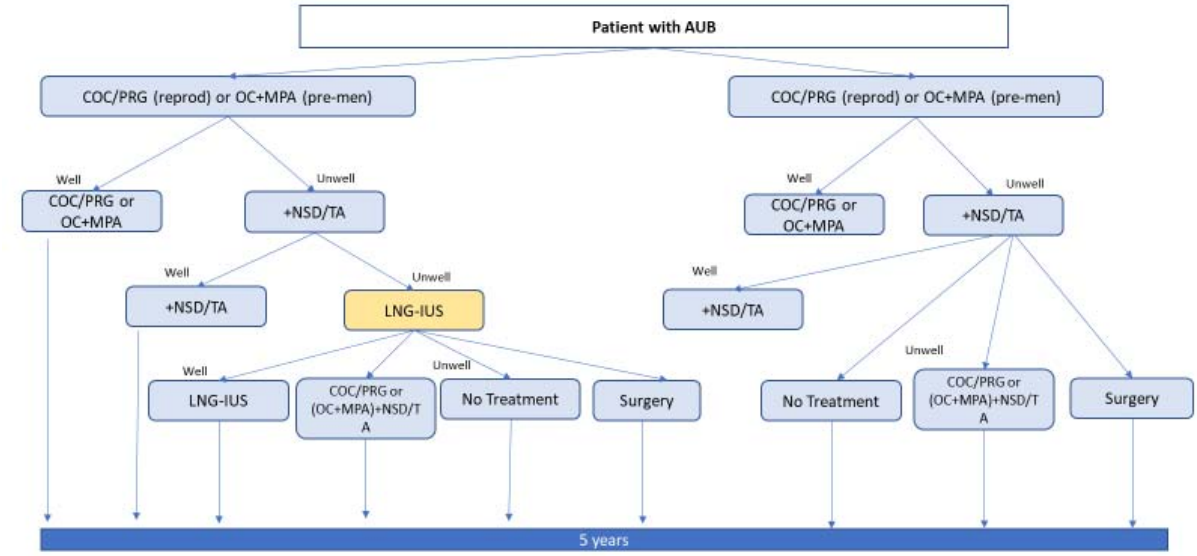

Figure 1. Clinical pathway for treatment of AUB in South Africa

5. Cost-effectiveness Analysis

5.1. Methodology

There are a number of models that have been used in the cost-effectiveness analysis of the LNG-IUS, however these models vary depending on their setting and perspective. Furthermore, these models are complex markov models which require considerable resources to develop and collect input data.

Following discussion with the EML Adult Hospital Level Expert Review Committee, it was agreed to use a more simplified decision-analysis model based on an agreed clinical pathway as presented to the Committee on 15th February 2018 and in consultation with Prof Gebhardt, a member of this Committee. The model was modified a number of times based on discussions with members of the EML as well as other experts in order to arrive at a scenario that was most likely to reflect the South African public healthcare setting. A more complex markov model structure was also proposed but this would be resource intensive and it was unlikely the outcomes would differ significantly to the decision-analysis model. A proposed markov structure is included in

Appendix A. Markov Model Structure – proposal in the event that a more complex model is to be pursued.

The decision-tree model was structured in 3-month cycles for the first year and yearly thereafter up to a final time horizon of 5 years based on the 5 year life of the LNG-IUS model. International health economics models have typically selected a 5-year time horizon (Ganz et al, 2013; Sanghera et al, 2014; Spencer et al, 2017).

Clinical outcomes based on published data are generally only available up to 1 year following the initiation of treatment. An assumption was made that patients would cycle through all the available treatments within the first year and whichever health state a patient was in at the end of Year 1, they would remain in that health state until the end of the model (5 years)

The model structure included 2 cohorts per arm of initial treatment; COC/PRG (oral contraceptive or progestin alone) ie women in their fertile years (wanting to fall pregnant or requiring contraception) and OC+MPA (conjugated estrogens and medroxyprogesterone acetate) ie women in the pre- or peri-menopausal stage of their lives.

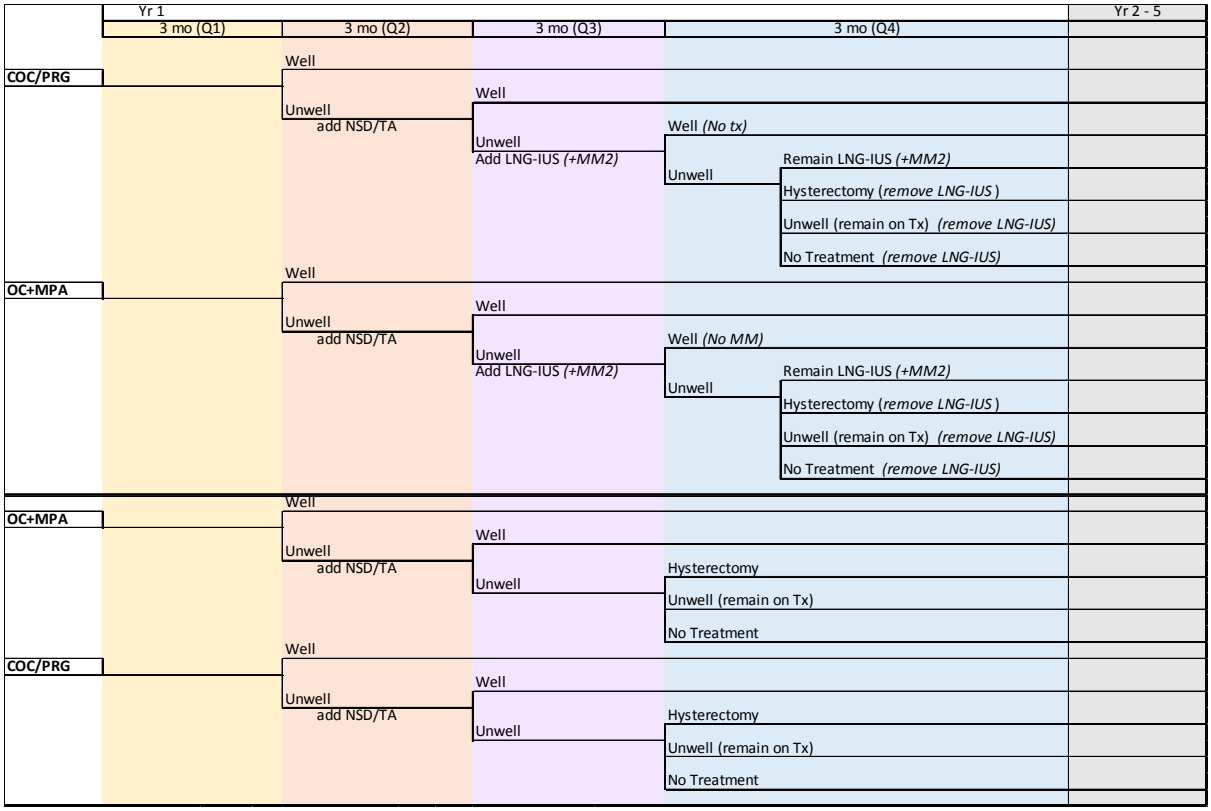

Figure 2. Decision-tree model of treatment options and timelines

A state for surgery (hysterectomy) was included, however it was assumed that the uptake for this treatment option would be low considering the current practice in South Africa. The majority of patients would either remain symptomatic on treatment or stop treatment altogether if they failed medical management.

Pregnancy and the impact on AUB was not considered in the model. It is possible that patients with AUB who fall pregnant will no longer experience AUB after the birth (ie cured after pregnancy). Furthermore, patients who fall pregnant will not be eligible for AUB treatment for the duration of the pregnancy in the model. Introducing a pregnancy state and the impact on AUB could be considered in a more complex model.

The model assumed that all patients continued with the LNG-IUS for 5 years once a patient was well on LNG-IUS or elected to continue with the LNG-IUS despite symptoms although it is possible that patients may request to have the LNG-IUS removed before the 5-year expiry date,

The analysis was carried out from a South Africa public healthcare perspective in a secondary level care setting where only direct costs to the funder (ie that of the Department of Health) were taken into consideration.

5.2. Clinical Inputs

The clinical inputs to the model were based on probabilities of treatment success (well) or treatment failure (unwell) as well as the quality of life experience by patients in each treatment arm (as determined by utilities). Since there are no data available in South Africa on the probabilities or utilities for treatment options in AUB, published data was used to inform the inputs.

Probabilities of treatment success or failure were obtained from the Sanghera study where medical management was categorised as either first line (MM1) or second line (MM2). Depending on the fertility status of the cohort (ie requiring OCs/progesterone alone or requiring hormone replacement therapy), the second line treatment of NSAIDs or tranexamic acid was in addition to the hormonal treatment of the first line therapy (Sanghera et al, 2014). Probabilities of treatment success or failure were validated against data obtained from the Lethaby Cochrane meta-analysis (Lethaby et al, 2015) where the probabilities were found to be similar to the values from the Sanghera study.

It was assumed that the probabilities for success (well) and failure (unwell) of Medical management Treatment 1 and Treatment 2 were the same. When patients failed 2nd line treatment and the LNG-IUS was not available in that cohort, it was assumed that the majority of patients would continue on treatment, albeit unwell.

Treatment modality	Probability*	Source	Verification	
Medical management 1 well	0.402	*Sanghera et al, 2014*	0.44	*Lethaby et al, 2015*
Medical management 1 unwell	0.598	*Sanghera et al, 2014*	0.56	Assumption
Medical management 2 remain well	0.402	*Sanghera et al, 2014*	0.44	*Lethaby et al, 2015*
Medical management 2 unwell	0.598	*Sanghera et al, 2014*	0.56	Assumption
LNG-IUS well	0.639	*Sanghera et al, 2014*	0.635	*Lethaby et al, 2015*
LNG-IUS unwell	0.361	*Sanghera et al, 2014*	0.365	Assumption
LNG-IUS remain	0.907	*Sanghera et al, 2014*		
Hysterectomy	0.017	*Sanghera et al, 2014*		
Unwell remain on tx	0.035	*Sanghera et al, 2014*		
No treatment	0.041	*Sanghera et al, 2014*		
Patients failing Medical Management 2 (no LNG-IUS)				
Hysterectomy	0.017	*Sanghera et al, 2014*		
Unwell remain on tx	0.942	*Assumption*		
No treatment	0.041	*Sanghera et al, 2014*		
**Probability of treatment success - ie pt remains in that health state*				

Table 1. Probabilities of health states in treatment arms

In addition to published probabilities, certain assumptions were made about the probability of patients selecting certain treatment options. For example the number of patients who would chose to take COCs because they require contraception was assumed to be 70% and that the balance of patients would chose to take progestin either because they wanted to fall pregnant or because they couldn't tolerate the COCs and chose to use other methods of contraception. The probability of patients taking NSAIDs in the first line of therapy was based on assumptions around availability and cost where an assumption

was made that the NSAIDs would be more commonly available in secondary level healthcare facilities than tranexamic acid and that NSAIDs are considerably less expensive than tranexamic acid. The probability was increased to 50% in the second-line of treatment where it was assumed that if patients were not responding to NSAIDs then they would be more likely to be prescribed tranexamic acid. These probabilities were tested in the sensitivity analysis to determine the impact of varying these inputs (see cells in blue).

Treatment modality	Probability**
COC	0.7
Progestin alone	0.3
NSD (Q1)	0.8
TXA (Q1)	0.2
NSD (Q2+)	0.5
TXA (Q2+)	0.5
** probability of utilisation of that modality	

Table 2. Probabilities of treatment selection for COC vs progestin and NSAIDs vs tranexamic acid

Where hysterectomy was a treatment option, the probability of undergoing the surgery was assumed to be low (1.7%) in comparison to patients remaining on medical management or the LNG-IUS. This is reflective of clinical practice in South Africa where few patients go on to have surgery for menorrhagia. Hysterectomy may also not be an acceptable treatment option in patients who are wanting to fall pregnant.

No underlying mortality rates were taken into consideration as it was assumed that there was no difference in mortality rate between the different treatment groups, including that of hysterectomy.

Utility values were available from a number of studies and varied somewhat. It was decided to take the format of the Ganz study which provided utilities for medical treatment (respond and fail) and apply to all the oral treatments available in this study (Ganz et al, 2013). The utilities for the LNG-IUS and hysterectomy were taken from the Spenser study (Spenser et al, 2017)

In the Sanghera study (based on the ECLIPSE trial by Gupta et al), utilities were derived from 2 different methods of measuring quality of life, the EQ-5D and the SF-6D. On the whole, there was a substantial difference between the 2 measures where the SF-6D utility values were consistently lower than the EQ-5D values as well as lower than the utility values used in other models (Sanghera et al, 2014). Based on this uncertainty it was decided not to use the SF-6D values, except in the sensitivity analysis.

Treatment Modality	State	Utility	Source
COC/Prog	CCP_well	0.84	*Ganz et al, 2013*
	CCP_unwell	0.76	*Ganz et al, 2013*
OC+MPA	OCM_well	0.84	*Ganz et al, 2013*
	OCM_unwell	0.76	*Ganz et al, 2013*
add NSD/TA	aNT_well	0.84	*Ganz et al, 2013*
	aNT_unwell	0.76	*Ganz et al, 2013*
Add LNG-IUS			
well	aLNG_well	0.89	*Spencer et al, 2017*
symptomatic	aLNG_unwell	0.76	*Ganz et al, 2013*
Hysterectomy	HYS_well	0.87	*Spencer et al, 2017*
Unwell remain on tx	Any_unwell	0.76	*Ganz et al, 2013*
No treatment	No_unwell	0.76	*Ganz et al, 2013*

Table 3. Utility values for decision-tree model

In the first year, treatment lines were presented in 3-month treatment cycles and therefore the QALYs for each quarter in Year 1 were calculated as; QALY (Q1) = p*(u*0.25), QALY (Q2) = p*(u*0.25) etc. Thereafter QALYs for each arm were calculated according to utilities and probabilities per annum.

Benefits (QALYs) were discounted at a rate of 5% as per the South African Pharmacoeconomic Guidelines (NDoH 2013).

5.3. Costs

Medicine costs were obtained from the Master Procurement Catalogue, February 2018. Where more than one product was available for a particular treatment, the order quantity was used to derive a weighted average cost for each treatment. Average monthly and annual costs were determined based on dose, frequency and duration recommendations from the STGs.

In the first and second lines of medical treatment there are substantial cost differences between oral contraceptives and progestins alone as well as between non-steroidal anti-inflammatories and tranexamic acid. The model, however assumes that either one or the other of these treatment options are used per health state (e.g. COC or progesterone alone, NSAIDS or tranexamic acid). Therefore, the probability of utilisation of these different treatment options in each health state was based on assumptions that the less expensive treatment option would have a higher utilisation in the first 3 months of initiating treatment and in the event of treatment failure the more expensive treatment option would be prescribed to more patients in the next 3 months and thereafter.

The costs of visits to a primary healthcare clinic were assessed from a number of different sources; the Health Financing Group study with clinic visit costs for family planning services (Hariharan et al, 2017) and the HE^{2}RO Cost and Cost modelling of Family Planning Services (IPiC) study (HE^{2}RO). It was assumed that the overhead, equipment, laboratory, medical equipment and human resource costs are the same per visit regardless of whether a patient is seen at the clinic for a first consultation, treatment failure consultation and whether they receive oral contraceptive treatment or treatment with non-steroidal anti-inflammatories or tranexamic acid. Since the clinic visit costs from the above studies included the cost of medicines, each clinic visit cost per treatment modality was calculated as the total clinic visit cost less the cost of the medicines from those studies. Costs were inflated to 2018 and an average clinic visit cost of R66.11 was determined. However in discussion with the Adult Level Expert Review Committee it was determined that most patients would access care at a secondary level facility and therefore the UPFS 2018 tariffs for an out-patient visit were used. The variance in costs is addressed in the sensitivity analysis.

The price of the LNG-IUS device was set as per the National Department of Health contract circular RT283-2017 (valid 10/01/2017 to 30/09/2020) at a unit price of R898.00.

The costs of the insertion of the IUS was based primarily on the HE2RO Cost and Cost modelling of Family Planning Services (IPiC) study conducted in 2015 where the personnel services were calculated as total of R163.00 per patient for either removal or insertion of the device, supplies were R3.73 and equipment R 5.02 per patient [unpublished]. The total cost of inserting the LNG-IUS was R201.28 (not including the cost of the device).

The costs for a hysterectomy were obtained from the UPFS 2018 tariffs where a Vaginal Hysterectomy Without Repair is considered a Major Theatre Procedure Category C. A Level 2 facility fee was selected as was the professional fee for a Specialist to perform the procedure.

Summary of Costs in 2018 (ZAR)		
	per month	**per annum**
Combined Oral Contraceptives	2.61	34.04
Progestins	155.38	2 025.55
Conjugated Oestrogens+MPA	168.12	2 191.50
NSAIDs	5.28	68.81
Tranexamic Acid	89.24	1 163.29
Ferrous Sulphate (oral)	9.39	122.39
	per event	
Clinic Visit	198.00	
LNG-IUS (insert)	1099.279	
LNG-IUS (remove)	201.28	
Hysterectomy	6 309.00	

Table 4. Direct cost components

For patients who remained unwell on treatment or with no treatment, an ongoing monthly cost for iron supplementation was included.

The model has not included any costs for sanitary products in women who continue to experience heavy menstrual bleeding despite various treatment lines.

Discounting was carried out at a rate of 5% as per the South African Pharmacoeconomic Guidelines (NDoH 2013). For the hysterectomy and LNG-IUS_well cohorts no further costs were attributed in Years 2-5, however the benefits (QALYs) were still accrued. For patients who did not respond to the LNG-IUS, additional medical management costs accrued over the 5-year time period unless patients elected not to have any treatment at all.

A table of event costs per annum is presented in Appendix B. Summary of Event Costs per year.

5.4. Results

The total costs and QALYs were determined for each arm of the decision-tree and presented as an Incremental Cost Effectiveness Ratio (ICER) of Cost/QALY with a time horizon of 5 years. A 1-year time horizon was also considered for the sensitivity analysis.

COC/PRG	QALYs	Incremental QALYs	Costs	Incremental Costs	ICER (R/QALY)
LNG-IUS	3.79		6 326.61		
No LNG-IUS	3.68	0.11	8 008.62	- 1 682.01	Dominant
OC+MPA	**QALYs**		**Costs**		**ICER (R/QALY)**
LNG-IUS	3.79		11 995.13		
No LNG-IUS	3.68	0.11	14 813.20	- 2 818.07	Dominant

Table 5. Costs and QALYs for a 5-year time horizon

COC/PRG	QALYs	Incremental QALYs	Costs	Incremental Costs	ICER (R/QALY)
LNG-IUS	0.82		1 878.67		-
No LNG-IUS	0.81	0.01	1 823.65	55.02	6 443.26
OC+MPA	**QALYs**		**Costs**		**ICER (R/QALY)**
LNG-IUS	0.82		3 346.64		-
No LNG-IUS	0.81	0.01	3 205.84	140.80	19 235.43

Table 6. Costs and QALYs for a 1-year time horizon

For the 5-year time horizon, the LNG-IUS had improved clinical benefits and fewer costs, thereby making it dominant over the medical management option. For the 1-year time horizon, the incremental benefits were lower than the 5 years but the total costs were slightly higher compared to medical management resulting in an ICER of R6 442/QALY and R19 235/QALY for the 15-44 year cohort and the 45-59 year cohort respectively. This is in line with other published cost-effectiveness analyses where the LNG-IUS has been shown to be dominant compared to medical and surgical management (Ganz et al, 2013; Calaf et al, 2015; Spencer et al, 2017).

The total costs for the peri-menopausal cohort were nearly twice that of the patients in their fertile years (ie taking oral contraceptives or progestins) due to the higher cost of the conjugated oestrogens and medroxyprogesterone acetate combination treatment over the 5-year time period.

5.5. Sensitivity Analysis

A one-way sensitivity analysis was conducted on key variables. The inputs most sensitive to changes are presented as minimum and maximum ICERs per category of variables (ie probabilities, utilities and costs) in Table 7

Variable		Value	15-44 years (COC/PRG)			45-59 years (OC+MPA)		
			Incr. QALYs	Incr. Costs	ICER	Incr. QALYs	Incr. Costs	ICER
Probabilities								
	p_No_treatment (LNG)	0.8	0.11	646.94	5 854.15	0.11	1 003.17	9 077.69
	p_TXA uptake	0.75	0.11	- 1 928.77	Dominant	0.11	- 3 064.83	Dominant
Utilities								
	u_Any_unwell	0.5	0.37	- 1 682.01	Dominant	0.44	- 2 818.07	Dominant
	u_LNG_unwell	0.55	0.02	- 1 682.01	Dominant	0.02	- 2 818.07	Dominant
Costs								
	c_clinic visits	99	0.11	- 1 360.28	Dominant	0.11	- 2 496.34	Dominant
	c_LNG	449	0.11	- 1 842.57	Dominant	0.11	- 2 978.63	Dominant
	c_TXA	44.62	0.11	- 1 430.25	Dominant	0.11	- 2 566.31	Dominant
	c_OC+MPA	84.06		n/a		0.11	- 1 927.84	Dominant
	c_OC+MPA	336.24		n/a		0.11	- 4 598.67	Dominant

Table 7. Incremental Costs and QALYs for key variables sensitivity analysis

In most instances the model remained dominant regardless of changes in the variable inputs. The model was most sensitive to the probability of patients no longer receiving treatment following treatment failure with first and second line medical management or LNG_IUS. This was the only parameter that shifted the ICERs from being dominant to an increased cost for the LNG-IUS with an increased clinical benefit. However, even with a probability of 80% of patients no longer receive any treatment, the ICERs were still below R10 000/QALY

A threshold analysis shows that the model crosses over from being dominant to having an incremental cost for the incremental benefit at the point where the probability is 0.59 (ie nearly 60%) of patients no longer receiving any treatment despite continuing to be unwell.

When the probability of increasing tranexamic acid uptake in the second line of treatment was increased to 75% the incremental costs increased as the costs of the non LNG-IUS arm were increased. In terms of utilities, the model dominance was most sensitive to reductions in utilities of being unwell so as the

utility of patients in the LNG-IUS model who have not responded to the treatment is reduced, so the incremental QALY difference changes.

Changes in costs of treatment, either medical management, the LNG-IUS or clinic visits did not shift the dominance. However, as the cost of the LNG-IUS is reduced to 50% the cost difference between the arms is increased as the LNG-IUS arm becomes even less costly. If the price of the conjugated oestrogens or tranexamic acid is reduced by 50%, the incremental costs are reduced but the model remains dominant.

6. Budget Impact Analysis

A simplified decision analysis model was used to determine the budget impact analysis (BIA). Whereas for the cost-effectiveness analysis (CEA) the model followed treatment pathways from the point of diagnosis, the budget impact analysis starts at the decision node of LNG-IUS or no LNG-IUS. The 2 cohorts of patients either in their fertile years (age 15-44 years) or peri-menopausal (age 45-59 years) were considered as the type and cost of hormonal treatment in each cohort differs. Based on recommendations from the Adult Level Expert Review Committee, a sensitivity analysis was conducted to determine the impact of reducing the age bands in the peri-menopausal cohort to 45-54 years of age as it was debated whether patients 55 years and older would be eligible for this treatment intervention.

It was assumed that any patient entering the model had failed both 1st line (e.g. hormonal treatment) and 2nd line treatment (non-steroidal anti-inflammatories or tranexamic acid). Patients were allocated to either receive the LNG-IUS or No LNG-IUS. Where patients were in the cohort that did not receive the LNG-IUS they were allocated to either receive medical management, no treatment or undergo a hysterectomy. Where treatment with the LNG-IUS failed, patients were allocated to either retain the LNG-IUS but return to medical management or have the LNG-IUS removed and receive medical management, no treatment or undergo a hysterectomy.

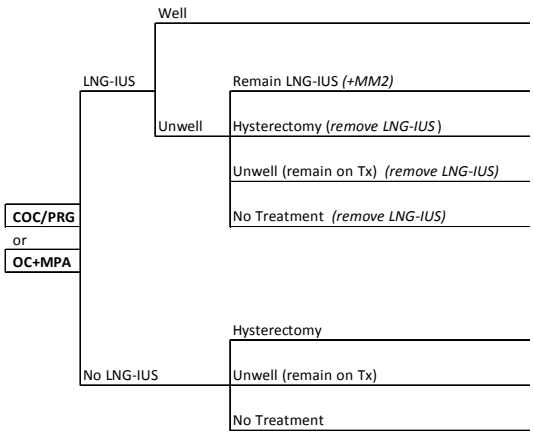

Figure 3. Model structure for budget impact analysis

6.1. Probabilities

The probabilities of moving into different branches of the decision tree were based on the probabilities used in the cost-effectiveness analysis. These were tested in the sensitivity analysis. See Table 1. Probabilities of health states in treatment arms.

6.2. Costing Inputs

The time horizon for the model was 5 years, although a Year 1 cost was also calculated. The 2018 costing inputs for the BIA were taken from the CEA spreadsheets. An average annual inflation rate of 5% was used to inflate costs year on year. It was assumed that with the exception of ongoing medical management, all treatments occurred in the first year. The cost of the LNG-IUS and Hysterectomy were single event costs.

Summary of Costs (ZAR)		2018	2019	2020	2021	2022	Total
	per month	per annum	per annum	per annum	per annum	per annum	
Combined Oral Contraceptives	2.61	34.04	35.75	37.53	39.41	41.38	188.11
Progestins	155.38	2 025.55	2 126.82	2 233.17	2 344.82	2 462.06	11 192.42
Conjugated Oestrogens+MPA	168.12	2 191.50	2 301.08	2 416.13	2 536.94	2 663.79	12 109.45
NSAIDs	5.28	68.81	72.25	75.87	79.66	83.64	380.24
Tranexamic Acid	89.24	1 163.29	1 221.45	1 282.52	1 346.65	1 413.98	6 427.89
Ferrous Sulphate (oral)	9.39	122.39	128.51	134.93	141.68	148.76	676.28
	per event						
Clinic Visit	198.00		207.90	218.30	229.21	240.67	
LNG-IUS (COC/PR) (insert)	1 527.08		1 603.43	1 683.61	1 767.79	1 856.17	
LNG-IUS (OC+MPA) (insert)	1 917.08		2 012.94	2 113.58	2 219.26	2 330.23	
LNG-IUS (remove)	201.28		211.34	221.91	233.01	244.66	
Unwell (MM2 - COC/PRG)		2 284.32	2 398.54	2 518.46	2 644.39	2 776.61	12 622.32
Unwell (MM2 - OC+MPA)		3 844.33	4 036.55	4 238.38	4 450.29	4 672.81	21 242.36
No treatment		122.39	128.51	134.93	141.68	148.76	676.28
Hysterectomy	6 309.00		6 624.45	6 955.67	7 303.46	7 668.63	

Table 8. Summary of medicine and event costs for 2018 to 2022

6.3. Patients eligible for treatment

The total number of patients eligible for treatment was based on 2 age-band cohorts;

- All women aged 15-44 years; in their fertile years, treatment options COC or progestins
- All women aged 45-59 years; peri-menopausal, treatment options conjugated oestrogen combined with medroxyprogesterone acetate

Another cohort of women aged 45-54 years was also considered for the peri-menopausal treatment options.

The total number of women eligible for treatment in the public sector was determined by deducting women eligible in the medical scheme population from the country total population. In light of the impending National Health Insurance, a sensitivity analysis was conducted to determine the budget impact of all eligible women in the total population of South Africa, i.e. including the medical scheme patients.

The epidemiological data on women seeking treatment for heavy menstrual bleeding is limited, particularly in developing countries and in a majority black population. Prevalence data was determined from 3 key studies; Marsh et al (2014) who reported in African America women in the USA, Fraser et al (2015) who reported on a survey of women aged 15-57 in 5 European countries and Zimmerman et al (2012) who reported on a survey of women aged 15-49 years in the US and Europe.

Furthermore, Marsh and Fraser reported on the number of patients who sought treatment for their AUB at 38.9% and 46% respectively. An average of 14.5% patients seeking treatment was used in the model with a lower limit of 10.6% and an upper limit of 20.8%. This is similar to the 11-16% reported in the Harlow study of patients in developing countries reporting AUB to their physician (assuming seeking treatment) (Harlow et al, 2004)

It was assumed that not all patients who seek treatment for AUB will opt for the LNG-IUS and so an uptake rate of 20% in Year 1 was assumed followed by an increase in uptake with each subsequent year as acceptance of the treatment

A Total Cost, Average Cost/patient for each cohort was determined as well as an incremental budget cost of LNG vs No LNG-IUS

	SA Populations 2017	Medical Scheme Population	(Excluding Medical Scheme Members)	
Total Population	56 521 948	8 878 081	47 643 867	
Women	28 901 306	4 694 968	24 206 338	
Women age 15-44	13 984 808	2 063 060	11 921 748	
Women age 45-59	3 823 658	871 522	2 952 136	
Women age 45-54	2 723 515	624 375	2 099 140	
	Aged 15-44 years (COC/PR)	**Aged 45-59 years (OC+MPA)**	**Aged 45-54 years (OC+MPA)**	
Pts eligible for treatment	4 458 734	1 104 099	785 078	*Zimmerman, 2012*
Upper Limit	6 366 213	1 576 441	1 120 941	*Marsh et al, 2014*
Lower Limit	3 242 715	802 981	570 966	*Fraser et al, 2015*
Pts seeking treatment	1 734 447	429 494	305 395	*Fraser et al, 2015*
Upper limit	2 476 457	613 235	436 046	*Fraser et al, 2015*
Lower limit	1 261 416	312 360	222 106	*Fraser et al, 2015*
	Aged 15-44 years (COC/PR)	**Aged 45-59 years (OC+MPA)**	**Aged 45-54 years (OC+MPA)**	
Uptake Year 1	**Cohort n =**	**Cohort n =**	**Cohort n =**	
LNG-IUS (20% uptake)	346 889	85 899	61 079	

Table 9. Prevalence and predicted eligible patient numbers for 2018

6.4. Results

COC/PRG	Costs (Yr 1)	Difference	Costs (Yr 1-5)	Difference
LNG-IUS	815 598 885		2 037 953 566	
No LNG-IUS	785 393 171	30 205 715	4 171 417 216	**-2 133 463 651**
OC+MPA (45-59 yrs)				
LNG-IUS	281 033 742		789 950 877	
No LNG-IUS	320 714 819	-39 681 078	1 730 457 578	**-940 506 701**
OC+MPA (45-54 yrs)				
LNG-IUS	199 831 298		561 700 912	
No LNG-IUS	228 046 847	-28 215 549	1 230 455 752	**-668 754 839**

COC/PRG	Costs (Yr 1) per pt	Difference	Costs (Yr 1-5) per pt	Difference
LNG-IUS	2 351		5 875	
No LNG-IUS	2 264	87	12 025	**-6 150**
OC+MPA (45-59 yrs)				
LNG-IUS	3 272		9 196	
No LNG-IUS	3 734	-462	20 145	**-10 949**
OC+MPA (45-54 yrs)				
LNG-IUS	3 272		9 196	
No LNG-IUS	3 734	-462	20 145	**-10 949**

Table 10. Total and Average patient costs for 2018

The BIA shows that the Total costs of treating AUB run into hundreds of millions of rands per annum. The incremental difference in cost in patients aged 15-44 years (COC/PRG) is around R30 million per year (2018). However, for the patients ages 45-59 and 45-54 years a savings of R39 million and R28

million is achieved respectively with the use of the LNG-IUS. Furthermore, if the model is run over 5 years for that same cohort (ie receive LNG-IUS in Year 1) then the model shows that the LNG-IUS is cost saving in the longer term. The total budget impact is less in the 45-54 years population due to a reduction in numbers of people in that cohort.

The average cost increment per patient is just over R87 in Year 1 in patients who have had the LNG-IUS placed, however for patients who are peri-menopausal, a savings of around R462 is achieved in the first year. This is due to the higher cost of hormone treatment (R168 per month) contributing significantly to the total costs in this patient cohort. The incremental cost difference is the same for both the 45-59 and 45-54 year cohorts.

The budget impact analysis takes into account the prevalence of AUB rather than the incidence (new cases) year on year. The uptake in the first year is likely to be low, however this may increase with greater acceptability in subsequent years.

Assuming a population growth rate of 1.6% (StatsSA) and an increase in annual uptake of 30% (2019), 40% (2020), 50% (2021) and 50% (2022) for the next 4 years, the total cost budget impact per year increases nearly two-fold for the NEW patients aged 15-44 years, however, when the annual ongoing cost of treating existing patients (on medical management) is taken into consideration, an incremental savings is achieved in the LNG-IUS group from the second year onwards. In the patients aged 45-59 years over the next 5 years a savings in the LNG-IUS group is predicted in the first year with an increase every year in savings.

Budget Impact over 5 years

Population	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Eligible for LNG-IUS					
Women age 15-44	1 734 447	1 762 372	1 790 746	1 819 577	1 848 872
Women age 45-59	429 494	436 409	443 436	450 575	457 829
Uptake of LNG-IUS	20%	30%	40%	50%	50%
Women age 15-44	346 889	424 645	407 685	320 179	174 737
Women age 45-59	85 899	105 153	100 953	79 285	43 269
Women age 15-44					
Average cost/pt (per annum) NEW					
LNG-IUS	2 351	2 469	2 592	2 722	2 858
No LNG-IUS	2 264	2 377	2 496	2 621	2 752
Average cost/pt (per annum) Existing					
LNG-IUS		881	925	971	1 020
No LNG-IUS		2 440	2 562	2 690	2 825
Total Cost (per annum)					
LNG-IUS	815 598 885	1 353 924 814	1 770 448 544	2 016 757 621	2 028 458 999
No LNG-IUS	785 393 171	1 856 017 014	2 994 545 693	4 011 759 029	4 716 568 050
Budget Difference	**30 205 715**	**- 502 092 200**	**- 1 224 097 149**	**- 1 995 001 408**	**- 2 688 109 052**
Women age 45-59					
Average cost/pt (per annum) NEW					
LNG-IUS	4 601	4 831	5 073	5 326	5 593
No LNG-IUS	5 251	5 513	5 789	6 078	6 382
Average cost/pt (per annum) Existing					
LNG-IUS		2 083	2 187	2 297	2 411
No LNG-IUS		5 770	6 059	6 362	6 680
Total Cost (per annum)					
LNG-IUS	395 233 203	686 945 499	929 976 955	1 092 902 692	1 137 308 875
No LNG-IUS	451 038 885	1 075 395 902	1 741 940 407	2 339 549 321	2 756 259 286
Budget Difference	**- 55 805 682**	**- 388 450 402**	**- 811 963 452**	**- 1 246 646 629**	**- 1 618 950 411**

Table 11. Total Cost and Average Cost per patient for 2018-2022

If an assumption is made that 80% of patients who fail 1st and 2nd line treatment (and the LNG-IUS in that cohort) *do not remain* on medical management, i.e. that they stop all treatment despite being symptomatic, then the budget implications change with an incremental cost in Years 1 to 3 in the age group 15-44 years, only turning to a savings in Years 4 and 5. Similarly, in the cohort 45-59 years, there is an incremental cost in Years 1 to 3, with a savings achieved in Years 4 and 5.

Population	Year 1	Year 2	Year 3	Year 4	Year 5
Women age 15-44					
Budget Difference	**413 064 126**	**401 541 721**	**233 036 712**	**- 43 592 429**	**- 394 537 565**
Women age 45-59					
Budget Difference	**168 926 187**	**147 135 904**	**55 418 945**	**- 81 833 604**	**- 246 803 735**

Table 12. Total Cost difference assuming 80% pts stop all treatment following treatment failure.

6.5. Sensitivity Analysis

The BIA is most sensitive to changes in probability of patients electing to have no treatment in both cohorts and the probability of being well with the LNG-IUS where the highest incremental budget costs are seen. If the probability increases to 80% of patients electing not to take any treatment despite being symptomatic following treatment failure, the total budget increment for 2018 increases to R413m pa in the cohort 15-44 years and R120m pa in the cohort of 45-59 years. However, over a 5-year period, a savings of R104m and R79m is reflected in those cohorts respectively. When the probability of being well with the LNG-IUS increases to 0.8 the model becomes cost saving (R97m) even in the age group 15-44 years in the first year.

If the cost of progestin treatment in the cohort 15-44 years is halved to R78pm, then the budget impact is increased to an incremental difference of R67m in the first year. However, this returns to a savings of over R1bn in the overall 5 year time horizon for that cohort.

In order for the model to be cost neutral in the 15-45 year cohort in the first year, the price of the LNG-IUS should be just less than R811.

If the total population of eligible women is considered (including public sector and private sector patients) the total cohort of patients utilising the LNG-IUS (assuming a 20% uptake) increases to over by 60 000 in the 15-44 years and by 25 359 and 18 168 in the 45-59 and 45-54 years cohorts respectively. The total budget impact for the whole population for 15-44 years is greater at R35 million in the first year, however over the full 5 years still results in a savings of over R2.5bn.

	Aged 15-44 years (COC/PR)	Aged 45-59 years (OC+MPA)	Aged 45-54 years (OC+MPA)
Uptake Year 1	**Cohort n =**	**Cohort n =**	**Cohort n =**
LNG-IUS (20% uptake)	406 919	111 258	79 247

COC/PRG	Costs (Yr 1)	Difference	Costs (Yr 1-5)	Difference
LNG-IUS	956 738 375		2 390 621 688	
No LNG-IUS	921 305 558	35 432 817	4 893 281 494	**-2 502 659 806**
OC+MPA (45-59 yrs)				
LNG-IUS	363 999 800		1 023 158 144	
No LNG-IUS	415 395 424	-51 395 624	2 241 318 815	**-1 218 160 671**
OC+MPA (45-54 yrs)				
LNG-IUS	259 269 766		728 775 051	
No LNG-IUS	295 877 839	-36 608 073	1 596 446 495	**-867 671 444**

The full details of the Total Cost and Average Cost budget impact sensitivity analysis are in Appendix C. Sensitivity Analysis of Total Cost Budget Impact and Appendix D: Sensitivity Analysis of Average Cost/Pt Budget Impact

7. Conclusion and Recommendations

The introduction of the LNG-IUS as a third line treatment for heavy menstrual bleeding in South Africa is shown to be dominant, ie costs less and has a better clinical benefit in both the younger and older cohorts. This is largely due to the ongoing pharmacotherapy treatment costs of patients year on year compared to the once-off cost of the LNG-IUS in the first year. Variations in input parameters in the sensitivity analysis fail to shift the dominance with the exception of increasing the probability of no treatment to 59%.

The budget impact analysis shows a substantial level of costs for the treatment of AUB. In the first year of treatment, the LNG-IUS cohort has higher costs in the 15-44 year age group compared to those on medical management (ie No LNG-IUS). In the older patient cohort (45-59 years) the budget impact shows a savings in the LNG-IUS group. Over a 5-year time period it is proven to be cost-saving for both cohorts (age 15-44 and age 45-59).

A recommendation may be to introduce the LNG-IUS in older patients (i.e. peri-menopausal) as this is shown to be cost-effective and cost-saving in the budget.

This evaluation has been based on clinical inputs from international studies as there is no local data to draw upon. Furthermore the prevalence of AUB in South Africa is unknown and hence there are considerable uncertainties in the model. It would be a recommendation that a costing analysis is conducted to determine how much treatment of AUB actually costs in South Africa in the public sector as well as a survey of numbers of patients requiring treatment and their treatment preferences.

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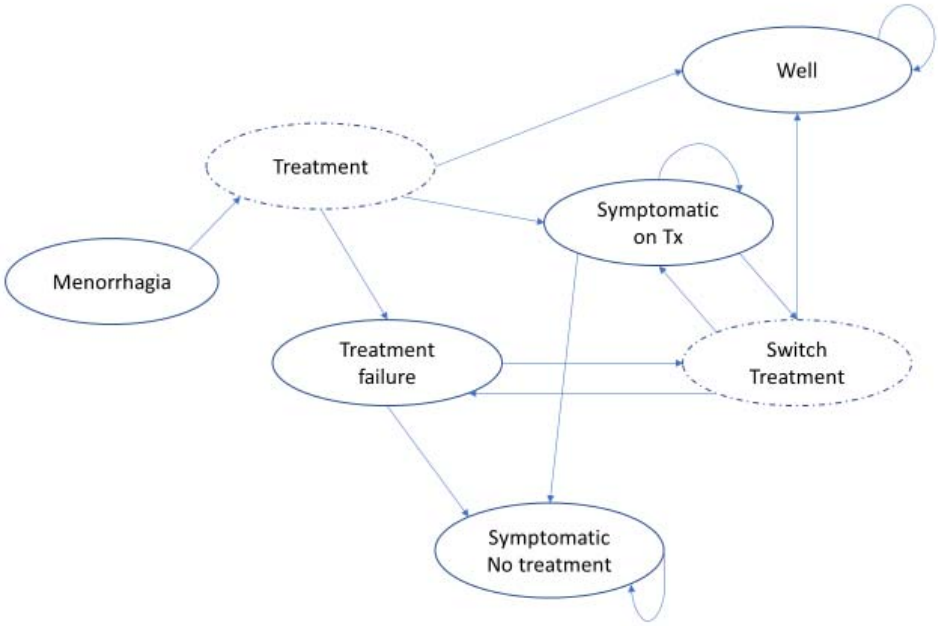
Appendix A. Markov Model Structure – proposal



Appendix B. Summary of Event Costs per year

Event Costs per Time Period									
	Q1	**Q2**	**Q3**	**Q4**	**Yr 1 Ann_Cost**	**Yr 2**	**Yr 3**	**Yr 4**	**Yr 5**
(COC/PRG)									
1st Line MM (well)	355.87	355.87	355.87	355.87	1 423.49	1 352.32	1 284.70	1 220.47	1 159.45
2nd Line MM (well)		427.80	427.80	427.80	1 711.20	1 625.64	1 544.36	1 467.14	1 393.78
2nd Line MM (unwell)		571.08	571.08	571.08	2 284.32	2 170.11	2 061.60	1 958.52	1 860.59
(OC+MPA)									
1st Line MM (well)	745.88	745.88	745.88	745.88	2 983.50	2 834.33	2 692.61	2 557.98	2 430.08
2nd Line MM (well)		817.80	817.80	817.80	3 271.21	3 107.65	2 952.27	2 804.66	2 664.42
2nd Line MM (unwell)		961.08	961.08	961.08	3 844.33	3 652.12	3 469.51	3 296.03	3 131.23
LNG-IUS									
LNG-IUS Initial (+MM2 COC)			1 527.08	0	1 527.08				
LNG-IUS Initial (+MM2 OC)			1 917.08	0	1 917.08				
R-LNG			201.28		201.28				
Unwell (MM2 - COC/PRG)			571.08	571.08	2 284.32	2 170.11	2 061.60	1 958.52	1 860.59
Unwell (MM2 - OC+MPA)			961.08	961.08	3 844.33	3 652.12	3 469.51	3 296.03	3 131.23
Hysterectomy			6309		6 309.00				
No treatment			30.60	30.60	122.39	116.27	110.46	104.93	99.69

Appendix C. Sensitivity Analysis of Total Cost Budget Impact

Sensitivity Analysis (Total Cost)		Year 1 (ZAR millions)		Year 1-5 (ZAR millions)	
Variable	**Value**	**Inc Cost (COC/PRG)**	**Inc Cost (OC+MPA)**	**Inc Cost (COC/PRG)**	**Inc Cost (OC+MPA)**
Probabilities					
p_LNG-IUS_Well	0.639	30.21	-39.68	-2 133.46	-940.51
	0.8	-97.29	-91.58	-2 806.11	-1 219.37
	0.48	156.12	11.57	-1 469.18	-665.11
p_LNG-IUS_remain	0.907	30.21	-39.68	-2 133.46	-940.51
	0.831	-5.89	-68.94	-2 090.56	-1 042.18
	0.22	-49.67	-76.83	-2 653.20	-1 165.17
p_Hysterectomy	0.017	30.21	-39.68	-2 133.46	-940.51
	0.05	1.60	-43.94	-2 086.45	-913.25
p_No_treatment (no LNG)	0.041	30.21	-39.68	-2 133.46	-940.51
	0.1	74.45	-20.82	-1 888.97	-836.28
	0.5	374.43	107.07	-231.39	-129.64
	0.8	599.42	202.98	1 011.80	400.35
p_No_treatment (both)	0.041	30.21	-39.68	-2 133.46	-940.51
	0.50	261.74	56.96	-906.47	-419.50
	0.80	413.06	120.12	-104.51	-78.96
Prevalence					
Women with AUB	37.40%	30.21	-39.68	-2 133.46	-940.51
	53.40%	43.13	-56.66	-3 046.18	-1 342.86
	27.20%	21.97	-28.86	-1 551.61	-684.00
Uptake of LNG-IUS	0.2	30.21	-39.68	-2 133.46	-940.51
	0.4	60.41	-79.36	-4 266.93	-1 881.01
	0.6	90.62	-119.04	-6 400.39	-2 821.52
Costs					
c_COC	2.61	30.21	-39.68	-2 133.46	-940.51
	1	32.00		-2 117.77	
c_ Progestins	155.38	30.21	-39.68	-2 133.46	-940.51
	77.69	67.30		-1 809.25	
	310.76	-43.98		-2 781.84	
c_OC+MPA	168.12	30.21	-39.68	-2 133.46	-940.51
	336.24		-105.94		-1 519.60
	84.06		-6.56		-650.98
c_LNG	898	30.21	-39.68	-2 133.46	-940.51
	811	0.03	-47.15	-2 163.64	-947.98
	673.5	-47.67	-58.97	-2 211.34	-959.79
	449	-125.55	-78.25	-2 289.22	-979.08

Appendix D: Sensitivity Analysis of Average Cost/Pt Budget Impact

Sensitivity Analysis (Ave Cost/Pt)		Year 1		Year 1-5	
Variable	**Value**	**Inc Cost (COC/PRG)**	**Inc Cost (OC+MPA)**	**Inc Cost (COC/PRG)**	**Inc Cost (OC+MPA)**
Probabilities					
p_LNG-IUS_Well	0.639	87.08	-461.95	-6 150.27	-10 949.00
	0.8	-280.46	-1 066.08	-8 089.34	-14 195.40
	0.48	450.04	134.67	-4 235.29	-7 742.92
p_LNG-IUS_remain	0.907	87.08	-461.95	-6 150.27	-10 949.00
	0.831	-16.98	-802.60	-6 026.60	-12 132.66
	0.22	-143.19	-894.39	-7 648.55	-13 564.42
p_Hysterectomy	0.017	87.08	-461.95	-6 150.27	-10 949.00
	0.05	4.61	-511.53	-6 014.74	-10 631.70
p_No_treatment (no LNG)	0.041	87.08	-461.95	-6 150.27	-10 949.00
	0.1	214.63	-242.36	-5 445.45	-9 735.60
	0.5	1 079.40	1 246.42	-667.03	-1 509.16
	0.8	1 727.98	2 363.00	2 916.78	4 660.66
p_No_treatment (both)	0.041	87.08	-461.95	-6 150.27	-10 949.00
	0.50	754.52	663.05	-2 613.13	-4 883.59
	0.80	1 190.77	1 398.35	-301.28	-919.27
Prevalence					
Women with AUB	37.40%	87.08	-461.95	-6 150.27	-10 949.00
	53.40%	124.33	-659.58	-8 781.40	-15 633.06
	27.20%	63.33	-335.96	-4 472.92	-7 962.91
Uptake of LNG-IUS	0.2	87.08	-461.95	-6 150.27	-10 949.00
	0.4	174.15	-923.90	-12 300.54	-21 897.99
	0.6	261.23	-1 385.85	-18 450.81	-32 846.99
Costs					
c_COC	2.61	87.08	-461.95	-6 150.27	-10 949.00
	1	92.25		-6 105.03	
c_ Progestins	155.38	87.08	-461.95	-6 150.27	-10 949.00
	77.69	194.01		-5 215.63	
	310.76	-126.77		-8 019.39	
c_OC+MPA	168.12	87.08	-461.95	-6 150.27	-10 949.00
	336.24		-1 233.27		-17 690.62
	84.06		-76.32		-7 578.46
c_LNG	898	87.08	-461.95	-6 150.27	-10 949.00
	673.5	0.08	-548.95	-6 237.27	-11 036.00
	627.5	-137.42	-686.45	-6 374.77	-11 173.50
	449	-361.92	-910.95	-6 599.27	-11 398.00