Cost-effectiveness of an Outpatient Uterine Assessment and Treatment Unit in Patients with Abnormal Uterine Bleeding

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I would like to dedicate this thesis to my dad, Major Patrick Bennett.

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TABLE OF CONTENTS

PREFACE

Contributions of the student

Alexandria Bennett is the primary author of all thesis content. The concept and methods for the studies were conceived by Alexandria Bennett, Drs. Kednapa Thavorn, Doug Coyle, and Sukhbir S. Singh. Alexandria analyzed data with the assistance of Kednapa Thavorn. Alexandria Bennett is the primary author of both manuscripts included in this thesis. All listed authors for each manuscript provided feedback and approval of the final versions presented in this thesis.

Contributions of authors

The authors included in these manuscripts adhere to the International Committee of Medical Journal Editors (ICMJE).

Approvals

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ACRONYMS AND ABBREVIATIONS

95% CI	95% confidence interval
ACOG	American College of Obstetricians and Gynecologists
AUB	Abnormal uterine bleeding
HMB	Heavy menstrual bleeding
MIS	Minimally invasive surgery
MRI	Magnetic resonance imaging
NIHR	National Institute of Health Research
OCCI	Ontario Case Costing Initiative
OHRI	The Ottawa Hospital Research Institute
OR	Operating room
PALM-COEIN	**P**olyps, **A**denomyosis, **L**eiomyoma, **M**alignancy (and hyperplasia), **C**oagulopathy, **O**vulatory disorders, **E**ndometrial, **I**atrogenic **N**ot otherwise classified
RCT	Randomized controlled trial
SIS	Saline infusion sonohysterography
SOB	Schedule of Benefits
SOGC	Society of Obstetricians and Gynaecologists of Canada
TOH	The Ottawa Hospital
TOHAMO	The Ottawa Hospital Academic Medical Organization
TOHDW	The Ottawa Hospital Data Warehouse
UATU	Uterine Assessment and Treatment Unit

ABSTRACT

Abnormal uterine bleeding (AUB) is one of the most common presenting complaints in our medical system with up to 30% of females affected by this condition. The current evaluation and management of AUB often requires multiple lengthy visits to both general practitioners and specialists. Advances in endoscopic technology have allowed clinicians to diagnose and treat women presenting with AUB in a single-visit within an outpatient uterine assessment and treatment unit (UATU). Unfortunately, the UATU is not the standard of care with very few locations in Canada providing this type of service. This thesis project aimed to synthesize data pertaining to efficacy and safety as well as to evaluate the cost-effectiveness of a UATU service model compared to usual care in diagnosing and treating AUB.

To address the main aim for this thesis project, the first manuscript focuses on the hysteroscopic procedures that may be offered in a UATU. The manuscript includes a systematic review that synthesizes outcome measures surrounding efficacy, patient safety, and cost data of outpatient hysteroscopy compared to hysteroscopy performed in the operating room. The second manuscript is a cost-effectiveness modelling study that compares cost and effectiveness outcomes, including time to diagnosis and time to treatment of a UATU versus usual care for women who present with AUB. Data used to populate the cost-effectiveness model were obtained from a retrospective review of patient charts and the published literature.

The systematic review found no statistically significant difference in the safety, efficacy, or patient tolerability between outpatient and intraoperative hysteroscopy procedures. This review helps provide further support for performing procedures outside of a traditional operating room without increasing patient harm or compromising efficacy. However, given the current available evidence and limited number of studies, findings should be interpreted with caution.

The cost-effectiveness analysis found that a UATU is cost-effective when compared to usual care in diagnosing and treating patients who present with AUB. These two studies combined provide evidence to support that the UATU has the potential to improve gynecologic care by reducing wait-times to receiving diagnosis and treatment and to lower overall costs to the health care system.

LIST OF FIGURES

Chapter 1: Background and Introduction

Chapter 2: Systematic Review and Meta-Analysis

Chapter 3: Cost-Effectiveness Analysis

LIST OF TABLES

Chapter 2: Systematic Review and Meta-Analysis

Chapter 3: Cost-Effectiveness Analysis

LIST OF APPENDICES

Chapter 2: Systematic Review and Meta-Analysis

Chapter 3: Cost-Effectiveness Analysis

CHAPTER 1: INTRODUCTION AND BACKGROUND

1.1 Introduction

The following introduction and background chapter introduces the objectives and structure of this thesis project. This chapter describes the importance of this thesis and provides a background section outlining abnormal uterine bleeding (AUB), a one-stop uterine assessment and treatment unit (UATU), the current Canadian standard practice for uterine assessment and treatment, and similar previous economic evaluations.

Research problem

AUB is one of the most common presenting complaints in our medical system with up to 30% of females affected by this condition.[1] The current evaluation and management of AUB often requires multiple lengthy visits to both general practitioners and specialists which, in turn, leads to longer wait-times, reduced access to care, impact on quality of life, and increased health care costs. Advances in technology have allowed women presenting with AUB to be assessed, diagnosed, and treated safely without general or regional anesthesia in a single-visit at an outpatient UATU,[2] where physicians can use high-definition, small diameter hysteroscopes to accurately visualize the uterine cavity and treat pathology.[3] Evidence suggests that hysteroscopy performed in an outpatient or office setting is preferred by most women, avoids complications, reduces costs, and allows for quicker recovery time.[4,5] Furthermore, the UK Royal College of Obstetricians and Gynaecologists have suggested the following in their 2011 guideline on this topic: *"All gynaecology units should provide a dedicated outpatient hysteroscopy service to aid*

management of women with abnormal uterine bleeding. There are clinical and economic benefits associated with this type of service."[6]

Although these approaches exist, an outpatient UATU is not standard practice in Canada's health care system and most hysteroscopic diagnostic and therapeutic procedures occur in formal operating rooms under general anesthesia. Cases that could potentially avoid formal operating rooms use a significant portion of elective surgical time and resources that could be allocated elsewhere.[7] The uptake of a UATU into clinical practice has been limited by a deficiency in training for providers, the need for outpatient clinic space, and lack of studies demonstrating its effectiveness and cost to the health care system.[4,8,9]

Objectives

The overall objective of this thesis project is to assess the cost-effectiveness of an outpatient UATU service model compared to the current standard practice of evaluating and treating AUB. The goal of an outpatient UATU service model aligns with the triple aim of improving the patient health care experience, population health by improving accessibility, and reducing the cost of the care provided. The specific objectives of this thesis project are to synthesize evidence regarding safety and efficacy of UATU and evaluate the cost-effectiveness of a UATU from the perspective of the Canadian health care system.

The need for a systematic review

To address the main objectives, the first part of this thesis aims to synthesize the available literature on current evidence surrounding the safety and efficacy of outpatient hysteroscopic procedures that would be performed in an outpatient UATU. The aim is to compare outpatient

hysteroscopy to hysteroscopy performed in the main operating room under general anesthesia. The objective of the systematic review is to characterize outpatient hysteroscopy by synthesizing outcome measures surrounding efficacy, patient safety, and cost.

The need for a cost-effectiveness analysis

The second part of this thesis aims to perform a cost-effectiveness analysis to assess whether the benefits of a UATU outweigh its costs. Conventional practice to evaluate and treat AUB is currently cumbersome for those involved (patient and provider) and costly to our system. If hysteroscopy is part of the pathway, then it is most often done under general anaesthesia in hospital. The costs associated with surgery and hospital admission for conventional practice of treating AUB have not been formally evaluated in a contemporary Canadian health economic evaluation. The National Institute for Health Research (NIHR) in the United Kingdom has conducted a health technology assessment (HTA) of outpatient uterine assessment and treatment and concluded that outpatient uterine treatment was non-inferior to inpatient treatment and more cost-effective. However, NIHR recommended that patients be aware that failure to treat uterine conditions is more likely with outpatient treatment and procedure acceptability was slightly lower. Currently there are no studies demonstrating the cost-effectiveness of outpatient uterine assessment from the perspective of the Canadian health care system.[8,10] Given the financial constraints of the Canadian health care system, the cost-effectiveness analysis will inform how to best allocate scarce health care resources. The following cost-effectiveness analysis aims to demonstrate the clinical benefit and the financial implications of a UATU to the hospital and the Canadian health care system.

Relevance to research

The results from this thesis project could help Canadian hospitals to better align health care delivery with best care practices by providing evidence-based tools to health care providers and policy makers. As it stands, there is little research investigating the cost-effectiveness of implementing a UATU as it is not the first-line treatment in many Canadian health care facilities. In the UK, the health technology assessment evaluating outpatient polypectomy has supported the procedure as being effective, acceptable and cost saving.[10] Further rigorous research is needed to evaluate the cost and benefits surrounding a UATU, especially in the Canadian setting.

Outpatient non-gynecologic endoscopic procedures (i.e. colonoscopy and cystoscopy) are available in most Canadian hospitals, so very little additional infrastructure and training would be required to begin offering a UATU service from a systems perspective. This research may help the local women's health care providers advocate for expansion of similar outpatient services for uterine conditions. The secondary impact that will be studied is the patient experience including timely access to care. It is important to consider the patient's quality of life as there's a need to advocate for greater accessibility to Canadian women in terms of gynecological care and to provide care that is timely, less expensive, and beneficial to the patient.[11] Through a systematic review and a health economic evaluation we aim to assess whether an outpatient UATU service could improve the patient experience and provide better health outcomes at lower costs.

Outline of thesis organization

This thesis project is organized by manuscript, with chapter 2 and 3 comprising of the manuscripts. Chapter 2 includes a systematic review that synthesizes the available literature,

while chapter 3 includes a cost-effectiveness analysis that simultaneously assesses the cost and effectiveness data surrounding a UATU. Chapter 4 summarizes the entire thesis project with an overall discussion and conclusion.

1.2 Background

Abnormal uterine bleeding

AUB is defined as "bleeding from the uterine corpus that is abnormal in volume, regularity, and/or timing that has been present for the majority of the last 6 months," and may include postmenopausal, irregular menstrual, or heavy menstrual bleeding.[12] AUB is a condition that affects approximately 30% of women during their reproductive years and accounts for more than 20% of referrals to the gynaecologist.[13] The impact of AUB on a woman's physical, social, emotional, and material quality of life is significant.[14–16] Since AUB heavily relies on the subjective experience of women, the American College of Obstetricians and Gynecologists (ACOG) uses the patient-centered definition of HMB, "excessive menstrual blood loss which interferes with a woman's physical, social, emotional, and/or material quality of life" as an indication for investigation and treatment options.[15]

Once bleeding is defined as being abnormal, the International Federation of Gynecology and Obstetrics (FIGO) classification system for causes of AUB provides a framework approach to inform treatment options and accurately diagnose AUB.[17] The PALM-COEIN framework categorises conditions causing AUB as structural (PALM) or non-structural (COEIN): **P**olyps, **A**denomyosis, **L**eiomyoma, **M**alignancy (and hyperplasia), **C**oagulopathy, **O**vulatory disorders, **E**ndometrial, **I**atrogenic, and **N**ot otherwise classified. PALM categories are assessed visually with the help of imaging and histopathology, while COEIN categories are assessed by history and lab tests.[18]

AUB is a common and debilitating condition that not only directly impacts women, but significantly burdens the economy and health services financially. One study aimed to estimate the total annual societal cost of uterine fibroids in the United States and found that direct costs

(surgery, hospital admissions, outpatient visits, and medications) were an estimated $4.1 to $9.4 billion annually.[19] The same study also found that estimated lost work costs ranged from $238 million to $7.76 billion annually. Another American study reported financial losses of over $2000 per patient per annum due to work absence and home management costs due to AUB,[20,21] while a Danish study of menstrual disorders estimated that they incurred health care resource use of 150 million Danish Kroner in 1991 ($US 28 million) and it is approximately 0.4% of the total Danish health expenditure.[22]

Outpatient UATU

When clinically evaluating AUB, the primary goal is to establish a specific diagnosis, including ruling out cancer, in the most efficient and least invasive manner possible. For this reason, outpatient hysteroscopy, when combined with pelvic transvaginal ultrasound and endometrial biopsy is invaluable to the investigation of AUB.[2,14] The outpatient UATU uses hysteroscopy to visualize the uterine cavity to diagnose and treat intrauterine pathology. Outpatient hysteroscopy is a gynecological procedure that uses a miniature endoscope to directly visualise and examine the uterine cavity, without the need for formal operating rooms or general anaesthesia.[23] Improvements in the design of the smaller-diameter hysteroscopes have also made it possible to carry out operative procedures to treat common intrauterine conditions in an outpatient setting. The hysteroscopic approach is suitable for a range of surgical

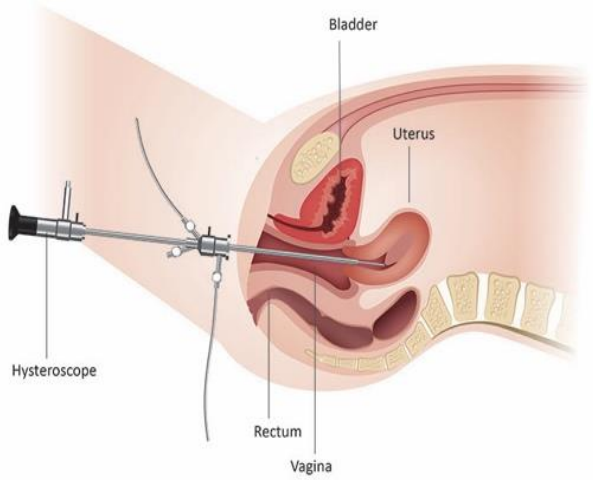

Figure 1.1: Hysteroscopic procedure courtesy of RCOG: *https://www.rcog.org.uk/en/patients/patient-leaflets/outpatient-hysteroscopy/*

interventions including endometrial biopsy, polypectomy, fibroid resection, endometrial ablation, and sterilization.[24] In this thesis project, we aim to model a UATU which is a one-stop, see-and-treat clinic that allows patient consultation followed by uterine assessment and treatment to occur in a conscious patient in one visit.

Moving gynecological procedures to the outpatient setting can save the patient from needing a major surgical procedure which reduces the risks and costs associated with surgery and anesthesia.[25] Post-procedure, studies have shown that outpatient hysteroscopy is associated with low rates of adverse events, high physician acceptance, and significant quality of life improvements up to 12 months post-procedure.[4,25,26] In addition to its safety benefits, the outpatient procedure also offers timely diagnosis and treatment. The outpatient hysteroscopy procedure takes between 5 and 10 minutes, with the total time at the clinic roughly adding up 30 to 60 minutes in total.[27] Although outpatient hysteroscopy has shown to be a more rapid and efficient method to diagnose and treat AUB, most uterine assessment and treatment still continues to occur in a formal operating rooms under general anesthesia.[28]

Figure 1.2: Outpatient hysteroscopy unit at The Ottawa Hospital. Courtesy of S.Singh and O. Bougie.

Current clinical practice

There has been poor adoption of best practice guidance for uterine therapy and as a result, most patient care continues to occur in major operating rooms where the patient is admitted for a surgical procedure.[26] At present, multiple visits to a health care provider to treat these common gynecologic conditions are required, and due to a delay in evaluation and treatment, many patients are often offered hysterectomy to completely remove the uterus instead of specific therapy that may have been successfully treated at hysteroscopy or other methods. Hysterectomy is one of the most common surgeries in Canada and is an invasive surgical procedure which presents significantly more complications and risks to the patient and increased costs to the health care system.[29,30]

Current clinical guidelines recommend that the hysteroscopic management of uterine conditions such as heavy menstrual bleeding, uterine fibroids, and lesions suspicious for uterine cancer is best done without general anesthesia.[13,15,31] Guidelines in the UK also recommend that all gynecology units provide uterine assessment and treatment in an outpatient setting outside the traditional operating room; however in Canada this intervention remains a major operative procedure requiring general anesthesia and multiple pre and post-operative visits.[24,31,32] In 2011, The Royal College of Obstetricians and Gynaecologists recommend that all services should have a dedicated outpatient hysteroscopy service away from the operating theatre with an appropriately sized and staffed treatment room.[23]

Previous economic evaluations

A recent economic evaluation and formal HTA was carried out alongside a randomized Outpatient Polyp Treatment (OPT) trial in the United Kingdom from the perspective of the UK

National Health Service (NHS). The HTA compared outpatient and inpatient polypectomy and concluded that the treatment of uterine polyps in the outpatient setting is less expensive than inpatient treatment and similarly effective, resulting in outpatient polypectomy being the cost-effective treatment option.[33,34] The findings from the HTA and OPT trial provides strong evidence to support outpatient polypectomy for women presenting with polyps from a UK prospective, whereas the following thesis aims to provide a broad Canadian perspective on not only polyps but all conditions that cause AUB.

Other cost-analyses have been conducted that compare costs across outpatient and inpatient hysteroscopy units, with many concluding that outpatient hysteroscopy is the less expensive treatment option.[8,29,35] An American study in particular concluded a surgical procedure performed laparoscopically cost US$3449 while a similar office procedure cost US$1374, yielding a US$2075 difference.[29] Although many studies evaluating outpatient hysteroscopy exist, the NHS HTA study by Diwakar et al. is the only formal cost-effectiveness and cost-utility analysis to our knowledge.

CHAPTER 2: SYSTEMATIC REVIEW AND META-ANALYSIS

Title: Effectiveness of Outpatient versus Operating Room Hysteroscopy for the Diagnosis and Treatment of Uterine Conditions: A Systematic Review and Meta-Analysis

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2.1 Abstract

Objective: Traditionally, hysteroscopy has been performed in the main operating room (OR) under general anaesthesia. Hysteroscopy performed in an office setting avoids the risks of general anaesthesia. The aim of this review is to evaluate the effectiveness of outpatient hysteroscopy compared to hysteroscopy performed in the OR to diagnose and/or treat intrauterine pathology.

***Methods*:** Relevant electronic databases were searched including Medline, EMBASE, and the Cochrane Library. Randomized controlled trials (RCTs) and non-randomized studies that compared the efficacy of outpatient hysteroscopy and traditional hysteroscopy performed in the OR were included. The primary outcome of interest was diagnostic accuracy and secondary outcomes included treatment success, adverse events, pain, patient satisfaction, and cost. The Cochrane risk of bias tool was used to assess RCTs and the Down's and Black tool was used for non-randomized studies.

Results: A total of 12,658 abstracts and 347 full-text articles were assessed, from which a total of 20 full-text studies met our eligibility criteria. No study compared the diagnostic accuracy of outpatient hysteroscopy to hysteroscopy performed in the OR. There was no significant difference between hysteroscopy performed in the outpatient and OR setting for treatment success, adverse events, and patient satisfaction. In the included RCTs, there was greater reported post-operative pain in the outpatient setting [SMD 0.19, 95% CI 0.01, 0.37]. All seven economic studies concluded that outpatient hysteroscopy (range US$97 - US$1258) is substantially less expensive than hysteroscopy performed in the OR (range US$258 - US$3144). Included RCTs presented with serious risks of selection, performance, and detection bias.

Conclusion: The results from this review demonstrate that implementing hysteroscopy in an outpatient setting without general anesthetic should be thoughtfully considered. The current available evidence demonstrates greater reported post-operative pain in the outpatient setting and no statistically significant differences in all other studied outcome measures between outpatient and intraoperative hysteroscopy procedures.

Keywords: Outpatient hysteroscopy, effectiveness, systematic review, abnormal uterine bleeding

PROSPERO trial registration: CRD42017057843

2.2 Introduction

Based on national and international guidelines, the ideal location for hysteroscopy procedures that manage uterine conditions would be in an outpatient or ambulatory setting that avoids general anaesthesia. [1,6,36,37] Hysteroscopy can be performed safely without the need for general anaesthesia outside of the conventional operating room (OR) setting to effectively evaluate the uterine cavity, increasing its use in gynecologic practice internationally.[37] Many non-randomized studies in the literature investigating outpatient hysteroscopy without general anaesthesia have reported on its high success rate with minimal complications.[38–41] When compared to hysteroscopy performed in the OR, outpatient or ambulatory hysteroscopy is a non-invasive alternative that has the potential to avoid invasive surgical procedures, improve patient experience, and provide overall better health outcomes.[42–44] The evaluation and management of intrauterine pathology is an essential part of gynaecologic practice and hysteroscopy can be used in the diagnostic evaluation of conditions in the uterine cavity such as abnormal uterine bleeding, neoplastic disorders, and infertility. Along with diagnostic evaluation, hysteroscopy serves as a therapeutic means to treat uterine conditions such as polypectomy, myomectomy, and endometrial ablation.[45,46]

Despite the evidence showing the benefits as well as the safety surrounding hysteroscopy performed in an outpatient setting, there has been limited uptake in the Canadian setting.[47] Currently, many gynaecological procedures in Canada continue to occur in a formal OR suggesting a need for more robust evidence demonstrating the effectiveness of hysteroscopy in an outpatient or ambulatory setting. This systematic review aims to provide a contemporary review of the literature in order to represent current evidence comparing outpatient or ambulatory hysteroscopy versus the traditional hysteroscopy performed in the OR. The main

question surrounds the efficacy, patient safety, and cost of each intervention. This review will provide guidance to policy makers or guideline developers to advocate for greater accessibility to Canadian women in order to provide hysteroscopy in the outpatient or ambulatory setting.

2.3 Methods

Search strategy

An electronic literature search strategy was developed by an experienced information specialist and members of our research team. We searched Medline, EMBASE, the Cochrane Library, CINAHL, and the Web of Science Citation Index from 1 January 1965 (first Medline citations) to 12 February 2017 with no restrictions on language. Reference lists of relevant studies were cross-checked to include any additional studies not identified by the original search. An additional search of grey literature was performed by searching independent organizations, conference proceedings, and registries.

Study selection and eligibility criteria

Two authors (A.B and K.T) independently screened all titles and abstracts identified by our literature search to determine their eligibility (stage I). In the event of a disagreement, the citation was included for full-text review.

To be included, all studies had to meet the following criteria: pre and postmenopausal women >11 years of age presenting with uterine disorders requiring gynecological consultation; hysteroscopic procedures performed in an outpatient setting to diagnose and/or treat intrauterine pathology compared to any gynecological hysteroscopic procedure performed in an OR under general anaesthesia. The primary outcome of interest was diagnostic accuracy reported as

sensitivity, specificity, negative or positive predictive values. Secondary outcomes included treatment success, adverse events, pain scores, patient satisfaction, and cost. For women with heavy menstrual bleeding, hysteroscopy treatment was considered a success if bleeding had reduced to acceptable levels and if there was an improvement in abnormal uterine bleeding[48]. To evaluate all relevant evidence, both experimental and observational studies with a control group (randomized and non-randomized) were included. We excluded full-text articles reporting procedures that focused on sterilisation, endometrial ablation, and laparoscopy. Reviews, editorials, case series, abstracts, and case reports were also excluded.

The full-text of the included studies in stage I of screening were retrieved and independently reviewed by two authors (A.B and C.L) to assess final eligibility (stage II). Disagreements were resolved by a third party if a consensus could not be reached. Once studies met inclusion criteria, the data of eligible studies were independently extracted by two authors (A.B and C.L) using a standardized data extraction form. The process of study selection is depicted by a PRISMA flow diagram[49] (Figure 2.1).

Quality assessment

The methodological quality of included studies was assessed independently by two authors (A.B and C.L). The methodological quality in RCTs was evaluated using the Cochrane Risk of Bias Assessment Tool.[50] The quality of non-randomized studies was evaluated using the Downs and Black tool.[51] Disagreements between review authors were resolved by consensus and then by a third party (K.T) if a consensus could not be reached.

Data synthesis and analysis

An evaluation of clinical and methodological characteristics of included studies were assessed for heterogeneity by stratifying relevant studies based on variations in specific study characteristics (i.e. type of outpatient hysteroscopy, type of OR, outcomes reported, study design, and study quality). If the methodology and clinical characteristics are deemed too heterogeneous to pool across studies, a qualitative review of the findings will be conducted. If a meta-analysis is deemed suitable, individual studies providing head-to-head comparisons of outpatient hysteroscopic procedures to OR hysteroscopic procedures will be pooled by meta-analysis. Diagnostic and therapeutic studies were analyzed independently. When appropriate, pooled effect estimates are presented as odds ratios with 95% confidence intervals (CI) using a random-effects model.

Dichotomous outcomes were analyzed using the Mantel-Haenszel approach, presenting the odds ratio for each trial with uncertainty being expressed as a 95% CI. Continuous outcomes were analyzed by computing mean differences (MD) or standardized mean differences (SMD) for each trial using the inverse-variance method with uncertainty expressed as a 95% CI. Randomized and non-randomized trials were analyzed separately. Sub-group analyses of premenopausal and postmenopausal women were conducted to investigate heterogeneity.

Statistical heterogeneity was evaluated by the I^2 statistic and χ^2 test. An I^2 statistic greater than 50% is considered to indicate substantial heterogeneity and a p value less than 0.05 was considered statistically significant. We assessed the possibility of publication bias by constructing Begg and Egger inverted funnel plots which will show asymmetry when publication bias is present.[52] All statistical analyses were performed using Review Manager Software, Version 5.3

(Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The study protocol is registered with PROSPERO (CRD42017057843).

2.4 Results

Result of the search

The search strategy identified 12,658 citations, from which 347 studies were retrieved for assessing final eligibility. A total of 20 full-text studies met our eligibility criteria. No additional studies were identified from reference lists or the grey literature. 327 full-text studies were excluded because their comparator was not performed in the OR or the study reported hysteroscopy but did not specify whether it was done in an outpatient setting (Figure 2.1).

Seven of the 20 studies were RCTs and 13 were non-randomized studies. The majority of studies were performed in England (n=9) and the USA (n=5), with the remaining performed in Scotland, Turkey, Netherlands, Israel, Brazil, and Slovenia. A total of ten studies were therapeutic focusing on the treatment of intrauterine pathology, eight were diagnostic, and two studies were both diagnostic and therapeutic (Table 2.1).

Data synthesis of diagnostic studies

Of the ten diagnostic studies, no study compared the diagnostic accuracy between outpatient hysteroscopy and hysteroscopy performed in the OR. Four of the ten diagnostic studies reported the diagnostic accuracy of outpatient hysteroscopy with hysteroscopy performed in the OR as the reference standard.[53–56] The sensitivity for outpatient hysteroscopy ranged from 72% to 90%, while the specificity ranged from 91% to 93% with hysteroscopy in the OR as the gold standard. Of those four studies, three studies evaluated office hysteroscopy compared to

transvaginal sonography. The three aforementioned studies[54–56] suggest that outpatient hysteroscopy is superior to transvaginal sonography in diagnosing intracavitary pathologic disorders in patients with abnormal uterine bleeding, however one review[56] suggested that outpatient diagnostic hysteroscopy is superior to transvaginal sonography in the assessment of polyps.

Data synthesis of therapeutic studies

Of the twelve therapeutic studies, five studies (two RCTs and three non-randomized studies) report the treatment success of hysteroscopy performed in either an outpatient or OR setting. The pooled estimate of RCTs suggest that there is no significant difference between the two groups in treatment success [odds ratio: 0.68, 95% CI 0.43, 1.05] (Figure 2.4A). Non-randomized studies show similar results in that there is no statistically significant difference between outpatient and OR hysteroscopy in treatment success [odds ratio: 0.95, 95% CI 0.49, 1.83] (Table 2.3). There was no evidence of heterogeneity (I^2=0%).

Adverse events were reported in eight of the twelve therapeutic studies (three RCTs and five non-randomized studies). In the pooled analysis, RCTs suggest that the number of adverse events did not significantly differ between the outpatient and OR [odds ratio: 0.29, 95% CI 0.04 to 2.23] (Figure 2.4B). Non-randomized studies also show that there is no significant difference between groups [odds ratio: 1.31, 95% CI 0.49 to 3.55], with no evidence of heterogeneity (I^2=0%) (Table 2.3).

Data on mean post-operative pain score was reported in four of the twelve therapeutic studies (two RCTs and two non-randomized studies). The pooled estimate of the RCTs suggest that there is greater reported post-operative pain in the outpatient room setting [SMD 0.19, 95%

CI 0.01 to 0.37] (Figure 2.4C), while the non-randomized studies also suggest a significant increase in post-operative pain in the outpatient setting [SMD 0.42, 95% CI 0.19 to 0.65] compared to an OR setting. The overall I^2 value suggests some heterogeneity (I^2=35%) in the non-randomized trials (Table 2.3).

Six of the twelve therapeutic studies reported on patient satisfaction (four RCTs and two non-randomized studies). The overall pooled estimate for RCTs showed that there is no significant difference between the two groups [odds ratio: 0.94, 95% CI 0.25 to 3.56] with considerable heterogeneity (I^2=80%) (Figure 2.4D). Non-randomized trials show similar results in that there is no significant difference in patient satisfaction between hysteroscopy performed in the outpatient or OR [odds ratio: 0.38, 95% CI 0.10 to 1.48] (Table 3).

Lastly, all seven studies reported the cost of outpatient and OR hysteroscopy; however, the cost estimates were reviewed qualitatively. All seven studies concluded that the cost for performing outpatient hysteroscopy (range US$97-US$1258) is substantially lower than hysteroscopy performed in the OR (range US$258-US$3144) (Table 2.2). Subgroup analyses of premenopausal and postmenopausal women were not possible because no study reported outcome data for postmenopausal and premenopausal women and because of the small number of eligible studies for each outcome. In addition, assessing publication bias was limited due to the small number of included studies.

Study quality

The RCTs presented with serious risks of selection, performance, and detection bias (Figure 2.2). Blinding of the participants, investigators, and the outcome assessment was poorly

reported and it was unclear whether allocation was appropriately concealed. One RCT[57] clearly stated that the patients were not blinded and thus ranked as a high risk of bias.

The Down's and Black quality assessment checklist[51] was used to evaluate the quality of reporting (questions 1 through 10), external validity (questions 11 through 13), internal validity (bias and confounding, questions 14 through 26), and power (question 27) in non-randomized studies (Figure 2.3). The quality of reporting was variable across studies and almost all studies presented with at least one serious risk of bias. More than 85% of studies clearly reported their objectives and main outcomes of interest in addition to clearly describing their study population, however, the characteristics of patients lost to follow-up and measures of probability values were poorly described. More than 60% of papers clearly described the source population where the population was being recruited. None of the non-randomized studies attempted to blind either subjects or outcome assessments. The risk of confounding was also high since more than 50% of studies did not appropriately report confounding or patients lost to follow-up.

2.5 Discussion

In patients requiring uterine cavity evaluation and/or treatment, this systematic review demonstrated that there is a lack of concrete evidence to conclude that hysteroscopy performed in either an outpatient or OR setting are comparable in terms of treatment success, adverse events, and patient satisfaction. This review suggests that there is an increase in post-operative pain in the outpatient unit, however due to the small number of studies and variable reporting, conclusions should be interpreted with caution. Although the meta-analysis did not support significant conclusions for the outcomes of interest, this systematic review did demonstrate that hysteroscopy

performed in an outpatient setting without the need for general anaesthesia is substantially less expensive than hysteroscopy performed in the OR.

Regardless of the lack of studies directly comparing the diagnostic accuracy of outpatient versus OR hysteroscopy, other studies and systematic reviews have supported the accuracy and feasibility of outpatient hysteroscopy.[56,58–60] Hysteroscopy can be successfully performed in the outpatient setting with significantly shorter time spent away from home, faster recovery, and increased preference by patients.[61] In addition, patient satisfaction and tolerance of the procedure are important considerations if outpatient hysteroscopy were to be implemented. Our review found no significant difference in patient satisfaction between outpatient hysteroscopy and hysteroscopy performed in the OR. One study by Filiz et al. found higher patient satisfaction in office procedures however they state that it may be attributed to the patient being able to pick the procedure they would prefer.[62] More well conducted and scientifically sound trials are needed to evaluate patient satisfaction and acceptability in the outpatient setting compared to the OR.

Pain management and control is also an important consideration when transferring surgical procedures from the OR setting to an outpatient environment. Some patients still prefer OR procedures because they believe there will be less pain.[25,63–67] This review suggests that there is a significant increase in post-operative pain in the outpatient unit, however due to the small increase and small recorded VAS pain measurements in Cooper et al. 2015 and Kremer et al. 2000, 3 is considered mild pain.[68] The studies reporting on post-operative pain in this review were small in number and varied in the time at which post-operative pain was measured suggesting the results should be interpreted with caution. More well-conducted studies investigating the reduction of patient pain in outpatient hysteroscopy units compared to the OR are necessary.

There are a number of limitations related to this review. The quality of the meta-analyzed studies is poor as many studies present with at least one serious risk of bias, particularly RCTs since allocation concealment and blinding were not clearly reported. In addition, the meta-analysis combined studies with varying methods to evaluate patients' pain and satisfaction (i.e. one on one interview versus a survey, the way in which the questions were administered, etc.), varying definitions and timing for adverse events (i.e. some studies identified vaso-vagal reactions as an adverse event while others identified shoulder pain), and differing populations (i.e. pre- versus post-menopausal women, race, parity, etc.). Further investigation of subgroups to examine the magnitude of the effect of these study differences was limited due to small numbers of included studies and deficient and variable reporting.

2.6 Conclusions

The results from this review demonstrate that implementing hysteroscopy in an outpatient setting without general anesthetic should be carefully considered. The current available evidence supports no statistically significant difference in the safety, efficacy, or patient tolerability between outpatient and intraoperative hysteroscopy procedures. There was greater reported post-operative pain the outpatient setting, however this finding should be interpreted with caution given the limited number of studies. The poor methodological quality of the included studies observed in this review highlights the need for improvements in study reporting which includes defining the source population, patients lost to follow-up, and whether confounding was considered. Although outpatient hysteroscopy is less expensive as it avoids general anesthesia, further health economic evaluations are required to evaluate whether its benefits outweigh its costs. The findings from this

systematic review can help inform the design of future experimental studies investigating patient tolerability and pain outcomes in the outpatient unit.

Acknowledgements

The authors would like to thank information specialists Ms. Becky Skidmore and Mr. Daniel Raymond for their help and support with the electronic literature searches and Ms. Lena Faust for the interpretation of the non-English language studies.

TABLES AND FIGURES FOR CHAPTER 2

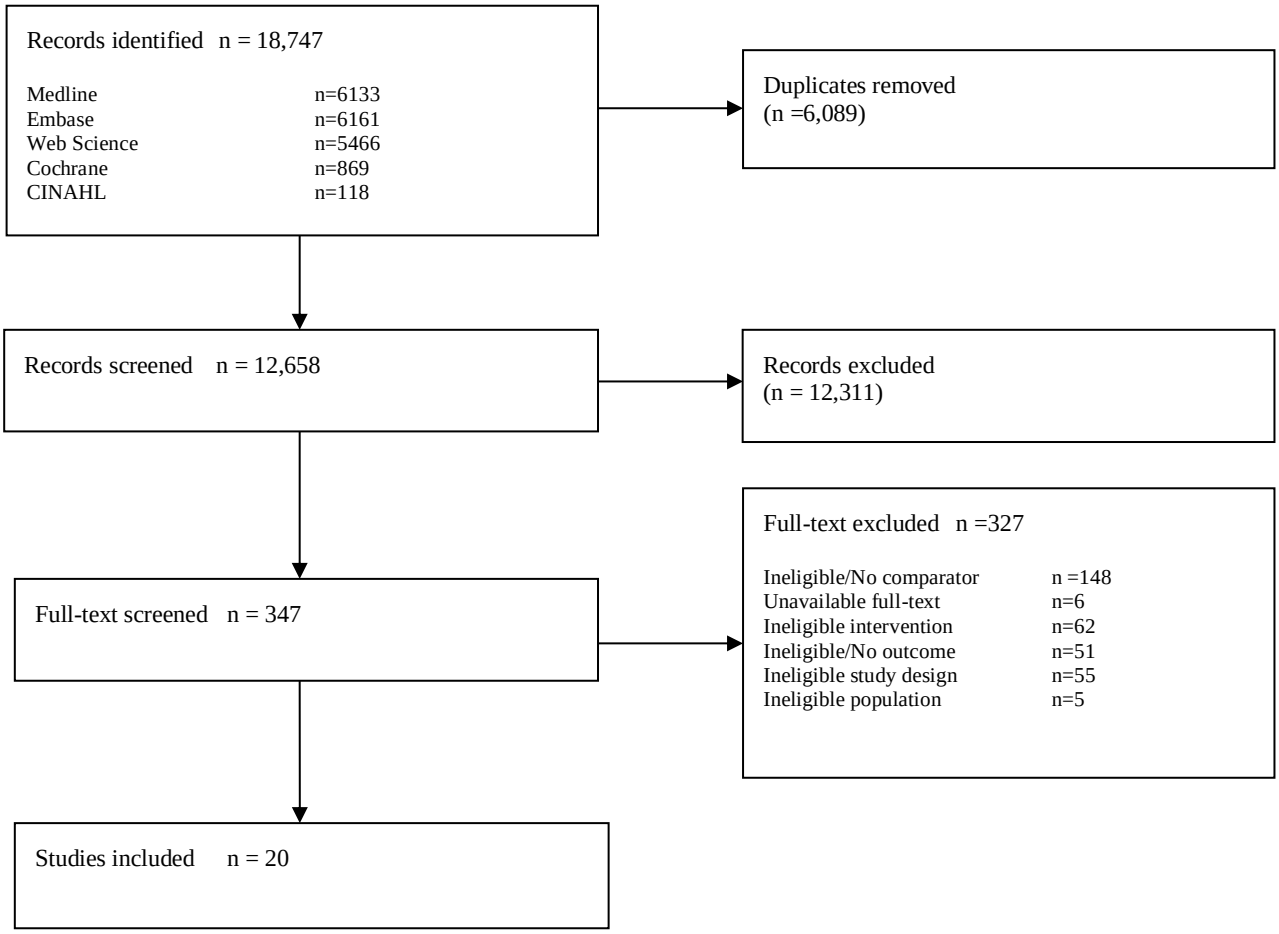


Figure 2.1: PRISMA flow diagram

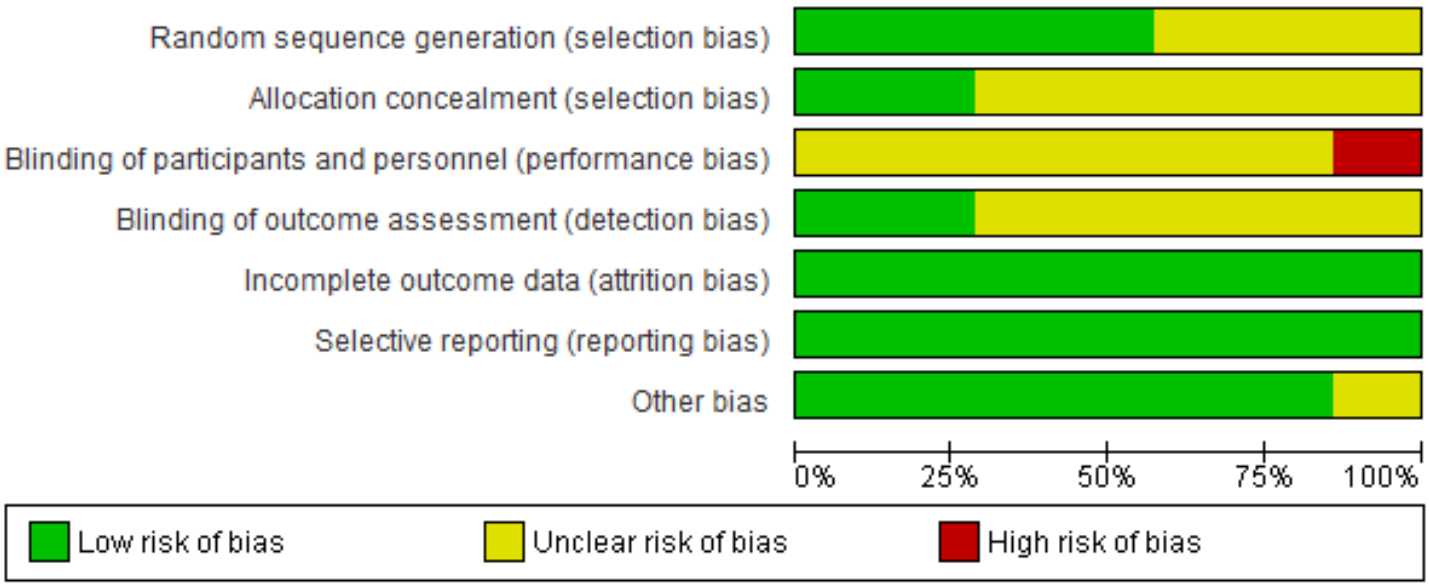


Figure 2.2: Cochrane Risk of Bias assessment for RCTs

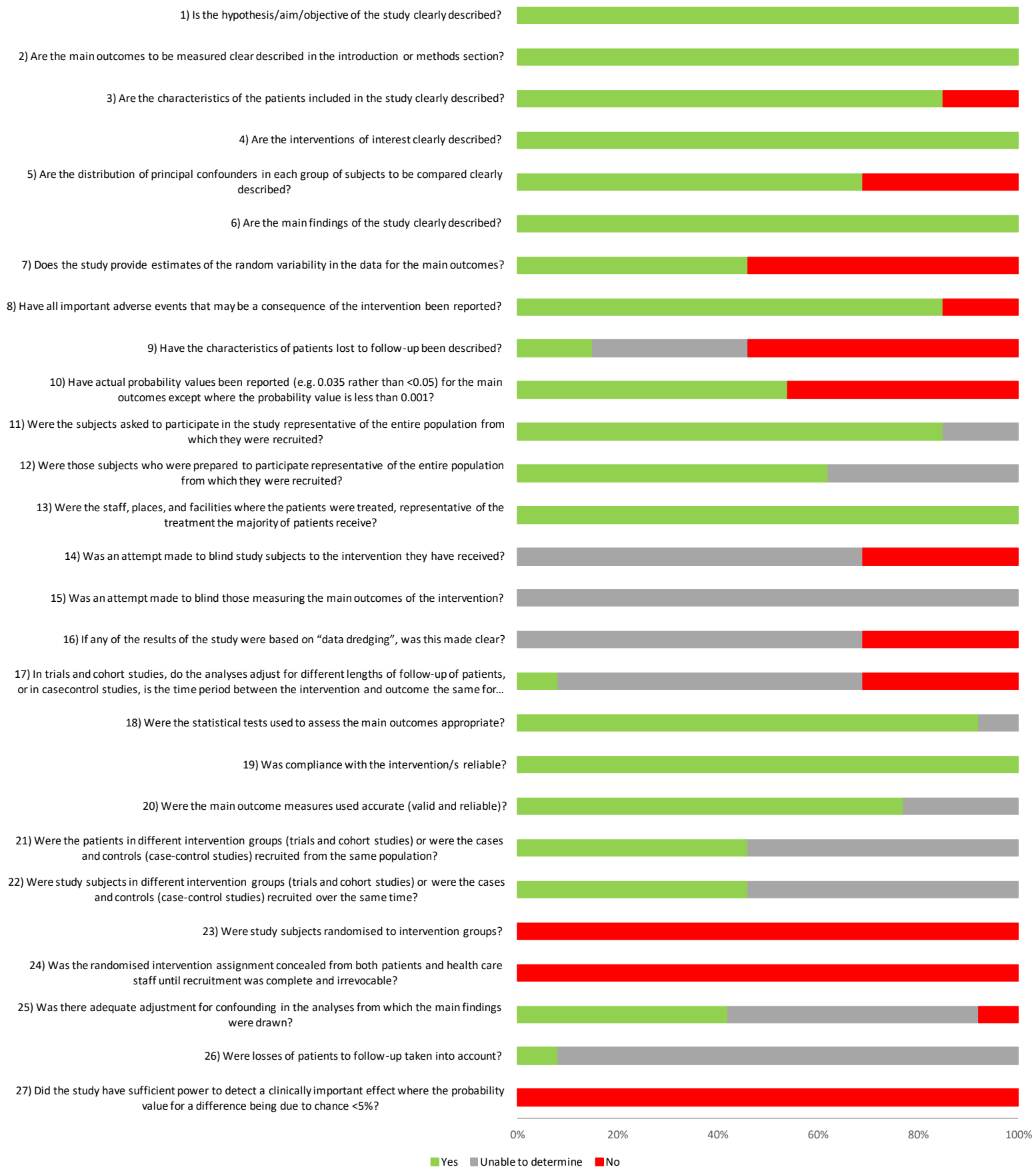


Figure 2.3: Down's and Black risk of bias for non-randomized studies

Table 2.1: Characteristics of 20 included studies

Study author (year)	Country	Study type	Total sample size	Outpatient technique	OR technique	Reason for procedure	Diagnostic, Therapeutic, or both
Bergamo et al. (2012)	Brazil	Cross-sectional	60	Outpatient polypectomy	Conventional polypectomy	Polyps	Therapeutic
Brown et al. (2000)	USA	RCT	42	Office hysteroscopy	Operative hysteroscopy	Infertility investigation	Diagnostic
Clark et al. (2002)	England	Prospective cohort	34	Ambulatory polypectomy	Inpatient polypectomy	Polyps	Therapeutic
Cooper et al. (2016)	England	Prospective cohort	338	Office polypectomy	Inpatient polypectomy	AUB and polyps	Therapeutic
Cooper et al.(2015)	England	RCT	474	Outpatient polypectomy	Inpatient polypectomy	AUB and polyps	Therapeutic
Filiz et al. (2009)	Turkey	Prospective cohort	123	Office hysteroscopy	Operative hysteroscopy	AUB	Both
Hidlebaugh et al. (1996)	USA	Retrospective cohort	568	Office hysteroscopy	Hospital hysteroscopy and dilation and curettage	AUB	Diagnostic
Kremer et al. (2000)	England	RCT	100	Outpatient hysteroscopy	Daycase hysteroscopy	AUB	Therapeutic
Mackenzie et al. (1992)	Scotland	Case-control	167	Outpatient hysteroscopy	In-patient dilation and curettage	AUB	Diagnostic
Marsh et al. (2006)	England	RCT	36	Outpatient polypectomy	Daycase polypectomy	AUB and polyps	Therapeutic
Marsh et al. (2004)	England	RCT	97	Outpatient hysteroscopy	Daycase hysteroscopy	AUB	Therapeutic
Raju (1992)	England	Prospective cohort	350	Outpatient hysteroscopy	Hysteroscopy with anaesthesia	Menstrual symptoms or endometrial assessment	Diagnostic
Rubino et al. (2015)	USA	RCT	74	Office hysteroscopic morcellation	Hysteroscopic morcellation in surgical center	AUB, polyps, and fibroids	Therapeutic
Scheiber et al. (2016)	USA	Prospective cohort	278	Office hysteroscopic morcellation	Hysteroscopic morcellation in surgical center	AUB, polyps and/or submucosal myomas, infertility, postmenopausal bleeding	Therapeutic
Schwarzler et al. (1998)	England	Prospective cohort	98	Office hysteroscopy	Operative hysteroscopy	AUB	Diagnostic
Shinar et al. (2014)	Israel	Retrospective cohort	132	Office hysteroscopy	Operative hysteroscopy	AUB	Diagnostic
Smits et al. (2016)	Netherlands	Retrospective cohort	258	Office hysteroscopy	Operative hysteroscopy	AUB, fibroids, polyps, placental remnants	Both
Tahir et al. (1999)	England	RCT	400	Outpatient hysteroscopy	Inpatient hysteroscopy and curettage	AUB	Diagnostic
Takac et al. (2007)	Slovenia	Retrospective cohort	146	Office hysteroscopy	Dilation and curettage	Endometrial cancer	Therapeutic
Towbin et al. (1996)	USA	Prospective cohort	65	Office hysteroscopy	Operative hysteroscopy or hysterectomy	AUB, polyps, and myomas	Diagnostic

AUB: Abnormal uterine bleeding
RCT: Randomized controlled-trial
OR: Operating room

Table 2.2: Outpatient and OR hysteroscopic details and outcomes of 20 included studies

Study	**Procedures**		**Outcome assessed**									
Author	**Outpatient technique**	**ORS technique**	**Patient satisfaction***		**Mean (SD) post-operative pain score¶**		**Post-operative adverse events**		**Treatment success†**		**Mean cost (USD)‖**	
			Outpatient	OR	Outpatient	OR	Outpatient	OR	Outpatient	OR	Outpatient	OR
Bergamo et al. (2012)	Polypectomy	Conventional polypectomy	NR	NR	2.93	1.43	0	2 (uterine perforation and false passage)	NR	NR	NR	NR
Brown et al. (2000)	Hysteroscopy	Operative hysteroscopy	NR	NR	5.3	NR	NR	NR	NR	NR	NR	NR
Clark et al. (2002)	Endoscopic polypectomy	Inpatient polypectomy	14 (78%)	14 (88%), NS	NR	NR	0	0	11 (92%)	13 (93%), NS	$1003 ($937-$1070)	$1598 ($1444-$1752), p=0.0001[1]
Cooper et al. (2016)	Office polypectomy	Inpatient polypectomy	283 (94%)	62 (98%), p=0.21	2.7 (2.4)	2.0 (2.4), p=0.03	5% vaso-vagal reactions (16/324)	3% vaso-vagal reactions (2/75)	231 (82%)	45 (82%), NS	NR	NR
Cooper et al.(2015)	Polypectomy	Inpatient polypectomy	200 (90%)	186 (96%), p=0.009	2.8 (2.3)	2.3 (2.2), p=0.03	0	4 (2%) uterine perforations	166 (73%)	168 (80%), NS	NR	NR
Filiz et al. (2009)	Hysteroscopy	Classic hysteroscopy	81.8%	NR	1.5 (1.6)	NR	NR	NR	43‡ (91.5%)	39‡ (92.9%)	$144 ($113-$152)	$520 ($290-$953), p<0.001[2]
Hidlebaugh et al. (1996)	Hysteroscopy	Hospital hysteroscopy and dilation and curettage	NR	NR	NR	NR	9 (1.9%) (3 vagal reactions, 2 post procedure endometritis, 1 heavy bleeding, 2 lidocaine reaction, 1 shoulder pain)	4 (4.2%) (2 heavy bleeding, 1 post-operative pneumonia, spinal headache dural patch)	439 (92.8%)	92 (96.9%)	$97	$2828
Kremer et al. (2000)	Hysteroscopy	Daycase hysteroscopy	41 (84%)	37 (77%)	0.4 (0-1.2)	0.3 (0-2.2), p=0.34	NR	NR	48 (96%)	NR	NR	NR
Mackenzie et al. (1992)	Hysteroscopy	In-patient dilation and curettage	NR	NR	NR	NR	NR	NR	121 (88%)	NR	$171	$352
Marsh et al. (2006)	Polypectomy	Daycase polypectomy	44 (90%)	28 (67%), p<0.0005	58% said no pain	28% no pain, p=0.09	0	0	18 (95%)	20 (100%)	NR	NR
Marsh et al. (2004)	Hysteroscopy	Daycase hysteroscopy	NR	NR	NR	NR	NR	NR	NR	NR	$118	$258
Raju (1992)	Hysteroscopy	Hysteroscopy with anaesthesia	140 (95.9%)	52 (25.5%), p<0.001	24 (16.4%), experience pain	120 (58.8%), p<0.0001	NR	NR	NR	NR	NR	NR
Rubino et al. (2015)	Hysteroscopic morcellation	Hysteroscopic morcellation in surgical center	40 (95.5%)	32 (100%)	1.8 (1.8)	NR	1 (2.4%), pain	1 (3.1%), diarrhea and food poisoning	NR	NR	NR	NR

Table 2.2 continued

Study	Procedures		Outcome assessed									
Author	**Outpatient technique**	**ORS technique**	**Patient satisfaction***		**Mean (SD) post-operative pain score¶**		**Post-operative adverse events**		**Treatment success†**		**Mean cost (USD)‖**	
			Outpatient	OR	Outpatient	OR	Outpatient	OR	Outpatient	OR	Outpatient	OR
Scheiber et al. (2016)	Hysteroscopic morcellation	Hysteroscopic morcellation in surgical center	NR	NR	NR	NR	3.6%	1.6%, p=0.4143	NR	NR	NR	NR
Schwarzler et al. (1998)	Hysteroscopy	Operative hysteroscopy	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Shinar et al. (2014)	Hysteroscopy	Operative hysteroscopy	NR	NR	5 (during procedure)	NR	NR	NR	NR	NR	NR	NR
Smits et al. (2016)	Hysteroscopy	Operative hysteroscopy	NR	NR	1 (0-8)	0 (0-7), median pain, p=0.466	2/129 (1.6%), infection needing antibiotics	2/129 (1.6%), uterine perforations, p=0.659	NR	NR	No numerical data, financial analysis states outpatient is ½ cost	NR
Tahir et al. (1999)	Hysteroscopy	Inpatient hysteroscopy and curettage	5	5 (median acceptability), p=0.526	3.5 (median)	1.5, p<0.0001	NR	NR	NR	NR	NR	NR
Takac et al. (2007)	Hysteroscopy	Dilation and curettage	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Towbin et al. (1996)	Hysteroscopy	Operative hysteroscopy or hysterectomy	NR	NR	Little discomfort	No discomfort	Few complications	Few plus anaesthetic complications	NR	NR	$1258	$3144

NR = Not reported, NS = Not significant.

*Patient satisfaction was measured as the number of patients who would recommend the procedure to other patients or were satisfied with the procedure, unless stated otherwise

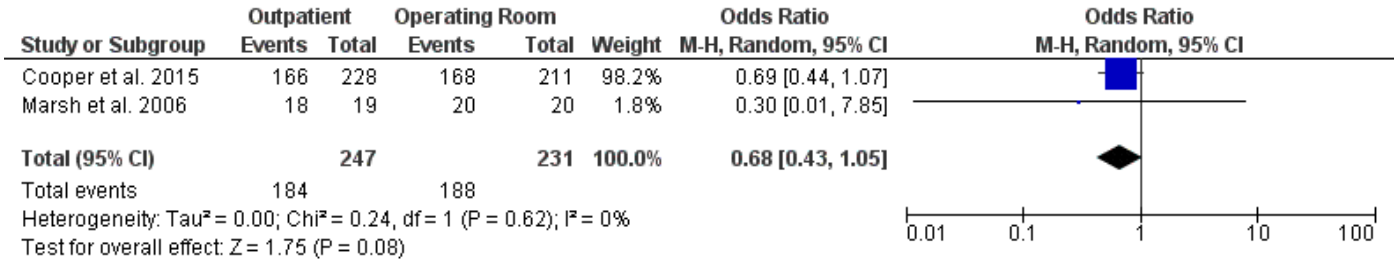
¶The mean pain score used the visual analog scale (VAS) and was measured from 0-10, where 0 is no pain and 10 is the worst pain imaginable. Timing post-surgery varied from right after the procedure to 60 minutes.

†For women with heavy menstrual bleeding, treatment was considered a success if bleeding had reduced to acceptable levels and improvement of abnormal uterine bleeding. Number of successful treatments presented.

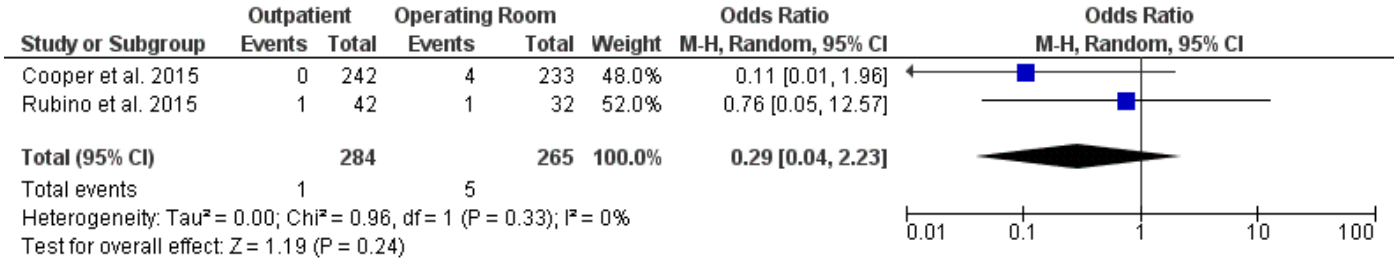
‡Reported values are only among pre-menopausal women.

‖All cost values have been converted to 2017 USD

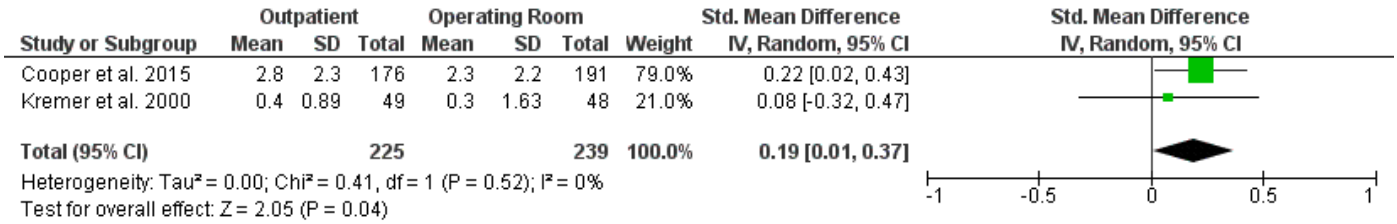
A) Treatment success



B) Adverse events



C) Post-operative pain



D) Patient satisfaction

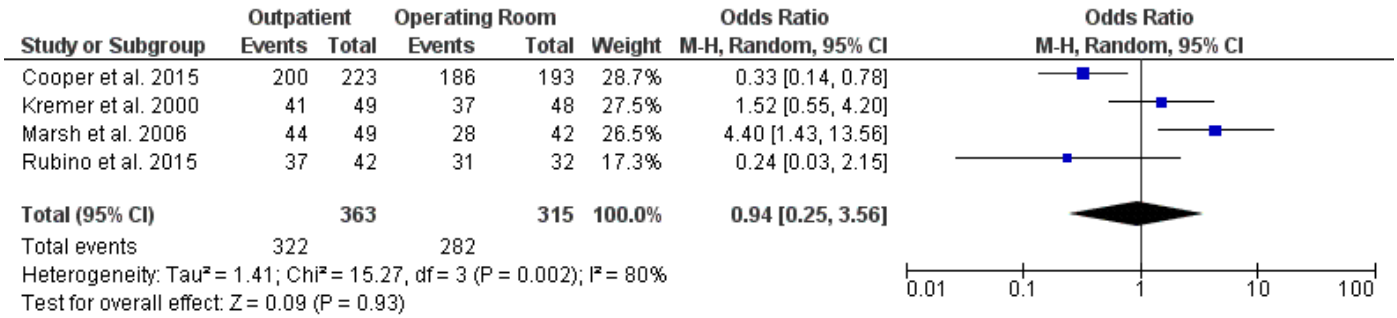


Figure 2.4: Forest plots of RCTs comparing outpatient hysteroscopy and hysteroscopy performed in the OR for selected outcomes; A) Events were considered the number of patients who had reduced levels of bleeding after the procedure, B) Events were considered the number of patients who experienced an adverse event as defined by the study, C) The mean value of pain experienced post-operatively as measured by the visual analog scale, D) Events were considered the number of patients who reported a positive experience with the procedure as defined by the study. Abbreviations: M-H, Mantel-Haenszel test.

Table 2.3: Outcome results from meta-analyses in RCTs and non-randomized

Outcome	N of studies	N of participants	Citations	Estimate of outpatient effect [95% CI]
Randomized trials				
Treatment success	2	478	24, 28	OR 0.68 [0.43 to 1.05], I^2= 0%
Adverse events	3	585	24, 28, 42	OR 0.29 [0.04 to 2.23], I^2= 0%
Post-operative pain	2	464	24, 31	SMD 0.19 [0.01 to 0.37], I^2=0%
Patient satisfaction	4	678	24, 28, 31, 41	OR 0.94 [0.25 to 3.56], I^2=80%
Non-randomized trials				
Treatment success	3	453	15, 27, 29	OR 0.95 [0.49 to 1.83], I^2= 0%
Adverse events	5	1029	15, 27, 37, 43, 44	OR 1.31 [0.49 to 3.55], I^2= 0%
Post-operative pain	2	565	15, 44	SMD 0.42 [0.19 to 0.65], I^2= 36%
Patient satisfaction	2	397	15, 27	OR 0.38 [0.10 to 1.48], I^2= 0%

OR = Odds ratio, SMD = Standard mean difference, I^2= test for heterogeneity

CHAPTER 3: COST-EFFECTIVENESS ANALYSIS OF AN OUTPATIENT UTERINE ASSESSMENT AND TREATMENT UNIT

Title: Cost-Effectiveness of an Outpatient Uterine Assessment and Treatment Unit in patients with Abnormal Uterine Bleeding: A Modelling Study

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3.1 Abstract

Objectives: To assess the cost-effectiveness of a single-visit uterine assessment and treatment unit (UATU) compared with the current standard of care to diagnose and treat women with abnormal uterine bleeding (AUB).

Design: A cost-effectiveness analysis using a decision tree model from the perspective of the publicly funded health care system in Canada.

Setting: An ambulatory women's health clinic at a tertiary academic health sciences center (The Shirley E. Greenberg Women's Health Center at The Ottawa Hospital (TOH)).

Methods: We developed a probabilistic decision tree to simulate the total costs and outcomes of women receiving a UATU and usual care over a one-year time horizon. Effectiveness of the UATU and usual care was obtained from a systematic review, while probabilities, resource use and time associated with each treatment option was obtained from a retrospective chart review of 200 randomly selected patients presenting with AUB at TOH between April 1st 2014 and March 31st 2017. Results were expressed as overall cost and time savings per patient. A series of sensitivity analyses were conducted to assess the robustness of the study findings. Costs are reported in 2018 Canadian dollars.

Results: Compared to usual care, the UATU was associated with a decrease in overall cost ($1,331.90 [95% CI -1,337 to -1,326.8]) and a decrease in overall time to treatment (-74.50 days [95% CI -74.70 to -74.40]), dominating usual care. 100% of the Monte Carlo simulations all lie

in the bottom right quadrant of the cost-effectiveness plane illustrating that the UATU is both time and cost saving. The point at which the UATU would no longer be cost-savings is if the cost to maintain and operate the UATU is greater than $1,600 per patient. The cost-effectiveness results were robust to changes in model assumptions and input parameters.

Conclusions: An outpatient UATU is more cost-effective than usual care from the perspective of Canada's health care system.

Key words: Cost-effectiveness, hysteroscopy, outpatient, uterine assessment and treatment unit, abnormal uterine bleeding

3.2 Introduction

Endometrial evaluation and hysteroscopic treatment of uterine conditions such as heavy menstrual bleeding, uterine fibroids, and lesions suspicious for cancer is best done outside of the operating room (OR) without general anesthesia.[13,17,31,69] The use of hysteroscopic technology allows physicians to directly visualize the uterine cavity to diagnose and treat intrauterine pathology. Hysteroscopy is traditionally performed under general anesthesia in hospital, however, advances in technology and training have made it possible to perform hysteroscopy in a conscious patient in an outpatient setting.[23,28] Many studies have demonstrated that hysteroscopy can be performed in an outpatient setting with a high degree of safety and patient satisfaction.[25,26,47,70] In addition, outpatient hysteroscopy improves access to gynecologic care for women by providing timely assessment and treatment with the aim of improving the efficiency of care by reducing wait-times, improving patient experience, and lowering costs to the health care system.[15,71–73]

Despite the clear advantages of outpatient hysteroscopy, there has been poor adoption of best practice guidance for uterine therapy. As a result, most patient care continues to occur in major operating rooms where the patient is admitted for a surgical procedure.[15,32] In these cases, the additional risks of general or regional anesthetic present significantly more risks to the patient and have been shown to be more costly to the health care system compared to procedures out of the OR.[8,29] Outpatient hysteroscopy is not the primary line of treatment in many health care facilities and its uptake into clinical practice has been limited due to a lack of training for providers, the need for outpatient clinic space, and a lack of studies demonstrating its cost-effectiveness.[9]

The combination of technical advances in endoscopes, patient demands for timely treatment and diagnosis, and system-wide financial constraints suggests that there could be an economic advantage in establishing outpatient hysteroscopy as a first line diagnostic procedure. Therefore, the aim of this study is to evaluate the cost-effectiveness of a single-visit outpatient uterine assessment and treatment unit (UATU) compared to the traditional standard of care to diagnose and treat intrauterine pathology from the perspective of the publicly funded health care system in Canada. This study will help facilitate further decisions relating to the implementation of a UATU in Canadian hospitals.

3.3 Methods

Overview – Decision Problem

We conducted a cost-effectiveness analysis of a UATU compared to usual care from the perspective of the publicly funded Canada's health care system over a 1-year time horizon. Discounting in our model was not necessary since costs and outcomes did not occur beyond a year. Probabilities, cost data, and outcome measures were derived from a retrospective chart review of the medical charts of 200 randomly selected patients from an ambulatory women's health clinic at a tertiary academic health sciences center (The Ottawa Hospital's Shirley E. Greenberg Women's Health Center at the Riverside Campus) and a review of the existing literature.

Model structure

We constructed a decision tree model to compare the costs, probabilities, time to diagnosis, and time to treatment between a single-visit UATU and usual care. The decision tree

model was used to illustrate the typical management pathway a patient encounters at the hospital in both service models. Typical usual care management includes the patient's first initial consultation for AUB, followed by further assessments until a final diagnosis and treatment has been reached. Possible assessments include transvaginal ultrasound, saline infusion sonohysterography (SIS), magnetic resonance imaging (MRI), biopsy, and/or hysteroscopy.

In a UATU, typical management includes the patient's first initial consultation for AUB where diagnosis is obtained immediately the same day by hysteroscopy in an outpatient setting. Biopsy and/or treatment may be also completed in a subset of patients while others are directed into the appropriate pathways for diagnosis specific care (i.e. no further treatment, medical treatments or hysterectomy for malignancy). Cost and time data were assigned to each branch and were multiplied by the respective probabilities to calculate the expected outcomes for both the UATU and the standard of care services. The structure of the model is depicted in figure 3.1.

Setting and Population

This study focused on women who presented with AUB to the Ottawa Hospital's Shirley E. Greenberg Women's Health Center at the Riverside Campus. TOH is a large tertiary level academic health sciences center with 1,232 beds and the Shirley E. Greenberg clinic is part of TOH's Department of Obstetrics, Gynecology and Newborn care.

Costs

This study considered costs borne to the publicly funded health care system in Canada. Hospital cost data were obtained from the Ontario Case Costing Initiative (OCCI) database, a single source of integrated financial/statistical and clinical information at the patient/resident

level and reflects actual patient care costs. Direct hospital costs included costs related to the provision of care such as the costs of nursing, surgical equipment (including disposables), diagnostic imaging, pharmacy, laboratory services, and food services. Indirect hospital costs included overhead expenses relating to hospital operations, and included administration, finances, human resources, and plant operations. Cost data for physician services were obtained from the Ontario Schedule of Benefits Physician Services under the Health Insurance Act. The physician fees listed are the amounts payable by the government of Ontario (OHIP). The listed physician services in the Ontario Schedule of Benefits include provision of the premises, equipment, supplies, and personnel used in the performance of common and specific elements of the service. For patients who received medications as their primary treatment, the drug costs were considered out-of-pocket costs and not costs borne to the government. The costs and codes relating to surgical and physician fees were verified by a clinical expert in the field of gynaecology (S.S.). The costs are adjusted to 2018 Canadian dollars using a consumer price index reported by Statistics Canada.[74]

Outcomes

The primary clinical outcome of interest is time to diagnosis. Time to diagnosis was measured as the total time in days from the initial consult to the date of the final consult where a diagnosis and management plan was discussed between the physician and patient. The final diagnoses reported in patient charts for AUB were defined by the FIGO PALM-COEIN (polyp, adenomyosis, leiomyoma, and malignancy/hyperplasia) criteria for defining pathologies and were verified by a gynaecologist.[75] Our secondary clinical outcome of interest is time to treatment. Time to treatment was measured as the total time in days from the initial consult to the first management attempt of AUB including either medical or surgical interventions. For medical

management, we measured the final time as the date of the consult where the prescription was prescribed or recommended. The date for surgical management was defined as the date of the surgical procedure. Although time to diagnosis and time to treatment were surrogate outcomes, they were important measures and have long been identified by patients, clinicians and governments as key area to improve. We did not use successful treatments as our outcomes because it would be challenging to define treatment success given that AUB can have many causes and may require different treatments depending on the causes and diagnoses.

Measure of effectiveness

We defined the effectiveness of the UATU as the relative risk of having a failed outpatient hysteroscopy procedure in the UATU requiring further uterine assessment compared to usual care. This variable was obtained from the results of a systematic review conducted by Clark et al[76] that determined the accuracy of hysteroscopy in diagnosing endometrial cancer and hyperplasia in women with AUB, and synthesized failure rates for hysteroscopy in an outpatient setting. We were interested in modeling the number of failed outpatient UATU hysteroscopic procedures that required an additional procedure or had to be sent to the operating room.

The baseline rate of patients requiring further uterine assessment for usual care was derived from the retrospective chart review of 200 patients. Using a random number generator, we randomly selected individuals from an eligible group of patients who had a visit at TOH Shirley E. Greenberg clinic for AUB between April 1st 2014 and March 31st 2017. To include a representative sample of women who would potentially be eligible for the UATU, we reviewed the charts of 200 patients referred for AUB including heavy menstrual bleeding, irregular menses, or post-menopausal bleeding. Patients were excluded if they were being assessed for

infertility or had an abortion, as well as patients with endometriosis. Information on age, date of first clinic visit, type of surgery, type of diagnosis, and date of final diagnosis and treatment were extracted. All extracted data was verified by an expert in the field of gynaecology (S.S.).

Assumptions

In our decision model, we assumed that all patients who were to visit the UATU consented to being treated in the outpatient setting. We did not take into account the patients who would have refused medical work-up in a UATU and preferred to have work-up outside of the outpatient setting as they will likely have the same outcomes as usual care and will be no effect on the results. In addition, we assumed that all patients requiring treatment under usual care were either acute inpatient or day surgery patients. There is currently a minimally invasive surgical (MIS) suite in place at the Ottawa Hospital that would function similar to a UATU, however, in our usual care model we treated as though the MIS suite did not exist. Of the total 87 patients in our population who required surgical treatment, only 20 patients had treatment in the MIS suite without general anesthesia. We also assumed that the cost to operate and maintain a UATU in the hospital setting was equal to usual care, since most of the hysteroscopic equipment is already in use in the main operating room.

Analysis

Our base-case analysis is carried out for two clinical outcomes (time to diagnosis and time to treatment) using an individual sampling model which models the progression of individuals rather than hypothetical cohorts.[77,78] We performed a series of one-way deterministic sensitivity analyses by varying individual model input parameters including effectiveness of

UATU and cost parameters to assess various assumptions and the reliability of our conclusions. A probabilistic sensitivity analysis of the base-case was performed to evaluate the uncertainties in the cost and outcome data. We used a Monte Carlo simulation with 5,000 replications and used the results to generate a cost-savings acceptability curve to illustrate the probability at which the additional cost per patient to maintain a UATU will be more expensive than usual care. The distribution around each parameter were presented with standard deviations (SD) and 95% confidence intervals (CI). All analyses were carried out using STATA 12® (StataCorp, Stata Statistical Software, College Station, TX, USA) and Microsoft Excel 2007® with Visual Basic Applications (Microsoft Corporation, Redmond, WA, USA).

Ethics

The study was approved by TOH's research ethic's board according to protocol # 20170665-01H. Funding was received from The Ottawa Hospital Academic Medical Organization Innovation Fund, a competitive internal peer reviewed grant.

3.4 Results

Base-case analysis

The results for the probabilistic base-case analysis are presented in table 3.3. For cost outcomes, we estimated a point estimate of the mean (SD) overall cost for time to diagnosis at $426.60 (27.7) for the UATU and $534.30 (43.9) for usual care, representing a total cost-savings of -$107.70 (95% CI -108.6 to -106.8). For time to treatment, mean (SD) overall costs were $1,092.90 (108.50) for the UATU and $2,424.80 (239.60) for usual care, representing a significant total cost-savings of -$1,331.90 (95% CI -1,337 to -1,326.80). For time outcomes, we

estimated a point estimate of the mean (SD) overall time for time to diagnosis at 23.5 (2.9) days for the UATU and 55.3 (5.0) days for usual care, a time difference of -31.8 days (95% CI -31.9 to -31.7). For time to treatment the overall mean (SD) time was 35 (4.5) days for the UATU and 109.5 (8.2) days for usual care, a time difference of -74.5 days (95% CI -74.7 to -74.4). The UATU significantly reduced time and health system cost for both time to diagnosis and time to treatment, dominating usual care.

Probabilistic Sensitivity Analysis

The results of the Monte Carlo simulations are presented in a cost-effectiveness plane in figure 3.2. The x-axis represents the incremental time savings and the y-axis represents the cost difference between usual care and the UATU. The resulting incremental cost and time ratios are located below the x-axis indicating that the UATU is less expensive than usual care, and to the right of the y-axis indicating that the UATU is time saving compared to usual care for both outcomes. The UATU is said to dominate usual care, illustrating that the UATU is cost-effective. The cost-savings acceptability curve is presented in figure 3.3 and illustrates the probability at which the additional cost per patient to maintain a UATU will be more expensive than usual care. Since the assumption of our model is that the cost to implement a UATU is equal to usual care, the graph provides a tool to quantify how much more the UATU would need to cost per patient before it was no longer cost saving. The horizontal dashed line indicates the cost at which the UATU is certain to be more expensive than usual care at roughly $1,600 per patient.

Univariate sensitivity analysis

The results of our sensitivity analysis are presented as a tornado graph in figure 3.4. Each horizontal bar represents the range in possible UATU cost savings as the corresponding model input parameter value is varied between two extreme but plausible values while holding all other baseline estimates constant. The two extreme values are used to calculate the difference in overall cost between the UATU and usual care, and then plotting the input parameter with the widest range at the top and the smallest range at the bottom. The input parameter with the widest range in cost savings is hospital costs for a surgical procedure ($513 and $2,857) followed by the cost of a further assessment ($1,225 and $1,776), UATU surgical costs ($1,039 and $1,504), surgeon and assistant costs ($1,104 and $1,438), outpatient hysteroscopy costs ($1,184 and $1,434), the relative risk (RR) of UATU ($1,230 and $1,429), and the cost of a re-ordered assessment ($1,317 and $1,351). The range in values represented by the horizontal bar is greater than 0, illustrating that the UATU service model will always be less expensive than usual care when we vary baseline estimates between two extreme but plausible values.

3.5 Discussion

Interpretation of findings

The results of the cost effectiveness analysis show that the UATU is both less expensive and time savings compared to usual care in both diagnosing and treating AUB (table 3.3 and figure 3.2). The robustness of our conclusions was explored with a deterministic sensitivity analysis (figure 3.4) by varying our baseline estimates between two extreme values and evaluating the impact on our overall conclusions. The varied estimates did not change our overall conclusions from the base-case analysis that the UATU is cost-saving compared to usual care.

Our cost-effectiveness results align with the results of a cost-utility and cost-effectiveness analysis conducted in the UK that compared outpatient polypectomy and standard inpatient polypectomy in treating patients with AUB.[34] Their study was carried out alongside a multi-centre randomized controlled Outpatient Polyp Treatment trial and measured outcomes surrounding patient-reported effectiveness of the procedure determined by the women's self-assessment of bleeding at 6 months, and quality-adjusted life year (QALY) gains at 6 and 12 months. The authors concluded that inpatient polypectomy was more expensive and marginally more effective, resulting in the likelihood of effectiveness being roughly equal for both inpatient and outpatient polypectomy at 6 and 12 months. The author's overall conclusions were that outpatient treatment of uterine polyps appears to be more cost-effective than inpatient treatment and should be recommended as the best use of limited resources. Our study differs in that we evaluated the overall process of AUB care and focused on time as our effectiveness outcome, while Diwakar et al. focused on polypectomy and patient reported outcomes. Although there are some differences between the two studies, the overall conclusions complement each other in that treating patients with abnormal uterine bleeding in an outpatient setting is cost-effective compared to usual treatment in the inpatient setting.

Study strengths and limitations

This study is unique in that we evaluated time as the outcome of interest, which is an important outcome for patients, health care providers, and the health care system. By presenting the cost-effectiveness of a UATU in terms of reducing the time to diagnosis and treatment, we aim to provide an alternative option to provide timely care in diagnosing and treating patients with AUB. Providing patients with timely access to health care remains a pan-Canadian

challenge. Canadians wait longer for primary, specialist, and emergency department care compared to citizens in most of the 11 countries surveyed by the Health Council of Canada.[79] While patients experience long wait times for diagnosis and/or treatment they may be experiencing considerable pain, mental stress, and may even have their condition worsen. The burden of waiting for health care will continue to incur high personal costs to the patient in terms of valuable time lost while waiting for treatment. A study by the Fraser Institute estimated that the average Canadian waits 9.8 weeks for treatment after seeing a specialist, and experienced a personal cost of $1,304 lost in productivity and income.[80] This estimate is conservative since it did not include the cost of wait-times from referral by a general practitioner or other delays in the health care pathway. Although time is an important clinical outcome to clinicians and patients, it presents some limitations in our economic model. The model does not factor in costs or other relevant outcomes if a patient were to require further healthcare resources beyond the set time-point of diagnosis or treatment. Future research is warranted to explore the economic implications beyond the one-year time horizon of failure to treat AUB in a UATU.

In addition, our study used individual patient level data through a retrospective review, providing the best estimate for probability, time, and cost data for our model. By performing a retrospective chart review, we were able to target our population of interest and map their encounters with the health care system to accurately illustrate the patient health care pathway. Patient level data was also verified by a second reviewer who was a specialist in the field, ensuring that our cost and time estimates were accurate. We also performed probabilistic analyses and multiple deterministic sensitivity analysis, validating the stability of our conclusions.

There are some limitations to note in the study. Firstly, we did not consider the costs of adopting and maintaining a UATU such as additional costs associated with administration, maintenance, or training. The total cost of the UATU is unknown and we took the assumption that the cost to implement a UATU is equal to usual care. The rationale behind this assumption is that the additional cost to adopt a UATU will be minimal for many large hospital centers because some hysteroscopic equipment available in the main operating room can be shifted to the outpatient setting to set up a UATU. Although this is applicable to large tertiary medical centers such as The Ottawa Hospital, it is important to consider implementing a UATU in smaller outpatient clinics where an operating room does not exist which will require additional costs for training and equipment. To address this limitation, we presented our findings using a cost savings acceptability curve (figure 3.3). This figure allows decision makers or policy makers to visualize how much more expensive the UATU would have to be per patient to implement and maintain a UATU before it was no longer cost-saving to the health care system. The decision maker would have to spend an additional $1,600 per patient to maintain and operate the UATU for it to certainly no longer be cost-effective.

In addition, the generalizability of our study is limited. The patient population from which we derived probability, time, and some cost parameters were included from the Ottawa Hospital. The Ottawa Hospital is a large academic health sciences center that may have varying clinical practice, experience, and techniques in instrument use compared to other institutions to treat and diagnose patients with AUB. Cost data obtained from OCCI only consider costs borne to participating hospitals in the Ontario provincial region and may not reflect what occurs outside the province or other countries, however our model can be adapted to answer other decision problems in varying jurisdictions. Moreover, our model did not consider the costs from the

patient perspective. We did not take into consideration associated costs to the patient such as time-off work, medications, and transportation while waiting for diagnosis and treatment that would negatively impact the patient's quality of life.

Finally, the effectiveness measure in the model worked under the assumption that all patients presenting with AUB are consenting to having an outpatient UATU and only those who had a failed UATU procedure required additional work-up. Based on the systematic review by Clark et al. from which we derived our effectiveness measure, a failed outpatient hysteroscopic procedure was a result of technical problems (i.e. cervical stenosis, anatomic factors, or structural abnormalities) or patient factors (i.e. pain or intolerance). We did not consider patients who may not be eligible for a hysteroscopic procedure in a UATU setting, such as extreme obesity, comorbid conditions, or pain intolerance. We also did not consider the percentage of patients who would refuse treatment in an outpatient setting, however there are studies that have evaluated women's views and experiences of an outpatient hysteroscopy procedure.[81] Many women find outpatient hysteroscopy acceptable and a high percentage of patients would have a repeat procedure.[82–85]

Suggestions for future research, policy and practice

A costing study and a budget impact analysis would be required to gain a further understanding of the total budget required to operate and maintain a UATU, as our study focused on a large tertiary medical center and not smaller outpatient clinics. Currently, there are no studies or budget impact analyses that assess the total cost of a UATU clinic and would therefore need to be explored. In addition, future studies should consider patient satisfaction or quality of life metrics associated with a UATU. Given that our study supports timelier diagnosis and

treatment, the UATU has the potential to optimize health system performance which aligns with the Triple Aim framework developed by the Institute for Health care Improvement. The framework describes an approach to optimizing health system performance by improving the patient experience of care (including quality and satisfaction), improving the health of populations, and reducing the per capita cost of health care.

The study results represent the first cost-effectiveness analysis evaluating a UATU, however future cost-utility analyses are necessary to incorporate patient quality of life outcomes. The results of a cost-utility analysis will provide patient preferences which can better inform the decision to allocate limited health care resources to offset-up, implement and maintain a UATU.

3.6 Conclusions

In conclusion, an outpatient UATU is more cost-effective than usual care in diagnosing and treating patients with AUB. The UATU should be offered as the first line approach as it would improve access to gynecologic care by reducing wait times, improving patient experience, and lowering overall costs to the health care system. The results from this cost effectiveness analysis provide a tool for objectively assessing the value of implementing an outpatient UATU while allowing clinicians and decision makers to make rational decisions regarding clinical care and resource allocation.

TABLES AND FIGURES FOR CHAPTER 3

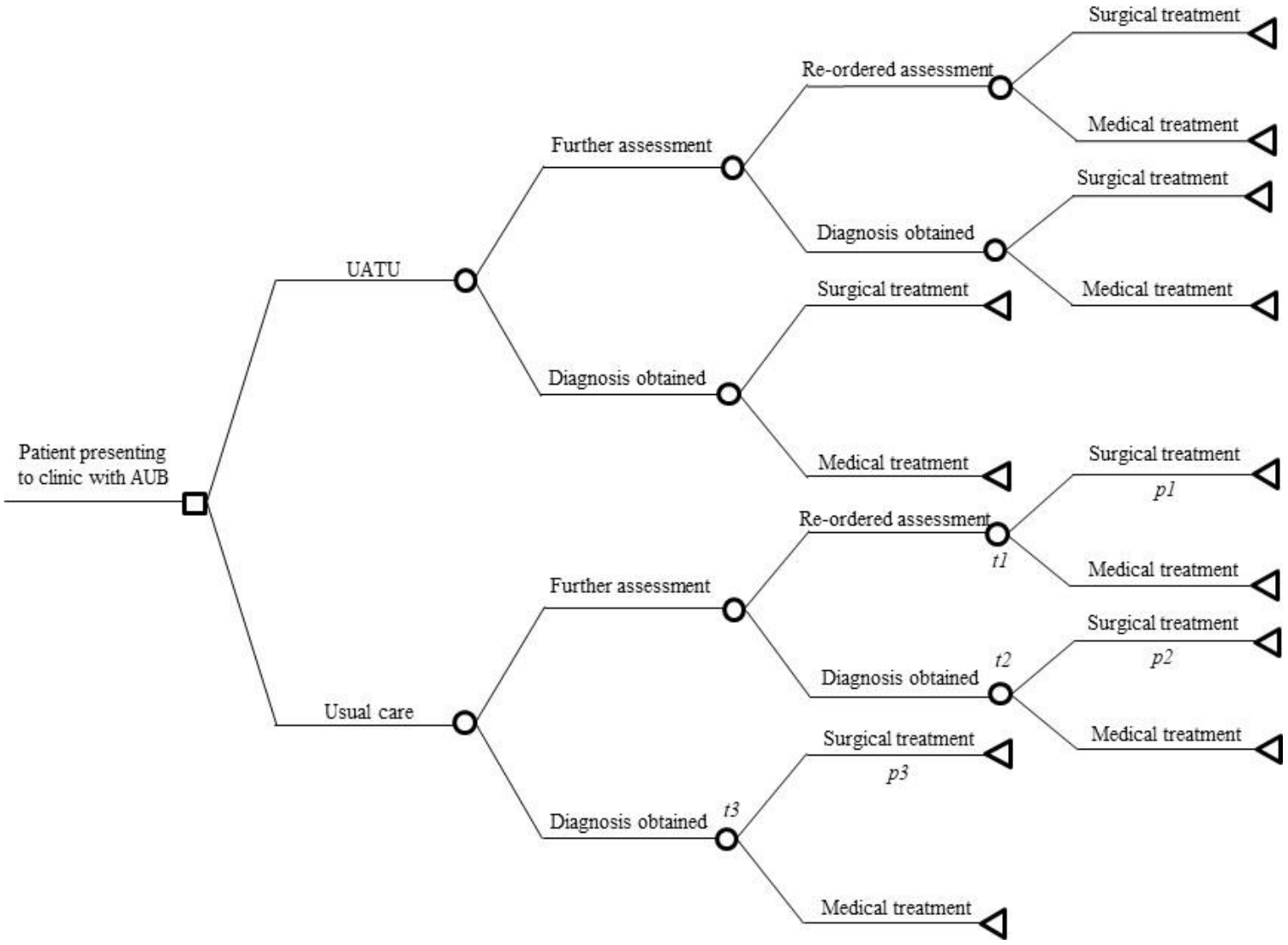

Figure 3.1: Decision tree model

Table 3.1: Variable estimates and probability distributions for our base-case decision analysis model. Costs were adjusted to 2018 CAD dollars.

Parameters	Baseline estimate	Standard error	Probability distribution[a]	Reference source
Outpatient UATU				
RR of UATU	0.412	0.09	Lognormal (0.347, 0.489)	Clark et al.[60]
Outpatient hysteroscopy costs	152	13.5	Gamma (128.1, 1.14)	OCCI
Physician costs for diagnostic hysteroscopy procedure	105.40		Fixed	Schedule of Benefits
Surgical procedure in UATU[b]	600	150	Gamma (16, 37.5)	Expert opinion
Further uterine assessment				
Probability	0.605		Beta (121, 79)	Chart review
Cost	689.80		Weighted average	Chart review, OCCI, Schedule of Benefits
Diagnosis obtained (*t2*)	77.5	6.1	Gamma (161, 0.48)	Chart review
Re-ordered uterine assessment				
Probability	0.19		Beta (23, 98)	Chart review
Cost	599.30		Weighted average	Chart review, OCCI, Schedule of Benefits
Time to diagnosis (*t1*)	146.9	19.1	Gamma (59, 2.49)	Chart review
Surgical treatment				
Probability (*p1*)	0.522		Beta (12, 11)	Chart review
Probability (*p2*)	0.408		Beta (40, 58)	Chart review
Probability (*p3*)	0.443		Beta (35, 44)	Chart review
Hospital costs	3514.34		Weighted average	Chart review, OCCI
Surgeon, assistant, and anaesthesiologist costs	1038.09		Weighted average	Chart review, Schedule of Benefits
Time to treatment (*p1)*	151	30.3	Gamma (24.8, 6.1)	Chart review
Time to treatment (*p2)*	90	14.7	Gamma (37.5, 2.4)	Chart review
Time to treatment (*p3)*	152	17.3	Gamma (77.2, 2)	Chart review

[a]Probability distributions are presented as gamma (shape, scale), beta (alpha, beta), and lognormal (lower limit, upper limit)
[b]The estimated mean cost of surgical disposables in the UATU. We set the uncertainty around the value at an assumed standard error of 25% of the mean and a gamma distribution

Table 3.2: Demographic characteristics of 200 women randomly selected to be included in retrospective cohort.

Variable	No. (%)
Mean age (SD)	45.3 (12.2)
Menopausal status	
Postmenopausal	47 (23.5)
Parity	
Parous	138 (69)
Nulliparous	62 (31)
Indication for clinic visit	
HMB	138 (69)
Postmenopausal bleeding	43 (21.5)
Irregular menstrual bleeding	19 (9.5)
Diagnosis[a]	
Submucosal fibroids	71 (35.5)
Normal cavity/Ovulatory dysfunction	60 (30)
Endometrial polyps	46 (23)
Abnormal endometrium(hyperplasia/cancer)	14 (7)
Adenomyosis	14 (7)

[a]Some patients were diagnosed with multiple pathologies (fibroids and polyps)

Table 3.3: Cost-effectiveness base-case results.

	UATU mean (SD)	Usual Care mean (SD)	Difference (95% CI)
Time to diagnosis			
Overall cost, $	426.6 (27.7)	534.3 (43.9)	-107.7 (-108.6 to -106.8)
Total time, days	23.5 (2.9)	55.3 (5.0)	-31.8 (-31.9 to -31.7)
ICER (Δ cost/Δ time)		UATU dominates usual care	
Time to treatment			
Overall cost, $	1092.9 (108.5)	2424.8 (239.6)	-1331.9 (-1337 to -1326.8)
Total time, days	35.0 (4.5)	109.5 (8.2)	-74.5 (-74.7 to -74.4)
ICER (Δ cost/Δ time)		UATU dominates usual care	

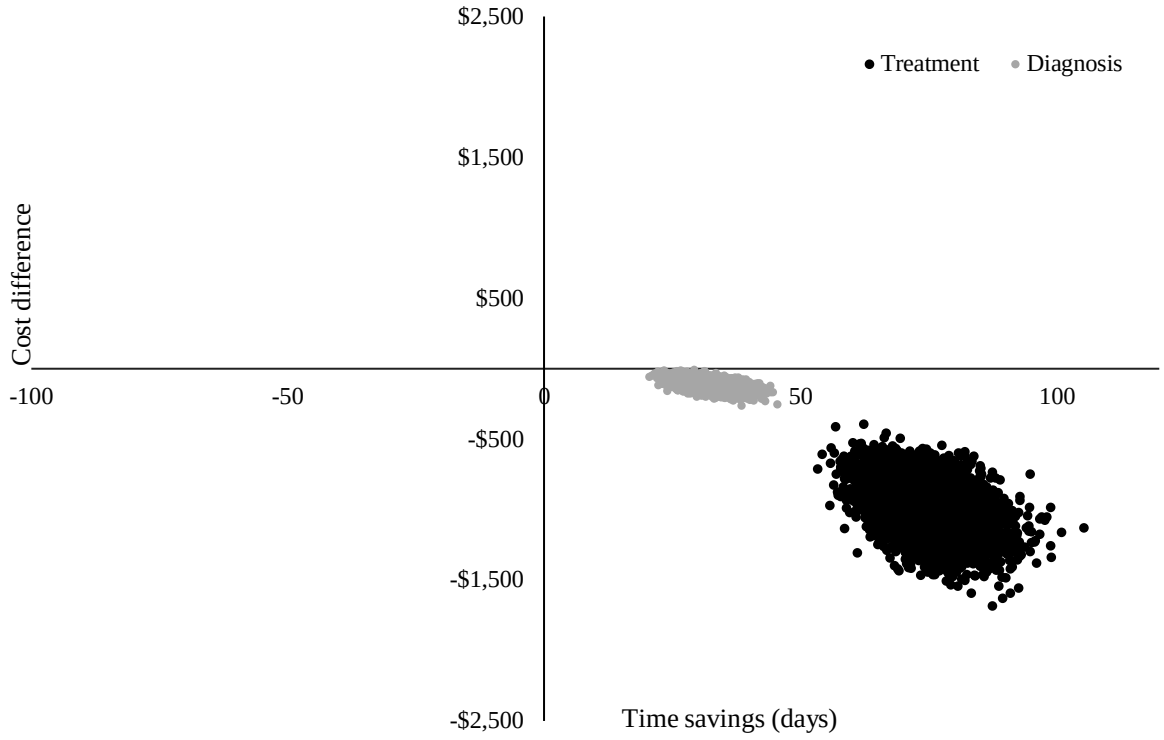

Figure 3.2: Probabilistic sensitivity analysis for time to diagnosis (grey) and time to treatment (black).

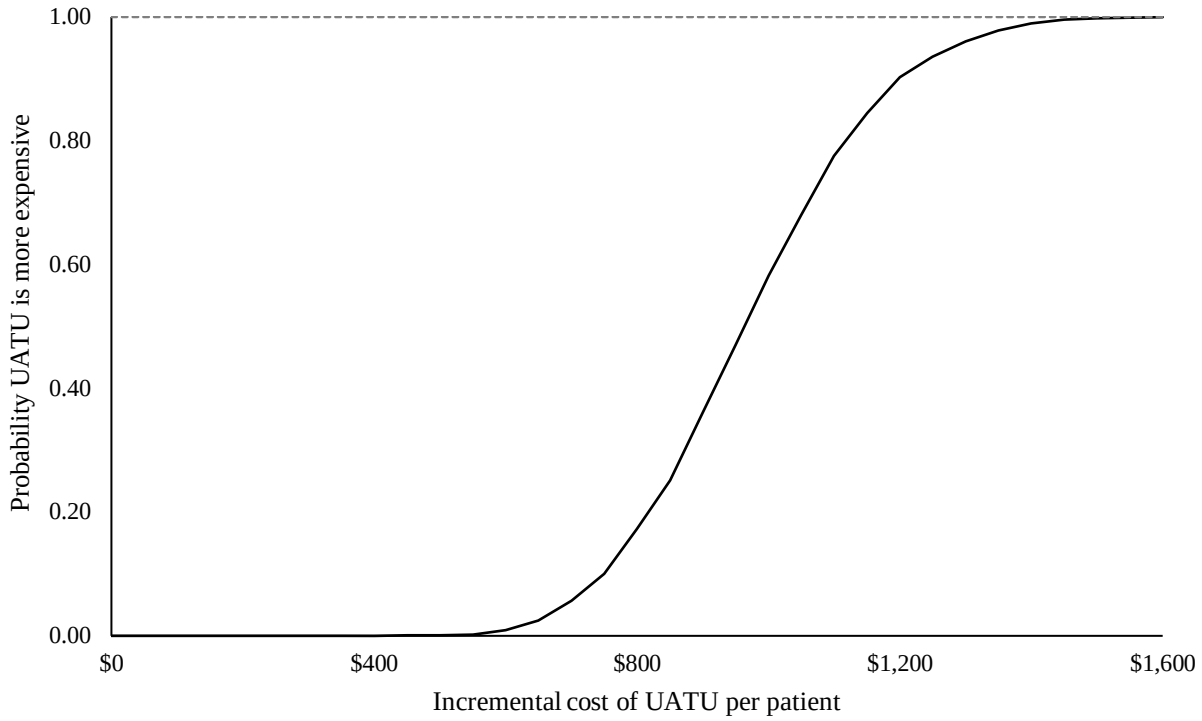

Figure 3.3: Cost savings acceptability curve representing the probability at which the additional cost per patient to maintain and operate the UATU will be more expensive than usual care. The dashed line represents the cost at which the UATU will be certainly more expensive than usual care.

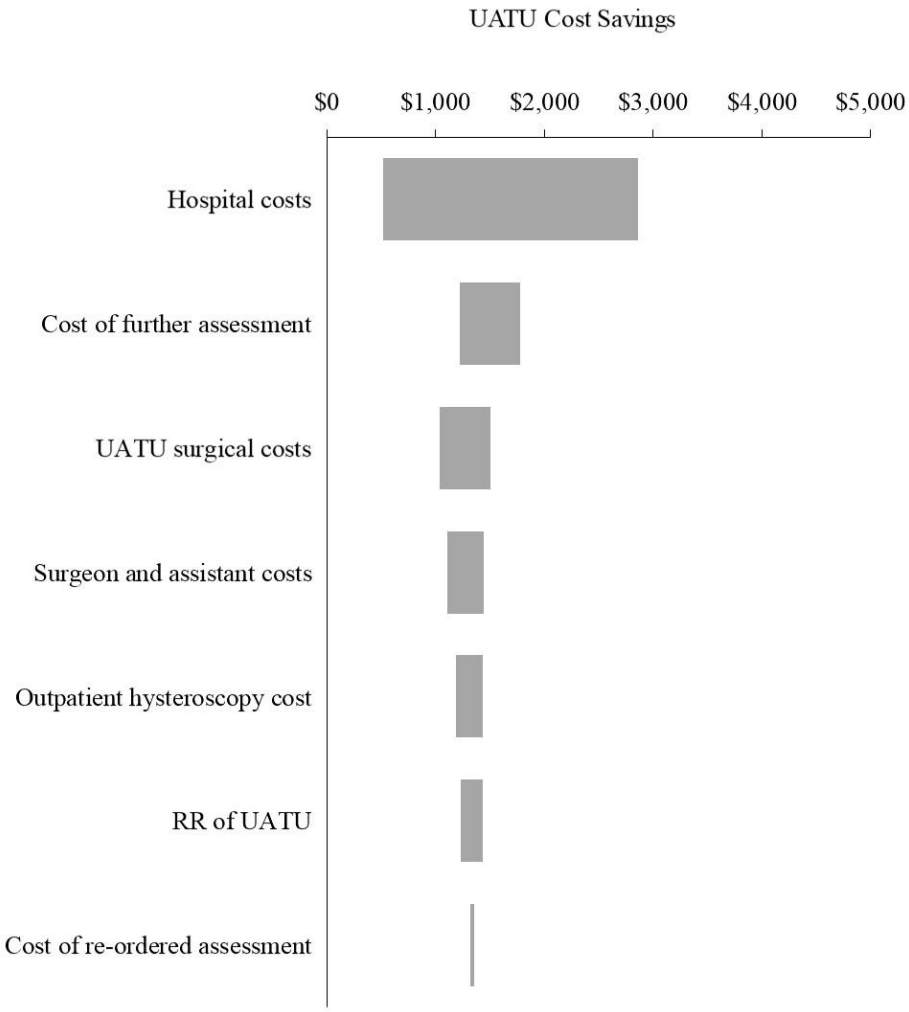

Figure 3.4: Univariate sensitivity analysis presented as a tornado plot. The range in possible cost savings between the UATU and usual care are presented by varying each input parameter between two extreme but plausible values. The input parameter with the widest range in cost savings is presented at the top.

CHAPTER 4: OVERALL DISCUSSION AND CONCLUSIONS

The following discussion chapter summarizes and discusses the main findings and limitations of the systematic review and cost-effectiveness studies that comprise this thesis project. Considerations for policy makers and clinicians are described, as well as future research suggestions and overall conclusions.

4.1 Summary of results

A UATU is an innovative approach in providing faster, effective, and satisfactory care to women presenting with AUB in our Canadian system. The decision to implement a UATU in an outpatient setting will prevent women from unnecessary encounters to the health care system and will provide timely diagnosis and treatment in one location. The overall objective of this thesis project is to assess the cost-effectiveness of an outpatient UATU service model compared to the current standard practice of diagnosing and treating AUB. Specifically, we aimed to synthesize and evaluate the costs and effectiveness data surrounding the proposed implementation of a UATU model. These aims were addressed in both Chapters 2 and 3 of this thesis through a systematic review and cost-effectiveness analysis, with an end goal to general evidence-based tools for decision makers and clinicians related to the implementation of an outpatient UATU.

The systematic review manuscript in Chapter 2 synthesized the available literature on current evidence surrounding the hysteroscopic procedure that would be utilized in the UATU setting. Since diagnostic work-up and therapy in the proposed UATU of this thesis includes hysteroscopic evaluation and no studies evaluate a UATU, we aimed to identify studies investigating outpatient and inpatient hysteroscopic procedures. The review looked at comparing outpatient hysteroscopy to hysteroscopy performed in the main OR under general anesthesia. We

synthesized outcome measures surrounding efficacy, patient safety, and cost of both interventions. The results of the systematic review suggest that it is unclear whether implementing hysteroscopy in an outpatient setting is more effective than hysteroscopy performed in the operating room. The current evidence supported no statistically significant difference in the safety, efficacy, or patient tolerability between outpatient and intraoperative hysteroscopy procedures, and given the current available evidence and limited number of studies, findings should be interpreted with caution. The review noted that there was greater reported post-operative pain in the outpatient setting, however there was high uncertainty surrounding this finding. The results of this review highlighted the need for improvements in study reporting and further clinical studies evaluating the clinical effectiveness of performing hysteroscopy in an outpatient setting.

The cost-effectiveness analysis manuscript in Chapter 3 aimed to assess whether the benefits of a UATU outweigh its costs. We aimed to evaluate the cost-effectiveness of a single-visit outpatient UATU compared to usual care in diagnosing and treating intrauterine pathology from the perspective of the publicly funded Canadian health care system. Our effectiveness measure of interest was comparing the UATU and usual care in terms of how much time it took from the initial consult until diagnosis and treatment was obtained. The results of this review illustrate that the UATU is more cost-effective than usual care in diagnosing and treating patients who present with AUB. All of the results of our Monte Carlo simulations are plotted on a cost-effectiveness plane located in the bottom right-hand quadrant, illustrating that the UATU is both less expensive time saving compared to usual care.

4.2 Significance of findings and future directions

With health care providers continuously searching for streamlined approaches to delivering effective health care, there is an increased demand for research of innovative methods to provide care that improves the quality of life for patients while managing or reducing costs. The findings of this thesis have the potential to inform decision makers and clinicians to drive practice change in redirecting patient care to the outpatient setting and improve how women are diagnosed and treated for AUB in the Canadian setting. The NHS in the United Kingdom recommends that the management of AUB is best done outside of the formal operating room. A formal HTA of outpatient versus inpatient polyp treatment for abnormal bleeding was conducted by the NHS.[10] An HTA is a comprehensive evaluation of the clinical effectiveness, cost-effectiveness, and may include the legal, ethical, and social implications of health technologies on patient health and the health care system.[86] The overall assessment by NHS concluded that in treating women with AUB associated with uterine polyps, outpatient polypectomy was similarly effective to inpatient polypectomy at 6 and 12 months and was more cost-effective, however, patients need to be made aware that failure to remove a polyp is more likely with outpatient treatment. The paper supports outpatient polyp treatment as effective, acceptable, and cost-effective while providing patients with realistic expectations of the outpatient treatment experience regarding pain, acceptability, and treatment failure. Both the NHS health technology assessment and this thesis project provide a reliable case to consider UATU as a first line of treatment in the Canadian setting.

In addition, this thesis aligns with the measures set by the Institute for Health care improvement (IHI) in the Triple Aim framework. The IHI has set to define a framework for new health technologies or programs to pursue three dimensions in health care: 1) improving the patient experience of care (including quality and satisfaction); 2) improving the health of

populations; and 3) reducing the per capita cost of health care.[87] Benefits of the Triple Aim are healthier populations, patients who can expect less complex and more coordinated care, and providing hospitals and health facilities with the flexibility to allocate health care resources to other important programs. The results of this thesis project and the NHS health technology assessment support UATU as achieving the results of all three Triple Aim dimensions. This thesis project supports UATU as being cost-effective and improving patient satisfaction with timely diagnosis and treatment, while the health assessment suggests outpatient treatment as being similarly effective to the standard practice of inpatient treatment.

Future research

Further research is warranted on characterizing the design and implementation costs of a UATU to health care facilities that would implement a UATU, especially in centers outside of Ontario. The cost-effectiveness analysis presented in Chapter 3 only focused on data from Ontario and may not reflect the overall health system costs in other Canadian provinces, territories, or outside of Canada. The Ottawa Hospital is a large academic medical center and may have different cost distributions than a small or private community hospital.

In terms of implementing a UATU, future research should also consider the numerous barriers in the implementation of a UATU in the Canadian setting. There is a current lack of knowledge and understanding on how to advocate for effective change in Canadian hospitals. Knowledge translation is a critical component to advocate for practice change within the hospital and among clinicians, and should be considered when designing future studies. Another barrier includes funding, as the Canadian health care system works with a global budget, resulting in health care programs being funded in silos. For instance, the money that would fund the

outpatient suite is independent from the money that funds the inpatient suite which poses challenges to deliver effective and efficient health care when there is such a disconnect between programs.

Given the results of this thesis project, further well-designed randomized-controlled trials and clinical studies evaluating effectiveness, cost-effectiveness, and patient experience should be conducted to further evaluate the outpatient hysteroscopic procedure and the UATU. These future studies would help characterize the UATU and further support practice change. In addition to focusing research on characterizing the UATU within hospitals, health care providers should also consider the possibility of expanding the UATU as a community-based service which may be more convenient to patients.

4.3 Methodological strengths and limitations

Strengths of this thesis project include systematically synthesizing all available evidence related to treating and diagnosing women presenting with AUB in an outpatient setting compared to the main operating room. Synthesizing available data allows us to summarize clinical effectiveness data on outpatient hysteroscopy to further understand and characterize the UATU service model. Also, performing a cost effectiveness analysis provides insight into the trade-offs and consequences between a UATU and usual care that would not be apparent thought assessment of clinical outcomes alone. The cost-effectiveness analysis is unique in that it explores time to diagnosis and treatment as outcomes which decision makers to visualize the clear differences between usual care and the UATU in providing fast, efficient, and reliable care.

In addition, the cost-effectiveness analysis took the perspective of the publicly funded Canadian health care system. This perspective considers all the costs borne to the health care

provider that will fund the intervention, however this thesis project did not explore the patient perspective. There are many out-of-pocket expenses incurred by patients attending appointments and consults that are important to consider. Out-of-pocket costs may include loss of time from work, transportation, parking, or medication that burden patients who are required to have multiple consultations or appointments and increased waiting-time for diagnosis and treatment. Although the patient perspective was not explored, we would anticipate that the UATU would decrease these out-of-pocket costs by minimizing appointments and consults to a one-day visit.

Health Utility

Our cost-effectiveness analysis did not measure QALYs as an outcome which limits conclusions we can draw regarding patient health related quality of life in the UATU. QALYs are measured by using utility weights, which reflect an individual's preference for a given health state on a scale ranging from 1.0 (perfect health) to 0 (death).[88] The use of QALYs in cost-effectiveness studies is favoured because they can be measured and compared over a wide variety of health conditions.[89] Indirect methods exist where study participants complete generic health state classification surveys (i.e. EuroQol or the Medical Outcomes Study Short-Form 36) where utilities from reference populations for each health state is defined by the survey.[90,91]. In terms of our thesis project, we only identified one other study that evaluated QALYs for patients with abnormal bleeding and this was measured in patients who only received outpatient polypectomy and did not accurately reflect the health utility of patients in our study.[57] In the outpatient UATU, patients will receive other procedures to treat AUB other than polypectomy that may impact the quality of life score a patient experiences. In addition, collecting data from a generic health state classification survey was out of the scope of this thesis project, however

measuring health utilities would be useful for future cost-utility analyses evaluating the UATU. Overall, we decided time to diagnosis and time to treatment were clinically relevant outcomes for both patients and clinicians since delivering timely and streamlined health care are important to health care providers and patients.

Costing

It is important to note that there was some uncertainty surrounding the cost estimates in our cost-effectiveness model. To estimate cost, we were unable to obtain the total cost per patient but rather obtained an overall average cost per procedure or visit and applied this to our population. The primary administrative database used for this research project was the OCCI database and then for surgeon, assistant, and anaesthesiologist costs we used the Ontario Schedule of Benefits. The primary limitation of using OCCI costs was that only participating hospitals in Ontario that have a case costing system were included. Most large hospital centers are captured in the OCCI which can provide an accurate estimate, however smaller hospitals which may have valuable cost data were not included. Additionally, cost data in the OCCI for procedures with very few cases were not available which limits the cost data available to this study.

Patient self-reported outcomes

Although the results of this thesis project have the potential to inform decision makers about moving uterine assessment into the outpatient setting, there are some limitations to note. One limitation to consider is the heterogeneity of synthesized outcomes in the meta-analysis. Due to the small number of studies and large uncertainty surrounding estimates in each study, we

could not confidently support or refute performing hysteroscopy in the outpatient setting. A major drawback to study outcomes included patient self-reported outcomes using response scales. Many outcomes such as treatment success, patient satisfaction, and post-operative pain relied on the patient's self-assessment using instruments such as a questionnaire or interview. To measure post-operative pain intensity, many studies commonly used the Visual Analogue Scale (VAS). It provides a continuous scale for magnitude estimation and consists of a straight line, the ends of which are defined in terms of the extreme limits of pain experience.[92] For the evaluation of patient reported outcome instruments, validity and reliability must be established.[93–95] Validity is the degree to which evidence and theory support the interpretations of test scores entailed by the proposed uses of tests, while reliability is the ability to yield reproducible and consistent estimates of a true treatment effect. In studies evaluating post-operative pain, the reliability and validity of using the VAS to assess pain experience was not discussed. Pain is also difficult to compare and measure because of differences in cultural and environmental influences. Various psychologic aids play an important role in reducing anxiety and pain, such as nurse assistance and explanation of the procedure.[83]

Similarly, successful treatment was determined by the patient's assessment of their bleeding using a dichotomous (success or fail) outcome measure. For women with heavy menstrual bleeding, treatment was considered a success if bleeding had reduced to acceptable levels.[57] Overall patient satisfaction was also based on the patient's perceived experiences. One study asked patients to complete a hospital anxiety and depression questionnaire, while another assessed the acceptability of the procedure using a Likert scale and structured questions.[57,82,96] These methods to assess overall satisfaction are likely to differ from one another in how the questions are phrased and how the patient interprets and answers them. Patient self-reported

outcomes can bias the observed estimate since the individual has the tendency to bias their estimate. This may be explained by fear of disease, a desire to maintain self-esteem, and unwillingness to displease the doctor.[83,97] The biased results could explain why we observed such variable results in the pooled estimates of the meta-analysis.

The design and implementation costs of UATU

In this thesis we did not consider the cost of implementing a UATU in an outpatient setting. For hospitals and other institutions other than the Ottawa Hospital that would be interested in implementing a UATU in their clinic would require a costing study that evaluated all the costs associated with implementing and maintaining a UATU clinic. There may be costs associated with administration, physician training, other endoscopic technologies, or additional running costs that would need to be considered. We rationalized that the cost to implement a UATU will be minimal for many large tertiary hospital centers such as the Ottawa Hospital since the hysteroscopic equipment in the main operating room would be moved to the UATU. For this reason, the findings in this thesis have a limited generalizability to other smaller centers that may not already have these instruments in place and require additional training for practitioners who may not have adequate experience in performing hysteroscopic procedure in the outpatient setting.

Retrospective chart review

The retrospective chart review provided accurate probability, time, and cost estimates to populate the economic model. By performing a retrospective chart review, we were able to target our population of interest and map their encounters with the health care system to illustrate the

current patient health care pathway. Our patient sample was deemed to be a representative of women who present with AUB at the Ottawa Hospital as we used a random sampling approach. Although there were advantages to performing a retrospective chart review, there are also some notable limitations to report. Some limitations include incomplete or missing documentation and poorly recorded information. Misclassification bias may be present as there may be discrepancies in charts leading patients to be assigned to a different category than they should. This can lead to incorrect associations being observed and the relationships between time and receiving a diagnosis or treatment can either increase or decrease our observed association.[98] In our review, we anticipate misclassification bias to be minimal as there was a clinician with expertise in gynecology as a second reviewer ensuring that relevant all fields were abstracted accurately, along with a standardized abstraction form in excel with explicit inclusion and exclusion criteria. Performing a retrospective chart reviews alongside our economic model offers many advantages. There is a wealth of clinically relevant data providing relevant individual-level data giving best estimates to populate our model and answer our relevant research questions.[99,100]

4.4 Conclusions

Overall, this thesis project addressed its main objectives in synthesizing and evaluating the cost and effectiveness data surrounding an outpatient UATU. While the systematic review had some limitations in drawing reliable and definite conclusions, the cost-effectiveness analysis provides a strong case to support that a UATU provides less costly and timely care to women requiring diagnosis and treatment for AUB. The conventional approach to treating patients with AUB involves multiple investigations, multiple primary care and specialist appointments, and unnecessary surgical procedures performed in an operating theatre under general anesthesia. The

conventional approach comes to a cost to the patient with increased time in-hospital, increased time away from work, and the discomfort of multiple procedures. An outpatient UATU is an innovative approach to improve access to gynecologic care by providing timely assessment and treatment with the aim of improving the efficiency of gynecologic care by reducing wait-times, improving patient experience, and lowering costs to the health care system. Although this thesis project was limited in drawing conclusions regarding clinical effectiveness suggesting future research is warranted, the health technology assessment performed by the NHS in the UK concluded that outpatient treatment of uterine polyps was effective, acceptable to patients, and cost-effective.[10] The results of this thesis project along with the NHS suggest that the UATU should be considered in Canada as an option to diagnose and treat women who present with AUB.

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APPENDICES

Appendix 2. 1 - Systematic Review Search Strategy

Ovid Multifile
2017 Feb 11

Database: Embase Classic+Embase <1947 to 2017 February 10>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---

1 Hysteroscopy/ (14514)
2 Hysteroscopes/ (1146)
3 hysteroscop*.tw,kw. (15981)
4 uteroscop*.tw,kw. (37)
5 (endoscop* adj3 (uterine or uterus or uteri or intrauterin* or intra-uterin*)).tw,kw. (305)
6 or/1-5 (19447)
7 male/ not (female/ and male/) (5034984)
8 6 not 7 [MALE-ONLY REMOVED] (19407)
9 exp Infant/ not (exp Infant/ and exp Adult/) (1599723)
10 exp Child/ not (exp Child/ and exp Adult/) (3069124)
11 8 not (9 or 10) [CHILD-ONLY REMOVED] (19127)
12 exp Animals/ not (exp Animals/ and Humans/) (16251786)
13 11 not 12 [ANIMAL-ONLY REMOVED] (13838)
14 (comment or editorial or interview or news).pt. (1701612)
15 (letter not (letter and randomized controlled trial)).pt. (1924858)
16 13 not (14 or 15) [OPINION PIECES REMOVED] (13056)
17 16 use ppez [MEDLINE RECORDS] (6442)
18 hysteroscopy/ (14514)
19 hysteroscope/ (1146)
20 hysteroscop*.tw,kw. (15981)
21 uteroscop*.tw,kw. (37)
22 (endoscop* adj3 (uterine or uterus or uteri or intrauterin* or intra-uterin*)).tw,kw. (305)
23 or/18-22 (19447)
24 male/ not (female/ and male/) (5034984)
25 23 not 24 [MALE-ONLY REMOVED] (19407)
26 exp juvenile/ not (exp juvenile/ and exp adult/) (2243223)
27 25 not 26 [CHILD-ONLY REMOVED] (19113)
28 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (44705165)
29 exp humans/ or exp human experimentation/ or exp human experiment/ (35109177)
30 28 not 29 (9597676)
31 27 not 30 [ANIMAL-ONLY REMOVED] (18881)
32 editorial.pt. (957820)
33 letter.pt. not (randomized controlled trial/ and letter.pt.) (1919510)
34 31 not (32 or 33) [OPINION PIECES REMOVED] (17910)
35 34 use emczd [EMBASE RECORDS] (11383)

36 17 or 35 [BOTH DATABASES] (17825)
37 limit 36 to yr="2012-current" (5720)
38 remove duplicates from 37 (4217)
39 limit 36 to yr="2004-2011" (5333)
40 remove duplicates from 39 (3736)
41 limit 36 to yr="1990-2003" (5294)
42 remove duplicates from 41 (3372)
43 36 not (37 or 39 or 41) (1478)
44 remove duplicates from 43 (969)
45 38 or 40 or 42 or 44 [TOTAL UNIQUE RECORDS] (12294)
46 45 use ppez [MEDLINE UNIQUE RECORDS] (6133)
47 45 use emczd [EMBASE UNIQUE RECORDS] (6161)

****

Cochrane Library

Search Name: Hysteroscopy
Date Run: 13/02/17 00:50:20.828
Description: OHRI (Ked Thavorn) - 2017 Feb 12

ID Search Hits
#1 [mh Hysteroscopy] 396
#2 [mh Hysteroscopes] 27
#3 hysteroscop*:ti,ab,kw 862
#4 uteroscop*:ti,ab,kw 0
#5 (endoscop* near/3 (uterine or uterus or uteri or intrauterin* or (intra next uterin*))):ti,ab,kw 15
#6 {or #1-#5} 872
#7 [mh male] not ([mh female] and [mh male]) 119
#8 #6 not #7 872
#9 [mh Infant] not ([mh Infant] and [mh Adult]) 14868
#10 [mh Child] not ([mh Child] and [mh Adult]) 158
#11 #8 not (#9 or #10) 869

DSR - 19
DARE – 31
CENTRAL – 782
Methods - 3
HTA - 16
NHS EED – 18

CINAHL
Sunday, February 12, 2017 8:10:19 PM

#	Query	Limiters/Expanders	Results
S12	S9 NOT S10	Limiters – Exclude MEDLINE records Expanders - Apply related words Search modes - Boolean/Phrase	118
S11	S9 NOT S10	Expanders - Apply related words Search modes - Boolean/Phrase	532
S10	(MH "Animals+") NOT ((MH "Animals+") AND (MH "Human"))	Expanders - Apply related words Search modes - Boolean/Phrase	31,137
S9	S7 NOT S8	Expanders - Apply related words Search modes - Boolean/Phrase	533
S8	(MH "Child+") NOT ((MH "Child+") AND (MH "Adult+"))	Expanders - Apply related words Search modes - Boolean/Phrase	257,153
S7	S5 NOT S6	Expanders - Apply related words Search modes - Boolean/Phrase	534
S6	(MH "Male") NOT ((MH "Female") AND (MH "Male")))	Expanders - Apply related words Search modes - Boolean/Phrase	153,212
S5	S1 OR S2 OR S3 OR S4	Expanders - Apply related words Search modes - Boolean/Phrase	534
S4	TI ((endoscop* N3 (uterine or uterus or uteri or intrauterin* or intra-uterin*))) OR AB ((endoscop* N3 (uterine or uterus or uteri or intrauterin* or intra-uterin*)))	Expanders - Apply related words Search modes - Boolean/Phrase	8

S3	TI uteroscop* OR AB uteroscop*	Expanders - Apply related words Search modes - Boolean/Phrase	0
S2	TI hysteroscop* OR AB hysteroscop*	Expanders - Apply related words Search modes - Boolean/Phrase	381
S1	(MH "Hysteroscopy")	Expanders - Apply related words Search modes - Boolean/Phrase	386

Web of Science
2017 Feb 12

# 4	5,466	#3 OR #2 OR #1 Indexes=SCI-EXPANDED Timespan=All years
# 3	124	**TOPIC:** ((endoscop* NEAR/3 (uterine or uterus or uteri or intrauterin* or intra-uterin*))) Indexes=SCI-EXPANDED Timespan=All years
# 2	8	**TOPIC:** (uteroscop*) Indexes=SCI-EXPANDED Timespan=All years
# 1	5,364	**TOPIC:** (hysteroscop*) Indexes=SCI-EXPANDED Timespan=All years

Appendix 2. 2 – Systematic review data extraction sheet

ARTICLE IDENTIFIER

Reference ID:	
First author:	
Year:	
Country:	

PATIENTS TREATED IN THE OUTPATIENT SETTING

Name of procedure:	
Details of procedure:	
Indication for procedure:	
Type of evaluation:	
Was the procedure diagnostic or therapeutic or both?	

PATIENTS TREATED IN THE MAIN OPERATING ROOM

Name of procedure:	
Details of procedure:	
Indication for procedure:	
Type of evaluation:	
Details of general anesthesia administered:	
Was the procedure diagnostic or therapeutic or both?	

DETAILS OF THE STUDY

Study type (i.e. RCT, cohort, case-control, etc.)	
Study population inclusion criteria:	
Study population exclusion criteria:	
Number of centers included:	
Total sample size included:	
Sample size analyzed:	
Mean age:	
Ethnicity:	
Menopausal status:	
Parity:	
Comorbidities present:	
Follow-up time:	

OUTCOMES

Diagnostic accuracy (i.e. sensitivity, specificity, PPV, NPV, etc.):	
Safety (i.e. adverse events, infections, hospitalization, etc.):	
Effectiveness (i.e. treatment success):	
Health related quality of life outcomes (i.e. SF-36 scores, VAS, etc.)	
Practitioner satisfaction:	
Cost:	
Additional comments:	

Appendix 2. 3 – Cochrane risk of bias tool for RCTs

Item	Description
Sequence generation	Was the allocation adequately generated? *(yes/no/unclear)*
Allocation concealment	Was the generation adequately concealed before group assignments? *(yes/no/unclear)*
Blinding of participants and personnel	Was knowledge of the allocated interventions adequately hidden from the participants and personnel after participants were assigned to respective groups? *(yes/no/unclear)*
Blinding of outcome assessors	Was knowledge of the allocated interventions adequately hidden from the outcome assessors after participants were assigned to respective groups? *(yes/no/unclear)*
Incomplete outcome data	Were incomplete outcome data adequately addressed? *(yes/no/unclear)*
Selective outcome reporting	Are reports of the study free of suggestion of selective outcome reporting? *(yes/no/unclear)*
Other sources of bias	Was the study apparently free of other problems that could put it at risk of bias? *(yes/no/unclear)*

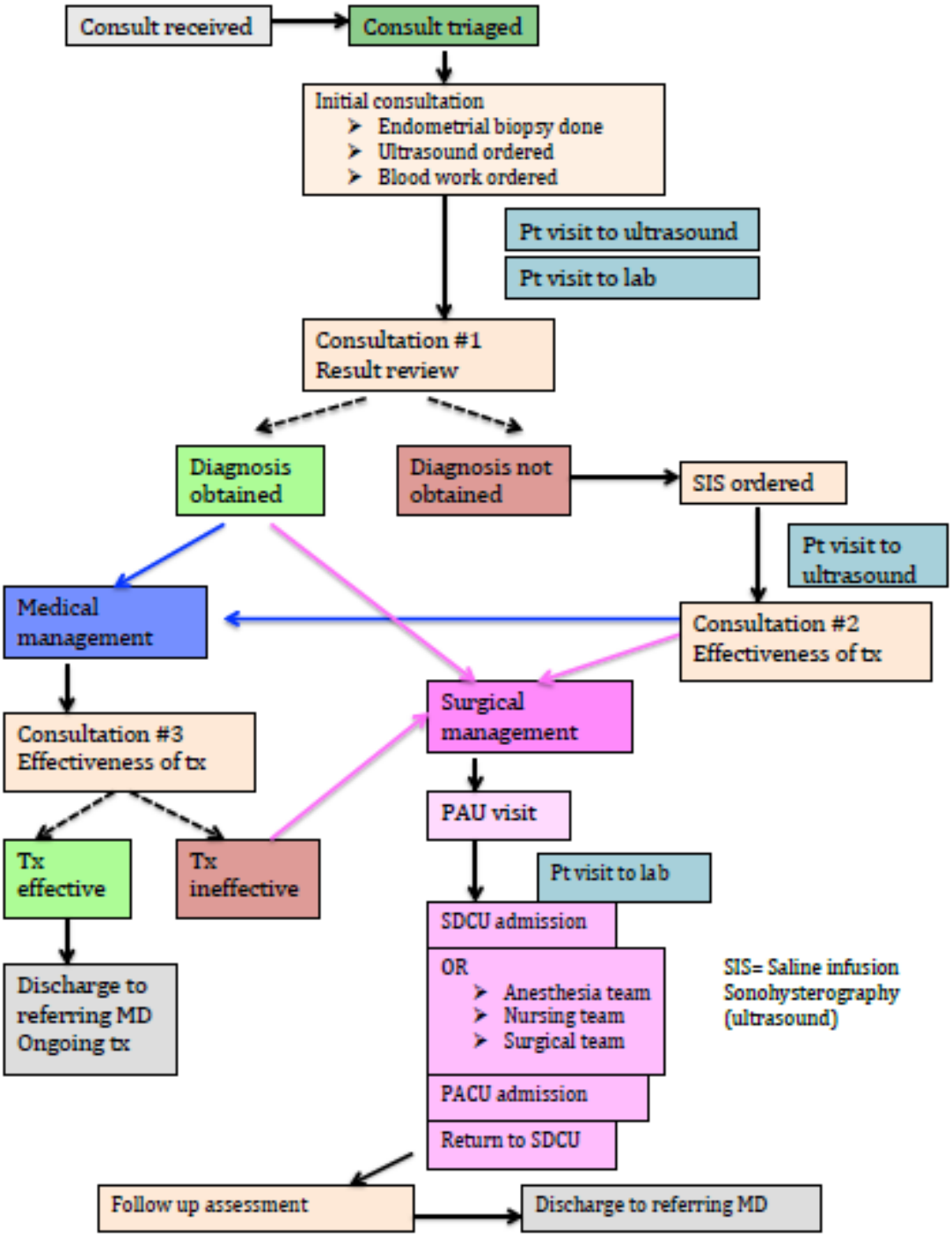
Appendix 2. 4 – Downs and Black checklist for methodological quality of non-randomized studies

Item	Criteria	Description
Reporting		
1	Is the hypothesis/aim/objective of the study clearly described?	*Must be explicit. (yes/no)*
2	Are the main outcomes to be measured clear described in the introduction or methods section?	*If the main outcomes are first mentioned in the results section, the question should be answered no. All primary outcomes should be described for is yes. (yes/no)*
3	Are the characteristics of the patients included in the study clearly described?	*In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given. Single case studies must state source of patient (yes/no)*
4	Are the interventions of interest clearly described?	*Treatments and placebo (where relevant) that are to be compared should be clearly described (yes/no)*
5	Are the distribution of principal confounders in each group of subjects to be compared clearly described?	*A list of principal confounder is provided YES=age, severity (yes/no)*
6	Are the main findings of the study clearly described?	*Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (yes/no)*
7	Does the study provide estimates of the random variability in the data for the main outcomes?	*In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. (yes/no)*
8	Have all important adverse events that may be a consequence of the intervention been reported?	*This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events (COMPLICATIONS BUT NOT AN INCREASE IN PAIN). (yes/no)*
9	Have the characteristics of patients lost to follow-up been described?	*If not explicit = NO. RETROSPECTIVE – if not described = UTD; if not explicit re: numbers agreeing to participate = NO. Needs to be >85% (yes/no)*
10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	*(yes/no)*

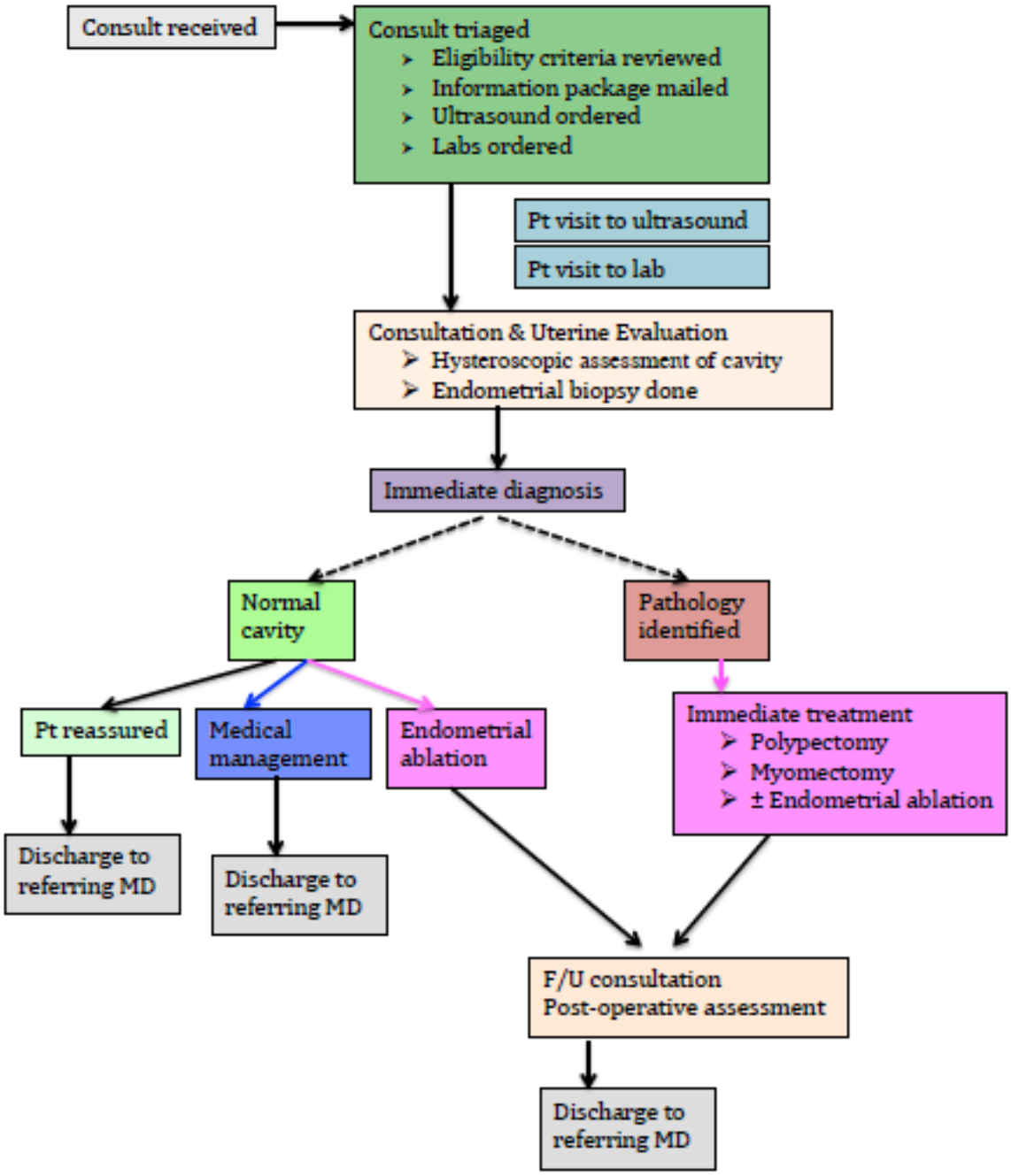
External validity		
11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	*The study must identify the source population for patients and describe how the patients were selected. (yes/no/unclear)*
12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	*The proportion of those asked who agreed should be stated. (yes/no/unclear)*
13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	*For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. Must state type of hospital and country for YES. (yes/no/unclear)*
Internal validity - bias		
14	Was an attempt made to blind study subjects to the intervention they have received?	*For studies where the patients would have no way of knowing which intervention they received, this should be answered yes. Retrospective, single group = NO; UTD if > 1 group and blinding not explicitly stated (yes/no/unclear)*
15	Was an attempt made to blind those measuring the main outcomes of the intervention?	*Must be explicit. (yes/no/unclear)*
16	If any of the results of the study were based on "data dredging", was this made clear?	*Any analyses that had not been planned at the outset of the study should be clearly indicated. Retrospective = NO. Prospective = YES (yes/no/unclear)*
17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case control studies, is the time period between the intervention and outcome the same for cases and controls?	*Where follow-up was the same for all study patients the answer should yes. Studies where differences in follow-up are ignored should be answered no. Acceptable range 1 yr follow up = 1 month each way; 2 years follow up = 2 months; 3 years follow up = 3months.....10years follow up = 10 months (yes/no/unclear)*
18	Were the statistical tests used to assess the main outcomes appropriate?	*The statistical techniques used must be appropriate to the data. If no tests done, but would have been appropriate to do = NO (yes/no/unclear)*
19	Was compliance with the intervention/s reliable?	*Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. Surgical studies will be YES unless procedure not completed. (yes/no/unclear)*
20	Were the main outcome measures used accurate (valid and reliable)?	*Where outcome measures are clearly described, which refer to other work or that demonstrates the*

		outcome measures are accurate = YES. ALL primary outcomes valid and reliable for YES (yes/no/unclear)
Internal validity - confounding (selection bias)		
21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	*Patients for all comparison groups should be selected from the same hospital. The question should be answered UTD for cohort and case control studies where there is no information concerning the source of patients (yes/no/unclear)*
22	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time?	*For a study which does not specify the time period over which patients were recruited, the question should be answered as UTD. Surgical studies must be <10 years for YES, if >10 years then NO (yes/no/unclear)*
23	Were study subjects randomised to intervention groups?	*Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. (yes/no/unclear)*
24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	*All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no. (yes/no/unclear)*
25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	*In nonrandomised studies if the effect of the main confounders was not investigated or no adjustment was made in the final analyses the question should be answered as no. If no significant difference between groups shown then YES (yes/no/unclear)*
26	Were losses of patients to follow-up taken into account?	*If the numbers of patients lost to follow-up are not reported = unable to determine. (yes/no/unclear)*
Power		
27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance <5%	*Sample sizes have been calculated to detect a difference of x% and y%. (yes/no)*

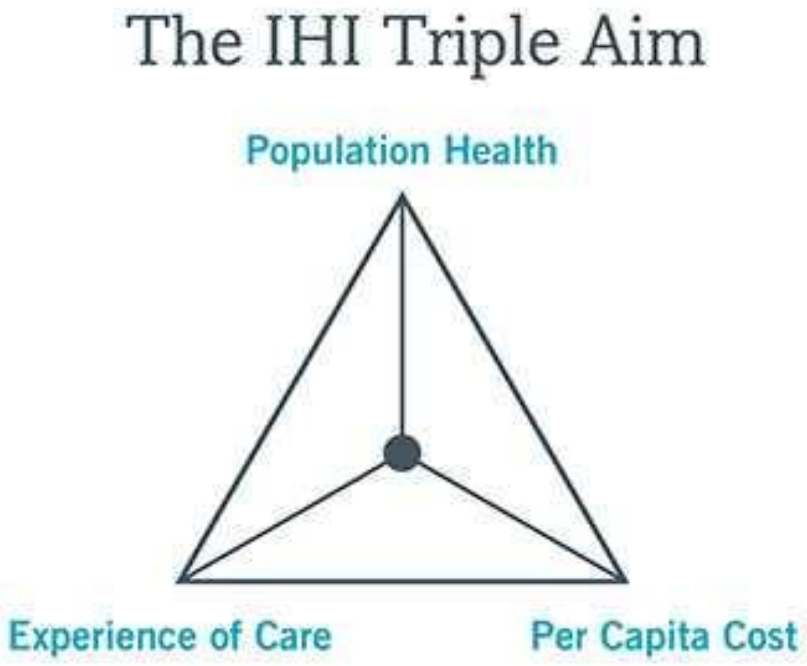
Appendix 3. 1 - Usual care patient pathway



Appendix 3. 2 – Proposed UATU patient pathway



Appendix 3. 3 – Institute for Health care Improvement Triple Aim Initiative



Appendix 3. 4 - Retrospective chart review data extraction sheet

PATIENT DEMOGRAPHIC INFORMATION

MRN:	
DOB (YYYY-MM-DD):	
Peri-menopausal status:	yes/no
Post-menopausal status:	yes/no
Nulliparous:	yes/no

WORK-UP

Date of initial consultation:	
Age at initial consultation:	
Was a uterine evaluation ordered at consult (ultrasound, saline infusion, hysteroscopy, etc.):	yes/no
Type of evaluation:	
Was an additional uterine evaluation after the first evaluation ordered? (SIS, hysteroscopy, etc.)	yes/no
Type of additional evaluation:	

DETAILS OF INTERVENTION

Indication:	
Diagnosis:	
Date of final diagnosis and treatment plan:	
Was the patient's final treatment plan medical or surgical?	

Was the initial surgical procedure under general anesthesia:	yes/no
Did the patient visit the outpatient hysteroscopy suite?	yes/no
Type of surgical procedure:	
Surgical procedure code:	
Date of surgical procedure:	
Drugs prescribed for the medical treatment plan:	

Appendix 3. 5 – Detailed retrospective review methods

Patient collection

A list of all patients who had a clinic visit to the Ottawa Hospital's Shirley E. Greenberg Women's Health Center at the Riverside Campus between April 1st 2014 and March 31st 2017 were obtained from a methodologist at the Ottawa Hospital Data Warehouse. A list of 5,283 patients were obtained and assigned a random number from a random number generator in Microsoft excel. The list was then ordered by the randomly assigned number to generate a random list of patients.

Using the patient's MRN number, we were able to access and review each patient's chart to assess whether they met eligibility criteria. Eligible patients were those who presented with AUB including heavy menstrual bleeding, irregular menses, or post-menopausal bleeding. We excluded patients visiting the clinic for infertility, abortion, or patients with endometriosis. If the patient met the inclusion criteria, we abstracted information using the detailed abstraction form presented in appendix 3.4. Abstracted data was verified by a second reviewer who was an expert in the field of gynecology. We reviewed each chart in the list until we reached 200 eligible patients.

Time to diagnosis calculation

Time to diagnosis was measured by calculating the difference in time between the date of initial consult and the date of consult when a diagnosis and treatment plan was discussed between the physician and patient.

Time to treatment calculation

Time to treatment was measured by calculating the difference in time between the date of consult when a diagnosis and treatment plan was discussed and the date of the first surgical procedure. This time was then added to the time to diagnosis to obtain a total time to treatment from the initial consult.

Further evaluation

We defined patients as requiring further evaluation if a transvaginal ultrasound, saline infusion sonohysterography (SIS), magnetic resonance imaging (MRI), biopsy, and/or hysteroscopy was ordered at initial consult.

To calculate the cost of a further uterine assessment, we used cost data from both OCCI and the Ontario schedule of benefits (SOB). We added both costs from the OCCI and the Ontario SOB to get an estimate for the cost borne to each patient. We then took a weighted average over all patients of the costs to get an overall estimate for further evaluation costs. Costs were adjusted to 2018 dollars accordingly.

Surgical intervention

The type of surgical procedure and surgical codes were abstracted from patient charts and were then linked to the Canadian Classification of Health Intervention codes as reported by OCCI with the help of a gynecologist (S.S). We then calculated a weighted average for each procedure to get an overall estimate of surgery based on hospital costs.

To calculate anaesthesiologist, assistant, and surgeon costs, we used the codes and data from the Ontario SOB. The costs of surgeons are presented as such, and if more than one SOB code, the costs were added accordingly. For anaesthesiologists and assistant fees, the Ontario

SOB uses time units to calculate the unit fee. Time is determined per operation, excluding any time spent waiting between surgical procedures. There is a number of basic unit listed next to each code, which is used to calculate the total units which are calculated for each 15 minutes or part thereof. For assistant fees, each unit block is $12.04. The unit value of each 15 minute period is: during the first hour or less is 1 unit, after the first hour is 2 units, and after 2.5 hours is 3 units. For anaesthesiologists the unit fee is $15.01. The unit value of each 15 minute period is: during the first hour is 1 unit, after the first hour up to and including the first 1.5 hours is 2 units, and after 1.5 hours is 3 units. A weighted cost over all patients were then added to obtain an overall estimate of surgeon, assistant, and anesthesiologist costs. These costs were then added to the hospital costs to get an overall surgery cost.

Appendix 3. 6– List of participating Ontario hospitals included in the OCCI

BARRIE Royal Victoria	ORANGEVILLE Headwaters HC
TORONTO North York General	KITCHENER Grand River
CLINTON Public	WINDSOR Regional
CAMBRIDGE Memorial	THUNDER BAY Regional Health Sciences
HAMILTON St Joseph's	LONDON Health Sciences
KINGSTON Hotel Dieu	HAMILTON Health Sciences Corp
KINGSTON General	TORONTO University Health Network
KITCHENER St Mary's	TORONTO Addiction & Mental Health
RICHMOND HILL Mackenzie Health	BRAMPTON William Osler
LONDON St Joseph's	OSHAWA Lakeridge Health Corp
NEWMARKET Southlake Regional	TORONTO Sunnybrook HSC
OTTAWA Montfort	BELLEVILLE Quinte Health Care
ST MARYS Memorial	OTTAWA The Ottawa Hospital
ST THOMAS Elgin General	Health Sciences North
SEAFORTH Community	TORONTO Scarborough Hospital
STRATFORD General	ST CATHARINES Niagara Health System
TORONTO Hospital for Sick Children	SARNIA Bluewater Health
TORONTO St Michael's	NORTH BAY Regional Health Centre
TORONTO East General	MISSISSAUGA The credit valley hospital and trillium health centre
TORONTO St Joseph's	Sinai Health System
MARKHAM Stouffville	

Appendix 3. 7 – Uterine assessment Schedule of Benefit codes

Table A1: Corresponding codes and physician costs for further and re-ordered assessments according to the Ontario Schedule of Benefits.

Code	Description	Cost
A205	Initial consultation	101.7
A203	Follow-up consult	47.45
A204	Minor follow-up consult	26.35
J162	Pelvic ultrasound	75.3
J165	SIS ultrasound	133.1
Z770	Office biopsy	34.05
Z582	Hysteroscopy, diagnostic	105.4
Z583	Hysteroscopy, with biopsy and/or D&C	131.4
X461	Pelvic MRI	73.35

Abbreviations: D&C, dilation and curettage; MRI, magnetic resonance imaging

Appendix 3. 8 - Uterine assessment Ontario Case Costing Initiative codes

Table A2: Corresponding codes and hospital costs for further and re-ordered assessments according to the OCCI.

Code	Description	Cases	Average Cost	SD	Min	Max
2RM70BA	Ambulatory hysteroscopy	23	146	62	45	225
2RM70BA	Day surgery hysteroscopy	254	1348	593	220	3922
2RM71BA	Ambulatory hysteroscopy with biopsy	90	354	158	69	818
2RM71BA	Day surgery hysteroscopy with biopsy	93	857	643	195	2814
3RZ30DA	U/S only	2,331	487	294	14	4438
3RZ30LA	U/S transvaginal approach	3,502	501	232	13	3360
	Combined average*	5,833	495	259	13	4438
2RM71CR	Biopsy orifice approach with scraping of cells	787	232	186	46	2387
3OT40VA	MRI abd cav without contrast	182	840	427	101	3465
3OT40WC	MRI abd cav with contrast	60	710	391	161	1895
	Combined average*	242	808	421	101	3465

Abbreviations: U/S, ultrasound; abd cav, abdominal cavity
*The combined average was calculated by the OCCI and was used to calculate the estimated total cost for ultrasound or MRI.

Appendix 3. 9 – Detailed cost calculation: further uterine assessment ($689.80)

Table A3: Further uterine assessment estimate includes physician costs from the Ontario schedule of benefits, follow-up cost (A203), and OCCI cost.

	Cost	**Proportion***
Cost of ambulatory hysteroscopy and biopsy	532.85	0.025
Cost of biopsy	313.5	0.339
Cost of biopsy and SIS	941.6	0.124
Cost of biopsy, SIS, and MRI	1822.95	0.008
Cost of biopsy and ultrasound	883.8	0.174
Cost of MRI	928.8	0.008
Cost of pelvic ultrasound	617.75	0.223
Cost of SIS	675.55	0.099

*The proportion reflects the number of patients (n=121) who had a further uterine assessment out of the 200 patient cohort.

Appendix 3. 10 – Detailed cost calculation: re-ordered uterine assessment ($599.30)

Table A4: Re-ordered estimate includes physician costs from the Ontario schedule of benefits, follow-up cost (A204) and OCCI costs.

	Cost	**Proportion***
Cost of ambulatory hysteroscopy	277.75	0.087
Cost of ambulatory hysteroscopy and biopsy	511.75	0.174
Cost of biopsy	292.4	0.217
Cost of SIS	654.45	0.391
Cost of ultrasound	596.65	0.130

*The proportion reflects the number of patients (n=23) who had a re-ordered assessment out of the 121 patients who also had a further uterine assessment.

Appendix 3. 11 – OCCI costs and codes for surgical procedures

Table A5: The codes and costs for surgical procedures as reported by the OCCI. The cost data are presented in the 2016/2017 fiscal year as reported by the OCCI.

ACUTE INPATIENT						
Code	**Description**	**Cases**	**Average cost**	**SD**	**Min**	**Max**
1RD89LA	Laparotomy	696	7981	6061	2330	57069
1RM87LAGX	Myomectomy (open approach)	881	5792	2694	1532	34723
1RM89CA	Vaginal hysterectomy	2283	4679	10810	1037	514371
1RM89DA	Laparoscopic hysterectomy	1262	6009	2372	1647	43334
1RM89LA	Abdominal hysterectomy	4050	6988	6938	1860	214608
DAY SURGERY						
1RM59BAGX	Endometrial ablation (rollerball)	674	1608	606	284	5330
1RM87BAAK	Hysteroscopic D&C, and/or polypectomy	1290	1726	636	460	9317
2RM71BA	Diagnostic hysteroscopy	93	857	643	195	2814

Abbreviations: D&C, dilation and curettage

Appendix 3. 12 – Detailed cost calculation: proportion of patients receiving a surgical procedure

Table A6: OCCI codes and proportion of patients receiving surgical procedures (n=87) in our 200 patient cohort.

	Total cost	**Proportion**
1RD89LA	7981	0.011
1RM87LAGX	5792	0.011
1RM89CA	4679	0.023
1RM89DA	6009	0.276
1RM89LA	6988	0.092
1RM59BAGX	1608	0.103
1RM87BAAK	1726	0.253
2RM71BA	857	0.230

Appendix 3. 13 – Detailed cost calculation: surgeon, assistant, and anaesthesiologist costs based on the Ontario Schedule of Benefits

Table A7: Total costs for surgeons, assistants, and anaesthesiologists with the corresponding schedule of benefit codes.

Code	Total cost	Proportion*
S745, Z582	944.18	0.01
S757	1295.45	0.09
S757, E862	1735.80	0.28
S764	1216.35	0.08
S764, S772	996.26	0.02
S764, Z583	909.01	0.02
S772	368.75	0.09
S772, S764, Z583	1127.66	0.02
S772, Z770	402.80	0.01
S779, Z770	653.55	0.01
S816	994.93	0.02
Z582, S772, Z770	508.20	0.01
Z583	281.50	0.02
Z583, S772	500.15	0.01
Z587	350.10	0.21
Z587, S764	977.61	0.03
Z587, S772	568.75	0.03
Z587, Z770	444.19	0.01

* The proportion reflects the number of patients (n=87) who had a surgical procedure out of the 200 patients included in the cohort.

Appendix 3. 14 –Detailed cost calculation: surgeon, assistant, and anaesthesiologist costs based on the Ontario Schedule of Benefits

Table A8: Schedule of benefit codes and the corresponding costs for assistants, anaesthesiologists, and surgeons.

Code	Description	Procedural time (hours)	Assistant total cost	Anaes. total cost	Surgeon costs	Total cost
S757	Abdominal hysterectomy	3	337	495	463	1295
Z582, S772, Z770	Diagnostic hysteroscopy, ablation, biopsy	1	0	150	358	508
Z583	Diagnostic hysteroscopy, D&C	1	0	150	131	282
S772	Endometrial ablation	1	0	150	219	369
S772, Z770	Endometrial ablation, biopsy	1	0	150	253	403
S764, S772	Hysteroscopic endometrial ablation, myomectomy	1.5	169	225	603	996
Z587	Hysteroscopic polypectomy	1	0	150	200	350
S779, Z770	Hysteroscopic septum resection, biopsy	1	120	150	383	654
Z583, S772	Hysteroscopy, D&C, endometrial ablation	1	0	150	350	500
S772, S764, Z583	Hysteroscopy, endometrial ablation, myomectomy, D&C	1.5	169	225	734	1128
S757, E862	Laparoscopic hysterectomy with mini laparotomy	4	482	675	579	1736
S745, Z582	Laparotomy, cystectomy, diagnostic hysteroscopy	2	217	315	412	944
S764	Myomectomy	3	337	495	384	1216
Z587, Z770	Myomectomy and ablation, biopsy	1.5	0	210	234	444
S764, Z583	Myomectomy, curettage, hysteroscopy	1.5	169	225	515	909
Z587, Z772	Polypectomy, biopsy	1	0	150	419	569
Z587, S764	Polypectomy, myomectomy	1.5	169	225	584	978
S816	Vaginal hysterectomy	2	217	315	463	995

Appendix 3. 15 – Schedule of Benefits cost calculation assistant fee

CALCULATION OF FEE PAYABLE: BASIC UNITS AND TIME UNITS

Except where "nil" is listed opposite the service in the column headed with "Asst", the amount payable for the surgical assistant service is calculated by adding together the number of basic and time units and multiplying that total by the unit fee.

Assistant Unit Fee	**$12.04**

Basic Units: The number of basic units is the number of units listed opposite the service in the column headed with "Asst", except

a. where multiple or bilateral surgical procedures are performed during the same anaesthetic, the number of basic units is that listed in the column headed with "Asst" opposite the service that describes the major procedure; or

b. where no basic unit is listed opposite the service in the column headed with "Asst" and where "nil" is not listed opposite the service in the column headed with "Asst", the number of basic units is that listed opposite the service under the column headed with "Anae". This type of service is *only eligible for payment* upon authorization by a *medical consultant* following submission of a letter from the surgeon outlining the reason the assistant was required. Submit claims for this type of service using fee code M400B.

Where "nil" is listed opposite the service in the column headed with "Asst", the assistant's service is *not eligible for payment*.

Time Units: For the purpose of calculating time units, time is determined per operation as the total of the following, excluding any time spent waiting between surgical procedures:

a. time spent by the physician in direct contact with the patient in the operating room prior to scrub time to assist with patient preparation; and

b. time spent by the physician assisting at the patient's surgery starting with scrub time and ending when the physician is no longer required to be in attendance with that patient.

Time units are calculated for each 15 minutes or part thereof. The unit value of each 15 minute period or part thereof is:

During the first hour or less	1 unit
After the first hour	2 units
After 2.5 hours	3 units

Appendix 3. 16 – Schedule of Benefits cost calculation anaesthesiologist fee

CALCULATION OF FEE PAYABLE – BASIC AND TIME UNITS

The amount payable for the anaesthesia service is calculated by adding the number of basic and time units and multiplying the total by the anaesthesiologist unit fee.

Anaesthesiologist Unit fee	**$15.01**

Basic Units: The number of basic units is the number of basic units listed opposite the service in the column headed with "Anae" except,

a. where multiple or bilateral surgical procedures are performed during the same anaesthetic, the number of basic units listed in the column headed with "Anae" opposite the service that describes the major procedure; or

b. where the basic units are listed as IC, or where no basic units are listed, the amount payable is calculated by adding the appropriate time units to the basic units listed for a comparable procedure (taking into account the region, modifying conditions, or techniques).

Time Units: Time units are calculated on the basis of time spent by the anaesthesiologist and commence when the anaesthesiologist is first in attendance with the patient in the OR for the purpose of initiating anaesthesia and end when the anaesthesiologist is no longer in attendance (when the patient may safely be placed under customary post-operative supervision). Time units are calculated for each 15 minutes or part thereof. The unit value of each 15 minute period or part thereof is:

During the first hour	1 unit
After the first hour up to and including the first 1.5 hours	2 units
After 1.5 hours	3 units

Appendix 3. 17 – UATU cost estimate calculation

The UATU was estimated using the OCCI cost for ambulatory hysteroscopy plus the Ontario Schedule of Benefit physician fee (code Z582 for diagnostic hysteroscopy, $105.40) to get a total estimated outpatient diagnostic hysteroscopy cost of $251.40. Surgical disposable equipment in the UATU were estimated by a gynaecologist at roughly $600. Depending on the surgical procedure (Novasure ablation or Myosure polypectomy/myomectomy) surgical disposables could range from around $400 up to $900 and this was considered in the sensitivity analysis.

Table A9: OCCI costing for ambulatory hysteroscopy

Code	Cost (SD)	Minimum cost	Maximum cost	Number of cases
2RM70BA	146 (62)	45	225	23

Appendix 3. 18 – UATU relative risk calculation

A relative risk was used as the effectiveness measure to quantify the effectiveness of the UATU in the decision tree model. We aimed to model the number of failed outpatient hysteroscopic procedures that would occur in the UATU causing patients to need further uterine assessment. The values we used to calculate the relative risk were derived from a systematic review conducted by Clark et al.[101] The study by Clark et al. aimed to determine the accuracy of hysteroscopy in diagnosing endometrial cancer and hyperplasia in women with abnormal uterine bleeding. The study synthesized 65 full-text studies including 26,346 women. Failure rates were reported in 36 of the 65 studies, while failure rates for an outpatient procedure was reported in 755 of 18,126 women [4.2%; 95% CI, 3.9%-4.5%].

Using the number of patients who required a further evaluation in the usual care service model (n=121) and the number of failed outpatient hysteroscopic procedures (n=755) based on Clark et al. we were able to calculate the relative risk as illustrated below.

Table A10: Relative risk calculation in a 2x2 table

	UATU	**Usual care**
Diagnosis obtained	17,371	79
Further evaluation needed	755	121
Totals:	**18,126**	**200**

$$\left(\frac{79}{200} \div \frac{17{,}371}{18{,}126}\right) = \mathbf{0.412}\ \ [95\%\ \text{CI},\ 0.347 - 0.489]$$

$$\left(\frac{79}{200} \div \frac{17{,}371}{18{,}126}\right) = \mathbf{0.412}\ \ [95\%\ \text{CI},\ 0.347 - 0.489]$$

Appendix 3. 19 – Tornado plot values

Table A11: Input parameters for the tornado plot

	Base value	Min	Max	Cost difference lower bound	Cost difference upper bound
Hospital costs	3514.34	850	8000	513	2,857
Cost of further assessment	689.80	300	1850	1,225	1,776
UATU surgical costs	600	100	1000	1,039	1,504
Surgeon and assistant costs	1038.09	280	1300	1,104	1,438
Outpatient hysteroscopy cost	152	50	300	1,184	1,434
RR of UATU	0.412	0.347	0.489	1,230	1,429
Cost of re-ordered assessment	599.30	200	700	1,317	1,351