Cost-analysis of Misoprostol and Mifepristone versus Misoprostol and Methotrexate when used for medical termination of pregnancy in women of gestational age of 7 weeks and less at Embhuleni Hospital in Elukwatini, Mpumalanga

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2019

This is to certify that the contents of this thesis are the original research work of Miss

Thembelihle Nomsa Qiosandra Siyaya

As the candidate's supervisor, I have approved this thesis for submission.

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PREFACE and DECLARATION

I, Thembelihle Nomsa Qiosandra Siyaya, the researcher, declare that the work presented herein is my original work submitted to the University of KwaZulu-Natal in fulfilment of the requirements of the degree of Master of Pharmacy – Pharmaco-economics.

I declare that:

i. The research reported in this dissertation, except where referenced is my original work

ii. This dissertation has not been submitted for any degree or examination at any other university

iii. This dissertation does not contain other persons' writing, ideas, pictures, graphs or other information unless specifically acknowledged as being sourced from other persons.

iv. Where I have reference to a publication for which I am a principal author, I have referenced the "in press" publication.

The full bibliography of referenced material or texted used herein has been sighted in the reference appendix.

30 May 2019

Thembelihle Siyaya **Date**

Dedication

I would like to thank the Almighty God for His love and mercy towards me as I undertook this Master's degree. To my husband, Donovan who encouraged me when I felt like giving up, proofread my work and was self-reliant while I was working on this research; thank you for being the wind beneath my wings. My sister, Thuba your prayers for me were not in vain. Special gratitude goes to my colleagues at Embhuleni Hospital, who were patient with me during this study. My late parents always encouraged me to be better and their words kept me going. Onwards and forward ever.

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LIST OF APPENDICES

KEYWORDS

Cost analysis; mifepristone; misoprostol; methotrexate; termination of pregnancy (ToP); abortion

ABBREVIATIONS

cToP- choice of termination of pregnancy
ToP-Termination of pregnancy
MXT-methotrexate
SDG-Sustainable Development Goals
UN-United Nations
STG-Standard treatment guidelines
MVA-Manual Vacuum Aspiration
PV-Per vagina
SL-sublingual
WHO-World Health Organisation
EML-Essential Medicines List
SRR-Success Rate Ratio
DNA- Deoxyribonucleic acid
UKZN-University of Kwa-Zulu Natal
BREC-Biomedical Research Ethics Committee
UKZN- University of Kwa-Zulu Natal

ABSTRACT

Background: The purpose of the Republic of South Africa Choice on Termination of Pregnancy Act 92 of 1996 is to provide a safe and effective alternative to the rife illegal abortions taking place in South Africa. The Department of Health's standard treatment guidelines recommend a regimen of 200mg Mifepristone orally stat followed by 800mcg of Misoprostol sublingually after 24 to 48 hours (for up to 9 weeks or 63 days gestation) for termination pregnancy. Mifepristone has a relatively high cost and cost-effective alternatives would be beneficial to alleviate the strain on the National Healthcare budget caused by the official termination of pregnancy regimen.

Aim: To perform a budget impact analysis and calculate potential savings if Methotrexate/Misoprostol combination is used for termination of pregnancy in women of gestational age less than or equal to 7 weeks compared to the current regimen of Mifepristone/misoprostol

Setting: This study was undertaken at Embhuleni hospital, a 220-bed district hospital located in the Chief Albert Luthuli sub-district in Mpumalanga.

Method: Three hundred and twelve (n=312) medical records of patients who visited the Choice of Termination of Pregnancy clinic during the 2017/2018 financial year, were retrieved and analyzed. Only medical termination of pregnancy medicines cost was considered. The total cost for the medicine (Misoprostol and Mifepristone) used to bring about an abortion was calculated using the information gathered from personal details and treatment regimen. Tender prices for 2017 were used for the medicines on national tender.

Results: The current regimen of misoprostol/mifepristone costs R289.25 per case. The total cost incurred by the hospital in the 2017/2018 financial year for this medicine regimen was R90, 246.00 for a total of 312 patients. The proposed regimen comprising of methotrexate tablets and misoprostol costs R32.50 per patient whilst the total cost of using methotrexate injection and misoprostol tablets is R61.61 per patient. The current regimen impacted the medicine budget by 0.95% (0.51% if used for women of gestational age 7 weeks or less), 0.05% using the Methotrexate (MXT) tablets and 0.11% using the MXT injection. The alternative regimens were still cost-saving when tested through a sensitivity analysis.

Conclusion: Both MXT injection and tablets are registered in South Africa and have local manufacturers and distributors. Currently in the public sector, Mpumalanga Department of Health formulary, the MXT 2.5mg tablets are on tender. If MTX tablets had been used, the total cost savings would have been 48% and 43% for the injection. In order to bring about change which will recommend for the indications of MXT to include Medical termination of pregnancy. More studies need to be done across the country to determine the overall financial impact the current regimen has and how much money could be saved from amending the guidelines to include the cost-effective regimen of MXT and misoprostol in combination. This study was not without limitations, it studied only the medicine required to bring about an abortion, for a more comprehensive budget impact analysis more variables will need to be considered.

CHAPTER 1 BACKGROUND AND SIGNIFICANCE

1.1 Background.

In 2015, the United Nations (UN) member states adopted the 2030 Agenda for Sustainable Development and its 17 Sustainable Development Goals (SDGs) to replace the Millennium Development Goals (MDGs). UN SDG number 3 is the ensuring of healthy lives and promotion of well-being for all at all ages. Regarding maternal health, the SDG states that although maternal mortality has fallen by almost 50% worldwide, there is still a need for a reduction in maternal mortality to less than 70 women per 100,000 live births. Also, SDG number 5 involves the achievement of gender equality and empowerment of all women and girls. One of the ways it seeks to do this is by ensuring that all women have full access to sexual and reproductive care services (United Nations, 2015).

Access to contraceptive options, especially to women in developing countries is vital in the attempt to reduce maternal deaths. Whilst this goal mainly entails the provision and increased access to preventative contraceptive methods to women, the addition of mifepristone to the WHO Essential Medicines List (EML) in 2005 (WHO, 2005) showed that access to safe abortions is also key to those women who have unwanted pregnancies irrespective of the reason. South Africa has very progressive laws regarding abortion or Termination of Pregnancy (ToP) and is one of only four countries in Africa that legally allows ToP. (Guttmacher Institute, 2018) The legalization of ToP is legislated by Act 92 of 1996, Choice on Termination of Pregnancy Act. However, various factors still hinder access to safe ToP for many women, resulting in the proliferation of "abortion clinics" and self-described abortion doctors (STG, 2012). According to the WHO, (2014), the Government of South Africa, through the Provincial Departments of Health, has played a role in increasing access to free, safe abortions through ToP clinics and the provision of guidelines for ToP. Historically, the national ToP regimen has been as follows:

i. In 1998, two years after the passing of Act 92 of 1996, non-drug treatment was evacuation of the uterus whilst drug treatment involved use of Oxytocin IV 20-40IU in 1 litre of 5% Dextrose to aid in uterine contraction. However, the aforementioned regimen was for second trimester abortion (13-22 weeks gestation). The guidelines did not indicate the regimen for first trimester abortion. (STG and EML, 1998)
ii. In 2006, the specific first trimester (0-12 weeks) non-drug treatment was manual vacuum aspiration of the uterus with sublingual (SL)/per vagina (PV) Misoprostol 400mcg two hours before vacuum aspiration added where difficulty with cervical dilation was expected. The drug treatment (offered if woman commits to return for follow up) is as follows:
    - Misoprostol, SL/PV, 800 mcg daily for 2 doses, e.g. 800 mcg PV on day 1. Supply 800 mcg for sublingual use at home on day 2 and review with ultrasound on day 3. (Standard Treatment Guidelines and Essential Medicines List, 2006)

iii. In 2012, non-medicinal management involved manual vacuum aspiration of the uterus with sublingual (SL)/per vagina (PV) Misoprostol 400mcg three hours before routine vacuum aspiration added where difficulty with cervical dilation was expected. The medicinal treatment is:

- Mifepristone, oral, immediately as a single dose.
  - Up to 9 weeks gestation: 100–200 mg.
  - 9– 13 weeks gestation: 200 mg.
- Followed 24–48 hours later by Misoprostol, PV, 800 mcg.
- If expulsion has not occurred 4 hours after misoprostol administration, a second dose of misoprostol 400 mcg oral/PV may be given.
- Review with ultrasound on day 7, (Standard Treatment Guidelines and Essential Medicines List, 2012).

The 2018 South African guidelines, which are in line with current international guidance, state that for first trimester pregnancy ToP, the following regimen should be followed:

- Oral administration of 200mg Mifepristone stat followed by 800mcg of Misoprostol sublingually after 24 to 48 hours (up to 9 weeks or 63 days gestation)
- Oral administration of 200mg Mifepristone stat followed by 600mcg of Misoprostol sublingually after 24 to 48 hours followed by Manual Vacuum Aspiration (MVA) after 2-3 hours (9-12 weeks or 63-84 days gestation).

This is in line with WHO Clinical practice handbook for Safe abortion (WHO, 2014).

The purpose of the Choice on Termination of Pregnancy Act 92 of 1996 and the above regimens is to provide a safe and effective alternative to the rife illegal abortions taking place in South Africa. The Public Health sector is playing a significant role in the provision of safe and effective pregnancy terminations, with approximately 197 confirmed facilities throughout South Africa providing choice of Termination of Pregnancy (cToP) services, (Joan van Dye, 2017). This adds a benefit to safety and efficacious termination by adding "affordable" as an incentive to avoid illegal abortions. The provision of such a service by public health facilities comes at a cost. The most recent data shows the costs of providing cToP services for complete medical abortion as USD64.06 (Lince-Deroche N et al, 2017). At Embhuleni hospital alone, the total number of abortions during the 2017/2018 financial year was approximately 300. Using the costs derived from the aforementioned study done in KwaZulu Natal, the cost of medical terminations was USD4317/year based on the 2015 ZAR/USD exchange rate of 14.39. Due to efforts by the national DoH to encourage patients to have safe pregnancy terminations, the figure is likely to increase and to assist policymakers in Government, it is important that ways be found to continue to provide this critical service whilst bringing down the cost to the National budget. One of these ways is by finding medical abortion alternatives that are less of a financial strain on the already overburdened national budget. A possible alternative is the use of methotrexate in place of Mifepristone.

The American College of Obstetricians and Gynecologists includes Methotrexate with Misoprostol as an alternative regimen that can be used up to 7 weeks (49 days) of gestation (Moreno-Ruiz NL, 2007). The dosing regimen used in Canada is MXT 50 mg oral/Misoprostol 800 mcg vaginal for less than or equal to 56 days gestational age and MXT 50mg oral or intramuscular/misoprostol 800 mcg vaginally for women with gestational age less than or equal to 63 days. (Costescu D, 2016) The focus of this study will be mainly on medical ToP, rather than surgical ToP, as this is the main method utilized by Embhuleni Hospital. Embhuleni Hospital sees at least 40 cToP patients a month. This translates to an estimated ZAR10283 a month spent on the procurement of Mifepristone and Misoprostol tablets used for the medical termination of pregnancy.

Embhuleni Hospital, in Elukwatini, Mpumalanga, sees approximately 40 medical abortion patients every month. Patient age demographics range from teenagers to adult women. The current regimen of oral administration of 200mg Mifepristone stat followed by 800mcg of Misoprostol sublingually after 24 to 48 hours (up to 9 weeks or 63 days gestation) and oral administration of 200mg Mifepristone stat followed by 600mcg of Misoprostol sublingually after 24 to 48 hours followed by Manual Vacuum Aspiration (MVA) after 2-3 hours (9-12 weeks or 63-84 days gestation) is costly due to the high price of mifepristone
Mifepristone has a single unit cost purchase price of approximately ZAR240 in 2018. The CToP unit is costing the hospital approximately ZAR6 240 per month, in purchase of medical abortion medication alone. This figure can be theoretically brought down by finding an alternative regimen that is more cost-effective. One such alternative regimen is Methotrexate (injection or tablets), which, when used together with intra-vaginal Misoprostol, can also result in complete abortion, (American College of Gynecology,2014).

1.2 Hypothesis

Despite inclusion of Mifepristone tablets in the WHO EML in 2005, the medicine is relatively expensive and as a result, the usage of the medicine may result in a significant cost to the Department of Health, in particular, Embhuleni hospital. We hypothesized that for pregnancies meeting the criteria (<7 weeks since Last Menstrual Period), the regimen of methotrexate and misoprostol would translate to a lower cost to the Embhuleni cToP clinic compared to Mifepristone and misoprostol.

1.3 The purpose of the study

The purpose of the study was to:

- Determine whether it was possible to lower the costs of running a ToP clinic by substituting methotrexate which costs R43.59 for the injection and R15.42 for 20 tablets in place of mifepristone which costs R272.17. The current regimen and protocol proved to be costly (R90 246.00) and the study will look for a cost-effective alternative.
- To do a cost analysis on the cToP program at Embhuleni Hospital in order to determine the budget

impact of a change in regimen.

1.4 The objectives of the study

This retrospective study was done to

- Investigate what the budget impact is of using methotrexate/misoprostol vs. mifepristone/misoprostol in medical termination of abortion at less than 7 weeks. A budget analysis will be done to see what the potential cost savings will be, if any.
- Determine the mean difference in costs between the two regimens.
- To do a comparison of efficacy between regimens using reviews of the efficacy literature available on both regimens
- To determine how patients with gestational age less than 7 weeks will affect the budget, if they were to get misoprostol/methotrexate regimen

1.5 The research questions

i. What is the average acquisition cost misoprostol/mifepristone vs. the calculated extrapolation of methotrexate/misoprostol in the medical termination of pregnancy?
ii. What is the potential cost saving for Embhuleni Hospital from the introduction of the methotrexate/misoprostol combination for early (≤49 days gestation) terminations?

CHAPTER 2 LITERATURE REVIEW

2.1 INTRODUCTION

Abortion was legalized in South Africa in the year 1996. In 1997 a total of 26455 women had abortions and in 2015 this number had risen to 84220 women (Health Systems Trust, 2017). In 1996 the abortion protocol consisted of manual vacuum aspiration (MVA). Medical abortion was introduced in the public sector in 1998, with approved regimen being misoprostol 400mcgrams sublingual or per vagina. Mifepristone was approved for CTOP in 2001.

2.2 Pharmacodynamics properties

Methotrexate

Methotrexate is an antineoplastic antimetabolite with immunosuppressant properties. [PubChem

(Methotrexate), 2005]

Mifepristone

Mifepristone is a synthetic steroid with anti-progestational effects indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy. [Pubchem (Mifepristone), 2005]

Misoprostol

Misoprostol is a prostaglandin E1 (PGE1) analogue used for the treatment and prevention of stomach ulcers. Misoprostol has also been shown to increase the amplitude and frequency of uterine contractions during pregnancy via selective binding to the EP-2/EP-3 prostanoid receptors. [Pubchem (Misoprostol), 2005]

Embhuleni Hospital stocks methotrexate 2.5mg, misoprostol 200mcgrams and mifepristone 200mg. Methotrexate injection is registered in South Africa.

2.3 Studies on the efficacy of methotrexate-misoprostol

Methotrexate is cost-effective and readily available in many parts of the world (Potts, M, 1995). The study revealed that experimental protocols have used approximately 80mg (intramuscular) of methotrexate followed by 800mcg misoprostol (vaginally) 5-7 days later. This regimen was 88-97% effective when given to women who had had their last menstrual period 56-63 days prior. It was also observed that at ≤42 days after last menstrual cycle, methotrexate alone was effective to bring about complete abortion.

An experimental study on the effectiveness for early abortion of a single dose (75 mg intramuscularly) of methotrexate, followed 5-6 days later by 800 mcg of misoprostol vaginally, was investigated in 99 women presenting to a US hospital with pregnancies of <50 days gestation. Complete abortion occurred in 94 patients (94.9%). There were no significant differences in this rate by gestation (up to 42 days vs. 43-49 days). In 70 cases (70.7%), abortion occurred in the 24 hours following the initial or repeat misoprostol dose. Overall, 77.8%, 86.9%, and 91.9% of women had expelled the fetus by 14, 28, and 35 days, respectively, after receiving methotrexate. Vaginal bleeding lasted an average of 17 days in women who aborted in 24 hours and 11 days in those with delayed abortion. Side effects associated with methotrexate included nausea (47%), warmth/hot flashes (43%), diarrhea (22%), dizziness (21%), headache (16%), and vomiting (12%). These results are comparable to those obtained with an intramuscular dose of 50 mg/sq. m or an oral dose of 50 mg of methotrexate. The lowest effective dose of methotrexate, when combined with misoprostol for abortion, remains to be determined. (Creinin MD, 1997, Kulier R, 2011) This above study demonstrates the efficacy of methotrexate when used at 50 mg/sq. intramuscular and at 50mg orally in combination with 800mcg of misoprostol. The combination managed to bring about complete abortion in 94.4% of the sample.

A retrospective study (Aldrich, T, and Winikoff, B, 2007) done at an anonymous women's health center in Latin America compared efficacy of four medical abortion regimens used in one clinic. The comparison was

done as follows:

- (1) misoprostol alone,
- (2) oral methotrexate + buccal misoprostol,
- (3) oral methotrexate + vaginal misoprostol,
- (4) intramuscular methotrexate + vaginal misoprostol. (Aldrich, T, Winikoff, B, 2007)

A total of 8678 records of women with gestations less than 56 days, who wanted a medical abortion between April 2002 and December 2004 were utilized. Success rates for the three methotrexate regimens ranged from 81.7 to 83.5% and no significant difference was found among the three regimens. Misoprostol-alone regimen had a success rate of 76.8%. Efficacy was considerably higher for the three combined methotrexate regimens when compared with misoprostol alone and remained so in the multivariate model (OR = 1.35). In this real-use setting, methotrexate appears to have a significant advantage over misoprostol alone for early medical abortion. The authors concluded that this observation is paramount for settings where mifepristone remains unavailable or expensive. Additional factors such as gestational age limits and patient preference should be considered in regimen selection.

Intramuscular and oral methotrexate followed by misoprostol administration 3 to 7 days later appears to have comparable efficacy. (Moreno-Ruiz et al, 2007) In women with gestational age less than 49 days, the reported success rate after administration of oral methotrexate followed by intra-vaginal misoprostol was between 90% and 91%. When intramuscular methotrexate followed by intra-vaginal misoprostol in women with gestational age less than 49 days, the observed success ranged between 75% and 95%. The success rates of alternative regimens using misoprostol alone and methotrexate with misoprostol are around 90%, and these 2 regimens are inexpensive and available in many parts of the world. The following complications: incomplete abortion, bleeding, and infection seem to be similar for the 2 (methotrexate with misoprostol and misoprostol alone) regimens and for mifepristone regimens as well. Although the methods using misoprostol alone and methotrexate followed by misoprostol have lower success rates than those using mifepristone, these methods are safe and acceptable choices for women who desire an abortion early in the first trimester. (Morena, et al, 2006)

The combination of misoprostol plus methotrexate was more effective when misoprostol was administered 7 days after methotrexate as compared to 3 days, leading to a complete abortion rate of 98%. (Roudsari FV, . Sedigheh A, Saghafy N,2010).

Methotrexate, combined with a prostaglandin, has been used in some studies with an effectiveness of mostly > 90%,(Kulier R, 2011). An evaluation of the efficacy of misoprostol and methotrexate was done on 300 pregnant women with a maximum gestational age of 56 days, the results found that 90% of women with a gestational age of 49 days and 81.6% with a gestational age of 50-56 days had complete abortion. Creinin et al, (1996)

2.4 Studies on the efficacy of mifepristone-misoprostol regimen

An efficacy study of Mifepristone 200 mg given orally followed 48 hours later by Misoprostol 600 mcg per vaginally in women undergoing medical termination of early pregnancy (up to 73 days of gestational age) was done in India. Fifty pregnant women requesting termination of pregnancy in first trimester (up to 93 days of gestational age) were recruited for the study. The study revealed that 50% of the women were between 36-50 days of gestational age and overall 94% of the patients had complete abortion and 4% had incomplete abortion, it also further showed that 72% of the patients had a complete abortion within 10 hours and 84% had a complete abortion within 15 hours and almost all the patients within 24 hours of prostaglandin administration. Most of the adverse effects reported were of the gastrointestinal system - nausea, abdominal pain, vomiting and diarrhea. The authors concluded that the mifepristone-misoprostol regimen is an efficient and safe procedure in early pregnancy (up to 73 days) (Yamini Shobha Vani P, 2016)

A safety and efficacy study was conducted using 200 mg of mifepristone orally followed by home use of 800 mcg misoprostol buccally 24-48 h later through 63 days estimated gestational age, (Gatter M, 2015). The study focused on women presenting for medical abortion over a five-year period. The primary outcome of the study was successful abortion. Logistic regression was used to identify predictors of successful abortion. From the study; 13 373 women completed the follow-up and efficacy of the regimen among these women was 97.7%. Efficacy was at its highest at the following gestational ages: 29 to 35 days (98.8%) and 36 to 42 days (98.8%) and lowest at 57 to 63 days (95.5%). The odds of requiring manual vacuum aspiration for any reason were highest at later gestational ages. The study concluded that 200mg of mifepristone orally followed by 800mcg of buccal misoprostol 24-48 hours later was safe and effective through 63 days gestational age.

In 2014 an observational cohort in Australia analyzed 15 008 women attending one of 16 Marie Stopes International clinics in Australia for an early medical abortion (gestational age ≤ 63 days). Women were given 200 mg oral mifepristone at the clinic, followed by 800μg buccal misoprostol 24-48 hours later administered at home. The success of the study was defined as complete abortion without requiring surgical abortion. 87.14% (13 078/15 008) of the women were available for follow-up and 95.16% of the women who were available for follow up had successful medical abortions (12 445/13 078). Higher patient gestational ages were associated ($P < 0.001$) with a slight increase in method failure, which was defined as incomplete abortion requiring surgical intervention and continuing pregnancy. There were 674 serious adverse events (5.15%), mainly due to method failure. Overall mifepristone-buccal misoprostol was concluded to be an effective and safe alternative to surgical termination of pregnancy up to 63 days gestation. (Goldstone P, 2017)

2.5 Studies on the efficacy of both regimens- misoprostol-mifepristone and methotrexate-misoprostol

A review on the efficacy of mifepristone-misoprostol vs. methotrexate-misoprostol, looked at the pharmacology of methotrexate and misoprostol. It summarizes research on the regimen's effectiveness and

acceptability and presents a sample protocol of its clinical use. The methotrexate-misoprostol regimen has a longer treatment-abortion interval than the mifepristone-misoprostol combination; other limitations include transient gastrointestinal effects and a risk of potential teratogenicity from methotrexate's cytotoxicity. (Narrigan D, 1998) However, both regimens had similar acceptable success rates of 74.5% in the methotrexate group and 90.4% in the mifepristone group (Wiebe E, 2002a).

A clinical trial was conducted to compare the effectiveness, side effects, and acceptability of medical abortions induced by methotrexate and misoprostol with abortions induced by mifepristone and misoprostol. The design of the study was a multi-centered, randomized, non-blinded, controlled trial comparing 50 mg/m^2 of methotrexate followed 4-6 days later by 800mcg of vaginal misoprostol with 600 mg of oral mifepristone followed 36-48 hours by 400mcg of oral misoprostol. The trial comprised of 518 women in the methotrexate group and 524 women in the mifepristone group. In the methotrexate group, 386 (74.5%) had completed the abortion by day 8 compared with 474 (90.5%) in the mifepristone group, and the mean number of days from beginning to completion was 7.1 for methotrexate and 3.3 for mifepristone 'P $\leq$.001'. There were no differences in complications, and side effects were similar. Acceptance was slightly higher with mifepristone (88.0%) than with methotrexate (83.2%). The clinical trial therefore concluded that abortions induced with mifepristone completed faster than those induced with methotrexate, but the overall success rates, side effects, and complications were similar. Acceptance rates were slightly higher with mifepristone than methotrexate 'P =.03',(Wiebe E, 2002b).

Another was study done to evaluate the efficacy, side-effect profile, and follow-up rates in women who obtain a medical abortion in a non-research setting. This study was done from December 1, 2000, to June 30, 2001, where 218 women of gestational age up to 63 days were prospectively followed. The women received either mifepristone 200 mg orally followed 1 to 2 days later by self-administered misoprostol 800 mcg vaginally or methotrexate 50 mg/m^2 intramuscularly followed 3 to 7 days later by self-administered misoprostol 800 mcg vaginally. Out of 218 women, 174 women had medical abortions, 148 women (85%) chose mifepristone/misoprostol, and 26 women (15%) chose methotrexate/misoprostol. In women up to 49 days of gestation, complete abortion occurred by the first follow-up visit in 82 of 86 women (95%; 95% CI, 89-99) and in 21 of 25 women (84%; 95% CI, 64-95) women, respectively. In women who used mifepristone/misoprostol from 50 to 63 days of gestation, complete abortions occurred in 56 of 59 women (95%; 95% CI, 86-99) women. Four women (2%; 95% CI, 1-6) were lost to follow-up. The study revealed that medical abortion with mifepristone/misoprostol and with methotrexate/misoprostol can be provided in a non-research setting with efficacy similar to that reported in the medical literature for research protocols. (Creinin MD, 2003)

2.6 Other countries using Methotrexate for medical termination of pregnancy

In the Canada clinical guidelines intramuscular/oral methotrexate and vaginal/buccal misoprostol is used for the termination of pregnancy up to 63 days. It is 84-97% effective when used within this gestational age. The risk of ongoing pregnancy is 0.4 to 4.3%. The regimens are as follows MXT 50 mg oral and misoprostol 800 mcg vaginally for women of gestational age less than 56 days and MXT 50 mg oral or intramuscular/misoprostol 800 mcg vaginal for women of gestational age lea than 63 days,(Costescu D, 2016)

3.0 CHAPTER THREE SUBMITTED MANUSCRIPT

3.1 INTRODUCTION

In order carry out this research ethical clearance was obtained from the University of Kwa-Zulu Natal's Biomedical Research and Ethics Committee (BREC) and can be found in Appendix A .Also attached is the ethical approval from the Mpumalanga department of health and the letter of approval to access patient records from Embhuleni Hospital (Annexure C).

Approval of the research proposal by the ethics bodies was partially on grounds that findings of the research need to be shared locally and internationally to the relevant stakeholders. As a means of dissemination, a manuscript of this research was compiled and submitted to the South African Medical Journal (SAMJ) for publication. Presentation of the manuscript was structured and formatted as per the journal requirements (Appendix D).

This chapter hence presents the submitted paper as per the journal stipulated format and limitations in terms of graphs, tables and word count.

3.2 Submitted manuscript

Cost-analysis of Misoprostol and Mifepristone versus Misoprostol and Methotrexate when used for medical termination of pregnancy in women of gestational age of 7 weeks and less at Embhuleni Hospital in Elukwatini, Mpumalanga

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Key words: Cost analysis; mifepristone; misoprostol; methotrexate; termination of pregnancy (ToP); abortion

ABSTRACT

Background: The purpose of the Republic of South Africa Choice on Termination of Pregnancy Act 92 of 1996 is to provide a safe and effective alternative to the rife illegal abortions taking place in South Africa. According to the Department of Health standard treatment guidelines, the recommended regimen for termination of pregnancy is 200mg Mifepristone orally stat followed by 800mcg of Misoprostol sublingually after 24 to 48 hours (for up to 9 weeks or 63 days gestation) Mifepristone has a relatively high cost and cost-effective alternatives would be beneficial to alleviate the strain on the National Healthcare budget caused by the official termination of pregnancy regimen.

Aim: To perform a budget impact analysis and calculate potential savings if Methotrexate/Misoprostol combination is used for termination of pregnancy in women of gestational age less than or equal to 7 weeks compared to the current regimen of Mifepristone/misoprostol.

Settings: This study was undertaken at Embhuleni hospital, a 220-bed district hospital located in the Chief Albert Luthuli sub-district in Mpumalanga.

Method: Three hundred and twelve (n=312) medical records of patients who visited the Choice of termination of pregnancy clinic during the 2017/2018 financial year, were retrieved and analyzed. Only medical termination of pregnancy medicines cost was considered. The total cost per abortion treatment option was calculated using the information gathered from personal details and treatment regimen. Tender prices were used for the medicines on national tender.

Results: The current regimen of misoprostol/mifepristone costs R289.25 per pregnancy successfully terminated. The total cost incurred by the hospital in the 2017/2018 financial year for the medicine regimen required to terminate a pregnancy came up to R90,246.00 for a total of 312 patients. The proposed regimen comprising of methotrexate tablets and misoprostol costs R32.50 per patient whilst the total cost of using methotrexate injection and misoprostol tablets is R60.67per patient based on the SEP database 2017. The total cost was estimated using the prices found in the Rx solution system (procurement system used at Embhuleni Hospital). Price of Methotrexate injection was taken from the Single exit Price (SEP) database of 2017, as it is not available at Embhuleni Hospital. The current regimen impacted the budget by 0.95% (0.51% if used for women of gestational age 7 weeks or less), 0.05% using the MXT tablets and 0.11% using the MXT injection.

Conclusion: Both MXT injection and tablets are registered in South Africa and have local manufacturers and distributors. Currently in the public sector, Mpumalanga Department of Health formulary, the tablets are on tender. In order to bring about change which will push for the indications of MXT to include Medical termination of pregnancy more studies need to be done across the country to determine the overall financial impact the current regimen has and how much money could be saved from amending the guidelines to include the cost-effective regimen of MXT and misoprostol.

INTRODUCTION

South Africa legalized medical termination of pregnancy (ToP) in 1996. In 1997 a total of 26455 women had abortions and in 2015 this number had risen to 84220 women (Health Systems Trust, 2017). In 1996 the abortion protocol consisted only of manual vacuum aspiration (MVA). Medical abortion was introduced in the public sector in 1998, with approved regimen being misoprostol 400micrograms sublingual or per vagina. Mifepristone was approved for CTOP in 2001.

In the 2017/2018 financial year Embhuleni Hospital, in Elukwatini, Mpumalanga, saw approximately 300 medical abortion patients. Patient age demographics ranged from teenagers to adult women. The current regimen of oral administration of 200mg Mifepristone stat followed by 800mcg of Misoprostol sublingually after 24 to 48 hours (up to 9 weeks or 63 days gestation) and oral administration of 200mg Mifepristone stat followed by 600mcg of Misoprostol sublingually after 24 to 48 hours followed by Manual Vacuum Aspiration (MVA) after 2-3 hours (9-12 weeks or 63-84 days gestation) is costly due to the high price of mifepristone

Mifepristone had a single unit cost tender price of ZAR272.17 in 2018. The cToP unit was costing the hospital approximately ZAR7 076.42 per month, in purchase of medical abortion medication alone. This figure could be theoretically reduced by finding an alternative regimen that is more cost-effective. One such alternative regimen is Methotrexate (injection or tablets), which, when used together with intra-vaginal Misoprostol, can also result in complete abortion. (American College of Gynecology, (2014).)

Despite inclusion of Mifepristone tablets in the WHO EML in 2005, the medicine was still relatively expensive and as a result, the usage of the medicine resulted in significant costs to the Departments of Health, in particular, Embhuleni hospital.

We hypothesized that for pregnancies meeting the criteria (<7 weeks since Last Menstrual Period), the regimen of methotrexate and misoprostol would translate to a lower cost to the Embhuleni ToP clinic compared to Mifepristone and misoprostol.

The purpose of the study was to determine whether it was possible to lower the costs of running a cToP clinic by substituting mifepristone with methotrexate which is relatively costlier. The current regimen and protocol proved to be less cost-effective when compared with the proposed regimen.

This retrospective study was done to

- Investigate what the budget impact of using methotrexate/misoprostol vs. mifepristone/misoprostol in medical termination of abortion at less than 7 weeks. A budget analysis was done to see what the potential cost savings were.
- Determine the mean difference in costs between the two regimens.
- To do a comparison of efficacy between regimens using systematic reviews on both regimens
- To determine how patients with gestational age less than 7 weeks would affect the budget, if they were to get misoprostol/methotrexate regimen

Method

Data was collected from patient records for all patients who had abortions in the 2017/2018 financial year at Embhuleni Hospital. The data was compiled and then extrapolated to get the costs of the methotrexate regimen. Data about methotrexate dosages required to bring about complete termination of pregnancy was obtained from reviews done on the efficacy of the methotrexate/misoprostol. The extrapolation of medicine costs was limited to the methotrexate/misoprostol combination showing efficacy similar to that of the mifepristone/misoprostol combination. For the purposes of the cost analysis, it was assumed that other service costs were identical and only the medical termination of pregnancy medicine costs was analyzed.

Study sample

Sample size was based on the number of patients who visited the cToP clinic during the 2017/2018 financial year. Medical records of all patients who had medical abortions were retrieved. Three hundred and twelve patient records were retrieved.

After data collection patients were classified into those below or equal to 7weeks gestational age and those above 7 weeks gestational age.

Inclusion and exclusion Criteria

Patients' medical records included in this study will be for all CTOP patients. The patients who are got abortions and were less than seven weeks pregnant will be a subset for investigation. These medical records must have a prescription of misoprostol and mifepristone tablets. There are no exclusion criteria

Data Collection

Data was collected over a period of two (2) months. Data collection tools were developed by the researcher to collect information on patient demographics, gestational age, number of mifepristone, misoprostol tablets used, date of abortion, efficacy studies of MXT and misoprostol, cost of misoprostol and mifepristone Continuous, categorical and nominal types of data were collected for the different variables that were examined. Patient records were investigated for parameters that included information outlined below:

a) *Participant Hospital Number*. This parameter offered confidentiality on patient records. The study included this element to protect the patient's confidentiality

b) *Date of Abortion.* Information on date of abortion from patients' records was used to determine when the abortion took place so as to remain within the study period

c) *Gestational age.* Information on gestational age was used to determine the patients of interest (7weeks pregnant and less).

d) *Number of misoprostol and mifepristone used*. This information was used to calculate how many tablets were used and subsequently the cost of the regimen

e) *Number of methotrexate tablets and injection required to induce an abortion.* This information was used for the extrapolation of costs of the proposed regimen.

f) *Efficacy studies of MXT and misoprostol*. This information was needed to extrapolate and estimate the efficacy of the proposed regimen

Cost calculations

Figure 1 illustrates the various cost components that can be analyzed in any cost analysis study.

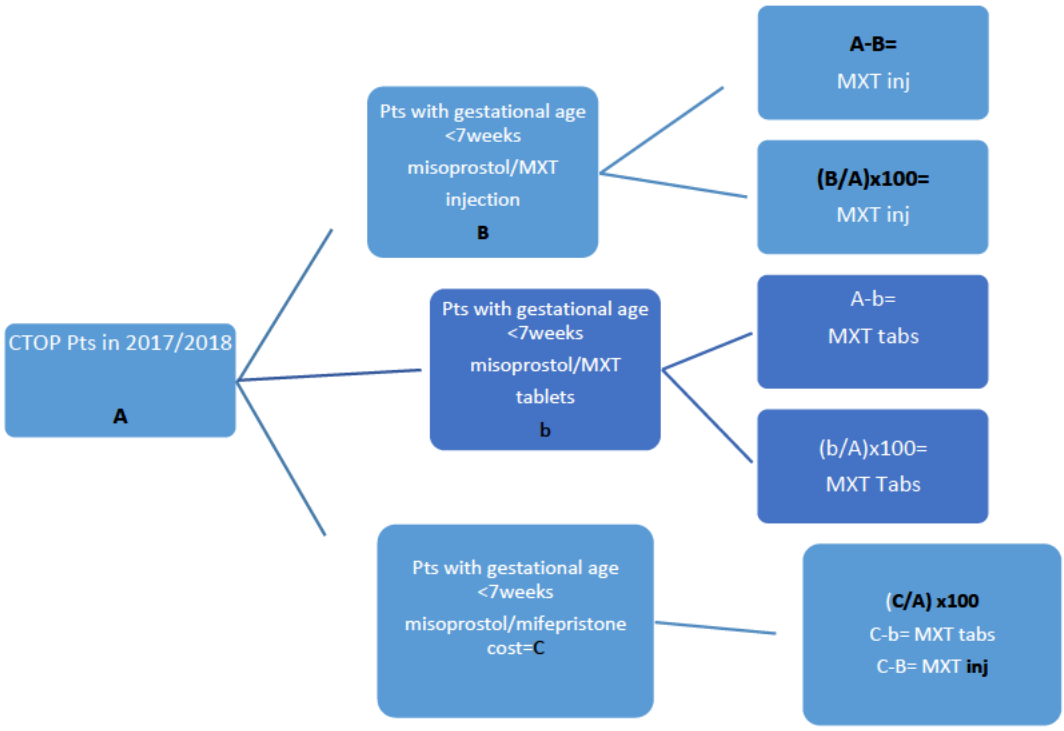

Figure 1: Schematic representation of patient sample and subsets, as well as simplified cost calculations

Statistical Analysis

For each of the study objectives data was analyzed and presented as shown in the results section of this paper. Statistical analysis was performed using SPSS software and Excel was used for the sensitivity analysis

The total cost was estimated using the prices found in the Rx solution system (procurement system used at Embhuleni Hospital). Price of Methotrexate injection was taken from the Single exit Price (SEP) database of 2017, as it is not available at Embhuleni Hospital

Ethical considerations

Ethical procedures followed were in accordance with the ethical standards of the University of Kwa-Zulu Natal (UKZN) Biomedical Research Ethics Committee (BE443/18), Provincial Health Research Committee Mpumalanga (PHRC MP_201812_005) and the Embhuleni hospital. To ensure confidentiality of information source(s), patient hospital numbers rather than names were used for patient identification.

Results

312 patient files were reviewed in the study. 168 (54%) patients had gestational age equal to or less than 7 weeks. All the patients received misoprostol and mifepristone. 17 (5%) patients had an incomplete abortion and had to repeat the procedure. 2 patients with gestational age under 7 weeks had an incomplete abortion and had to repeat the procedure (1.2%). The ages of the patients varied from 15 years to 44.

Cost of treatment options

The current regimen of 4x200mcg misoprostol tablets and 1 mifepristone tablet costs R289.25 per treated patient. The total cost incurred by the hospital for the medicine required to terminate pregnancy came up to R90,246.00. [prices were obtained from the stock procurement system Rx solution]. The proposed regimen comprising of giving 20x 2.5mg tablets of methotrexate and 4x200mcg tablets of misoprostol costs R32.50 per patient [prices were obtained from the stock procurement Rx solution]. The total cost of using 3x25mg/2ml ampoules and 4x200mcg misoprostol tablets is R60.67 per patient [SEP database 2017]

Cost of treatment analysis

The cost of both the current and proposed regimen could not be analyzed for normality because they had no variance. The methotrexate tablets option was the least expensive.

Table 1: Cost of the regimens per termination of pregnancy.

Treatment option	Cost per abortion
1xMifepristone tablet /4xmisoprostol tablets	ZAR 289.25
20x methotrexate tablets/ 4x misoprostol tablets	ZAR 32.50
3x25mg/2ml methotrexate injection/4xmisoprostol tablets	ZAR 60.67

ZAR/USD exchange rate 13.32 (average exchange rate for 2017 as published by the South African Reserve Bank).

Budget impact analysis

Total budget allocated for all medication in the hospital for the 2017/2018 financial year was ZAR 9,499,000. The cToP unit used ZAR 90, 246.00 in the medication used for medical termination of pregnancy, or 0.95% of the budget.

If the Mifepristone-misoprostol regimen was used for women with gestational age less than or equal to 7 weeks, the budget impact would have been:

ZAR (48,594.00/9,499,000.00) x100= **0.51% using the current regimen**

Yet if the MXT-misoprostol combination, if used for women with gestational age less than or equal to 7 weeks, the budget impact would have been:

ZAR (5,459.33/9,499,000.000x100= **0.05% using the MXT tablets**

ZAR (10,192.56/9,499,000.00) x100=**0.11% using the MXT injection.**

The total costs for women presenting at later than 7 weeks is derived from the total cost of medication used to bring about an abortion for all the women minus the cost for women who presented at the cToP clinic with gestational age below 7 weeks. ZAR 90 246 minus ZAR 48 594 which is ZAR 41 652.

For the budget impact analysis calculation, the cost for women presenting at later than 7 weeks would be the same for both MXT-misoprostol and Mifepristone-misoprostol regimens, ZAR 41 652. If the MTX tablets had been used, the total cost savings would be 90,246.00 less (41 652.00+ 5 459.33) = 43,134.67 **or 48%.** If MTX injection were used, the total cost savings would have been R90,246.00 less (41 652.00+10,192.56) = 38,401.44 **or 43%**

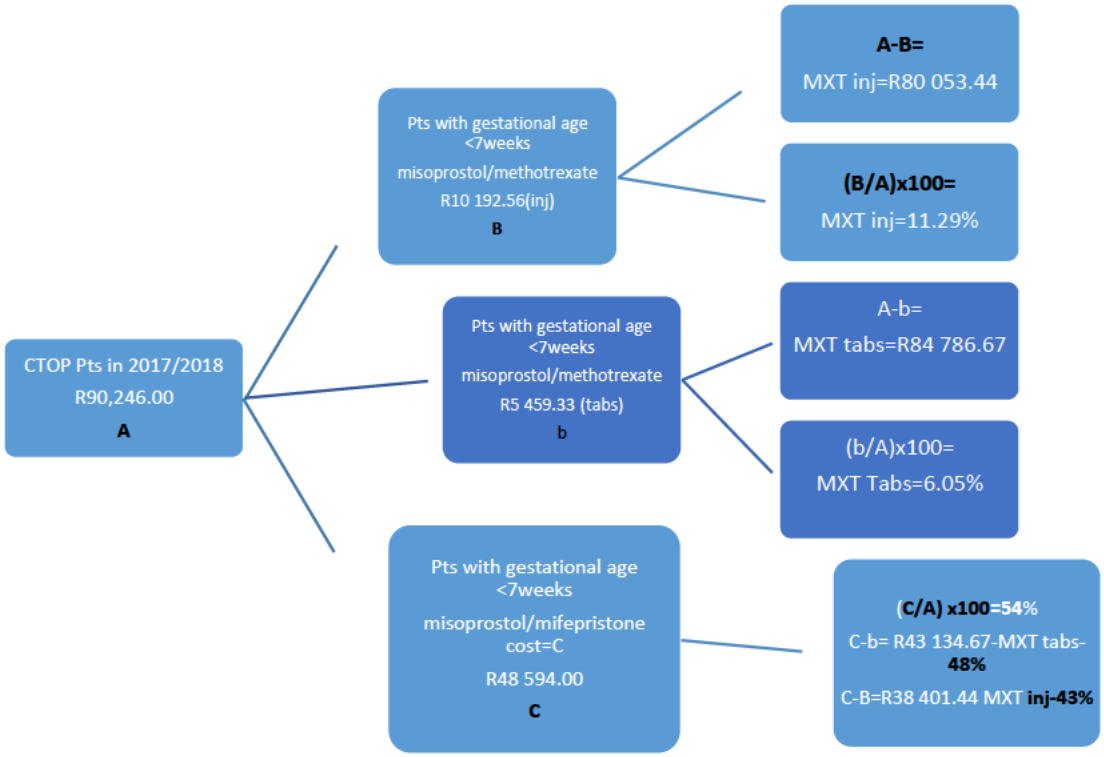

Figure 2: The budget impact analysis. ZAR/USD exchange rate 13.32 (average exchange rate for 2017 as published by the South African Reserve Bank).

Figure 2 shows the budget impact analysis in a diagram.

A- was the total cost of abortions in the 2017/2018 financial year. =R90 246.00

B- was the extrapolated cost of MXT injection (75mg) if would have been administered to women who had a gestational age equal to 7 weeks. =R10 192.56

b- Was the extrapolated cost of MXT tablets (50mg) if they had been given to women who had a gestational age equal to 7 weeks. = R5 459.33

C- Was the total cost of the current regimen when used for women of gestational age less than 7 weeks. =R48 594.00

A-B shows that R80 053.44 would have been saved on medication to bring about an abortion as opposed to spending R90 246.00 if MXT injection would have been used for the target group.

A-b shows that savings of R84 786.67 would have been made if MXT tablets would have been used for the target group.

C/A has 3 values, the first one shows that using the current regimen for the target group used 54% of the expenditure of termination of pregnancy medication on the 2017/2018 financial year. Yet if the MXT injection or tablets were used 43% and 48% of the expenditure would have been saved respectively

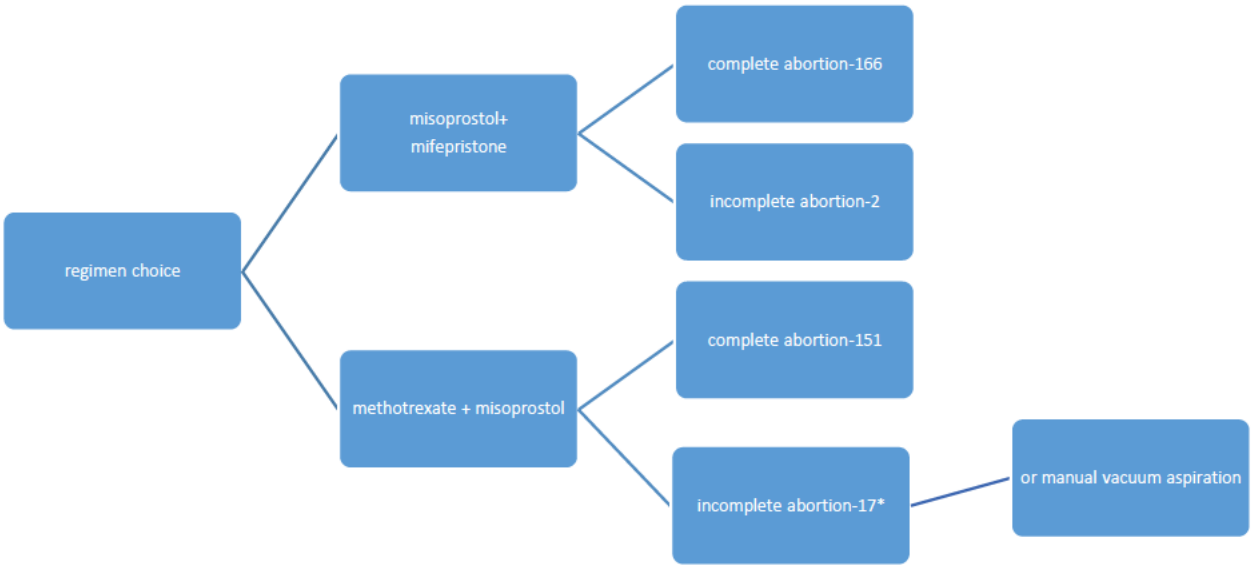

Figure 3: Schematic representation of data analysis guide

*-90% efficacy was taken from the Systematic Review- (Kulier R, 2011)

Figure 3 represents the data analysis guide for the success rate ratio (SRR), if 2 groups of the target population of 168 was subjected to either regimens. Then for the current regimen we would expect 2 failed abortions as that is what was observed from the data. For the theoretical regimen was 90%* of the women in the target group would have a complete abortion. The cost of 168 patients using the current regimen was R48 594.00. In the extrapolation 151 patients would have a complete abortion with the theoretical regimen, this would translate to R4 907.5 for the tablets and R9 161.17 for the MXT injection.

SRR= (Cost $_{\text{Mifepristone-misoprostol}}$ - Cost $_{\text{MXT-misoprostol}}$)/ (Patients with complete abortion $_{\text{Mifepristone-misoprostol}}$- Patients with complete abortion $_{\text{MXT-misoprostol}}$)

	Mifepristone-misoprostol combination	MXT-misoprostol combination
Pts with complete abortion	168	151
Costs	R48 594.	R4 907.5-MXT tablets R9 161.17-MXT injection
SRR	(Cost $_{\text{Mifepristone-misoprostol}}$ - Cost $_{\text{MXT-misoprostol}}$)/ (Patients with complete abortion $_{\text{Mifepristone-misoprostol}}$- Patients with complete abortion $_{\text{MXT-misoprostol}}$) = per patient with complete abortion **R2 917.61** per patient with complete abortion using the MXT tablets **R2 586.82** per patient with complete abortion using the MXT injection	

Table 2: Calculation of SRR. ZAR/USD exchange rate 13.32 (average exchange rate for 2017 as published by the South African Reserve Bank).

*-90% efficacy was taken from the Systematic Review- (Kulier R, 2011)

A one-way sensitivity analysis was done for the following variables, 1) efficacy of the current regimen, 2) efficacy of the proposed regimen, 3) decreasing cost of current regimen, 4) increasing cost of the proposed regimen for both tablets and injection. Baseline efficacy was obtained from the results of the study for the current regimen and an extrapolation from (Kulier R, 2011)was used for the theoretical regimen. Range for the efficacy of both regimens was obtained from the Canadian guidelines.(Costescu D, 2016)

Table 3: one-way sensitivity analysis. ZAR/USD exchange rate 13.32 (average exchange rate for 2017 as published by the South African Reserve Bank).

Parameter	base	range	Source for range		results	
Effectiveness of current regimen	99%	95-98%	Canadian guidelines(Costescu D, 2016)		SRR TAB	SRR INJ
				95%	R5 135.00	R4 552.80
				98%	R3 209.38	R2 845.50
				99%	**R2 917.61**	**R2 586.82**
Effectiveness of proposed regimen	90%	87-98%	Canadian guidelines(Costescu D, 2016)		SRR TAB	SRR INJ
				87%	R2 174.09	R1 927.60
				90%	**R2 914.46**	**R2 584.02**
				98%	R31 716.18	R28 120.24
					SRR tab	SRR inj
cost of current regimen	R272.17-mifepristone Per tablet	180.39-289.27		R136.09	R1 369.56	R1 039.12
				R163.30	R1 678.51	R1 348.07
				R190.52	R1 987.46	R1 657.02
				R217.74	R2 296.41	R1 965.97
				R244.95	R2 605.36	R2 274.92
				R272.17	**R2 914.31**	**R2 583.87**
					SRR tabs	
Price of methotrexate tabs	0.77 per tab	23.44-39.06		**32.47**	**R2 914.84**	
				34.01	R2 897.36	
				35.55	R2 897.36	
				37.09	R2 862.39	
				38.63	R2 844.91	
				40.17	R2 827.43	
						SRR inj
Price of methotrexate injection	14.53/ampoule 61.61	36.97-61.61		**60.67**		**R2 294.84**
				65.02		R2 545.36
				69.37		R2 495.88
				73.73		R2 446.40
				78.09		R2 396.92
				82.45		R2 347.44

Discussion

The study identified that using MXT tablets or injection is cost-effective compared to the current regimen of misoprostol and mifepristone. Reviews of efficacy done for all 3 regimens show that the proposed MXT regimen has an acceptable efficacy of 90% in women of gestational age less than or equal to 7 weeks. In the 2017/2018 financial year the cToP clinic used 0.95% of the medicine budget. If the proposed regimen would have been used for women of gestational age less than or equal to 7 weeks, the budget impact would have been 0.05% for the MXT tablets and 0.11% for the MXT injection. In the 2017/2018 financial year the cToP

clinic used R90 246.00 yet if the proposed regimen would have been used the cToP unit would have used R43134.67 for the MXT tablets and R38 401.44 for the MXT injection.

In the 2016 Canadian guidelines methotrexate and misoprostol can be used up to 63days' gestation in medical termination of abortion. Canada is using MXT for the medical termination of pregnancy. The safety and efficacy of the MXT in combination with misoprostol has been established and it can be a viable option to curb the relatively high costs of providing ToP services.

The number of patients requiring ToP services is increasing and this translates to an increase in the cost of proving the service, a cost-effective regimen i.e. MXT and misoprostol can go a long way in preserving the already limited budget.

At baseline the SRR for the tablets and injection was R2 917.61 and R2 586.82 respectively, which means that although the intervention is not as effective as the current regimen it is cost-effective and the efficacy is acceptable to bring about a complete medical abortion.

Table 3 shows the parameters varied for uncertainty and sensitivity analysis and their ranges. The base price of the current regimen (mifepristone /misoprostol) as quoted on the tender system in South Africa was R289.25.

Decreasing the effectiveness of the current regimen from the baseline of 99% to 94 % showed an increase in SRR from R2 586.82 and R2 917.61 to R4 552.80 and R5 135.00 per complete abortion for both MXT injection and tablets respectively. This means that if the efficacy of the current regimen decreases to 94 %, the SRR increases and so does the cost saving per complete abortion.

Varying the effectiveness of the proposed regimen from the baseline of 90% with SRR of R2 914.46 and R2 584.02 by decreasing said effectiveness to 87% and then increasing it to 98% showed an increase in SRR from R2 174.09 and R1 927.60 to R31 716.18 and R 28 120.24 for MXT tablets and injection respectively per complete abortion. This means that as the efficacy for the MXT regimen increases, so does the SRR and this increases the cost savings per complete abortion using this regimen.

Reducing the cost of the current regimen by half reduced the SRR from a baseline of R2 917.61 for the MXT tablets to R1 369.56 and R2 586.82 for the MXT injection to R1 039.12, translating to a 47% and 40% decrease in SRR respectively. Reducing the cost of MXT will reduce savings per complete abortion.

Increasing the price of MXT tabs regimen from R32.47 to R40.17 showed a steady decrease in the SRR from R 2 914.84 to R 2 827.43. A similar decrease in SRR was observed for the MXT injection. Increasing the price between R60.67 -R82 45 showed a decrease in the SRR per complete abortion from the baseline SRR of R 2 594.84 to R2 347.44 when the price was increased by 50%.

Conclusion

Both MXT injection and tablets are registered in South Africa and have local manufacturers and distributors. Currently in Mpumalanga formulary the tablets are on tender. In order to bring about change which will push for the indications of MXT to include Medical termination of pregnancy more budget impact analysis studies need to be done across the country to determine the over financial impact the current regimen has and how much money could be saved from amending the guidelines to include the cost-effective regimen of MXT and misoprostol.

It must be recognized that the MXT-misoprostol combination, although much less expensive than the mifepristone-misoprostol combination, also lower efficacy than the mifepristone-misoprostol combination. A failed termination of pregnancy can have significant impact on the mother and has added costs, and resource utilization in general. Both of these factors may render the MTX combination undesirable despite potential cost savings. However, this analysis will assist in determining what level of cost savings can be traded for a decrease in efficacy of the regimen, if any at all.

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CHAPTER 4 SYNTHESIS

4.1 SYNTHESIS

The study revealed that in the 2017/2018 financial year 312 patients used the ToP services at Embhuleni Hospital, R90 246.00 was spent on medicine used to terminate pregnancy. The regimen used for the medical termination of pregnancy was in line with 2015 STGs as well WHO guidelines. The ages of the patients varied from 15 years to 44. Had the proposed regimen of MXT/misoprostol been used for women with gestational age less than or equal to 7 weeks the costs would have resulted in 48% and 43% cost savings for the MXT tablets and injection respectively.

4.2 CONCLUSION

The budget impact analysis showed how much the current is affecting the budget and suggested how much could be saved if the theoretical regimen of MXT and misoprostol were to be used in women of gestational age 7 weeks or less. The mifepristone/misoprostol regimen has higher efficacy but systematic reviews showed that the efficacy of MXT/misoprostol, is acceptable if used for the target group only. Canada is an example of country that has incorporated MXT/misoprostol in its guidelines for ToP

4.3 RECOMMENDATIONS

The retrospective study was limited to the cost of medication used for ToP, more multi-faceted studies need to be conducted to analyse the overall cost of using either MXT tablets or injection for ToP. Studies that will look into cost of administration of both regimens, the sundries required for both procedures, the compensation given to the staff at the cToP clinic for administration of the regimen. There is a need to analyse the cost to the patients in terms of initial visits and follow up visits as well as the management of side effects of the proposed regimen.

4.4 STUDY LIMITATIONS

This study was not without limitations, it studied only the medicine required to bring about an abortion, for a more comprehensive budget impact analysis more variables will need to be considered. The record keeping system was not the best as some of the file numbers in the registers were difficult to locate due to ineligible handwritings. Some of the sonar grams were not stapled on the files and were missing making it impossible to get the gestational age of the patients. The sample size could have been bigger but some files had missing critical information.

Of the direct medical costs, this study considered the medicines needed for an abortion, this led to the neglect of clinical outcomes against medicine given to the patients. Further research will be necessary if treatment costs were to be examined in relation to treatment outcome and follow up visits.

4.5 DISSEMINATION

A manuscript of this research has been prepared and submitted for possible publication in the South African Medical Journal (SAMJ). Results of this study are yet to be shared with the Research office at the Mpumalanga Provincial office and made available on the national database. A copy of the study will be given to the Embhuleni hospital management as well as the Pharmacy and Therapeutic Committee (PTC) for review. The findings of the study will be presented at the South African l Association of Hospital and Institutional Pharmacists 63rd Annual Conference.

APPENDIX A – DATA COLLECTION INSTRUMENT (Patient records)

Entry number	Ref. Number	Age	Gestational age	mifepristone	misoprostol	Date

APPENDIX B- DATA COLLECTION INSTRUMENT FOR SYSTEMATIC REVIEWS

Name of article	Authors	Misoprostol tablets (Y/N)	Methotrexate injection (Y/N)	Methotrexate tablets (Y/N)	Efficacy results

Appendix C-Letter of permission from the Hospital

health
MPUMALANGA PROVINCE
REPUBLIC OF SOUTH AFRICA

MPUMALANGA
THE PLACE OF THE RISING SUN

No.3, Government Boulevard, Riverside Park, Ext. 2, Mbombela, 1200, Mpumalanga Province
Private Bag X11285, Mbombela, 1200, Mpumalanga Province
Tel I: +27 (13) 766 3429, Fax: +27 (13) 766 3458

Litiko Letemphilo | Departement van Gesondheid | UmNyango WezeMaphilo

Letter of Support Signed by Chief Director (CD)/CEO/District Manager (DM)/Programme Manager (PM)

1. Name & contact no. of Applicant	THEMBELIHLE SIYAYA 0781799804		
2. Title of Study: Cost analysis of Misoprostol & Mifepristone versus Misoprostol & Methotrexate when used for medical termination of pregnancy in women of gestational age of 7 weeks and less at Embhuleni Hospital, Ehlanzeni MP			
3. Aim and population target: To determine whether it is possible to lower the cost of running a ToP clinic by substituting methotrexate in place of mifepristone in women of gestational age 7 weeks			
4. Period to undertake the study	From: 24/12/18 to: 31/01/19		
5. Resources Required from Facility/Sub-district/Community			
5.1: Facility Staff Required to assist with the Study	**Yes**		**NO**
	How many:		
	Nurses:	N/A	
	Doctors:	N/A	
	Other, please specify:	N/A.	
5.2: Patient Records/Files	**Yes**		**NO**
5.3: Interviewing Patient at Facilities	**Yes**		**NO**
5.4: Interviewing Patients at Home	**Yes**		**NO**
5.5: Resource Flow (Are there benefits to Patients/community)	**Yes**		**NO**
	Please list:		
5.6: Resource Flow (Are there benefits to Facility/District)	**Yes**		**NO**
	Please list:		
6. Availability of Required Clearance			
6.1: Ethical Clearance	**Yes**	**Pending**	**NO**
	Clearance Number: BE 443/18		
6.2: Clinical Trial	**Yes**	**Pending**	**NO**
	Clearance Number:		
6.3: Vaccine Trial	**Yes**	**Pending**	**NO**
	Clearance Number:		
6.4: Budget	**Yes**		**NO**
	Source of fund: Self.		

Declaration by Applicant:
I Mr/Ms/Dr/Prof/Adv. T. N SIYAYA agree to submit/present the result of this study back to the CEO/Institution/District.

Comment by CEO/CD/DM/PM: **Supported ~~Not Supported~~**

Supported for study purposes

[redacted]

12/12/18

Signature of CEO/CD/DM/PM **Stamp/Date:**

Name: TWC MASHABA

Please email completed form to: JerryS@mpuhealth.gov.za or ThembaM@mpuhealth.gov.za

MPUMALANGA
THE PLACE OF THE RISING SUN

Appendix D: Mpumalanga PHREC Approval

health
MPUMALANGA PROVINCE
REPUBLIC OF SOUTH AFRICA

Indwe Building, Government Boulevard, Riverside Park, Ext. 2, Mbombela, 1200, Mpumalanga Province
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Litiko Letemphilo | Departement van Gesondheid | UmNyango WezeMaphilo

Enq: 013 766 3766/3511
Ref: MP_201812_005

Provincial Research Approval Letter

TO: **Ms Thembelihle Siyaya**
Stand No. 40B
Diepgezet
Elukwatini
1192

TITLE: COST-ANALYSIS OF MISOPROSTOL AND MIFEPRISTONE VERSUS MISOPROSTOL AND METHOTREXATE WHEN USED FOR MEDICAL TERMINATION OF PREGNANCY IN WOMEN OF GESTATIONAL AGE OF 7 WEEKS AND LESS AT EMBHULENI HOSPITAL IN ELUKWATINI, MPUMALANGA

The provincial health research committee has approved your research proposal in the latest format you sent.

- Approval Reference Number: MP_201812_005
- Data Collection Period: February 2019 – March 2019
- Approved Data Collection Facilities:

  Embuleni Hospital

Kindly ensure that the study is conducted with minimal disruption and impact on our staff, and also ensure that you provide us with a soft or hard copy of the report once your research project has been completed.

Kind regards

[redacted]

MR. JERRY SIGUDLA
MPUMALANGA PHRC

MPUMALANGA PROVINCE
DEPARTMENT OF HEALTH
07-02-2019
DATE
PRIVATE BAG X11285
NELSPRUIT 1200

MPUMALANGA
THE PLACE OF THE RISING SUN

APPENDIX E: UKZN BREC APPROVAL LETTER

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

10 December 2018

Ms TNQ Siyaya (217030246)
School of Health Sciences
College of Health Sciences
thembiesiyy@gmail.com

Protocol: Cost analysis of Misoprostol and Mifepristone versus Misoprostol and Methotrexate when used for medical termination of pregnancy in women of gestational age of 7 weeks and less at Embhuleni Hospital in Elukwatini, Mpumalanga.
Degree: MPH
BREC Ref No: BE443/18

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received 23 July 2018.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 15 November 2018 to BREC correspondence dated 27 August 2018 has been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full **ethics approval** and may begin as from 10 December 2018. Please ensure that site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from 10 December **2018.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **noted** by a full Committee at its next meeting taking place on **11 December 2018.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

[redacted]

Professor V Rambiritch
Chair: Biomedical Research Ethics Committee

Supervisor:shelleym@samedical.org Postgrad Administrator: nenep1@ukzn.ac.za

Biomedical Research Ethics Committee
Professor V Rambiritch (Chair)
Westville Campus, Govan Mbeki Building
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Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

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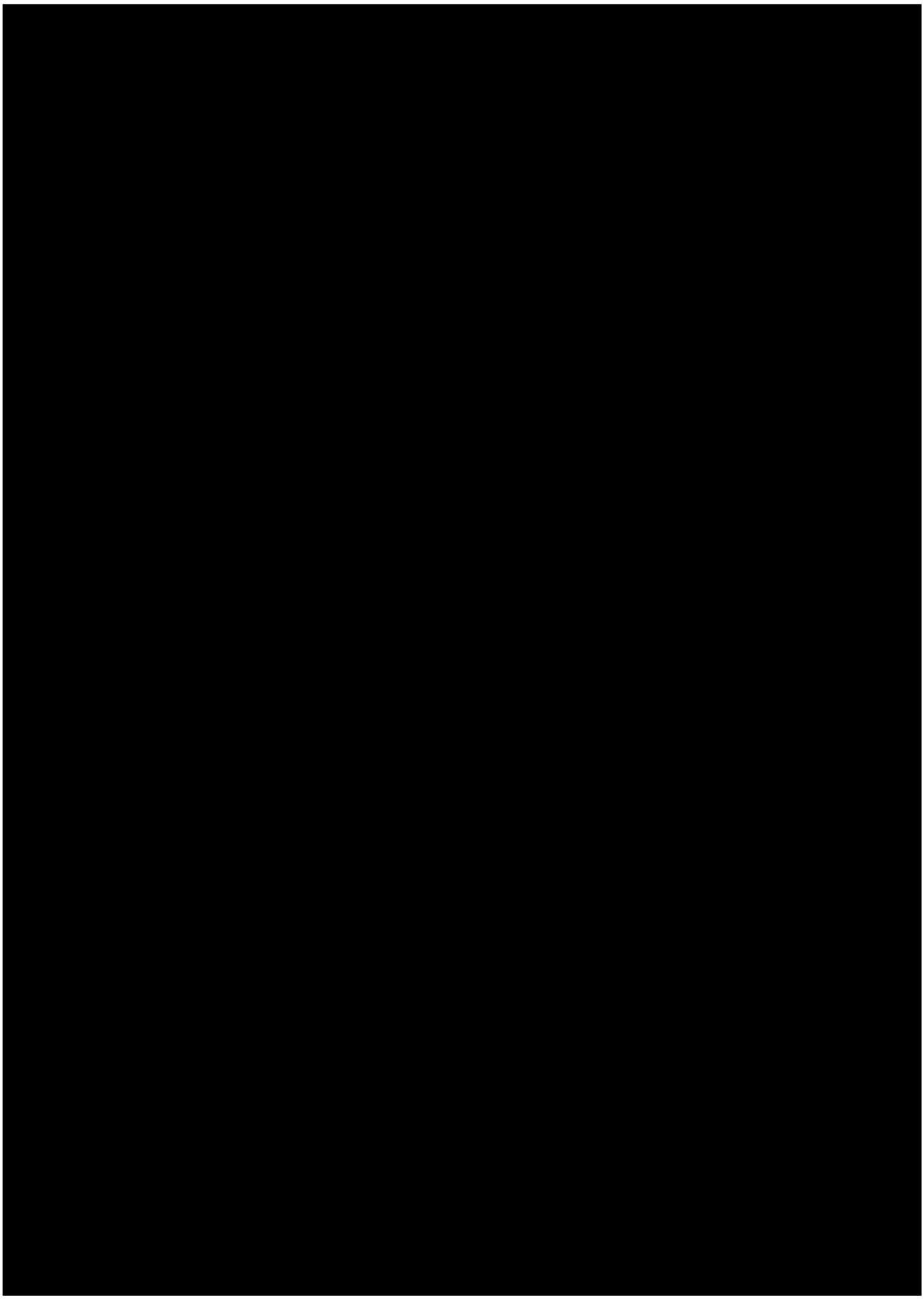
APPENDIX F: UKZN BREC APPROVAL LETTER AFTER AMENDMENTS



APPENDIX G: SAMJ FORMAT

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. μ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols