HEALTH TECHNOLOGY ASSESSMENT OF INTRAVENOUS TRANEXAMIC ACID USE IN MANAGEMENT OF PRIMARY POST-PARTUM HAEMMORHAGE IN INDIA

"HEALTH TECHNOLOGY ASSESSMENT OF INTRAVENOUS TRANEXAMIC ACID USE IN MANAGEMENT OF PRIMARY POST-PARTUM HAEMMORHAGE IN INDIA"

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LIST OF ABBREVIATIONS

ANC	Antenatal care
DCGI	Drug Controller General of India
DLHS	District level household survey
FDA	Food and Drug Administration
GOI	Government of India
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
ICU	Intensive care unit
ICUR	Incremental cost-utility ratio
IPHS	Indian Public Health Standards
I.V.	Intravenous
LSCS	Lower segment Caesarean section
NFHS	National Family Health Survey
PICOT	Population-Intervention-comparator-outcome-timeline
PHC	Primary Healthcare center
PPH	Post-partum Hemorrhage
QALY	Quality Adjusted Life Years
RCT	Randomized Control Trial
SBA	Skilled birth attendant
SOC	Standard of care
SRS	Sample Registration System
TXA	Tranexamic acid
UBT	Uterine Balloon Tamponade
WHO	World Health Organization
WTP	Willingness to pay threshold

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EXECUTIVE SUMMARY

Intravenous tranexamic acid (I.V.TXA) use in all women with primary PPH is recommended by the World Health Organization based on results from the 2017 WOMAN trial. This is an HTA submission to answer the policy question of whether this recommendation should be considered in the Indian public health system. A decision tree was constructed to answer this question. It was found from the decision analytic model that addition of I.V. TXA to the Indian public health system would be cost-effective at willingness to pay threshold of one-time GDP per capita of INR 1,45,742 (USD 2099) for year 2019. At this WTP threshold, addition of tranexamic acid to standard care treatment package is associated with an ICUR QALY value of INR 1,470 per QALY gained i.e. the society incurs an additional cost of INR 1,470 per patient with a gain in one QALY, indicating tranexamic acid addition to be a cost-effective intervention. Similarly, for DALY outcome measure, an ICER DALY value of INR 1,288 per DALY averted suggests that the society incurs an incremental cost of INR 1,288 for one associated DALY averted by adding tranexamic acid to PPH treatment. ICER DALY value suggests tranexamic acid to be cost-effective. As the incremental cost-effectiveness ratios for tranexamic acid addition were below the recommended threshold, this intervention was found to be cost-effective across DALY and QALY outcome measures. The modelling results were robust as sensitivity analysis shows that 94.6% of the 10,000 Monte Carlo ICUR QALY gained simulations (Mean incremental net monetary benefit of INR 11,980 (95% CI 11,833 - 12,128) and 93.1% of 10000 Monte Carlo ICER DALY averted simulations (Mean incremental monetary benefit of INR 2195 (95% CI 2,168 - 2,224) were both cost-effective across analysis. Budget impact analysis suggests an incremental cumulative increase in financial allocation by 2.3% over a five-year period to that currently allocated for management of primary PPH in Indian public health settings. Based on these results, the recommendations are as follows:

- To add I.V. TXA to the public health system of India for the management of PPH [one gm. in 10 mL (100 mg/mL) IV at one mL per minute (i.e., administered over 10 minutes) within three hours of birth and second dose of one gm. IV if bleeding continues after 30 minutes or if bleeding restarts within 24 hours of completing the first dose to all women who are diagnosed of primary PPH, irrespective of cause]

- All policy guidelines on PPH management, including DAKSHATA packages, training material etc. to be updated to reflect this recommendation if it is accepted.

A few points based on the inputs to the model have been highlighted to help policy makers to make an informed decision. (As the model results depend heavily on the inputs and assumptions)

- The clinical effectiveness of I.V. TXA is based on the results of a large globally conducted double-blinded placebo-controlled RCT called the WOMAN trial with 20,060 women enrollments. The trial showed reduction in mortality due to bleeding in the TXA arm. However, the confidence interval for this finding is not statistically significant. Despite this, the largeness of the RCT and the significance of preventing maternal deaths, has resulted in TXA being recommended for routine use in primary PPH by the World Health Organization. This analysis has used mortality related relative risk parameters as reported by the WOMAN trial results.
- The WOMAN trial did not report effectiveness of tranexamic acid in terms of prevention of any further intervention after tranexamic acid or standard care treatment as required. This analysis parameter was obtained from the WOMAN trial by indirectly cumulating the individual disaggregated reported interventions undertaken along with tranexamic acid or standard care as reported in the study.
- This model is specific to the Indian public health context. The decision model incorporates services available for PPH management across healthcare levels in India. Moreover, as recommended by the Indian guidelines, the model considers use of uterine balloon tamponade intervention for refractory atonic PPH cases in the decision model.
- The cost data is derived from a primary study done in four public health facilities. A sensitivity analysis has been done to improve generalizability of the model results.

CHAPTER 1: BACKGROUND

1.1 Background:

Maternal Mortality: Maternal mortality is still rampant in our world; 2.95 million women lost their lives either during pregnancy or within 42 days of childbirth[1] in the year 2017, of which 94% were from low and middle income countries[2]. To add to this, the pandemic of COVID-19 has adversely affected maternal health. A study done in 2020, in the midst of the COVID-19 pandemic, showed that there was a drop in institutional deliveries by 45% in a region in Northern India[3]. Another study estimated additional burden of the pandemic on maternal deaths by modelling and projected an 8.3-38.6% increase in maternal deaths per month during the ongoing pandemic in the 118 countries[4]. Sample registration system of India shows a decline in maternal mortality ratio (MMR) over the past decades. In 2015-17, the MMR was 122 per 100,000 live births, down by more than 100 points from the year 2004-05 when the MMR in India was 254 per 100,000 live births[5]. Despite the decline, we still have a long way to go to achieve the 'Sustainable Development Goals' target of reducing MMR to less than 70 per 100,000 live births by the year 2030; especially due to the pandemic impeding the world's progress.

Causes of Maternal mortality: A World Health Organization systematic analysis showed that 73% of maternal deaths are due to direct obstetric causes, of which hemorrhage, hypertensive disorders and sepsis were most common[6]. Post-partum hemorrhage (PPH) is the top preventable cause of maternal deaths. It is defined as blood loss of more than 500 mL during vaginal delivery and more than 1000 mL in caesarean delivery[7].

Postpartum hemorrhage management: PPH can be due to reduced tone in the uterus (atony), trauma, retention of placental bits and rarely, coagulation abnormalities. Post-partum hemorrhage can be controlled by timely and appropriate cause-specific care in a well-equipped health system. Appropriate management of PPH is a key factor in preventing maternal deaths. The algorithm for management of PPH, advocated by Royal College of Obstetricians & Gynecologists (RCOG) is shown in figure 1.

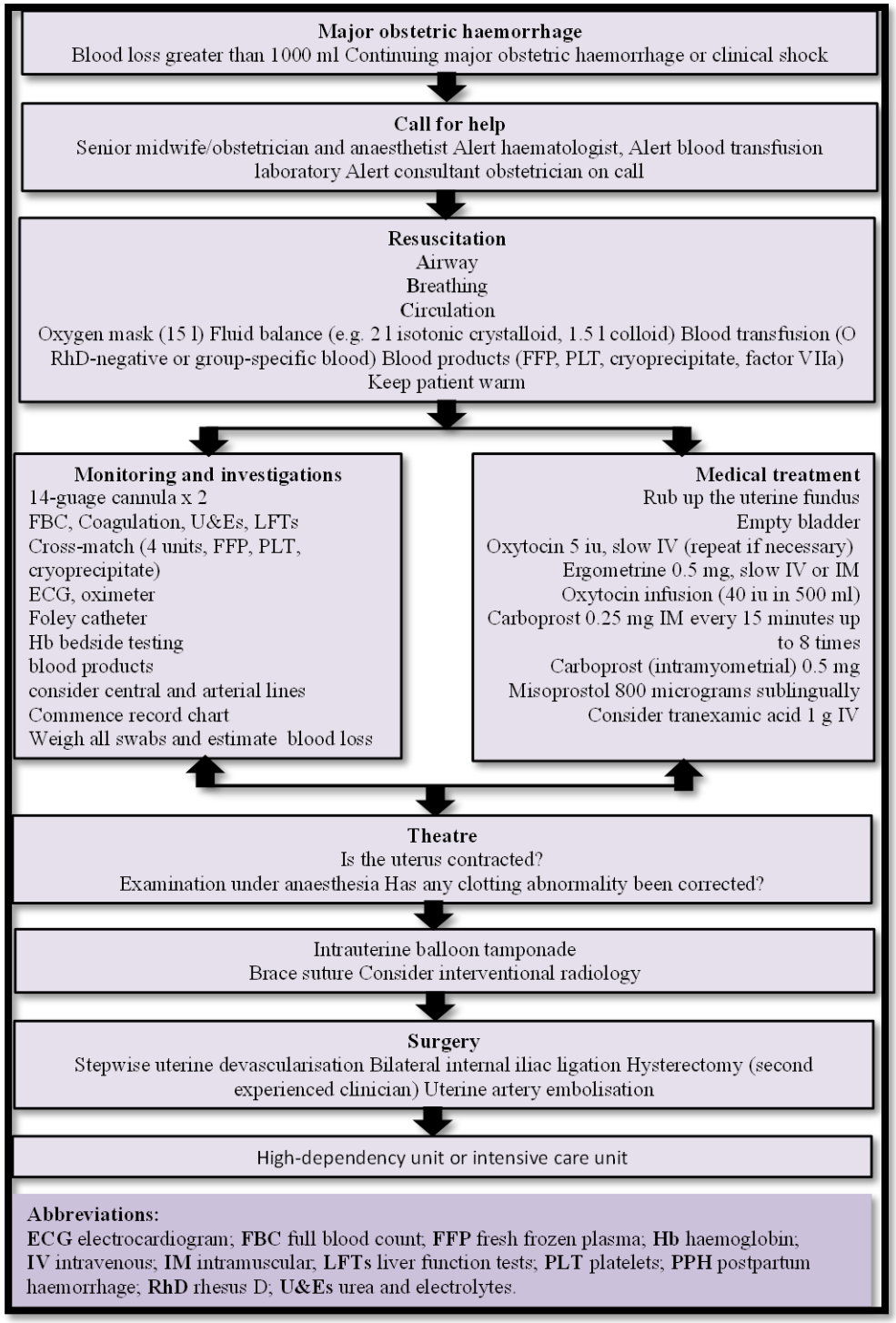


Figure 1: Algorithm for management of PPH by Royal College of Obstetricians & Gynecologists developed in the year 2016 [8]

The Algorithm is comprehensive and gives a clear flow of parallel activities that need to be done to control PPH effectively (Resuscitation, monitoring, investigation and treatment should occur simultaneously). The International Federation of Gynecology and obstetrics had developed an algorithm in the year 2012. This is depicted in figure 2.

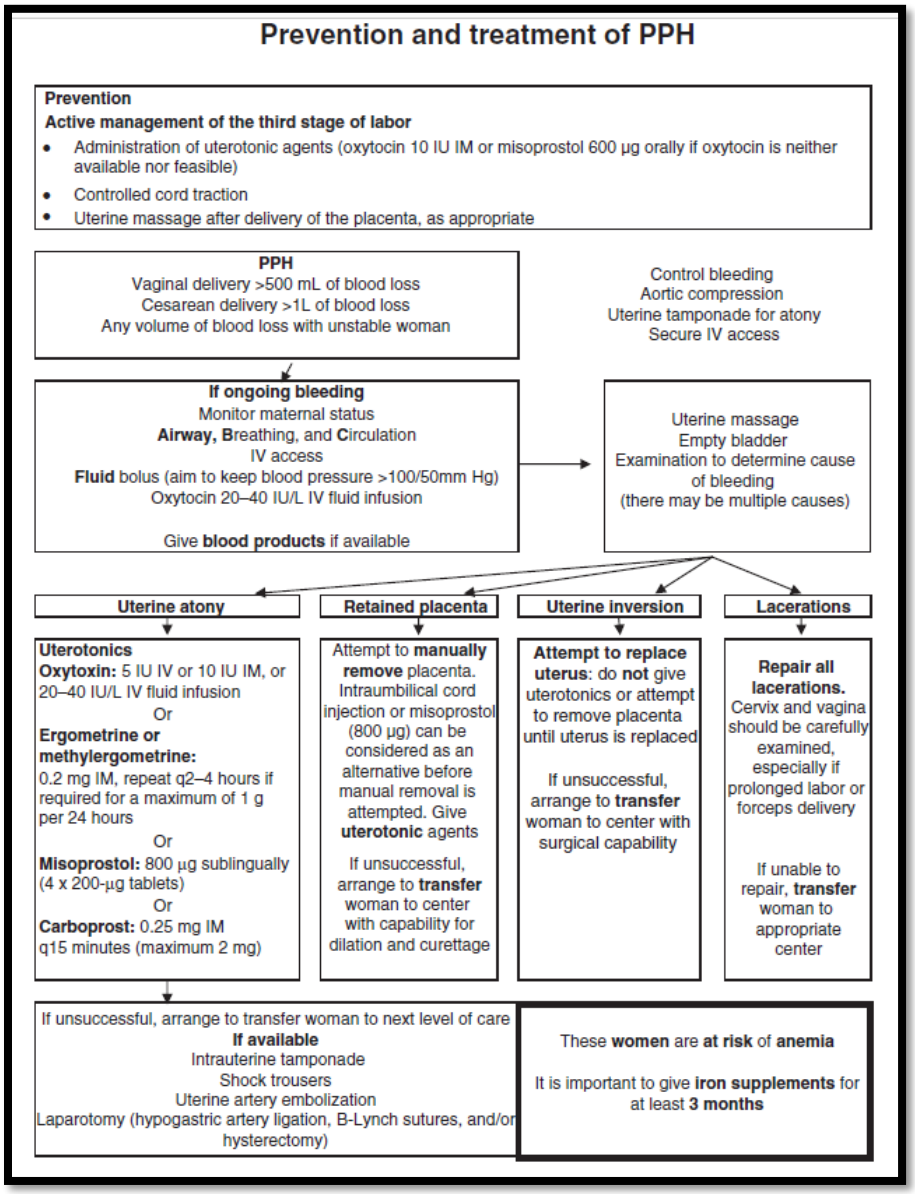


Figure 2: Algorithm of management of PPH (Cause-specific) by FIGO in 2012[9]

FIGO also enumerates the approach to prevention and treatment of PPH using medical management. This is depicted in figure 3.

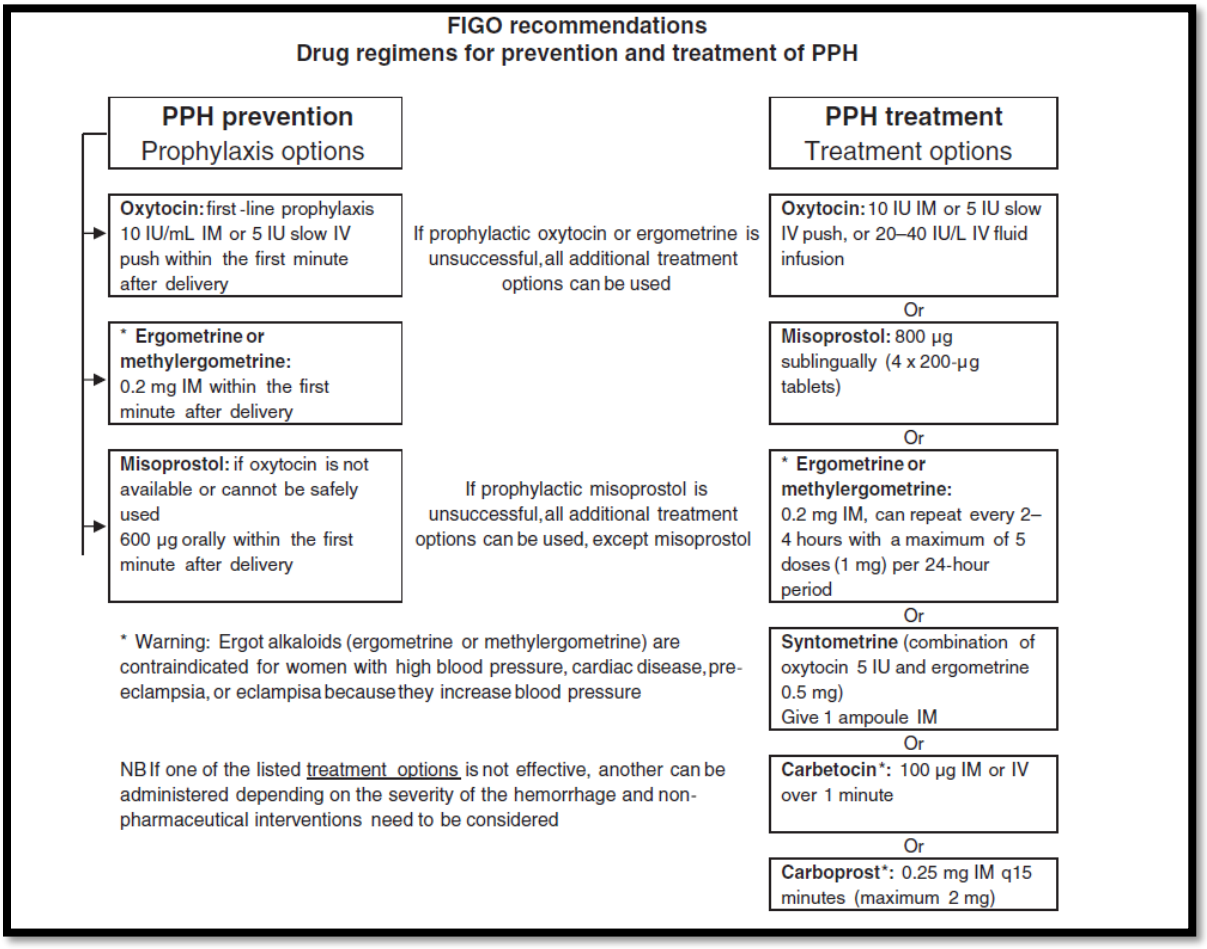


Figure 3: Drug regimens for prevention and treatment of PPH [9]

Tranexamic acid (TXA) use: TXA acts by competitively inhibiting plasminogen activation and by reduction of bleeding by inhibiting the breakdown of fibrinogen and fibrin clots. It was introduced in the 1960s. It is indicated in women with heavy menstrual bleeding and has long been used off-label to control bleeding in elective surgeries. I.V. Tranexamic acid is approved by US-FDA for patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction[9]. It is approved by Drug controller General of India for a) treatment of excessive bleeding in patients with hemophilia during & following tooth extraction and b) abnormal bleeding in which local hyper fibrinolysis is considered to be involved (pulmonary, hemorrhage, epistaxis, renal bleeding abnormal bleeding during or after prostate surgery)[10]. TXA had shown improvement in trauma

care outcomes. A few landmark trials in the use of TXA were the CRASH trials in 2010 and 2019 that explored use in trauma patients. Since the late 2000s, intravenous TXA use has been used in PPH.

Tranexamic acid use in PPH: In the early 2000s a Randomized control trial was done in France, to show the efficacy of Tranexamic acid in PPH [11]. The WOMAN trial, published in 2017 in the LANCET Global Health, was a huge, multi-country, double-blind, placebo-controlled study that showed the effectiveness of Tranexamic acid use in PPH.

Evidence for use of TXA in PPH: Ducloy-Bouthors et al conducted a randomized, controlled, multicenter, open-label trial in France in 2011[11] . Women with PPH >800 mL after vaginal delivery were randomly assigned to either receive TXA (loading dose 4 g over 1 hour, then infusion of 1 g/hour over 6 hours) or not receive TXA. A total of 144 women completed the protocol (72 in each group). Blood loss in the first six hours of enrolment was significantly lower in the TXA group than in the control group (median, 173 mL; first to third quartiles, 59 to 377) than in controls (221 mL; first to third quartiles 105 to 564) ($P = 0.041$). In the TXA group, bleeding duration was shorter and progression to severe PPH and packed RBC transfusion was less frequent than in controls ($P < 0.03$). Invasive procedures were performed in four women in the TXA group and in seven controls (P = NS). PPH stopped after only uterotonics and PRBC transfusion in 93% of women in the TXA group versus 79% of controls ($P = 0.016$). Mild, transient adverse manifestations occurred more often in the TA group than in the control group ($P = 0.03$) [11].

The WOMAN Trial (World Maternal Antifibrinolytic Trial) was a randomised, double-blind, placebo-controlled trial, which recruited women aged 16 years and older with a clinical diagnosis of post-partum haemorrhage after a vaginal birth or caesarean section from 193 hospitals in 21 countries. They randomly assigned women to receive either 1 g intravenous Tranexamic acid or matching placebo in addition to usual care. If bleeding continued after 30 min, or stopped and restarted within 24 h of the first dose, a second dose of 1 g of Tranexamic acid or placebo could be given. Between March 2010, and April 2016, 20,060 women were enrolled and randomly assigned to receive tranexamic acid (n=10 051) or placebo (n=10,009), of whom 10,036 and 9,985, respectively, were included in the analysis.

Results of the WOMAN trial: Death due to bleeding was significantly reduced in women given Tranexamic acid (155 [1.5%] of 10 036 patients vs. 191 [1.9%] of 9,985 in the placebo group, risk ratio [RR] 0.81, 95% CI 0·65–1·00; p=0·045), especially in women given treatment within three hours of giving birth. Hysterectomy was not reduced with Tranexamic acid. The composite primary endpoint of death from all causes or hysterectomy was not reduced with Tranexamic acid. Adverse events (including thromboembolic events) did not differ significantly in the Tranexamic acid versus placebo group [12].

Based on the WOMAN trial, the WHO recommended TXA use in all cases of PPH within three hours of delivery. The dose currently recommended is same for vaginal and cesarean deliveries. But, a TRACES study (Tranexamic acid to reduce blood loss in hemorrhagic Caesarean delivery) protocol published by Bouthors et al in 2018 et al hypothesizes that large variations in fibrinolytic activity during hemorrhagic caesarean section may need targeted TXA doses for clinical and biological efficacy. Hence they are conducting the TRACES randomized, double-blind, placebo-controlled trial for Therapeutic and pharmaco-biological, dose-ranging of TXA in cesarean deliveries[13]. The results of this study are awaited.

Recommendation by WHO: The dose recommended by WHO for use in PPH is one gm. in 10 mL (100 mg/mL) IV at one mL per minute (i.e., administered over 10 minutes) within three hours of birth and second dose of one gm. IV if bleeding continues after 30 minutes or if bleeding restarts within 24 hours of completing the first dose to all women who are diagnosed of Primary PPH, irrespective of cause. Following this trial, the World Health Organization changed its recommendation on TXA in PPH to warrant use in all cases of PPH; irrespective of cause [14]. In this recommendation, it is important to note that TXA is to be used within three hours of delivery as an adjunctive treatment to PPH and not to be used as mono-therapy.

(Note that in the figures 1 to 3, the RCOG algorithm was developed in 2016 and recommends use of Tranexamic acid while the FIGO algorithm does not recommend use of TXA, as it was formulated in 2012.)

TXA use in PPH in India: India's guidance note on management of PPH follows the WHO 2012 recommendations, where TXA use is advised more so in traumatic PPH and the dosage and timing of administration of the drug is not clear[15]. A program named 'Dakshata' was initiated by the Government of India in 2015 to build competencies in healthcare workers and to improve quality

of maternal and child health services in India[16]. Dakshata program has checklists for Obstetric conditions but the PPH management kit does not include TXA I.V. Injection. A policy question of whether TXA should be an integral part of management of PPH in India was proposed by the state government of Maharashtra.

Cost-effectiveness of TXA: To assess the evidence on cost-effectiveness of use of tranexamic acid in PPH treatment, a review of literature was undertaken. A very recent systematic review published in February 2021 looked at all available economic evidence for use of tranexamic acid exclusively in treatment of PPH. The primary outcome of interest in the review was incremental cost effectiveness ratio for tranexamic acid in PPH treatment as compared to without tranexamic acid intervention. Across available literature, the review found four studies that met the eligibility criteria. Two of the citations were conference abstracts for which authors could not obtain any additional data. The four studies aimed at analyzing cost-effectiveness of tranexamic acid in PPH treatment and were published between 2018-19. Two of these studies were undertaken in the USA, one was based on data from the WOMAN trial in Nigeria and Pakistan, and one study did not state the country. The studies all used a decision tree model. The two abstracts did not give information on model structure. Sudhof et al. model included timing of tranexamic acid use, laparotomy, brace sutures and death from PPH as the sequential branches in the decision tree. Li et al. looked at death due to bleeding and other causes through their model. The primary outcome assessed by Sudhof et al. was incremental cost, PPH related deaths averted, laparotomy avoided along with ICUR per QALY gained from the societal perspective. Li et al. evaluated costs, life years, QALYs and associated ICER values from healthcare provider perspective. The conference abstracts by Howard et al. And Wong et al. looked at ICERs QALYs but did not specify the perspective. The systematic review assessed the methodological quality of reviewed studies to report one study to be of high quality, one to be of moderate quality and unfortunate inability to assess quality of the conference abstracts as the complete studies were unavailable. Sudhof et al. reported tranexamic acid to be a cost saving intervention, Li et al. found tranexamic acid to be cost effective in reducing maternal mortality and morbidity caused by PPH. Wong et al reported tranexamic acid as not cost-effective in USA but reported that it may be cost-effective in settings with higher PPH probability. Howard et al. observed tranexamic acid to be a cost saving intervention. The review observed that there is limited evidence available regarding cost-effectiveness of TXA for PPH treatment with only two complete studies reporting such outcomes. The study identifies unavailability of evidence

especially from LMIC as a limitation. The authors state that while further evidence is required, it may be likely that TXA if available at a low price in PPH prevalent settings may likely be cost-effective. The review identifies a broad database search with inclusion of nine databases, duplicate screening and quality assessment as strengths of the study.

With this limited available evidence on cost-effectiveness of tranexamic acid in LMIC settings, especially for the Indian context where such economic evidence is unavailable, this present study aims to generate such evidence to act as a tool to assist evidence informed policy decision making in India. In this present study we aim to address two main questions that is to present the relevant clinical evidence for use of TXA I.V. supplemented primarily by undertaking cost-effectiveness analysis using relevant Indian data to determine cost-effectiveness of this intervention as an adjunct for PPH management in the public health system in India. While evidence on clinical and cost-effectiveness of TXA is key to decision making regarding modifying policy on TXA use in PPH in India, it is important to highlight the health system factors in the provision of maternal health in India.

Maternal health care in India: The maternal health care in India is improving over the decades but quality is still an issue of concern. The National Family Health survey-4 has measured certain indicators to assess maternal health care in India. Institutional births in total account for 78.9% and in public health system account for 52.1% [17]. A study done in 2013 in Delhi showed that correct diagnoses were rare, incorrect treatments were widely prescribed, and adherence to clinical checklists was higher in private than in public clinics [18]. This quality aspect is of utmost importance in achieving the predicted outcomes from a decision analytical model. Initiatives like DAKSHATA (to build competencies of health workers) and LAQSHYA (Labour room quality improvement initiative)[16, 19] have been brought out by the government of India, but their evaluation will be necessary.

1.2 Rationale for HTA:

In India, Tranexamic acid is currently recommended only in cases of clinically diagnosed PPH where, “oxytocin and other uterotonics fail to control bleeding or if bleeding is partly due to trauma”. However, recent WHO guidelines recommend use of Tranexamic acid in all cases of primary PPH. This HTA will help in justifying whether or not India should adopt recommending

use of I.V. Tranexamic acid in all cases of PPH within three hours of delivery. The rationale is summarized in the form of a timeline in figure 4.

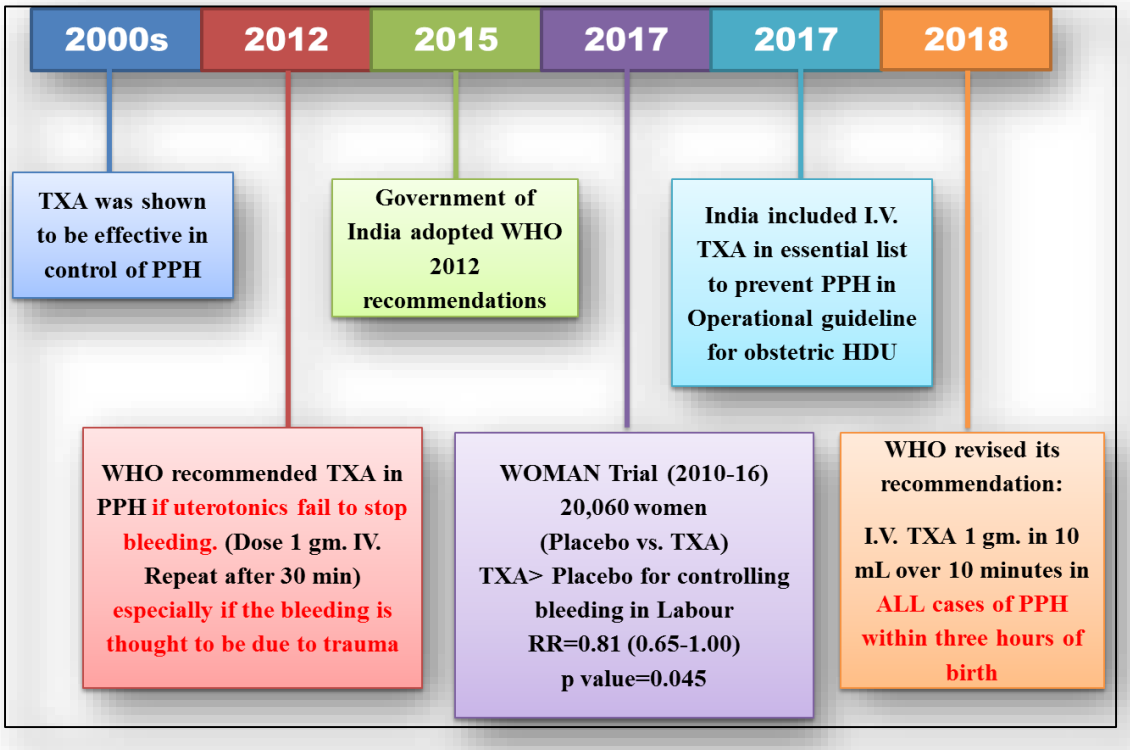


Figure 4: TXA use in PPH and rationale for HTA in India

1.3 Policy Question

Should Government of India recommend use of intravenous Tranexamic acid in all women with primary PPH in the public health system?

1.4 Aims and Objectives of the study

Aim of the Study: To conduct a Health Technology assessment on whether or not Intravenous Tranexamic acid should be recommended for use in all cases of Post-Partum Hemorrhage (PPH) in India

Objectives of the study:

- To collate evidence on clinical efficacy of intravenous Tranexamic acid use in women who experience Post-Partum Hemorrhage
- To determine the cost-effectiveness of recommending intravenous Tranexamic acid in all cases of PPH in the Public Health system of India
- To assess the budget implications for introduction of Tranexamic acid into the public Health program

1.5 Operational definitions:

PPH: Defined by the volume of blood loss i.e., estimated blood loss ≥500 mL after vaginal birth or ≥1000 mL after cesarean delivery

Primary PPH: PPH occurring in the first 24 hours after delivery is called primary PPH

Secondary PPH: PPH occurring from 24 hours to 12 weeks after delivery is called secondary PPH

CHAPTER 2: METHODOLOGY

2.1 Study design: A Health technology assessment (HTA) was conducted to answer the policy question put forward by the state government of Maharashtra, India. We have however aimed to answer this question for India as a whole. At the core of the HTA was an economic evaluation with a decision analytical model. The model type was a decision tree model as PPH is an acute event and the sequence of management is clearly linear in nature.
To populate the model, costing data, utility score data and epidemiological data were obtained by appropriate study designs and techniques as prescribed by the HTAIn Manual and are elaborated in chapter 3. The sections below describe the model characteristics, structure and flow.

2.2 Model characteristics: The model simulates a real-world scenario of PPH management through a decision tree model as per recommended algorithms of clinical guidance for management of PPH in India. The decision tree starts with the level of healthcare facility accessed by women following sequential course of medical, conservative and surgical management undertaken to control PPH. India recommends using uterine balloon tamponade intervention for management of atonic type of PPH whereas local or surgical measures are indicated for both atonic and traumatic causes of PPH. The model follows a lifetime horizon. The perspective of the model was that of disaggregated societal type. Model characteristics are summarized in table 1.

Table 1: Summary of characteristics of decision tree model for I.V. TXA in PPH management

Model Type	Decision Tree
Population	Women who had primary PPH in public health facilities in India
Comparators	TXA scenario vs. Current scenario
Perspective	Disaggregated societal
Time Horizon	Lifetime
Discounting of outcomes LYs and QALYs	3% (0-5%)
Model outcomes	Incremental cost-utility ratio (ICUR) i.e., Incremental cost per QALY gained, Incremental cost-effectiveness ratio (ICER) i.e.,

	incremental cost per DALY averted, maternal deaths averted, surgeries averted, ICU admissions averted.

The PICOTs elaboration of the model is as below:

Population: A hypothetical cohort of Indian women who are in reproductive age group (15-49 years) and who experience primary PPH during delivery (Vaginal and caesarean section) were chosen as the population who received the intervention. The cohort included Indian women with a median age of 21 years at first childbirth undergoing institutional delivery at public health facilities. Those delivering at home were assumed to access public health facilities for management of PPH and were included. In India, as per National Family Health survey- 4 (2015-16), 78.9% of the births are institutional; and of the total institutional births, 52.1% deliver in a public health facility [17]. As our policy question pertains to Public Health system of India, our study considered women who delivered in Government institutions at all levels of healthcare in India.

Intervention: Intravenous Tranexamic Acid (TXA) one gm. in 10 mL (100 mg/mL) I.V. at one mL per minute (i.e., administered over 10 minutes) within three hours of birth and second dose of one gm. I.V. if bleeding continues after 30 minutes or if bleeding restarts within 24 hours of completing the first dose to all women who are diagnosed of Primary PPH, irrespective of cause. This intervention is added on to the current healthcare scenario in the public health system. It is administered within three hours of birth and is an adjunct to the existing PPH medical management algorithm.

Comparator: The current scenario, where we assume that TXA is not being used in the management of PPH in the Public Health system of India. Though TXA is recommended in the guidance note on PPH in India, it is only for cases in which oxytocin and other uterotonics fail to control bleeding or if bleeding is partly due to trauma. The coverage of TXA use in India is unavailable. Also, the PPH management kit recommended by DAKSHATA (a Government of India Initiative to improve quality of Maternal Healthcare in India) does not include I.V. Tranexamic acid in the 'tray of medicines and emergency tray' list for Labour room. A newer guideline for obstetric HDU and ICUs in India mentions I.V. TXA in the list of essential medicines list to prevent PPH, but the dosage and indications are not explicitly mentioned.[20]

Outcomes:

Primary outcome: Cost effectiveness of I.V. TXA as an adjunct to current management of PPH (irrespective of cause of PPH; traumatic or atonic) as compared to current scenario (where TXA acid is not used) in terms of Incremental cost-utility ratio (ICUR per QALY gained) and incremental cost-effectiveness ratio (ICER per DALY averted)

Secondary outcomes: Cost effectiveness of adding I.V. TXA as an adjunct to current management of PPH (irrespective of cause of PPH; traumatic or atonic) as compared to current scenario (where TXA acid is not used) in terms of societal costs incurred, maternal deaths averted, surgeries averted and associated ICU admissions.

2.3 Model structure: A diagrammatic representation of the model is depicted in figure 5a and 5b.

Figure 5a: Short diagrammatic representation of decision tree for use of TXA in PPH

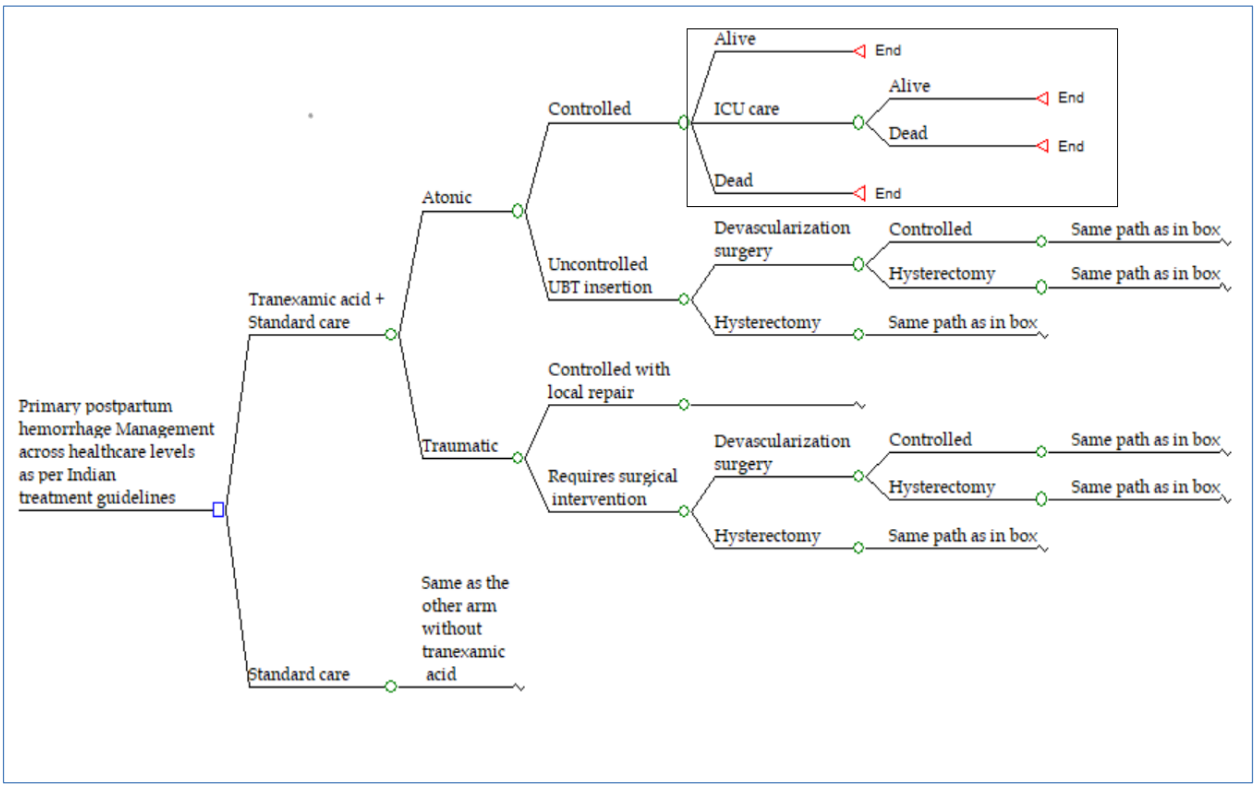
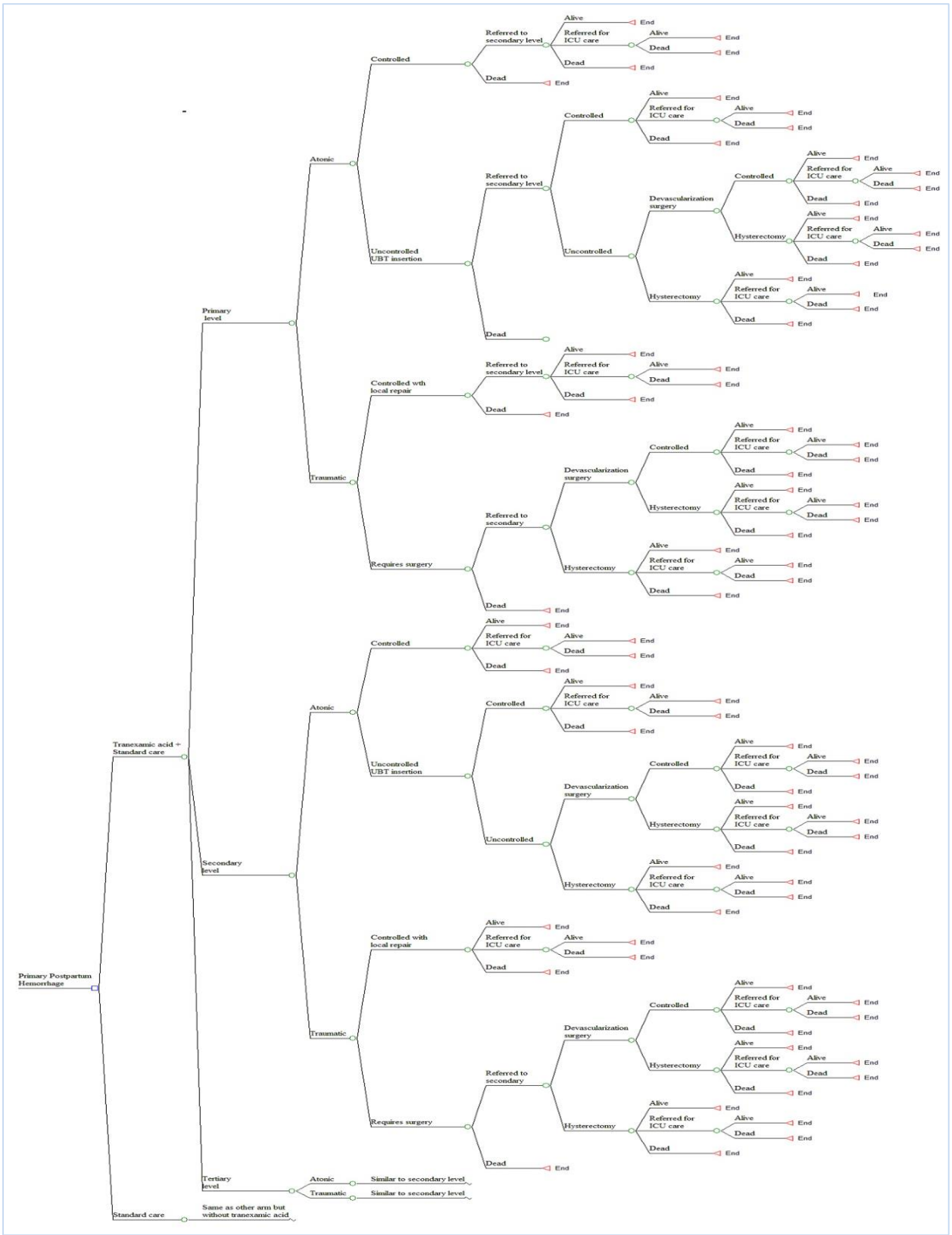


Figure 5b: Detailed decision tree diagram for use of TXA in PPH management in Indian public health system across healthcare levels



- As seen in figures 5a and 5b, chance nodes are designated by circles and terminal nodes are depicted by triangles. The square node at the beginning denotes the decision node wherein a decision is made regarding the intervention.
- Indian women who have experienced primary PPH in public health facilities in one year are present at the decision node (depicted as a square). This cohort has been derived by applying the incidence of PPH to the number of institutional public facility and home deliveries reported in India and is calculated to be 5,10,915 annually for the year 2019-20 [21].
- The cohort receives standard of care for primary PPH like monitoring, supportive treatment, uterotonics, ergometrine, Carboprost etc. as mentioned in the PPH management algorithms depicted in figures 1 to 3.
- At the decision node, the tree branches into the intervention i.e., tranexamic plus standard care and the comparator i.e., standard care alone. The current scenario is specified in the diagram as SOC (standard of care). The intervention and the comparator have been described in detail in section 2.2.
- In each of the branches after the decision node, the cohort divides depending upon the level of healthcare facility accessed and the course of action undertaken to control the specific type of PPH that is diagnosed. For atonic PPH, cases uncontrolled after medical management receive condom uterine balloon tamponade (UBT) intervention as a conservative measure as recommended in India. Here, there is an assumption that all women experiencing primary atonic PPH that are uncontrolled after medical management will receive the UBT intervention. UBT has been designated a separate chance node, as it is known to influence the number of surgeries that result after PPH. Also, UBT is a recommendation by the World Health Organization as well as Indian guidelines.
- UBT's clinical effectiveness has been applied at the chance node which branches into 'UBT controlled' and 'UBT uncontrolled'.
- The UBT 'controlled' branch, which translates to PPH controlled with UBT; is further subjected to alive, ICU admissions if required in management and maternal mortality rate as terminal nodes.
- The cohort in the UBT 'uncontrolled' branch, which translates to PPH not controlled with UBT, experience

(a) Devascularization i.e., uterus salvaging procedure like B-Lynch sutures or arterial ligation procedures either controlled or remaining uncontrolled, resulting in a lifesaving hysterectomy procedure subsequently.

Or

(b) A direct hysterectomy, where the uterus is removed surgically as a life-saving procedure depending on the clinical condition of the patient.

- For traumatic PPH, it is expected that the source of bleeding will be explored and repaired either locally or using conservative or surgical measures as mentioned above for uncontrolled cases.
- After the clinical course at each of these chance nodes, the branches terminate into 'dead' or 'alive' terminal nodes. Death can be either due to PPH or due to other causes.
- Those availing treatment at primary or secondary facility may need to be referred. Women at primary level are expected to be referred to secondary level care after initial stabilizing management or subsequently to tertiary level for ICU care as shown in the decision tree. Patients from secondary care may be referred to tertiary facilities for ICU admission as required.
- The decision tree pathway for standard care follows a similar path as that of intervention arm, however in this scenario, medical management is given without including tranexamic acid intervention in the package.

2.4 Model assumptions:

1) All primary atonic PPH cases receive condom-UBT as a part of standard PPH management. In the case of TXA+SOC, UBT is given for uncontrolled atonic PPH cases after TXA administration.

2) The standard of care is as per the recommendations and guidelines for PPH by the Indian Government. The staff in the public health facilities is well trained and the facilities are well-equipped as per Indian public health standards (IPHS).

2.5 Data Analysis for the model:

Microsoft Excel was used to construct the decision tree logically and using appropriate mathematical functions. The model outputs were derived as per the outcomes of ICUR and ICER mentioned above. The model follows a life time horizon by using life tables from SRS data. Standard discounting of 3 percent with a range of 0 to 5 percent in sensitivity analysis as recommended by the Indian reference case was used in the model. For this one-time intervention with life-time outcomes, differential discounting was used with one-time costs being kept undiscounted and outcomes being discounted at 3 percent for life-time horizon. A threshold of cost-effectiveness was set at one-time Gross Domestic Product per capita for India (GDP). This stands at USD 2099 or INR 1,45,742 for the year 2019. One-way and probabilistic sensitivity analysis (PSA) were done using Macros Visual basic applications (VBA) coding. Input parameters were varied by limits from literature/ by pre-fixed 20%. The one-way sensitivity analysis was done by varying each parameter to see which of the input parameters affect the ICUR and ICER the most. A tornado diagram was generated to show this. Appropriate distributions were assigned to input parameters for PSA; for example, cost parameters were assigned gamma distribution, all parameters with a range of 0-1 like utility parameters were assigned beta distribution. The sources of input parameters and the data analysis done in regard to costing data, is elaborated in chapter 3.

CHAPTER 3: DATA SOURCES USED AS INPUTS FOR THE MODEL

3.1 Evidence collation for clinical effectiveness of I.V.TXA in PPH:

As mentioned in the proposal of this HTA, submitted to Technical Appraisal Committee, HTAIn, the team set out to determine the need to conduct a systematic review to determine clinical effectiveness of I.V. TXA use in management of PPH. On literature review, it was found that there were multiple systematic reviews and reviews published on the exact same topic. Hence, it was decided to conduct a review of reviews.

Study design: Targeted Literature review of reviews and systematic reviews

Inclusion criteria:

- Population: Women experiencing PPH
- Intervention: Intravenous Tranexamic acid
- Comparators: Placebo, other drugs used in management of PPH
- Outcomes: Maternal mortality and morbidity including, but not limited to hospital stay, ICU admission, Surgeries.
- Type of study designs to be included: Targeted reviews and systematic reviews, meta-analysis
- Studies in English language

Search strategy: A search strategy was developed by using the PICO statement in the inclusion criteria. No time limit of publication was set for the studies.

Sources of search:

The search strategy was modified to suit each of the electronic databases that were searched. Namely: MEDLINE via PubMed; Web of Science and Cochrane database

Study selection: We conducted a two-stage screening process to select the studies. In the first stage, we screened abstracts for eligibility. In the second stage, we screened the full texts of the included abstracts. We used the PICO and inclusion criteria to decide which full texts met our selection criteria.

Data collection process: A form was used to collect the data from the selected studies. The data items were pre-determined and are listed in table 2.

Table 2: Summary of results of the review of reviews and systematic reviews on clinical effectiveness of I.V. TXA in PPH management:

Author	Year of publication	Type of review	Population	Interventions	Comparator	Outcomes	Number of studies included	Studies Included	Conclusion
Ferrer et al[22]	2009	Systematic Review	Women with PPH after vaginal delivery and LSCS	Antifibrinolytics: aprotinin, tranexamic acid and epsilon-aminocaproic acid	Placebo or no treatment	Primary: Mortality. Secondary: multiple.	3	Yang 2001, Gai 2004, Gohel 2007	TXA may reduce blood loss in PPH. The quality of the evidence is poor

Peitsidis et al[23]	2011	Review	Women with PPH after LSCS	TXA in pregnancy (obstetric haemorrhage) and up to 6 months postpartum	Placebo	Blood loss	35	6 RCT, 7 Observational, 22 case reports	32.5 ml reduction in blood loss (95% CI -4.1 -- 69.13; p = 0.08) in TXA as compared to placebo.
Mousa et al[24]	2014	Cochrane review	Women with PPH	Misoprostol, TXA, lower abdomen compression	Placebo	Maternal mortality, maternal morbidity, ICU admission, blood loss, blood transfusion, hysterectomy	10 (1 on TXA)	Ducloy bouthors 2011	No difference between TXA and placebo in maternal morbidity, ICU admission and hysterectomy
Agency for Healthcare Research and Quality	2015	Comparative effectiveness Review	Women with PPH	Surgical and non-surgical interventions	Multiple	PPH control, mortality, adverse effects	1 on TXA	Ducloy bouthors 2011	Rated poor quality for all outcomes
Sentilhes et al[25]	2015	Review	Women with PPH	TXA in prevention and	Placebo	Blood loss, hysterectomy	2 of 14	Ducloy bouthors 2011 and	Ducloy: Blood loss significantly decreases in TXA

				treatment of PPH				WOMAN trial	group. Nausea and vomiting significantly higher in TXA group; WOMAN trial was ongoing
Kachikis et al [26]	2018	Lit Review (consensus conference)	Women with PPH	TXA in prevention and treatment of PPH	Placebo	Blood loss, hysterectomy, Mortality	3 on treatment of 7	Ducloy bouthors 2011; Gillisen 2017 and WOMAN trial	Same as above.
Corte et al[27]	2018	Sys Rev and Meta-analysis	Women with PPH after vaginal delivery	TXA in treatment of PPH after vaginal delivery	Placebo	Hysterectomy, blood loss, mortality	2	Ducloy bouthors 2011 and WOMAN trial	Hysterectomy is significantly reduced in TXA group. No difference in other outcomes.
Ahmadzia et al [28]	2018	Review	Women with PPH	TXA in prevention and treatment of PPH	Placebo	Hysterectomy, blood loss, mortality	3 on treatment of 18	Ducloy bouthors 2011; Gillisen 2017 and	In PPH management, TXA use in non-risky

								WOMAN trial	
Feduniw et al [29]	2020	Review	Women with PPH	Pharmacological, surgical and blood products to manage PPH	Multiple	NA	2 of 50	WOMAN trial and Sentiles et al	TXA is recommended for treatment of PPH within 3 hours of delivery (0.5-2 g IV)

Results of the review: Nine studies fit our inclusion criteria out of 25 studies. Of these 9 studies, one was a Cochrane systematic review, three were systematic reviews, and the remaining five were targeted reviews. The year of publication, PICO (population, intervention, comparator, outcomes) parameters, the studies included in each review and the conclusion are presented in table 2. Eight of the 9 reviews include RCT by Ducloy Bouthers et al. Five of the 9 reviews include WOMAN trial. Studies included in Ferrer et al and Peistidis et al focused-on amount of blood loss outcome.

Implications of this review: The studies included in the reviews were used in the process to determine the clinical effectiveness of I.V.TXA. The most recent review in 2020 included the same studies mentioned above. We checked if there are any further studies (RCTs or observational studies) done on I.V. TXA use in PPH and found none. We chose findings of the WOMAN trial to derive relevant clinical effectiveness input parameters of using I.V. TXA in our decision tree model. The WOMAN trial study was a global multi-country, multi-centre, placebo-controlled randomized trial of 20,060 women in 193 hospitals across high, middle and low-oncome countries undertaken over a 6-year duration. The study randomization and blinding along with follow-up ensured reduction in potential biases and was successfully implemented across varied healthcare settings to demonstrate both clinical efficacy and feasibility of implementation of the intervention. Thus, primary parameters relevant to TXA intervention were obtained from this study. The large-scale RCT however did not report direct estimates of clinical effectiveness of UBT intervention in terms of its ability to control PPH bleeding without need for any further interventions. So, to populate the model for clinical effectiveness of tranexamic acid and standard of care management, the proportion of cases controlled with tranexamic acid and existing standard care was indirectly estimated from the reported conservative and surgical interventions consequent to use of medical management across both the study arms. Certain clinical parameters relevant to Indian settings such as UBT and its subsequent interventions were obtained from literature relevant to the Indian context as reported further in the section on input parameters.

Table 3 describes the clinical outcomes reported across the reviewed literature for tranexamic acid intervention. It is to be noted here that the TXA doses used in the three studies are different. WOMAN trial uses a 1 gm I.V. dose, Ducloy Bouthers et al uses 4 gm I.V. TXA and Gillisen et al mention a range of 0.1 to 3 gm I.V. TXA dose. However, WHO has made its recommendation based on WOMAN trial and recommends 3 gm I.V. TXA within 3 hours of delivery. These studies have been discussed more in detail in the background section of chapter 1.

Table 3: Identified studies reporting clinical effectiveness of I.V. TXA in PPH management

Author	Year	Study design	Country	TXA dose	Comparator	Mortality due to bleeding events TXA	Mortality due to bleeding events comparator	Hysterectomy in TXA	Hysterectomy in comparator	Adverse events
Woman trial [12]	2017	RCT-Double blind	21 countries	1 gm I.V. within 3 hrs of delivery AND additional 1 gm I.V. if bleeding restarted within 2 4 hours	Placebo	155 of 10036 (1.5%)	191 of 9985 (1.9%) P value of 0.045	358 (3.6%)	351 (3.5%) p value of 0.84	No difference
Gillisen et al [30]	2017	Retrospective cohort	Netherlands	0.1 to 3 gm TXA within one hour of first line therapy (uterotonics and blood products)	No TXA or TXA > 1 hour after first line therapy	2 of 247 (0.8%)	4 of 984 (0.4%)	28 of 247 (11.3%)	68 of 984 (6.91%)	NA
Ducloy Bouthors et al [11]	2011	RCT-open label	France	4 gm I.V. over 1 hour loading and 1 gm per hour for the next 6 hours	No TXA	NA	Blood loss was 48 ml lesser in TXA group as compared to no TXA (statistically significant, p=0.041)	0 of 77 (0%)	2 of 74 (2.7%)	Nausea, vomiting, dizziness higher in TXA

3.2 Estimation of Costs:

Study design: A primary bottom-up economic micro-costing study was conducted for a previous HTA on Uterine Balloon Tamponade use in PPH by the study team.

Ethical approval: This costing study was approved by the ethical committee for clinical studies in ICMR-NIRRH (Approval number: D/ICEC/Sci-29/31/2018).

Methods:

Study setting: A Primary Health Centers (PHC) (equipped with skilled birth attendants and a medical office), a secondary level Community Health Centers (CHC) and a sub-District Hospitals (SDH) (equipped with obstetrics-gynecology (OBGYN) specialist, operation theater (OT) and facilities for blood transfusion) and a tertiary level comprising of District Hospital (DH) and a medical colleges having additional advanced intervention and ICU facilities were represented in the study by enrolling four public health facilities from the state of Maharashtra in India. A convenience sample of one PHC, SDH, DH, and a tertiary medical college from Mumbai metropolitan region in Maharashtra was chosen for data collection.

Data collection and analysis: Data was collected from the written and electronic records of the chosen health facilities. Staffs were interviewed to understand time spent in various activities. Additional activities like measuring the floor area and observing the facilities were done.

Data analysis was done in three steps:

A) Deriving unit costs from the five apportioned parameters of

1) Drugs and consumables
2) Human Resources
3) Floor area rent
4) Medical and Non-medical equipment
5) Utilities (Electricity, Water, Transport, phone and others)

B) Deriving package costs from unit costs (at health facility level)

C) Deriving health system costs from package costs by weighting appropriately.

D) For generalizability of the model outputs to India level, a sensitivity analysis was done.

Results: The results of the costing study that were used in the model are presented in table 4 along with the other input parameters used in the model.

3.3 Utility scores used in QALY calculation: In the proposal submitted to TAC, HTAIn, it was proposed that a primary cross-sectional study be conducted to collect Health related quality of life. However, due to the COVID-19 pandemic, primary data collection for Health-related quality of life could not be done. Appropriate utility scores have been used from literature and reported in Table 4.

3.4 Review of literature: The list of input parameters and their sources are listed in table 4.

Table 4: List of input parameters used in the decision tree model

S No.	Input Parameter	Value	Source
1	Age start	21	[17]
2	Atonic PPH proportion	0.800	[31]
3	Relative risk of further interventions with TXA	0.955	[12]
4	Risk of further intervention events with SOC	0.234	[12]
5	UBT insertion for atonic PPH at primary	0.186	[17]
6	UBT insertion for atonic PPH at secondary	0.329	[17]
7	UBT insertion for atonic PPH at tertiary	0.485	[17]
8	Clinical effectiveness of condom-UBT	0.923	[32]
9	Relative risk for death due to bleeding with TXA	0.690	[12]
10	Risk of deaths due to bleeding with SOC	0.017	[12]
11	Direct hysterectomy for uncontrolled atonic PPH after UBT intervention	0.146	[33]
12	Hysterectomy after devascularization	0.220	[33]
13	Relative risk for all-cause mortality with TXA	0.880	[12]
14	Risk of all-cause mortality rate without tranexamic acid (Standard care intervention)	0.026	[12]
15	Risk of ICU admission for UBT uncontrolled cases	0.769	[34]
16	Risk of ICU admission for UBT controlled cases	0.025	[34]
17	Traumatic PPH controlled with suturing and local measures	0.455	[33]
18	Cost of medical management with TXA primary	451	From the primary costing study
19	Cost of medical management with TXA secondary	1685	
20	Cost of medical management with TXA tertiary	2812	
21	Cost of medical management with SOC primary	241	

22	Cost of medical management with SOC secondary	1475	
23	Cost of medical management with SOC tertiary	2601	
24	Cost of UBT insertion for atonic PPH at primary	281	
25	Cost of UBT insertion for atonic PPH at secondary	531	
26	Cost of UBT insertion for atonic PPH at tertiary	1303	
27	Cost of devascularisation at secondary level	4991	
28	Cost of devascularisation at tertiary level	8271	
29	Cost of hysterectomy at secondary level	7535	
30	Cost of hysterectomy at tertiary level	11462	
31	Cost of IPD admission for PPH at secondary	2230	
32	Cost of IPD admission for PPH at tertiary	3273	
33	Cost of ICU admission for PPH at tertiary	9901	
34	Cost of patient referral	1096	
35	Out of pocket expenditure for childbirth	3015	
36	Cost of training for TXA PPH	48	
37	Cost of local management for traumatic at primary	264	
38	Cost of local management for traumatic at secondary	387	
39	Cost of local management for traumatic at tertiary	689	
40	Disability weight of mild haemorrhage	0.114	[35]
41	Disability weight of severe haemorrhage	0.324	
42	Disability weight for infertility	0.005	
43	Utility death	0.000	
44	Utility at discharge (medical)	0.930	[12]
45	Utility for medical plus conservative measures period	0.895	
46	Utility short term devascularization (42 days)	0.565	[36]
47	Utility devascularization long term (Beyond 42 days)	0.909	
48	Utility hysterectomy short term	0.560	[37]
49	Utility hysterectomy long term (beyond 42)	0.880	
50	Utility ICU admission (1.5 days)	0.490	
51	Discount rate	0.030	[38]

CHAPTER 4: RESULTS

4.1 Model outcomes

The primary outcome of the HTA is Incremental Cost Effectiveness Ratio in terms incremental cost per QALY gained and incremental cost per DALY averted from a societal perspective. We have also reported base-case findings exclusively for the health system perspective. Adding tranexamic acid to the health system results in an incremental cost of INR 121 per patient resulting in a discounted incremental gain of 0.082 QALY per patient (Undiscounted gain of 0.18 QALYs). Similarly, discounted 0.094 DALYs (Undiscounted 0.21 DALYs) are averted by adding tranexamic acid to the medical management of PPH. Thus, from a societal perspective, the ICUR (QALY) value for tranexamic acid is INR 1,470/QALY gained whereas the ICER (DALY) value is INR 1,288 per DALY averted by including tranexamic acid. Thus, for both the societal and health system perspective, the ICER (DALY averted) and ICUR (QALY gained) were cost-effective and in favor of adding TXA to the public health system. The cost per woman in the cohort, from the decision tree model was higher in the TXA+SOC branch as compared to standard of care branch. For health outcomes, DALY lost were higher in standard of care (favorable for intervention) while QALYs gained (favorable for intervention) were higher in the TXA+SOC branch. Hence, the base-case analysis favors addition of TXA to the Indian public health system. The ICER and ICUR calculation is shown in table 5 from both the disaggregated societal and health system perspective.

Table 5: Incremental cost utility ratio comparing TXA+SOC and SOC

	TXA+SOC	SOC
SOCIETAL PERSPECTIVE		
Cost of PPH management (per patient)	**INR 6,607**	**INR 6,486**
QALY (Undiscounted)	**44.894**	**44.712**
QALY (Discounted)	**20.250**	**20.168**
DALYs (Undiscounted)	**1.48**	**1.69**
DALYs (Discounted)	**0.67**	**0.76**
Life years (Undiscounted)	**52.37**	**52.16**
Life years (Discounted)	**23.62**	**23.53**
ICUR QALY gained (Undiscounted)	**663**	
ICER DALYs averted (Undiscounted)	**581**	
ICUR QALY gained (Differential discounting)	**1,470**	
ICER DALYs averted (Differential discounting)	**1,288**	
HEALTH SYSTEM PERSPECTIVE		
Cost (per patient)	**INR 5,934**	**INR 5,782**
QALY (Undiscounted)	**44.894**	**44.712**
QALY (Discounted)	**20.250**	**20.168**
DALYS (Undiscounted)	**1.48**	**1.69**
DALYs (Discounted)	**0.67**	**0.76**
Life years (Undiscounted)	**52.37**	**52.16**
Life years (Discounted	**23.62**	**23.53**
ICUR QALY gained (Undiscounted)	**836**	
ICER DALYs averted (Undiscounted)	**733**	
ICUR QALY gained (Differential discounting)	**1,854**	
ICER DALYs averted (Differential discounting)	**1,624**	

The ICER DALY and ICUR QALY falls in the north-east quadrant of the cost-effectiveness plane below the WTP threshold, favoring the TXA plus SOC intervention. X-axis in the following graph denotes incremental QALY gained or DALY averted and Y-axis denotes incremental cost. The ICER is plotted as a red dot, the ICUR as a blue dot on the graph and is depicted in figure 6. The diagonal purple line denotes the threshold of cost-effectiveness set at one-time Gross Domestic

Product per capita for India (GDP). This stands at USD 2099 or INR 1,45,742 in 2019-20. The ICER DALY value of 1,288 and ICUR QALY value of 1,470 denotes that the values are below the Indian GDP threshold value and hence addition of TXA to the Indian public health system would be cost-effective from the health system as well as the societal perspective.

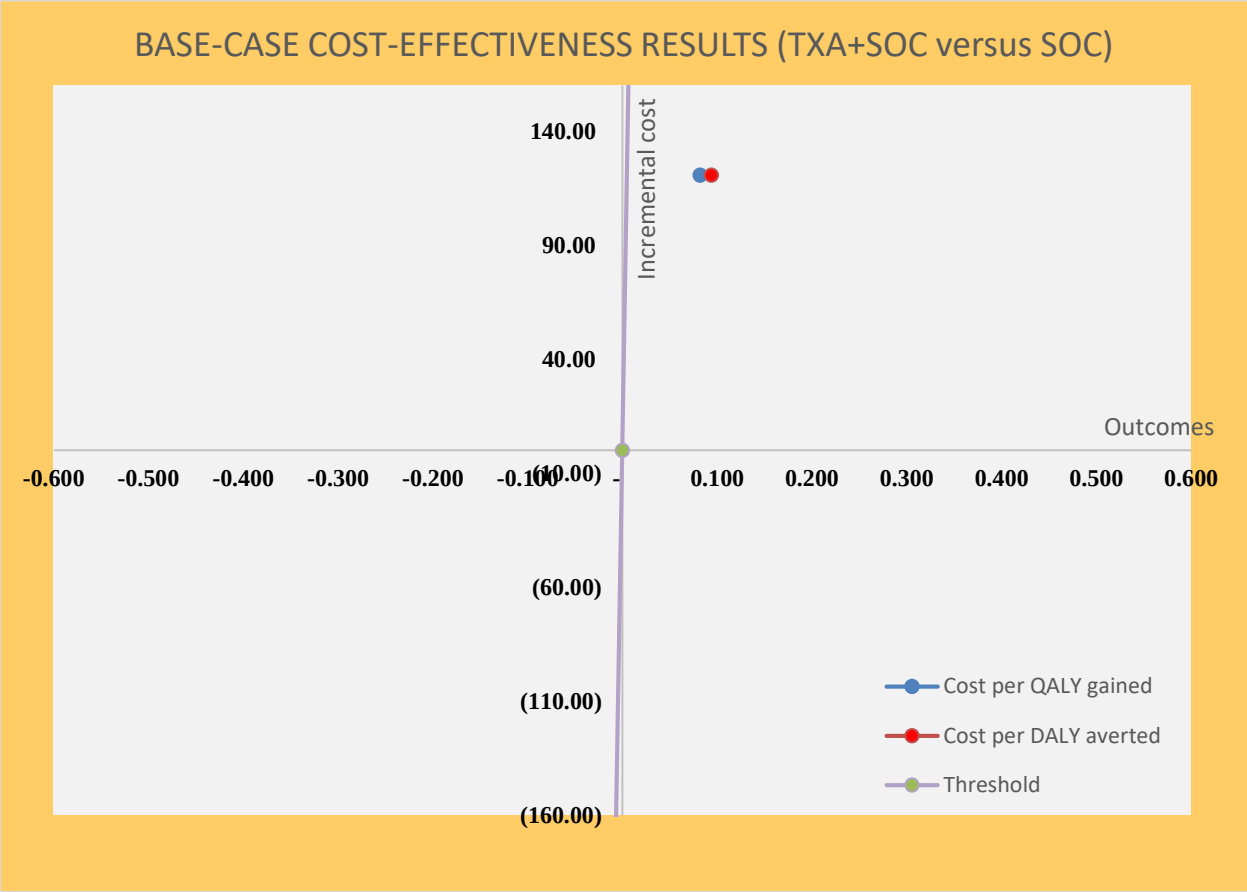


Figure 6: Base-case incremental cost-effectiveness results for Tranexamic acid with standard of care as compared to standard care alone for PPH management in Indian public health system

For an annual cohort size of 5,10,915 women who experience primary PPH the secondary outcomes of surgeries, ICU admissions and maternal deaths associated with either of the interventions are presented in Table 6. All three outcomes are higher in the SOC group as compared to the TXA+SOC group, hence favoring the addition of TXA to the Public health system of India at an incremental cost. The health system and societal perspective ICERs and ICURs for the aforementioned outcomes are listed in table 6 and favor addition of TXA.

Table 6: Surgeries, ICU admissions and maternal deaths associated with TXA+SOC versus SOC

	TXA+SOC	SOC	Increment /Averted with TXA
Health System cost (per woman in cohort)	INR 5,934	INR 5,782	INR 152 (increment)
Societal cost (per woman in cohort)	INR 6,607	INR 6,486	INR 121 (increment)
Total surgeries for annul cohort of 5,10,915 PPH cases	19,387	20,293	905 (averted)
Total number of ICU admissions for annul cohort of 5,10,915 PPH cases	27,181	27,836	655 (averted)
Total number of maternal deaths for annul cohort of 5,10,915 PPH cases	13,923	15,913	1990 (averted)

4.2 Results of Sensitivity analysis

4.2.1 One-way sensitivity analysis: This showed us the ten input parameters that affected the ICER or ICUR the most. The tornado diagram (figure 7a and 7b) shows that utility scores of uterus salvaging procedures and hysterectomy, mortality rate in the SOC and the TXA groups are the factors which influence the ICER or ICUR the most.

Figure 7a: One-way sensitivity analysis Tornado diagram ICUR (QALY)

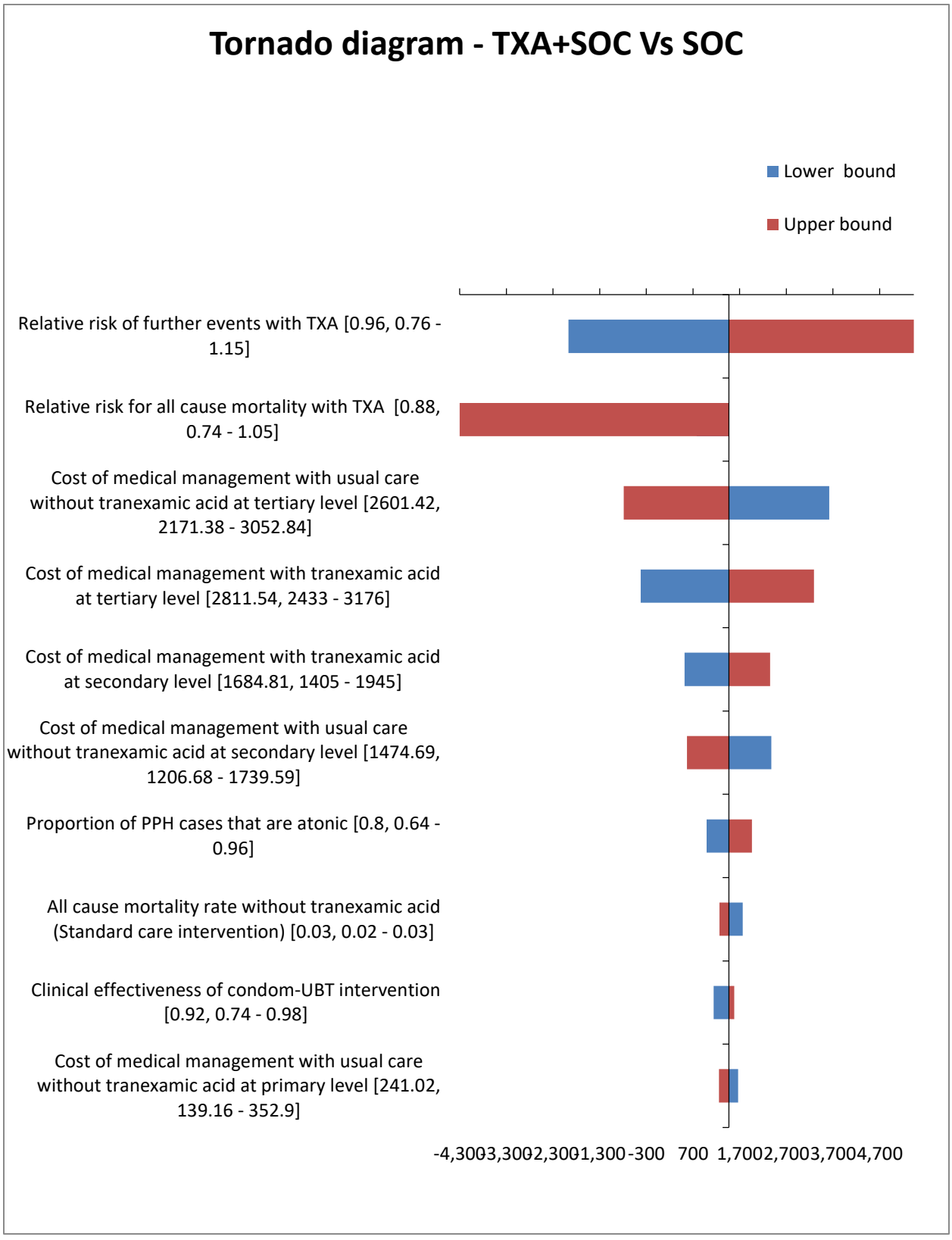
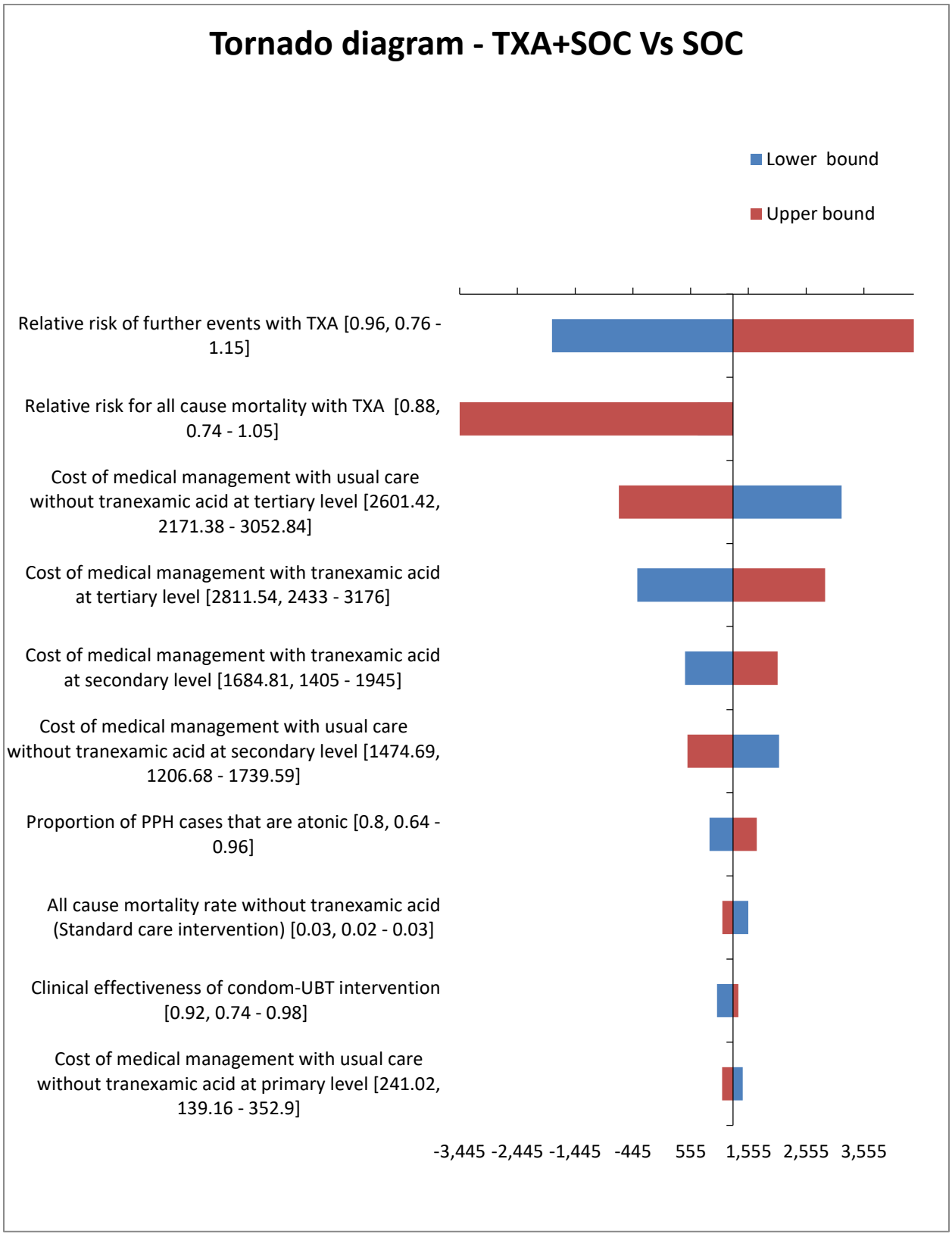


Figure 7b: One-way sensitivity analysis Tornado diagram ICER (DALY)



Interpretation of the tornado diagram: The red bars in figure 7a and 7b show the upper limit variation of the parameter and the blue bars show the lower limit variation of the respective parameter mentioned in the left margin of the graph. The central line represents the base case ICUR and ICER values respectively. The right or left sidedness of the bars determines the direction in which the ICER or ICUR both varies with the base case as reference. The first lower bound blue bar in the ICUR QALY tornado diagram in figure 7a for an ICUR value of INR -1970 per QALY gained suggests that tranexamic acid is a cost-saving intervention at lowered risk of further intervention events with tranexamic acid intervention. At the upper bound value represented by the first red bar in figure 7a for increased risk of further intervention with tranexamic acid addition as compared to standard care alone, an ICUR value of INR 5433 per QALY gain, the intervention is not cost-saving anymore however still remains very cost-effective as compared to the current Indian GDP per capita threshold value. For the second horizontal bar in figure 7a, variation of relative risk of all causes of mortality with tranexamic acid addition along the confidence interval limits reported by the WOMAN trial study, the red bar showing the upper bound variation i.e. an increased risk of death due to all causes with TXA intervention addition at an ICUR value of INR -4,300 per QALY gained suggests that tranexamic acid is not cost-effective. The blue bar indicating lower limit variation for risk of all-cause death is masked by the red bar at an ICUR value of INR 781 per QALY gained suggests that addition of tranexamic acid is cost-effective with reduced risk of all-cause mortality with the intervention.

Similarly, figure 7b representing ICER DALY tornado diagram in the first horizontal bar shows sensitivity of relative risk of further events with tranexamic acid parameter to the cost-effectiveness results. The first horizontal bar for lower bound variation of the relative risk parameter of further events with tranexamic acid as reflected by the first horizontal blue bar in figure 7b at an ICER value of INR -1,848 per DALY averted suggests that for lowered risk of further interventions with tranexamic acid, the intervention turns cost-saving with DALYs averted along with costs being saved. The same bar for the upper bound variation reflected by the red bar at an ICER value of INR 4,420 per DALY averted suggests that at increased risk of further events with addition of tranexamic acid, the intervention is still cost-effective but not cost-saving anymore. A similar interpretation can be applied for all the parameters giving the ten most sensitive parameters resulting in a change to cost-effectiveness results of this model. The tornado diagrams thus represent one-way sensitivity of cost-effectiveness results for each individual input parameter.

4.2.2 Probabilistic sensitivity analysis: The results of the PSA are presented in figure 8a and figure 8b.

Figure 8a: Probabilistic sensitivity analysis on ICUR-QALY gained plane for TXA+SOC compared to SOC

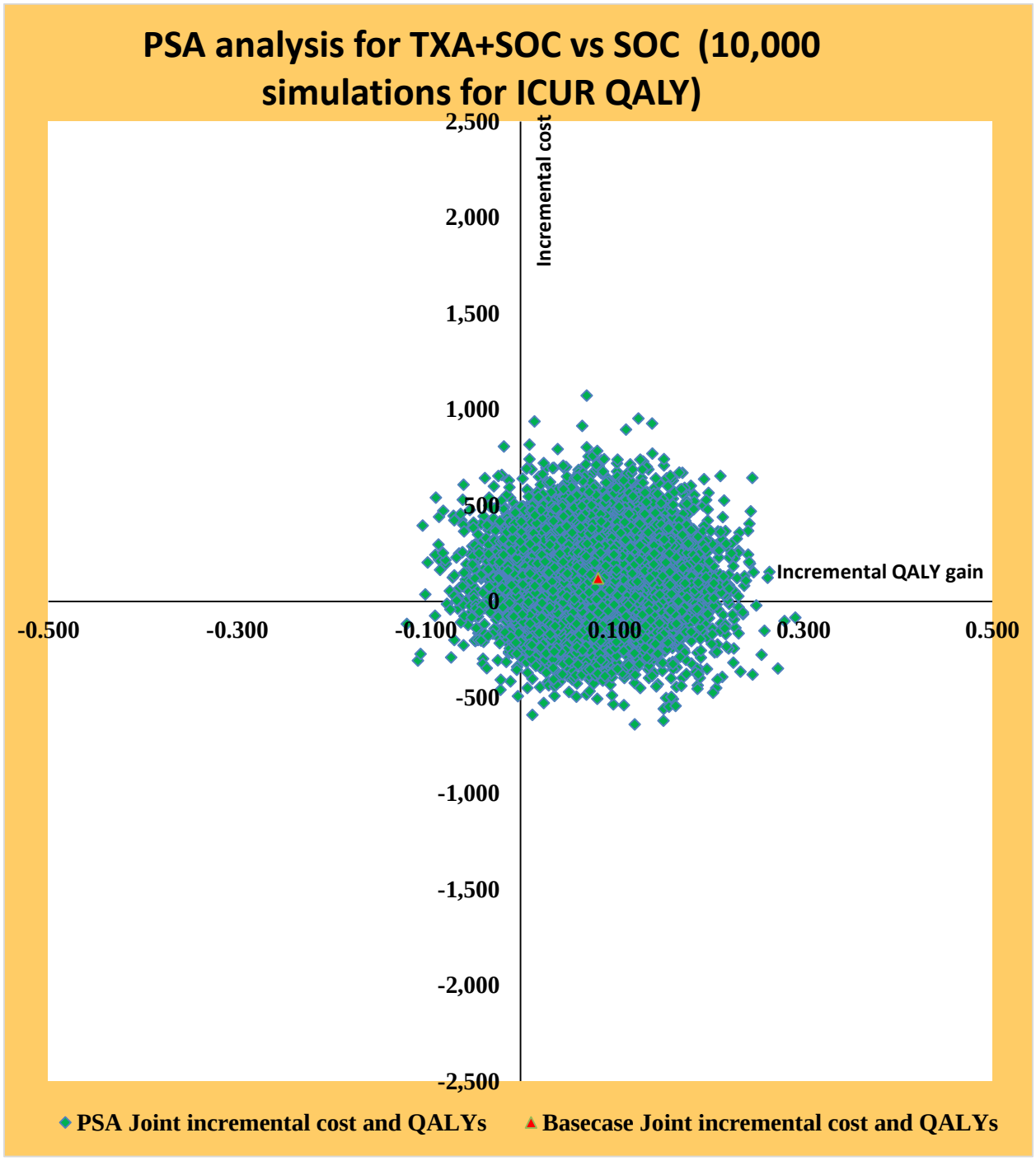
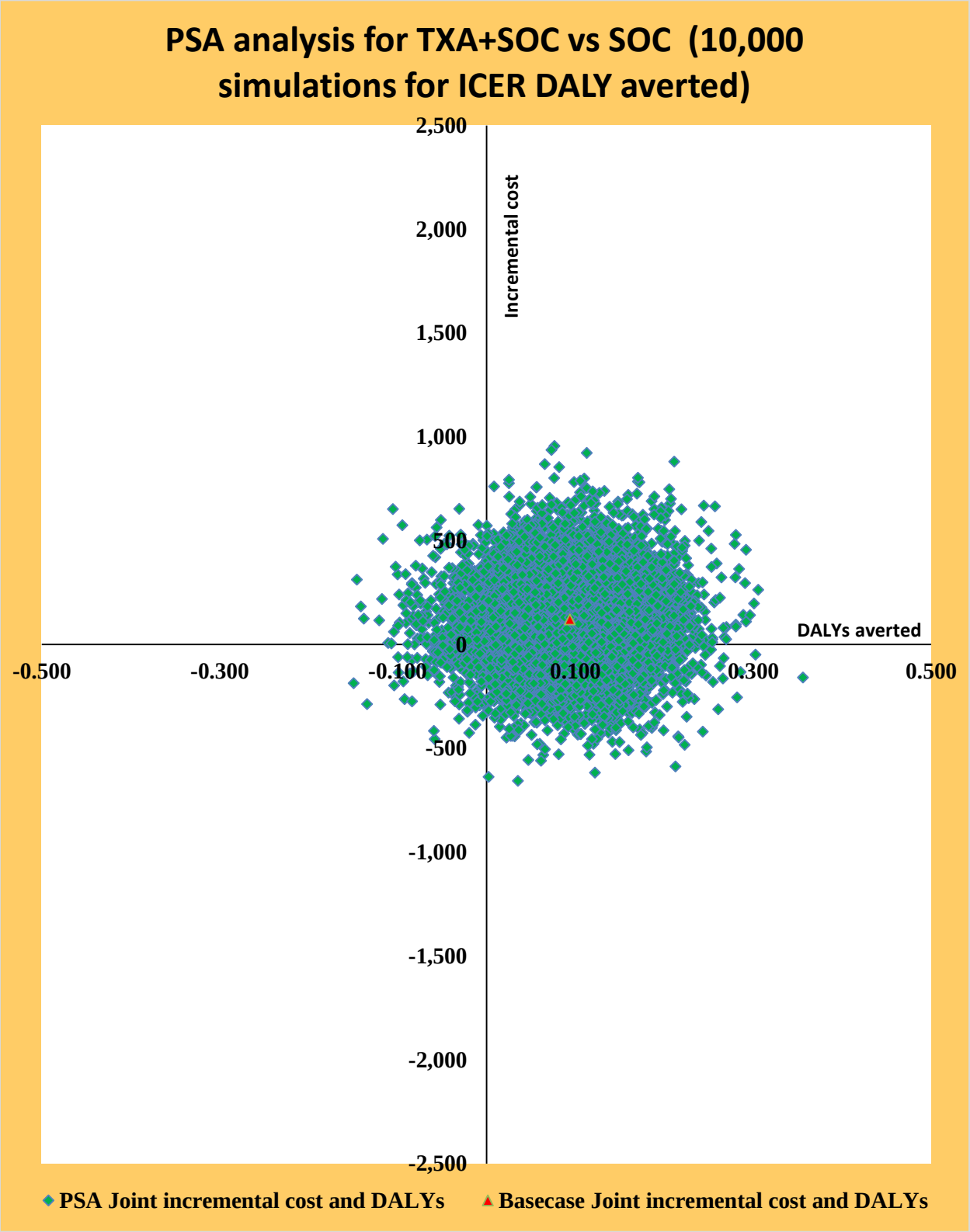


Figure 8b: Probabilistic sensitivity analysis for TXA+SOC compared to SOC (for DALY averted)



Interpretation of the ICUR plane: The 10,000 ICUR-QALY gained and ICER-DALY averted generated from the PSA are represented by green dots in figures 8a and 8b. The base case values are represented by the red dot. The X-axis is incremental QALYs gained in figure 8a and incremental DALYs averted in figure 8b while the Y-axis on both graphs indicates the incremental costs for the intervention. A societal willingness to pay threshold of one-time Indian gross domestic product (GDP) per capita passes through the origin for both graphs to determine cost-effectiveness of simulations. For ICUR-QALY gained graph as seen in figure 8a, 94.5% simulations were cost-effective whereas in case of the ICER-DALY averted graph as shown in figure 8b, 93.1% of the 10,000 simulations were cost-effective.

4.2.3 Cost-effectiveness acceptability curve (CEAC): This is depicted in figure 9. The probability of the intervention of TXA being cost effective is plotted on the Y-axis and the willingness to pay per QALY on the X-axis.

Figure 9a: CEAC curve for ICUR QALY gained between TXA+SOC versus SOC

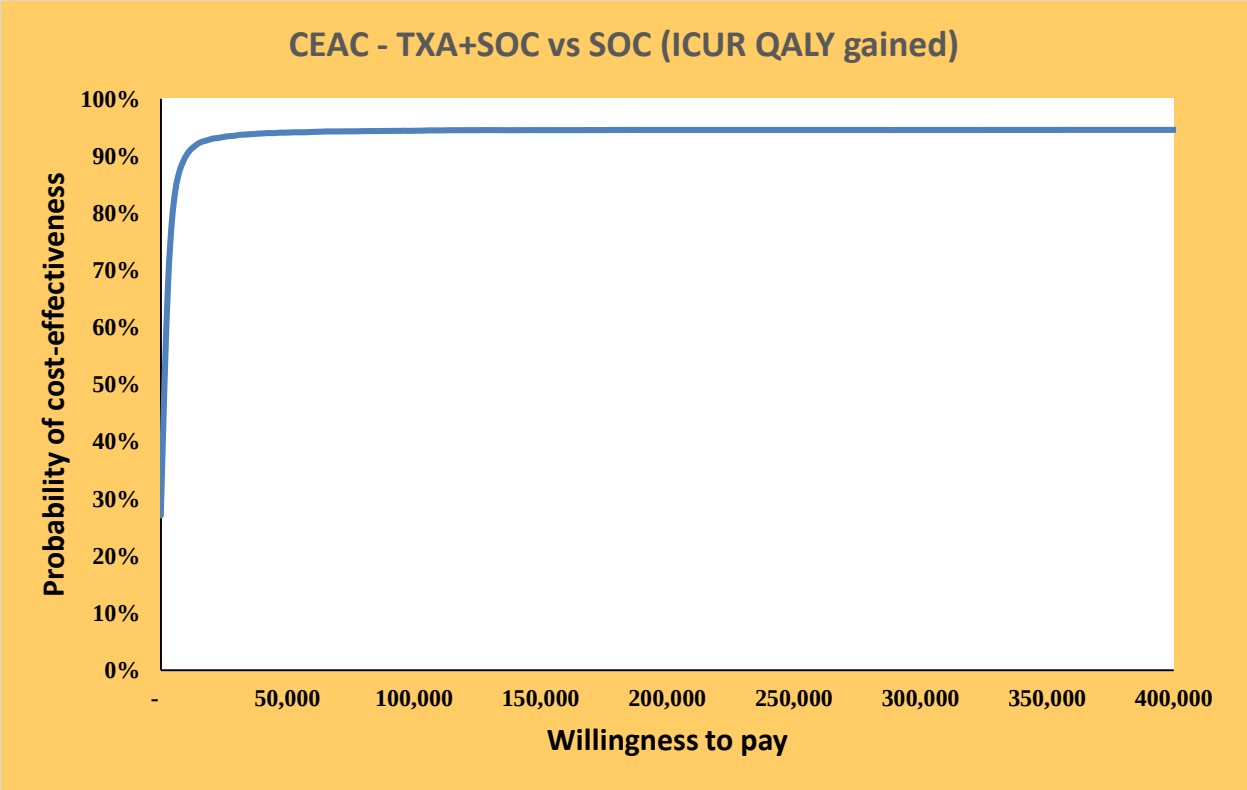
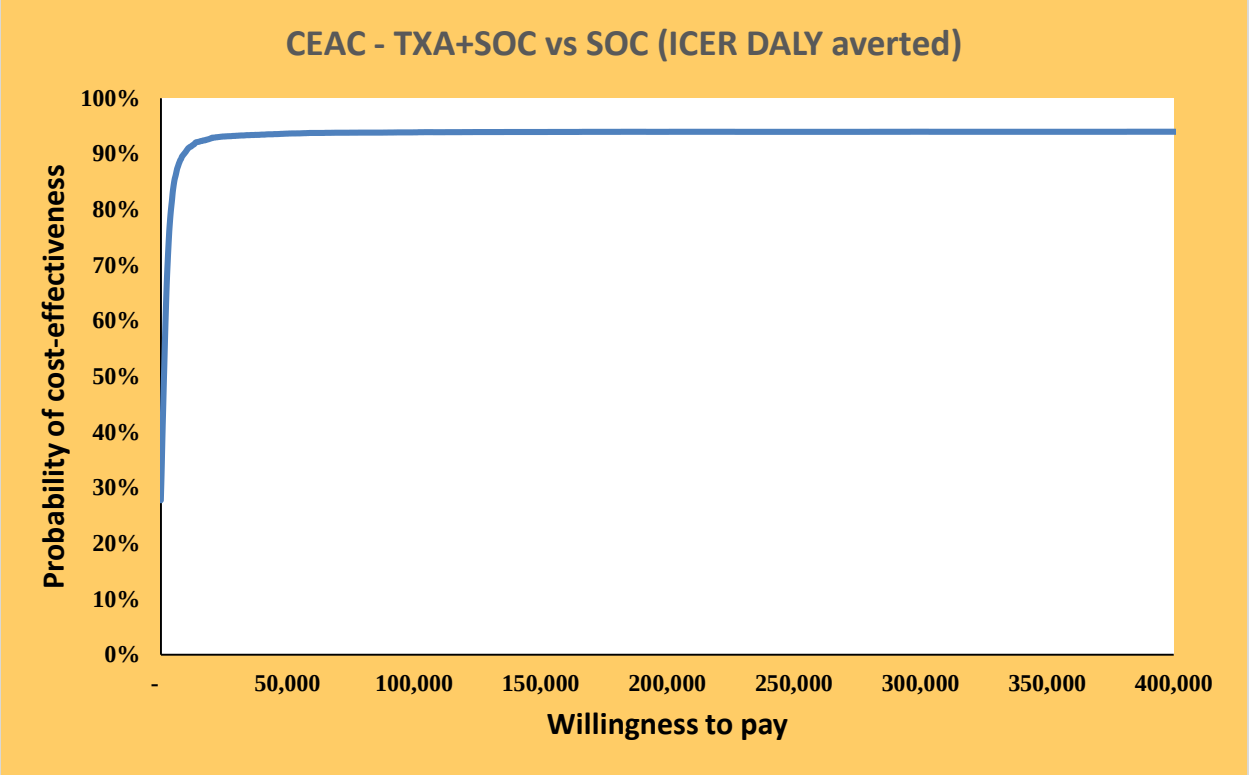


Figure 9b: CEAC curve for ICER DALY averted between TXA+SOC versus SOC



Interpretation of figure 9: This CEAC shows the probability of cost-effectiveness of adding TXA to current scenario at different willingness to pay thresholds. For ICUR QALY CEAC place as shown in figure 9a, at India recommended willingness to pay threshold of INR 1,45,742 i.e., one-time GDP for the year 2019, there is a 94.6% probability that adding tranexamic acid to the standard care is cost-effective. Even at higher willingness to pay, the probability plateaus at 95% suggesting low error probability of 5% around the model results. A similar ceiling probability of 93.1% ceiling cost-effectiveness is seen across the CEAC DALY plane as shown in figure 9b.

Given the availability of estimates of the health effect of changes in health expenditure using country level data to inform country specific assessment of health opportunity cost by applying estimated mortality effects (elasticities) to country-specific data on baseline epidemiology, demographics and health expenditure as reported by Ochalek et al as compared to using implicit threshold values through established norms that do not reflect evidence of health opportunity costs specifically for ICER DALY averted threshold, we undertook an analysis to reflect cost-effectiveness results using an inflation adjusted India specific cost per DALY averted threshold of INR 24,703 to assess cost-effectiveness of tranexamic acid intervention across DALY outcome

measure [39]. The study undertaken by Ochalek et al uses four different methods of calculating DALY thresholds for 97 different countries. For India, we chose the DALY 4 method that considers combined effect of changes in health expenditure on survival and morbidity burden of diseases using estimates specific to India. For India, DALY 4 method of INR 24,703 was the second highest threshold value amongst the estimated four values. The Indian threshold values ranged between INR 18,717 to INR 25,736 per DALY averted. For the threshold value of INR 24,703, our analysis suggests a 93% probability of cost-effectiveness out of 10,000 Monte Carlo simulations as also seen in the CAEC curve shown in figure 9b.

For sensitivity analysis, we also calculated the net incremental monetary benefit for tranexamic acid intervention. NMB as a summary statistic represents the value of an intervention in monetary terms when a willingness to pay threshold for a unit of benefit (QALY or DALY) is known. Incremental NMB is calculated as (incremental health benefit*threshold) – incremental cost. For the 10,000 Monte Carlo simulations of the QALY outcome measure, a mean net monetary benefit (NMB) of INR 11,980 (95% confidence interval limits 11,833 – 12,128) and similarly for DALY outcome measure, a mean NMB value of INR 2,196 (95% confidence interval limit 2,167 – 2,224) was estimated. As NMB value for the intervention across the mean and the 95% confidence interval limits are both positive i.e. greater than zero, the intervention remains cost-effective across NMB analysis. Similarly, the net health benefit (NHB) framework quantifies the cost-effectiveness results over net health benefit of the intervention and is calculated as [incremental health benefit – (incremental cost/threshold)]. For tranexamic acid intervention as compared to standard care, a mean NHB of 0.0822 in terms of QALY outcome measure (95% confidence interval limit 0.0812-0.0832) and mean NHB of 0.09 with DALY outcome (95% confidence interval limit 0.0877-0.09003) measure was estimated. Positive net monetary benefit and health outcomes across analysis suggest tranexamic acid intervention to be cost-effective.

CHAPTER 5: BUDGECT IMPACT ASSESSMENT

This analysis indicated addition of tranexamic acid to the standard medical treatment package for primary PPH cases to be a cost-effective intervention in the Indian public health settings across base-case results and across sensitivity analysis undertaken for associated uncertainties. To assess feasibility of such an introduction in the health system and determine financial sustainability of this intervention, we undertook a budget impact analysis for this given intervention.

This analysis aims to assist policy decision makers in predicting the financial consequences of adoption and diffusion of this intervention at the national level context. A similar analysis can be undertaken at regional or state level using state-specific parameters for the analysis. A societal perspective including both health system and out of pocket expenditure similar to that used in the decision modelling was considered for the analysis. A time horizon of five years was considered for this analysis. The available data used in the decision tree model was for the year 2019-20. Given that relevance of this analysis in the present and future context, we undertook budget impact assessment for a five-year period from year 2021 to 2025. The uptake of this intervention was considered to be bottom-up in nature and diffusion of the intervention was assumed to take place from primary level care in the first year to addition of secondary and tertiary levels subsequently in year two and three respectively.

The flow of patients eligible for tranexamic acid intervention across the Indian public health system was estimated using the predicted population growth rate of Indian females in the 15–49-year age group applied to the number of deliveries at public health facilities and home deliveries and the incidence of primary PPH obtained from literature [40]. Incidence of primary PPH was considered to remain constant across the years of budget impact analysis. As reported earlier, uptake share of the intervention was considered to take place across primary facilities in the first year followed by addition of secondary and tertiary care level in the subsequent years. Proportion of deliveries taking place in these healthcare levels as observed in India was 18.6% in primary facilities, 32.9% in secondary facilities and 48.4% in tertiary care as reported by NFHS 4 (2016-16). This proportion was used to determine uptake of tranexamic acid across the health system. Table 7 reports both the eligible patient flow projection and uptake to the intervention and standard care across the period for budget impact analysis.

Thus, from the Indian societal perspective as reported in Table 8, the addition of tranexamic acid to the current mix of management for primary PPH will result in a 2.3% increase in total costs for PPH management over a period of five years as compared to the standard of care being provided currently. The increase in costs gradually increases over the first three years of the scale-up for provisioning the intervention. The absolute increase in total cost in the first year is INR 2,51,55,540 which gradually increase to INR 13,99,89,556 in the third year and then correspondingly reduces over the years. Table 8 shows the total costs and budget impact of introducing tranexamic acid to the Indian public health settings.

Table 7: Eligible number of patients and treatment mix for budget impact duration

	2021	2022	2023	2024	2025
Total number of PPH patients in India	643,226	676,439	666,150	596,409	471,710
Current Scenario Patients eligible for available standard care	643,226 (100%)	676,439 (100%)	666,150 (100%)	596,409 (100%)	471,710 (100%)
Tranexamic acid introduction (a) Patients eligible for tranexamic acid intervention based on scale-up from tertiary to secondary to primary level care in subsequent years	119,704 (19%)	348,637 (52%)	666,150 (100%)	596,409 (100%)	471,710 (100%)
Tranexamic acid introduction (b) Patients receiving standard treatment care given the scale-up scenario for tranexamic acid	523,521 (81%)	327,803 (48%)	0 (0%)	0 (0%)	0 (0%)

Table 8: Total cost and budget impact of tranexamic acid introduction to Indian public health system

	Total cost of PPH management with tranexamic acid addition (INR)	Total cost of PPH management without tranexamic acid addition (SOC) (INR)	Budget impact (difference)	Percentage impact (% difference)
2021	4,21,28,16,600	4,18,76,61,060	2,51,55,540	0.6%
2022	4,47,71,59,957	4,40,38,94,864	7,32,65,093	1.7%
2023	4,47,68,94,328	4,33,69,04,772	13,99,89,556	3.2%
2024	4,00,81,98,438	3,88,28,64,695	12,53,33,742	3.2%
2025	3,17,01,51,163	3,07,10,22,610	9,91,28,552	3.2%
Cumulative	20,34,52,20,485	19,88,23,48,001	46,28,72,485	2.3%

CHAPTER 6: EQUITY

A descriptive review of literature was done to assess difference in patient access/ professional use of TXA in PPH in India. It was found that there was inequity at various levels in the Indian maternal healthcare scenario.

5.1 Equity in utilization of maternal health services in India

A study in Odisha, India in 2015 showed there was inequity in utilization of maternal health services in the rural area. The study conducted in-depth interviews and a qualitative analysis to show that some of the main barriers in utilizing timely maternal healthcare were lack of transport, financial constraints, and divergent concepts of etiology of maternal conditions, low perceived benefit of hospital care and different perceptions of danger signs[41]. On a larger scale analysis of the National Family Health survey data, trends of change in utilization from 2005 to 2015 were determined. This study, published in 2020 showed that the inequity in terms of accessing skilled birth attendants and utilizing complete Antenatal care had decreased from 2005 to 2015, however the decrease in ANC utilization was lesser as compared to access to SBA [42].

5.2 Equity in coverage of maternal health services in India

Coverage of maternal services in India was compared between states in India using the District Level Household and Facility Survey of 2007. The mean coverage was found to be 45% at the national level with wide differences between various states ranging from 31% in the state with lowest income quintile to 60% in the state with the wealthiest quintile. Almost half of the states and union territories of India recorded coverage of maternal health services to be less than 50%. This was back in 2007; however, even after a decade there is scope for much improvement [43].

5.3 Access to women physicians

A study published in 2020, used data from DLHS (2012-13) and NFHS (2015-16) to determine the association between maternal healthcare service utilization and presence of women doctors in PHCs in India and found that utilization was poorer in districts with fewer women doctors [44]. 72 of 256 districts (28.1%) reported >50% of PHCs with lady medical officers and these districts reported a higher prevalence of antenatal care visits and skilled birth attendance [44].

5.4 Availability of drugs at the health facility

A paper published in 2018 looked at health equity in India through the lens of social exclusion. The paper discusses various reasons for reduced access to healthcare. One of the most common reasons cited for lack of access to public health facilities is unavailability of drugs[45]. This could be a major barrier in the reception of quality emergency obstetric care services. Despite the low cost of I.V. TXA and its clinical, cost effectiveness, if procurement and supply chains are not adequate; then the predicted benefit of the drug cannot be translated from policy to practice.

CHAPTER 7: DISCUSSION

The benefit of I.V. TXA use in PPH was established in the 2000s. The landmark WOMAN trial led to the WHO recommending its use in all women with primary PPH. This HTA was conducted to answer the policy question of whether I.V. TXA should be added to the Indian public health system. A decision tree model was used to conduct an economic evaluation. The output of the model showed that adding TXA to the system would be cost-effective with an incremental cost of INR 1,470 incurred by the society with an associated gain in a QALY by introducing tranexamic acid for PPH treatment at the willingness to pay threshold of one-time GDP per capita for India as recommended by the HTAIn reference case. Similarly, across DALY outcome measure, an incremental cost of INR 1,288 is incurred to avert one DALY suggesting tranexamic acid to be cost-effective across DALY outcome measure for India. This study across base-case and across sensitivity analysis for given uncertainties shows that early treatment of post-partum haemorrhage with tranexamic acid is cost-effective for Indian public health settings. Across probabilistic analysis, tranexamic acid was found to be cost effective with 94.5% simulations turning cost-effective with plateauing at 95% probability across QALY outcome CEAC curve for higher willingness to pay thresholds [46].

The clinical effectiveness of tranexamic acid in preventing further interventions, associated mortality due to bleeding or all causes with and without TXA are important factors that affect the ICERs and ICURs. These have been derived from the multi-country double blinded, randomized controlled WOMAN trial [12, 46]. The cost-effectiveness study done in USA used the same measures as well. It is important to note here that the WOMAN trial showed a reduction in mortality in the TXA arm, but the difference was not statistically significant. However, as maternal mortality is a pressing public health issue, even a moderate reduction in mortality will help in preventing maternal deaths and reducing maternal mortality.

The cost data used in the model are from a primary study done in Maharashtra, India. Sensitivity analysis has been done, to improve generalizability of the study results. Also, the results of our costing study were cross-checked; with the national health system cost database [47] and it was found that they were in alignment.

Four studies from the systematic review undertaken by Aziz et al looked at cost-effectiveness of TXA use in PPH. Two of these studies were undertaken for USA context[48, 49], the third was

done in the context of Nigeria and Pakistan [46] and the abstract by Howard et al did not report the country. Our analysis reports an ICUR QALY value of USD 21 per QALY gained by using tranexamic acid intervention. This base-case value is comparable to two of the three studies that report ICUR QALY values. The reported ICUR values for these studies include USD 10.91 per QALY in the USA, USD 83 per QALY in Pakistan, USD 208 per QALY for Nigeria and USD 56,625 per QALY reported by Howard et al. Our base-case finding are comparable to the studies that report tranexamic acid intervention to be cost-effective across settings. Moreover, looking at secondary outcomes reported for the annual cohort of 5,10,915 PPH cases in Table 6, our results for Indian context suggests that by considering tranexamic acid intervention, 389 maternal deaths per 1,00,000 PPH cases, 177 surgeries per 1,00,000 cases and 128 ICU admission per 1,00,000 cases annually as obtained by our economic modelling analysis can be averted by considering addition of tranexamic acid to PPH management in the Indian public health system. The study by Sudhof et al in the USA reported 14 deaths per year and 1258 laparotomies to be averted annually with the intervention. Similarly, Howard et al reported 568 maternal deaths and 635 laparotomies per 1,00,000 cases to be averted by considering the intervention. Thus, though it may not be directly comparable, the estimations across analysis are along similar range as reported across globally available evidence in different contextual settings. The study from USA used a decision tree to conduct economic evaluation and showed that administering TXA to women in PPH is cost saving. The study done in Nigeria and Pakistan context showed that addition of TXA is very cost-effective. The results of our HTA show that addition of TXA to the Indian Health system is cost-effective. Our decision tree model is specific to the Indian context such that it incorporates clinical management across the various levels of healthcare facilities in the Indian public health system. The decision tree considers clinical guidelines for management of PPH in Indian settings. India recommends using the uterine balloon tamponade in case of atonic PPH management. Our model considers such management protocols along with India specific costs obtained from primary costing study to analyze and report results with best available data for the Indian context. However, some assumptions have been made to populate the model. Some assumptions made in our model pertain to the health system: that all women with PPH in the public health system will receive standard care according to the algorithm including appropriate medical, supportive management, timely referral, surgical and ICU care facilities under the care of trained health care personnel. The assumption that all women with PPH will always have access to good quality emergency obstetric

care may not be the case. Hence, our results of cost-effectiveness of tranexamic acid, reduction in maternal deaths, surgeries and ICU admissions as reported in the study are conditional to a fully functional and adept public health system.

Limitations of our study: The clinical effectiveness of tranexamic acid used in this study was obtained from a multi-country large scale RCT, however the study did not report direct clinical effectiveness measure of intervention in terms of control of PPH bleeding without need for any further intervention and neither did it include specific Indian settings in the study. However, as this was a robust global study with settings comparable to the Indian settings, an indirect measure of clinical effectiveness computed from available disaggregated data for further interventions undertaken in the study was used to determine the clinical effectiveness input parameter. The utility scores were derived from available literature. These may differ from the perception of Indian women, influencing ICER and ICUR values. For lack of availability of such India specific quality of life data used in economic evaluations, available literature was used.

CHAPTER 8: CONCLUSIONS & RECOMMENDATIONS

Conclusions:

- Based on the ICER and ICUR derived from the model, addition of I.V. TXA to public health system of India will be cost-effective as per current threshold of INR 1,45,741 for the year 2019
- The results of the model are robust as sensitivity analysis shows that 94.5% of the ICUR QALYs gained and 93.1% of DALYs averted are cost-effective. Across net benefit framework, tranexamic acid at a mean NMB of INR 11,980 across QALY outcome and mean NMB of INR 2,196 over DALY outcome measure suggests tranexamic acid to be cost-effective in Indian public health settings.
- Addition of tranexamic acid for primary PPH treatment in the Indian public health system will require an additional financial investment of 2.3% to the budget currently allocated for overall management of PPH in Indian public health settings.

Recommendations:

- To add I.V. TXA to the public health system of India for the management of PPH [one gm. in 10 mL (100 mg/mL) IV at one mL per minute (i.e., administered over 10 minutes) within three hours of birth and second dose of one gm. IV if bleeding continues after 30 minutes or if bleeding restarts within 24 hours of completing the first dose to all women who are diagnosed of Primary PPH, irrespective of cause]
- All policy guidelines on PPH management, including DAKSHATA packages, training material etc. to be updated to reflect this recommendation if it is accepted.

The aforementioned conclusions and recommendations need to be considered alongside the following key points on inputs to the model (as the model results depend heavily on the inputs and assumptions)

- The clinical effectiveness of I.V. TXA is based on the results of a large RCT called WOMAN trial. The trial shows reduction in mortality due to bleeding on the TXA arm. However, the confidence interval for this finding is not statistically significant and indirect cumulative measure of clinical effectiveness in terms of further interventions from WOMAN trial were used to populate the model. Despite this, the largeness of the RCT and

the significance of preventing maternal deaths, has resulted in TXA being recommended for routine use in primary PPH by the World Health Organization.

- The cost data is derived from a primary study done in only four public health facilities. A sensitivity analysis has been done to improve generalizability of the model results.

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