The University Of Sheffield.

Assessing the cost-effectiveness of interventions for Hypertensive Disorder of Pregnancy and Diabetes Mellitus in Pregnancy in Bangladesh

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List of abbreviations

ANC	Antenatal care
BBS	Bangladesh Bureau of Statistics
BDHS	Bangladesh Demographic and Health Survey
BDT	Bangladeshi Taka
BMMS	Bangladesh Maternal Mortality and Health Care Survey
CE	Cost effectiveness
CMDs	Cardio-metabolic diseases
DALYs	Disability Adjusted Life Years
DGFP	Directorate General of Family Planning
DGHS	Directorate General of Health Services
DHIS-2	District Health Information System 2
DMP	Diabetes Mellitus in Pregnancy
DW	Disability weight
EmONC	Emergency Obstetric and Newborn Care
EVPI	Expected Value of Perfect Information
GBD	Global Burden of Disease
GDM	Gestational Diabetes Mellitus
GDP	Gross Domestic Product
HDP	Hypertensive disorder during pregnancy

ICER	Incremental Cost Effectiveness ratio
LMICs	Low and Middle Income Countries
MDGs	Millenium Development Goals
MICS	Multiple Indicator Cluster Survey
MMR	Maternal Mortality Ratio
MMR	Maternal Mortality Ratio
MOHFW	Ministry of Health and Family Welfare
NCDs	Non-Communicable Diseases
NMR	Neonatal Mortality Rate
NVB	Normal Vaginal Birth
OR	Odds Ratio
PNC	Postnatal care
RR	Relative Risk
SD	Standard Deviation
SDGs	Sustainable Development Goals
USD	United States Dollar
WHO	World Health Organization
YLD	Years lived with disability
YLL	Years of life lost

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Executive Summary

Progress in reducing maternal mortality have stalled during the Sustainable Development Goals era both globally and in Bangladesh. Maternal mortality is often called the tip of the iceberg. The morbidities leading to maternal deaths often remain ignored. Long-term impact of these morbidities are rarely discussed. While hypertensive disorder is one of the leading causes of maternal deaths, there is a growing burden of diabetes in pregnancy. Economic evaluation models addressing either of the two Non-Communicable Diseases are scarce, especially in the context of low and middle income countries. Preventive interventions are highly recommended for addressing the burden of NCDs and are expected to be easier to implement given the capacity problems evidence in the Bangladesh health system. The aim of this thesis was to develop a cost-effectiveness model for interventions addressing hypertensive disorder and diabetes mellitus in pregnancy among Bangladeshi women. This was done in several steps including multiple reviews, stakeholder consultations and finally developing the model.

First, a review of World Health Organisation and Bangladesh clinical guideline review was undertaken to understand the two diseases and their recommended treatment pathways. The clinical guideline review led to the identification of the risk factors of the two conditions, their symptoms or diagnostic criteria and the treatment to be undertaken once they are detected. This review also identified the individual level risk factors of the two diseases and revealed that diabetes mellitus, both pre-existing and gestational are risk factors for hypertensive disorder in pregnancy. The review recommendations suggested antenatal care to be the key stage of the pregnancy continuum of care to address the two disease conditions. It also indicated antenatal period to be the most crucial stage for delivering preventive interventions.

Next, a systematic review of economic evaluation models assessing interventions related to hypertensive disorder and diabetes mellitus in pregnancy identified those methods that had been used previously. While decision trees represented the dominant model structures, markov state transition and microsimulation models had also been used. Interventions could be divided into several types; screening and diagnosis, treatment, diet and lifestyle, labour induction and others. Most models were built from a health system's perspective while some were focused on the payer's or societal perspective. Model time horizons ranged from pre-conception to the lifetime of the women and their offspring. A varied set of model outcomes were identified including immediate outcomes like development of hypertensive disorder to mortality and development of chronic conditions in the long-term. This review highlighted the lack of a consistent approach to modelling of these two disorders and the lack of a model that was suitable for decision making in Bangladesh. Both reviews also revealed the need for preventive care measures, specifically during the antenatal period.

The reviews led to the development of a detailed list of interventions relevant for Bangladesh and a draft conceptual framework. These were presented to stakeholders and amended via interviews. Both the reviews and interviews with stakeholders identified the antenatal care related interventions as the key to address the two diseases conditions. The antenatal care package was deemed to be the most important intervention in addressing the two conditions which contains multiple preventive interventions. Rather than modelling the whole package of intervention, a single preventive intervention was selected as an exemplar. The final intervention selected for the model was calcium supplementation among pregnant women in Bangladesh scaled up from 18% to reach 80% coverage level. Calcium supplementation is a recommended preventive intervention that is supposed to be delivered as part of the antenatal care package through the Bangladeshi health system. Methods for incorporating multiple intervention effect were explored and documented. The model programming ensured flexibility in incorporating additional interventions for future work.

The model took health system's perspective as suggested by the stakeholders. Model outcomes covered the development of hypertensive disorders and gestational diabetes mellitus in pregnancy, c-section, preterm births, stillbirths, newborn and maternal deaths. Long-term outcomes needed to account for development of chronic conditions among women for a lifetime and developmental delay among children for 5 years. The model took into account two pre-existing chronic conditions as risk factors; pre-existing chronic hypertension and diabetes mellitus.

An individual based markov microsimulation model was developed. Increased risks of events and outcomes were assigned from existing literature through ad hoc reviews. Costs of intervention and all downstream care-seeking were estimated based on Bangladesh national data. Disability Adjusted Life Years (DALYs) were estimated based on disability weights from Global Burden of Disease studies and country-specific life tables for women. DALYs were estimated both for pregnancy and long-term health conditions. Finally, a cost effectiveness analysis was undertaken and a probabilistic sensitivity analysis (PSA) was incorporated accounting for parameter uncertainty. The model was validated for the base case scenario against national prevalence levels and verified using a prescribed technical verification checklist. The model produced summary outputs in the form of Net Monetary Benefit, the Incremental Cost Effectiveness Ratio, the cost-effectiveness plane, cost-effectiveness acceptability curve. Selected scenario and sub-group analysis and deterministic sensitivity analyses were also conducted. The willingness to pay threshold was set at 1x and 3x Gross Domestic Product (GDP) per capita values based on stakeholder requirements.

The intervention reduced adverse pregnancy and birth outcomes for mothers and their babies. The direct impact of the intervention led to a reduction in the number of women developing gestational

hypertension, pre-eclampsia and eclampsia (23%, 40% and 36% reduction respectively). Caesarean-sections reduced by 7% through an indirect effect of the intervention. Preterm births and stillbirths reduced by 7% each and maternal deaths saw a 45% reduction through both direct and indirect impact. Newborn deaths were reduced by 8% through reduction in preterm births. Among the long-term outcomes, there was an 8% reduction in chronic hypertension while diabetes mellitus remained almost unchanged. The incremental cost per woman was estimated at BDT -5122 which indicates a cost saving for the scaled-up provision of care. The probability of the scaled-up provision to be cost-effective was 1 at both 1xGDP and 3xGDP per capita threshold level. The incremental net monetary benefit was positive at both threshold level and for all sub-group level analyses, which covered pre-existing conditions, age, education and wealth quintiles.

The model is novel and added to the existing evidence base in several ways. It is the first model that took into account two cardio-metabolic diseases; hypertensive disorder and diabetes mellitus in pregnancy together. Pre-existing conditions and risks related to them were incorporated as risk factors in the model while interaction between the two pregnancy related conditions were also considered. The model was strengthened in terms of its validity and relevance by use of a large number of country specific data and involving stakeholders at an early stage. Findings from this thesis can add value to the existing evidence base of economic evaluation of calcium in the context of low and middle income countries. The thesis reemphasised the need for ensuring access to calcium supplementation during pregnancy in Bangladesh to prevent hypertensive disorders in pregnancy. It also highlighted that this simple intervention can release resources, which can then be redirected to other areas of need. In order to ensure successful implementation of this intervention, there is value in exploring the most effective channel for delivering the intervention. Further research should also consider ways to improve compliance in calcium intake, alternative sources of calcium like food fortification during pregnancy and pre-conception and explore the optimum dose of calcium for Bangladeshi women.

1. Introduction

This chapter begins with establishing linkage between maternal and newborn health and non-communicable diseases like chronic hypertension and diabetes mellitus. The chapter then outlines the current status of maternal health in the global and Bangladeshi context in light of mortality, morbidity and the causes of death. The chapter explains why hypertensive disorders and gestational diabetes mellitus in pregnancy need attention and how pre-existing chronic hypertension and diabetes mellitus are linked to pregnancy-related complications. It also draws a brief outline of the health system structure of Bangladesh, status of coverage of services related to maternal health and preparedness of facilities in terms of availability of drugs and supplies, and service providers' knowledge and awareness on treatment protocol. Next, the chapter discusses the need to identify important interventions and assess cost-effectiveness to support evidence for scaling up coverage of interventions that can reduce the burden of hypertensive disorder and diabetes in pregnancy and their long-term health consequences. Finally, it presents the objectives of this research and provides an overview of the forthcoming chapters of this thesis.

1.1 Global situation of maternal and newborn health

1.1.1 Maternal mortality and morbidity

Maternal health conditions are responsible for almost 12% of deaths among women of reproductive age worldwide (1). In 2020, there were 800 deaths among women due to pregnancy and childbirth-related complications around the globe every day. More than 80% of maternal deaths took place only in 30 countries (2). Around 95% of the deaths were in low and middle-income countries, and a fifth took place in Southern Asia (3, 4). Southern Asia and sub-Saharan Africa contributes to around 87% of maternal deaths globally (3).

The maternal mortality ratio (MMR) as of 2023 data stands at 223 per 100,000 live births globally (5). The sustainable development goals have set the target to reduce MMR to less than 70 per 100,000 live births by 2030, which requires massive effort from countries (6). Between the 10 years from 1990 to 2000 there was only a small decline of 5.6% of MMR worldwide which accelerated to 37% between 2000 and 2017 (6). While much has been achieved during the Millennium Development Goals (MDG) era, the momentum in reducing maternal mortality at the beginning of the Sustainable Development Goals (SDG) era has stalled (5). Delays in seeking and receiving care, poor quality of care, shortage of supplies and lack of accountability of health systems are some key reasons behind poor maternal health performance (5).

Maternal deaths are categorised into direct and indirect causes. The direct causes include haemorrhage, high blood pressure, unsafe abortion, infection and obstructed labour (7). Around 75% of maternal deaths occur due to severe bleeding after delivery and other delivery-related complications, high blood pressure during pregnancy, infections after birth, and unsafe abortions. Haemorrhage and hypertensive disorder are the two leading causes of maternal death in developing regions (7). Indirect causes include causes not related to direct obstetric complications but diseases prevailing before pregnancy or developed during pregnancy such as diabetes and heart diseases (8).

Maternal deaths are often called the tip of the iceberg (9). The morbidities leading to deaths often remain ignored due to lack of data and challenges in measurement (1). Estimates show that 15% of all pregnancies are attached to severe complication that require skilled care (10). Maternal morbidities can lead to serious consequences beyond the outcome for mother and newborn at birth (1). The magnitude of these consequences often remains neglected and is not well understood. Globally, around 20 million women suffer the consequences of maternal complications each year. According to the Global Burden of Disease data in 2005, it was the third leading cause of Disability Adjusted Life Years (DALY) lost among women aged 15-44 (1, 11). In 2019, around 13 million DALYs were lost due to complications from pregnancy and childbirth (12).

1.1.2 Preterm births, stillbirths and newborn deaths

There has been a dramatic decline in global newborn mortality between 1990 and 2019 with a reduction from 5 million to 2.4 million deaths (13). Still, the first four weeks of life and time around birth are crucial for ensuring newborn survival. Almost half of global child deaths consist of newborn deaths. Preterm birth is the leading cause of death among newborns.

Global stillbirth rates, as of 2019 data, stands at 13.9 per thousand births (14). Between 2000 and 2019, the average annual rate of reduction in stillbirths was only 2.3% (15-17). While measurement of stillbirth has been difficult, especially in LMICs, HDP has been recognised as one key risk factor causing stillbirths.

1.2 Non-communicable Diseases and maternal health

Non-communicable diseases (NCDs) contributed to over 73% of global deaths in 2017 worldwide (18). Low and Middle Income Countries (LMICs) are disproportionately affected by the burden of NCDs with 86% of premature deaths due to NCDs taking place in these countries (19, 20). Around 65% of deaths among women occur due to NCDs and most of these are in low and middle-income countries. High blood pressure and raised blood glucose are among the leading metabolic risk factors contributing to

NCD-related deaths (21) (20). CVD account for the highest premature deaths while diabetes mellitus is the fourth largest contributor to premature deaths globally. CVD in the form of a heart attack and stroke are often caused by raised blood pressure or hypertension (22). There is also a disproportionate rise in cardio-metabolic diseases across LMICs.

A high-level United Nations meeting in 2011 recognised maternal and child health to be "inextricably linked with non-communicable diseases and their risk factors" (23). Pregnancy conditions are no longer considered as isolated incidents lasting only during pregnancy and postpartum (22). Pre-existing chronic conditions like chronic hypertension and diabetes mellitus can lead to serious adverse pregnancy and birth outcomes. On the other hand, complications specific to the pregnancy period like gestational diabetes mellitus and hypertensive disorder of pregnancy can also often lead to adverse effects around childbirth such as preterm birth, maternal deaths, stillbirths and newborn deaths (23).

Controlling the risks associated to NCDs is considered one of the most important ways to reduce the burden it poses to the health system and the overall economy of a country. Among the preventive interventions are reduction of tobacco and alcohol use, maintaining a healthy diet and an active lifestyle, reducing air pollution (24). Promotion of healthy diet, physical activity can help reduce premature death and disability and reduce burden on health system. The benefits of preventive measures go beyond protecting people from developing NCDs, it also helps reduce overall disease burden and the risk of developing comorbidities (25). Additionally, it can alleviate the immense financial burden posed to patients, their families and the health system. Management of NCDs is also critical and can be done through detection, screening and treatment of the diseases. Early screening and detection can also help prevent adverse conditions in pregnancy. Focus on preventive measures for NCDs especially in LMICs can help reduce the burden it poses to the already stressed health systems and also divert resources in other health priorities. Prevention of NCDs are among WHO's 'Best Buys' leading to higher return on investment along with benefits to individual and national health and social welfare (26).

1.2.1 Hypertensive disorder and diabetes mellitus in pregnancy

Hypertensive disorder during pregnancy (HDP) and gestational diabetes mellitus (GDM) are the two most common cardio metabolic[1] complications of pregnancy (27). Prevalence and burden of the two NCDs are unevenly distributed in the low-resource settings and require consolidated action by the governments for prevention and management (18). Table 1 below provides the clinical definitions of the two NCDs during pregnancy.

Table 1.1: Hypertensive disorders and diabetes mellitus during pregnancy (HDP): Definition

Condition	Definition
Chronic Hypertension	Chronic hypertension in pregnancy is defined as systolic blood pressure (SBP) ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg before pregnancy or 20 weeks of gestation. The other criteria includes women taking antihypertensive medication before pregnancy. Persistence of hypertension after 12 weeks postpartum is also classified as chronic hypertension (28, 29).
Gestational Hypertension	Hypertension during pregnancy is classified as the onset of a new episode of hypertension during pregnancy with diastolic blood pressure ≥ 90 mm Hg in the WHO recommendations (29, 30). The Bangladesh Maternal Health SOP follows a similar definition while restricting the blood pressure between 90-110 mm Hg 4 hours apart after 20 weeks of gestation (31).
Pre-eclampsia	According to WHO and NICE, pre-eclampsia is classified when persistent hypertension is coupled with substantial proteinuria of > 0.3 g/24 hours (29, 30). For Bangladesh the level is set lower at 0.2 g/ 24 hours (31).

[1] Cardiometabolic diseases include heart attack, stroke, diabetes, insulin resistance and non-alcoholic fatty liver disease.

Eclampsia	Eclampsia is the condition when women go through generalized seizures, generally in addition to pre-eclampsia symptoms. The same standard has been followed in WHO, NICE and national guidelines (29, 31).
Gestational Diabetes Mellitus (GDM)	The WHO suggests GDM to be diagnosed at any time in pregnancy if one or more of the following criteria are met: Fasting plasma glucose 5.1-6.9 mmol/l and/or 1-hour plasma glucose ≥ 10.0 mmol/l following a 75g oral glucose load and/or 2-hour plasma glucose 8.5-11.0 mmol/l following a 75g oral glucose load (32).
Pre-existing diabetes mellitus	In addition to the pregnancy-specific conditions, pre-existing diabetes mellitus is also part of the complications diabetes in pregnancy (29, 30, 32, 33). For detecting diabetes in pregnancy, WHO specified criteria suggests, fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) , 2-hour plasma glucose ≥ 11.1 mmol/l (200 mg/dl) following a 75g oral glucose load and random plasma glucose ≥ 11.1 mmol/l (200 mg/dl) in the presence of diabetes symptoms (32). The same classification is followed in the national guideline (34).

Estimates by the Institute of Health Metrics Evaluation (IHME) suggest a notable decline in deaths due to hypertensive disorders of pregnancy (21). Despite a decline in disabilities due to HDP by 37.5% between 1990 and 2017, it remains the second largest contributor of disability among maternal causes, leading to a loss of 191.7 DALYs in low-income countries in 2021 (18, 21). The World Health Organisation (WHO) estimates suggest an incidence of 2.8% of HDP in developing countries (4).

GDM on the other hand has become an 'emerging epidemic' worldwide with its prevalence ranging between 9 and 26% (17). Due to variation in diagnostic criteria of GDM, its prevalence is difficult to compare across countries and regions. Estimates suggest that worldwide, almost 17% of women in 2021 had hyperglycaemia[2] in some form during pregnancy and the majority of the cases (over 80%)

[2] Indicates high blood glucose level.

were due to GDM (35). Global prevalence of GDM ranges between 5% and 25.5% while an increasing number of women during the reproductive years are getting diagnosed with type 2 diabetes (36, 37).

GDM is associated with adverse pregnancy outcomes like increased risk of HDP among pregnant women and morbidity and mortality among newborns while increasing the risk of diabetes later in life (19, 38-40). Gestational hypertension and pre-eclampsia/eclampsia can lead to complications around childbirth, maternal deaths, preterm and stillbirths. Women with HDP are at risk of developing chronic hypertension after giving birth (14, 38).

Gestational hypertension and pre-eclampsia/eclampsia can lead to complications around childbirth, maternal deaths, preterm and stillbirths. Women with HDP are at risk of developing chronic hypertension after giving birth (14, 38, 41, 42). The long-term consequences of HDP to the mother include higher risk of Type 2 Diabetes Mellitus (T2DM), hypertension, cardiovascular diseases (CVD) (18).

The pregnancy and childbirth-related clinical consequences include impact on both mother and babies. HDP and GDM can lead to preterm birth and postpartum haemorrhage and can have adverse perinatal outcomes including maternal deaths, birth asphyxia, shoulder dystocia, stillbirth and neonatal deaths. Such conditions can increase the risk of HDP and preterm birth in subsequent pregnancies too (18). GDM also has impacts on women developing CVD in later life. They are also at a higher risk of developing T2DM compared to those with uncomplicated pregnancies.

Not only women but also their newborns have a higher risk of developing high blood pressure at a young age and CVD later in life (18). Diabetes mellitus among mothers during pregnancy increases the risk of diabetes among children. The offspring is also at a higher risk of developing cognitive and psychiatric disorders.

Women with HDP or hyperglycaemia are at higher risk of having stillbirth or premature births leading to newborn deaths (18, 43). Children born to mothers with GDM, HDP or pre-existing chronic hypertension and diabetes mellitus also have a higher likelihood of developing similar conditions later in their lives (14, 23, 38).

1.3 Maternal and newborn health in Bangladesh

1.3.1 Maternal mortality and morbidity

The fourth health, population and nutrition sector programme (HPNSP) of Bangladesh set a target of 105 maternal deaths per 100,000 live births in 2022 while the SDG target is set at 70 per 100,000 live births (44). Unfortunately, similarly to the global trend, the Bangladesh Maternal Mortality Survey

(BMMS) 2016 revealed that the MMR has stalled since 2010. This comes despite a significant reduction of MMR from 320 to 194 per 100,000 livebirths between 2001 and 2010 (45, 46).

Haemorrhage and eclampsia are the two leading causes of maternal mortality in Bangladesh (45). Pre-eclampsia/eclampsia is the second leading cause of death among women in Bangladesh and contributes to 24% of maternal deaths in Bangladesh. Still, pre-eclampsia/eclampsia accounted for 35 maternal deaths per 100,000 live births (47). Indirect causes occupy the third largest share, causing 20% of maternal deaths.

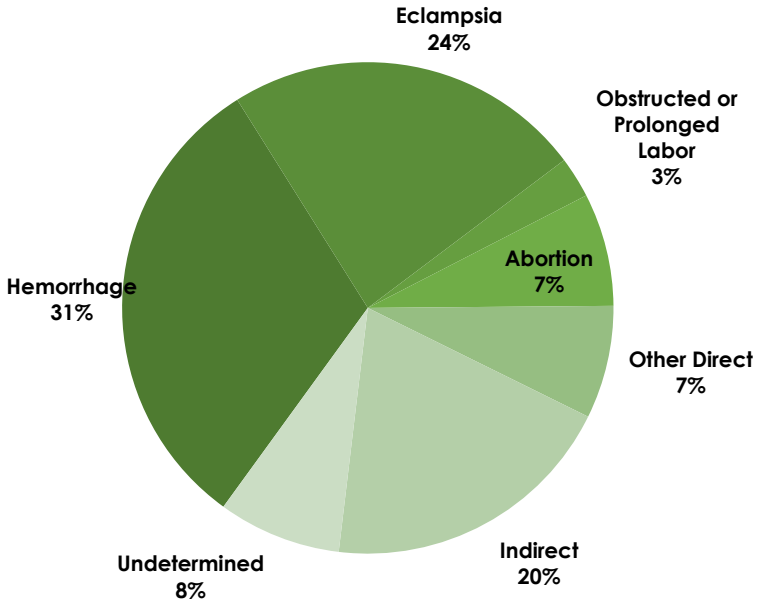


Figure 1.1: Causes of maternal deaths among women of reproductive age (15–49 years) in Bangladesh, 2016

[Produced based on data from the Bangladesh Maternal Mortality and Health Care Survey 2016] (42)

Data on morbidities or complications during pregnancy for Bangladesh are scarce. One reason is that the data capturing systems are relatively new and not yet widely used (47). Shortage of equipment also makes it more difficult to identify and measure the diseases, making things even more complex due to the low level of care-seeking practices. Data that are available have limitations as most are facility-based studies and pose the risk of biased estimates due to the type of study population they cover. One facility-based study followed women coming for antenatal care and estimated around 14% developed pre-eclampsia (48). Another facility based study reported a 9% prevalence of eclampsia (49). Considering it covered a large sample and was done in one of the largest medical college hospitals in Bangladesh, which receives patients from all over the country, the high rate is understandable. Knowledge among women regarding symptoms of complications was found to be low in BMMS 2016 (45). Less than 50% of women had knowledge on symptoms of pre-eclampsia while over 36% had

knowledge on convulsion. Around 37% women reported having symptoms of pre-eclampsia and 6% reported having convulsion/fits during pregnancy, at or after delivery.

For gestational diabetes mellitus, one study reported the prevalence to be around 9.7% following WHO diagnostic criteria (50). A recent study reported the prevalence at 35% but did not account for pre-existing diabetes mellitus among pregnant women (51).

1.3.2 Newborn death, preterm birth and stillbirth

Preventing maternal morbidity and mortality can help improve birth outcomes. One third of child deaths in Bangladesh take place during the newborn period (52). Newborn mortality stood at 28 per thousand live birth as of 2014 reports while a slight increase has been reported in 2018 to 30 per thousand live births (53). United Nations and Bangladesh Bureau of Statistics reported a lower rate at 26 per thousand live births (54). Prematurity is among the leading causes of newborn deaths in Bangladesh. Around 19% of newborns are born preterm in the country (55). According to national survey reports, the perinatal mortality[3] rate was 48 per 1000 pregnancies in 2018 and over half of these were stillbirths (52).

[3] Sum of the number of stillbirths and early neonatal deaths divided by the number of pregnancies of 7 or more months' duration.

1.3.3 Health system structure of Bangladesh

The health system in Bangladesh includes a large number of public sector agencies, non-governmental organisations (NGOs) and the private sector. The country is divided into seven administrative divisions and 64 districts (56). Under the districts, there are upazilas (sub-districts) and under upazilas, there are unions.

Under the Ministry of Health and Family Welfare, there are two divisions: Health Services Division and Medical Education and Family Welfare Division. Two agencies primarily responsible for healthcare service delivery are the Directorate General of Health Services (DGHS) and Directorate General of Family Planning (DGFP). Under DGHS, there are six tiers of health facilities: national, divisional, district, sub-district (upazila), union, and ward/community-level. At the divisional level, there are medical college hospitals and at district level, there are district hospitals. The sub-district or upazilas have upazila health and family welfare centres while the unions have union health centres and community clinics for every 6000 population (56). Under DGFP, there are healthcare facilities at central, divisional, district and sub-district level. At the central level, there are maternity hospitals and training centres while at division and district level, there are maternal and child welfare centres. The unions have union family planning centres (Figure 1.2).

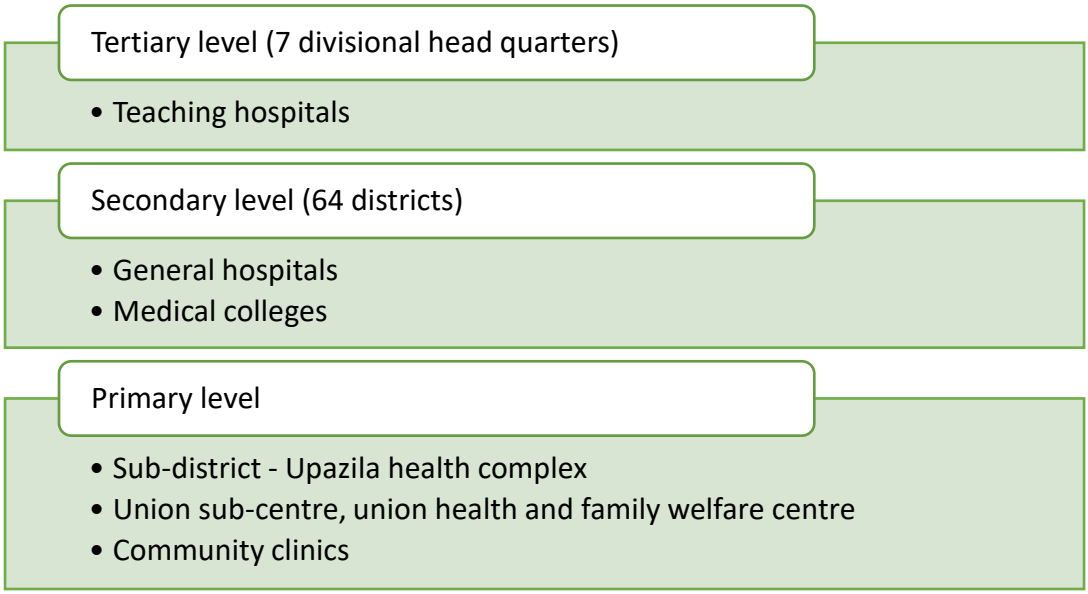


Figure 1.2: Tier of health facilities by administrative units in Bangladesh ***(45)***

In addition to the public health facilities, there are multiple cadres of domiciliary workers who provide home-based care and counselling. Under the DGHS, there are Health Assistants and under the DGFP, there are Family Welfare Assistants. Each of the domiciliary workers covers a population of approximately 5000-6,000 through monthly home visits (56).

1.3.4 Maternal health service coverage and availability in Bangladesh

Poor service coverage and readiness of facilities in providing maternity care are among factors responsible for the stagnated reduction in maternal and newborn mortality and disease burden. This section draws an overview of the coverage of antenatal care (ANC), care around the time of birth and postnatal care (PNC) in light of two latest surveys, the Bangladesh Demographic and Health Survey 2017-18 (BDHS) and the Bangladesh Health Facility Survey 2018 (BHFS) (52, 57).

According to the BHFS report, 99% of facilities had ANC services available (57). While 24% of facilities had normal delivery services available, 16% had the provision of all basic services[4] along with normal delivery services. Only 4% had c-section facilities available (figure 1.3).

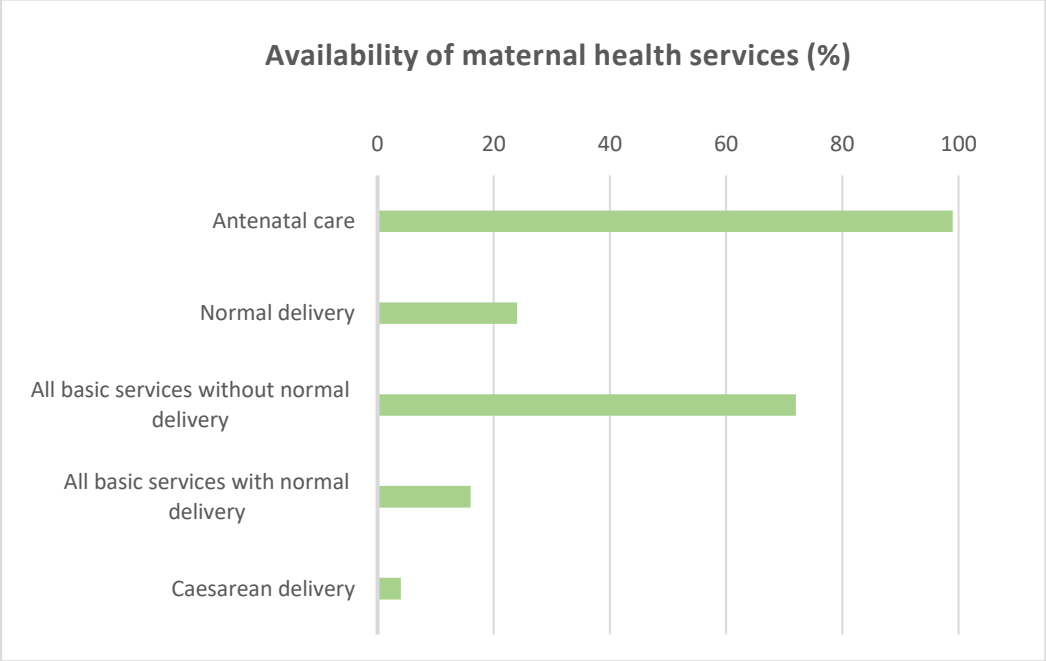


Figure 1.3: Availability of maternal health care at all facilities in Bangladesh

(Figure produced by author based on data from the Bangladesh Health Facility Survey 2017 (47))

[4] Includes the availability of service guidelines, staff with up-to-date training, basic items that support quality provision of delivery services, and items for infection control

1.2.4.1 Antenatal care

BDHS 2017-18 reported that about 64% of women received antenatal care during the three years preceding the survey (52). Around 47% received four antenatal check-ups from a medically trained provider. Only 25% of women received all components of ANC (weight and blood pressure measured, urine and blood sample taken, informed about danger signs of pregnancy) (Figure 1.4).

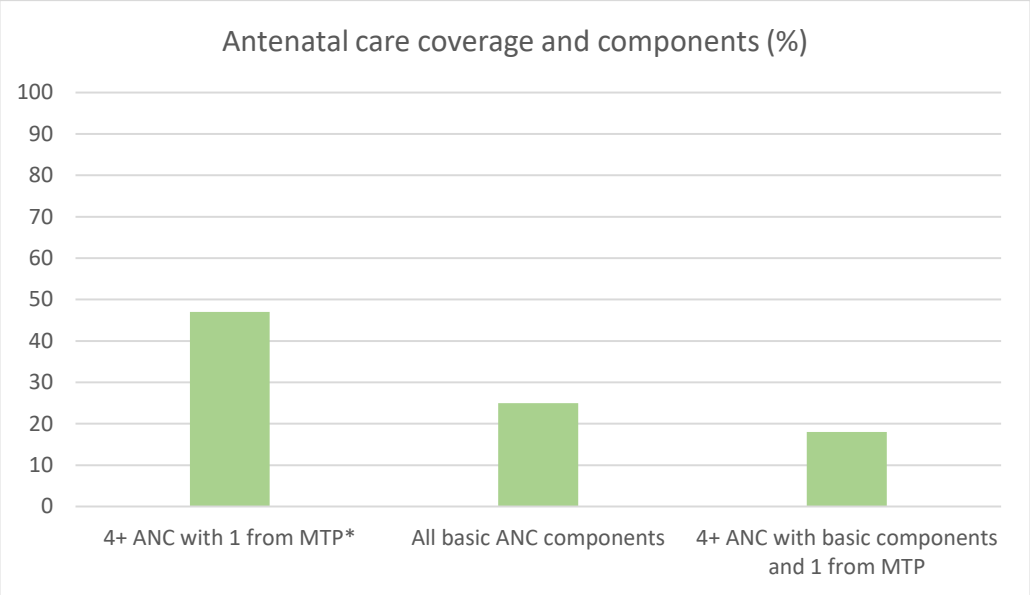


Figure 1.4: Coverage and quality of ANC in Bangladesh (*Medically Trained Provider[5])

(Figure produced by author based on data from the Bangladesh Demographic and Health Survey report 2017-18) (37)

1.2.4.2 Care around the time of birth

Overall, 37% of births took place in a health facility (52). Out of total deliveries, 38% took place through qualified doctors and 37% of births were assisted by untrained birth attendants. Around 14% births were assisted by nurse/midwives/paramedic/Family Welfare Visitors/Community Skilled Birth Attendants and 10% were assisted by trained traditional birth attendants (TTBA) (Figure 1.5).

[5] Qualified doctors, nurses, midwives, or paramedics; family welfare visitors (FWVs); community skilled birth attendants (CSBAs); and sub-assistant community medical officers (SACMOs)

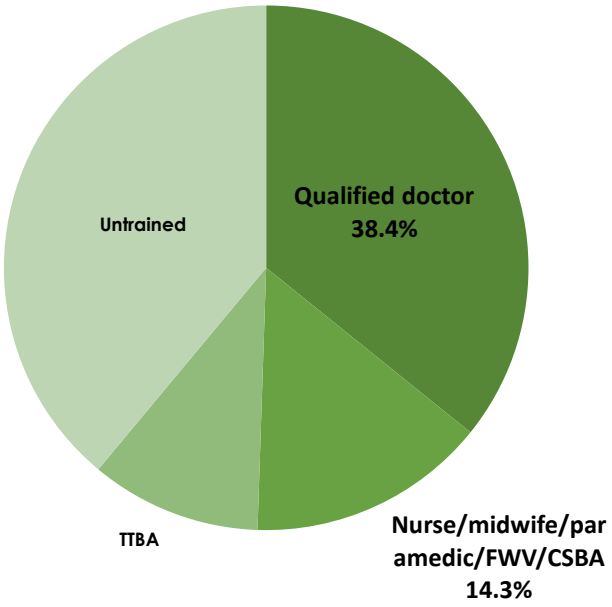


Figure 1.5 : Distribution of type of assistance for care during birth

(*Figure produced by author based on data from the Bangladesh Demographic and Health Survey report 2017-18* (37))

Availability of equipment and other resources in Bangladesh is mixed. While 83% of facilities had delivery packs available, only 45% had trained staff and only 14% had drugs in stock for treatment of preeclampsia/eclampsia (figure 1.6).

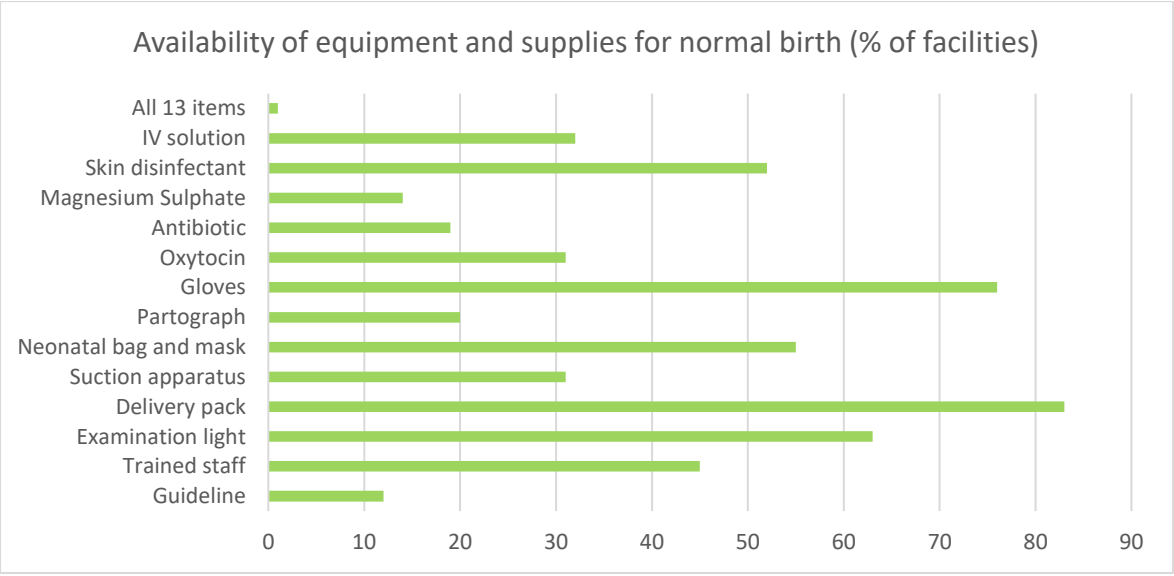


Figure 1.6: Readiness of Facilities to Provide Normal Delivery Services

(*Figure produced by author based on data from Bangladesh Health Facility Survey report 2017* (33))

1.3.5 Burden of hypertension and diabetes mellitus and availability of services in Bangladesh

In 2019, NCDs were the dominant cause of death among the population in Bangladesh. Fourteen out of the top 20 causes of death were NCDs (58). The BDHS report suggests that over 97% of people between the ages of 18 and 69 in Bangladesh have at least one risk factor[6] for NCDs (52). Raised blood pressure and raised blood glucose, two key intermediate factors for NCDs, are becoming more common among the Bangladeshi population in recent years.

Figure 1.9 shows that among women aged 18-34 the prevalence of hypertension was 12.5% and there was no difference between urban and rural prevalence in this age group (52). Overall, there was no notable difference between those living in urban and rural areas. Women without education had higher prevalence (43%) compared to those with secondary or higher education (16%). Among women over 70, over 60% have elevated blood pressure. More than half of hypertensive women were unaware of having the disease.

Among women over the age of 17, 10% were diabetic. Diabetes was evidently more prominent among urban women (14%) than their rural counterparts (8%) (52). Those without education were more likely to be diabetic compared to women with higher education (11% vs 8%). Women in the highest wealth quintile had higher prevalence at 16% compared to 6% in the lowest two quintiles. Among women over 70, over 13% were diabetic. Almost 60% of women were not aware of having a raised blood glucose level. (Figure 1.7)

[6] Includes unhealthy food habits, physical inactivity, high body mass index, substance abuse, high blood pressure and elevated blood glucose and plasma lipid levels.

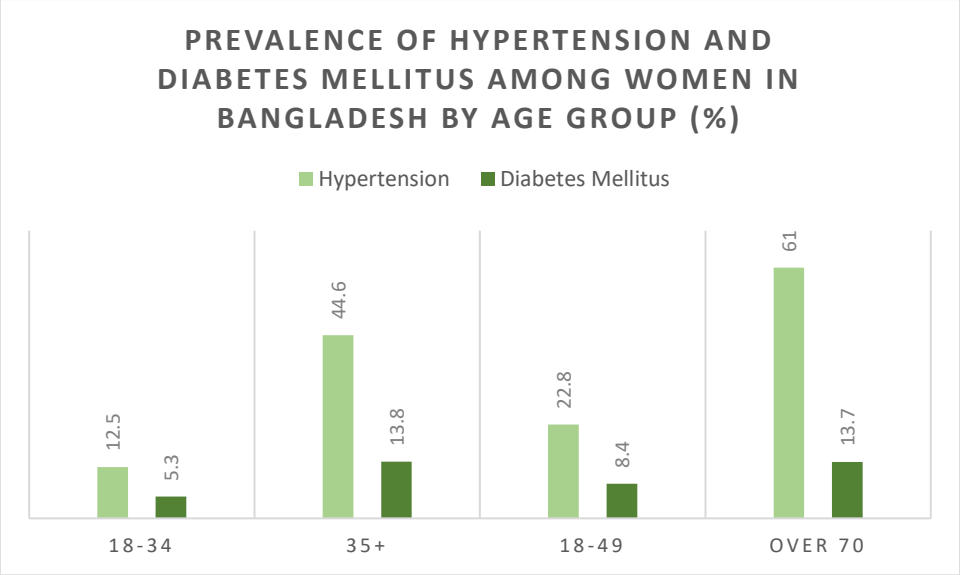


Figure 1.7: Prevalence of hypertension and diabetes among adult female population in Bangladesh

(*Figure produced by author based on data from the Bangladesh Demographic and Health Survey report 2017-18* (37))

As far as treatment for diabetes is concerned, 71% of district hospitals and upazila health complexes offer treatment while only 41% had a guideline available for diagnosis and management of diabetes (57). These proportions are as low as 11% and 15% respectively at union-level facilities. Within the public health system of the country, the community clinics refer diabetes patients to higher-level care while diabetic pregnant women are treated at the union level. Capacity for diagnostics including tests such as blood glucose, urine protein and urine glucose were available in over 30% of DHs and UHCs. Availability of blood-glucose-lowering medicines like metformin, glibenclamide, injectable insulin and injectable glucose solution was around 20% in these facilities. None of the union level facilities had provision of the diagnostics or availability of required drugs.

Diagnosis, treatment and management services for hypertension were commonly available in district hospitals, upazila health complexes and private hospitals (over 90% each) (57). Service availability was lower at union (65%) and community clinics (69%). Only 17% of facilities had a guideline available for managing hypertension. Ten percent of facilities had at least one trained staff who received training on hypertension treatment two years preceding the survey. Among medicines, 26% of facilities had calcium channel blockers available while only 3% had ACE inhibitors and 24% had angiotensin blockers available.

1.4 Need for developing decision analytic models addressing NCDs in pregnancy

Despite availability of proven interventions, the maternal mortality remains high. Both direct obstetric causes of maternal death like hypertensive disorder of pregnancy and indirect causes like diabetes mellitus in pregnancy are preventable but needs consolidated effort by the government in terms of

data generation and implementation of necessary interventions. Coverage of basic services like antenatal care is still low. While interventions are available throughout the maternal continuum of care; antenatal, birth and postnatal care, antenatal period provides the longest window to prevent the occurrence of gestational hypertension, pre-eclampsia, eclampsia or gestational diabetes mellitus. It also leads the way to prevent complications of pre-existing hypertension or diabetes mellitus from appearing among pregnant women and their offspring. Interventions beyond the antenatal period would focus on treatment and management of conditions and their associated consequences later in life.

The use of economic evaluation models as evidence in decision making in LMICs is despite the recognition of its significant need (59). As a result, there is a paucity of economic evaluation models around interventions addressing HDP and DMP in general. They are especially rare in the context of developing countries. Cost-effectiveness of health related in intervention in Bangladesh is very scarce (60). The link between NCDs and maternal morbidities are also not well recognised, especially in the Bangladeshi context. Whilst global and national evidence base has been widely adopted to inform policy discussions and decisions, there is still a need for country-specific economic analyses that are tailored to the needs of the relevant stakeholders and decision-makers. Decision analytic models can help identify what is feasible for the country, set priorities and mobilise resources accordingly.

Though the use of decision analytic modelling in Bangladesh has been minimal to date, there is a growing interest in its use from the government. Consequently, this thesis will explore the interventions with respect to HDP and GDM care, and develop a cost-effectiveness model to help inform investment decisions in Bangladesh. Prevention is the preferred way of intervening to tackle the increasing burden of NCDs as identified by both the WHO the NCD Alliance. Preventive interventions can lead to economic benefits both in terms of health and resource utilisation and hence this research will focus on preventive measures rather than the full breadth of continuum of care in addressing hypertensive disorders and diabetes mellitus in pregnancy. In doing so, the research also recognises the importance of exploring all possible interventions, preventive and curative in order to develop a comprehensive understanding of possible ways to mitigate the two NCDs throughout the pregnancy continuum of care.

1.5 Research aim and objectives

Aim

To assess the cost-effectiveness of interventions addressing hypertensive disorder in pregnancy and diabetes mellitus in pregnancy in government-funded health care facilities in Bangladesh.

Objectives

- To review global and national guidelines and treatment pathways of the two most common NCDs in pregnancy; hypertensive disorders and diabetes mellitus
- To conduct a systematic review of economic evaluation models focusing on interventions related to hypertensive disorders and diabetes mellitus in pregnancy and identify the methodological approach taken and key structural characteristics associated with the models
- To conduct a narrative review of generic antenatal care models to supplement the systematic review
- To develop a list of interventions related to hypertensive disorders of pregnancy and diabetes mellitus in pregnancy
- To inform and understand stakeholder views on the interventions and model specifications
- To develop a conceptual modelling framework based on the reviews and interviews with stakeholders in Bangladesh
- To develop an economic evaluation model addressing hypertensive disorders of pregnancy and gestational diabetes mellitus
    - During pregnancy, childbirth and postpartum; and
    - In the long-term
- To assess the value of conducting additional research related to implementation of the intervention
- To assess policy implications of the results

1.6 Brief overview of the rest of the thesis

The upcoming chapters in this thesis include literature review, stakeholder consultations and the cost-effectiveness model.

Chapter 2 presents a review of clinical guidelines related to HDP and GDM. The chapter defines the two conditions depending upon severity of disease, their risk factors, and symptoms, how they are detected and what treatment pathways are recommended. Two sets of clinical guidelines from the

WHO and national level guidelines have been reviewed and elaborated in the chapter. The chapter also points out the recommended preventive care pathways based on the clinical guidelines.

Chapter 3 presents details of a systematic review of literature on economic evaluation of interventions addressing hypertensive disorder of pregnancy and gestational diabetes mellitus.

Chapter 4 is divided into two sections. Section 4.1 presents the steps followed for selection of intervention for the model through a comprehensive list of interventions, informal and formal stakeholder interviews. This is followed by section 4.2, which details out the process of finalising the draft conceptual modelling framework based on the findings from chapters 2 and 3 and through incorporating inputs from stakeholder interviews. This section also identifies the final preventive intervention during the antenatal period for the model development.

Chapter 5 presents the detailed model development process. It provides the rationale for selection of the model structure, development of the current care model, estimating effect of scaled up provision of the interventions and incorporating long-run outcomes. Next, the chapter explains the methods for incorporating costs and aggregate benefits of the intervention. Finally, methods adapted for sensitivity analysis, analysis of model outputs, model validation and the steps for model verification are described.

Chapter 6 presents the model results and findings from the cost-effectiveness analysis. The section provides the impact of the intervention by presenting the intervention effect on the outcomes, costs, benefits, net monetary benefit, incremental cost-effectiveness ratio, the cost-effectiveness plane, cost-effectiveness acceptability curve and value of information analysis. Next, a few secondary analysis from the model is presented. Selected sub-group level analysis has been added. Finally, results from a few deterministic sensitivity analysis is presented.

Chapter 7 of the thesis is the discussion section that summarises key findings along with the approach taken to reach the findings. The discussion explains contribution of the thesis to existing evidence base of cost-effectiveness studies on calcium supplementation among pregnant women. The chapter also discusses how the model can be useful for policymaking and how it can be manipulated for further use. It further elaborates on possible scope for further research. Finally it discusses the strengths and weaknesses of the thesis before reaching the concluding remarks.

2. Understanding Hypertensive Disorders and Diabetes Mellitus in pregnancy: review of clinical guidelines and standard operating procedures to define clinical pathways

2.1 Introduction

Clinical pathways show the direction that a patient ideally should go through when a disease or complication appears. They are used to ensure quality and maintain a standard of care throughout a health system. It can be thought of as a guide for doctors or carers to provide the most appropriate level and type of care. It is also an optimization tool to ensure patient safety and accountability of the health workers (56). This chapter explores the risk factors, symptoms and recommended treatment along the pregnancy continuum of care, specific to women with hypertensive disorder or diabetes in pregnancy. How the two NCDs have been defined in the guidelines, why some women are more prone to develop them then others and how the health system or health service providers should act on are expected to add valuable information for model development. It will also highlight any deviation of national guidelines compared to recommended global practice by the WHO.

2.2 Objectives

The aim of this chapter was to conduct a review of clinical guidelines to understand the clinical pathways of the two conditions: HDP and DMP. The review aimed to understand the clinical definitions and diagnostic criteria of the two medical conditions during pregnancy and identify if they vary across the different guidelines.

The specific objectives to be attained through this review are as follows:

I. To identify a set of relevant clinical guidelines for HDP and DMP
II. To understand how screening, diagnosis, treatment and management are done for the two conditions at different stages of pregnancy as per the guidelines
III. To compare and identify what has been adopted in Bangladeshi national guidelines compared to the WHO recommendations

2.3 Methods

2.3.1 Selection of guidelines

The World Health Organisation (WHO), NICE and Bangladesh-specific guidelines were purposively selected as the sources for inclusion in this review. The WHO guidelines were added to the review to identify the adaptations made in the national guidelines and treatment pathways compared to the standards set in the WHO guidelines. For each source of guidelines, the WHO web page and google

were searched with keywords such as maternal health, gestational diabetes, diabetes in pregnancy, hyperglycaemia, hypertension in pregnancy, gestational hypertension, pre-eclampsia, eclampsia, pregnant women, antenatal care and postnatal care to find relevant guidelines. Some guidelines related to care around birth, which seemed relevant, were also included.

The WHO website was searched using the search terms mentioned above. The WHO clinical guidelines often referred as WHO recommendations specific to complications and their preventing or curative treatment were included. The WHO also has a set of documents relating to integrated management of pregnancy and childbirth (IMPAC) guidelines. Relevant recommendations and guidelines were shortlisted based on the titles.

The national documents were selected primarily based on prior experience and knowledge and discussion with experts working in the field of maternal and child health in Bangladesh. Some rapid Google searches were also done to identify additional relevant country-specific guidelines.

2.3.2 Identifying risk factors and recommended treatment/management plans

Clinical guidelines for each of the health conditions were summarised in the sequence following risk factors, symptoms, diagnosis, assessments, advice and treatment in the form of matrices (Tables 1-8, Appendix 2). Guideline summaries of HDP related conditions were organised in order of severity of conditions: chronic hypertension, pre-eclampsia, eclampsia and gestational hypertension. Similarly to HDP, a matrix was developed for DMP.

Risk factors were first recorded for each of the conditions, followed by assessment criteria based on symptoms of hypertensive disorder or diabetes in pregnancy; diagnosis; advice; and treatment or management of each of the conditions depending on the stage of pregnancy. For each condition, recommended treatment and management was summarised along the care pathway of pregnancy: antenatal, intra-partum and post-natal care. The initial summary was completed based on the review of the WHO guidelines.

Once the matrix was completed using all the available guidelines, a generic summary matrix was prepared combining all HDP-related conditions; gestational hypertension, mild and moderate pre-eclampsia, severe pre-eclampsia and eclampsia.

2.4 Results

2.4.1 Overview of sources of clinical guidelines

2.4.1.1 WHO guidelines

A WHO guideline is defined as “Information product developed by WHO that contains recommendations for clinical practice or public health policy”(61). The guidelines aim to aide in

achieving the best possible health outcomes for individuals. The guidelines contain a set of recommendations in regard to clinical interventions, diagnostic tests and public health measures that aide in evidence-informed decision-making. The guidelines help to answer questions related to when and how to act to improve health and health care services (61).

The WHO guidelines and recommendations follow a systematic approach to developing and presenting evidence summaries. The clinical practice recommendations are compiled through expert consultations and existing evidence based recommendations on its strength assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework (62). A set of recommendations with the level of strength of evidence and level of strength of recommendations are listed in each clinical guideline document.

The WHO guidelines related to IMPAC focused on managing complications for pregnancy and childbirth recommendations were included in the review. Recommendations covering pregnancy and antenatal care, management of pre-eclampsia and eclampsia, diagnosis of hyperglycaemia in pregnancy and management of severe pre-eclampsia before term were included in the review. Among the Standard Operating Procedures (SOPs), the WHO pocket book for hospital care for women was found to be relevant and included in the review. (Table 2.1)

2.4.1.2 Bangladesh-specific guidelines

National guidelines are usually developed following the WHO guidelines. These are adapted to country context, national health system and disease prevalence and severity. There is no single prescribed method that is followed at the country level for developing the guidelines. However, the process of developing national strategies and guidelines usually involves a large number of expert consultations and desk reviews which aligns with the process followed by WHO and NICE. There are two relevant programmes that are responsible for preventing, treating or managing HDP and DMP; the Non-Communicable Disease (NCD) programme and the Maternal Health Programme under the Ministry of Health and Family Welfare.

The Maternal Health Strategy (MHS) has recently been updated for the period 2019-2030 (63). The strategy was developed through repeated rounds of expert consultation and contains Standard Operating Procedures (SOPs) for broader and specific maternal health conditions. The SOPs also contain guidance for antenatal care. There is also a national action plan for management of eclampsia, which mostly focuses on clinical treatment. The NCD programme developed the national guideline for management of diabetes and hypertension (64). These include guidelines for the various tiers of public health facilities (primary, secondary and tertiary). (Table 2.1)

Table 2.1 below contains the list of recommendations and guidelines included in this review from each of the three sources.

Table 2.1 List of guidelines included in the review

Sl	WHO recommendations and guidelines
1	Integrated Management of Pregnancy and Childbirth: Managing complications in pregnancy and childbirth (10)
2	Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy (32)
3	WHO recommendations on antenatal care for a positive pregnancy experience (65)
4	WHO recommendations for Prevention and treatment of pre-eclampsia and eclampsia (29)
5	Policy of interventionist versus expectant management of severe pre-eclampsia before term (66)
6	Pocket book of hospital care for mothers (67)
	Bangladesh-specific guidelines
7	National Protocol for management of Diabetes and Hypertension and primary care facilities(64)
8	National guideline on Diabetes Mellitus (34)
9	Standard Operating Procedure: maternal and neonatal health Vol 1 (31)
10	Standard Operating Procedure: maternal and neonatal health Vol 2 (68)
11	National Action Plan for Maternal Health 2017-2022 (69)
12	Eclampsia and PPH Action Plan in Bangladesh 2017-2022 (70)

2.4.2 Key findings from the global and national guidelines

2.4.2.2 Risk factors

Risk factors for hypertensive disorder of pregnancy includes nulliparity, age over 40, a history of pre-eclampsia or gestational hypertension in previous pregnancy, high BMI, family history of pre-eclampsia and pre-existing conditions like CVD or kidney disease. Pre-existing diabetes mellitus of type 1 or type 2 also increase risks for severe pre-eclampsia and eclampsia (30). The WHO guideline identified obesity, chronic hypertension and diabetes among the risk factors of pre-eclampsia. It also includes nulliparity, adolescent pregnancy and conditions like twin pregnancy among the risks (29). Country specific guidelines do not highlight the risk factors, but rather focus on prevention, treatment and management (31). The maternal health strategy however highlights the role of undernutrition on adverse maternal and newborn health outcomes (63). (Table 2.2)

Among the risk factors for gestational diabetes mellitus are BMI above 30 kg/m2, a previous macrosomic baby weighing 4.5 kg or above, previous gestational diabetes and family history of diabetes (first-degree relative with diabetes) (33). (Table 2.3)

The common risk factors for the two conditions include maternal age, high BMI (overweight/obesity) and dietary pattern. Pre-existing chronic hypertension or diabetes also increases the risk of developing hypertensive disorders in pregnancy (30, 33).

2.4.2.3 Recommended pathway for treatment

i) Antenatal Care (ANC)

Number of visits

The WHO ANC model recommends minimum eight contacts for pregnant women. The government of Bangladesh in its guideline has ratified four contacts till now but as per the WHO guideline has accommodated more than four ANCs when it comes to recording ANC practices in the revised ANC visit case notes (ANC card) (31, 65). The treatments recommended by both sources were similar. An increased number of visits are recommended in the Bangladesh guideline for women with a high risk of developing NCDs or those with pre-existing NCDs. (Table 2.2)

Maternal and fetal assessment

The maternal assessment is a key part within antenatal care in order to identify women with risk of developing NCDs in pregnancy or with pre-existing NCDs.

The WHO recommendation suggests classification of hyperglycaemia to diabetes mellitus or GDM between 24 and 28 weeks of pregnancy following the diagnostic criteria mentioned above (71). The Bangladesh national guideline however does not specify any gestational age for testing of hyperglycaemia.

Assessment of HDP are done after 20 weeks following definitions provided in section 2.4.2.1 (31).

Nutrition counselling and supplements

Among the nutrition related interventions that directly affect HDP or DMP, counselling on healthy diet and exercise and calcium supplements for population with low dietary intake of calcium are recommended (31, 65).

Health system

Generic health system related WHO recommendations include personalised case note held by pregnant women with the aim to inform pregnancy and health related information. The second

intervention offers flexibility among the health workforce in counselling on health related behaviour and distribution of nutrition supplements covering lay health workers, nurses, midwives and doctors. The recommendations also cover midwife-led care throughout pregnancy, childbirth and postpartum and community mobilization to deliver antenatal care intervention to improve utilization especially in rural areas. Finally, group antenatal is recommended as an alternative to individual level care. These interventions can also be helpful in reducing maternal and foetal complications and their adverse outcomes.

Referral

For HDP, Bangladesh guidelines suggest that , women to be referred to higher-level facilities if diastolic BP was more than 90. At secondary and tertiary-level facilities, women can be allowed to proceed to normal labour and childbirth. The WHO guidelines, being more generic towards evidence-based treatment globally, are focused more around what treatment is recommended. The national guideline also recommends referral of all diabetic pregnant women or women at risk of GDM to secondary or tertiary-level facilities for treatment.

Drugs/supplements for prevention and treatment of HDP

Methyldopa is listed as an essential medicine in the WHO model list and a recommended drug of treatment for hypertension (28, 30). At secondary and tertiary-level facilities, if diastolic BP reaches 95, treatment with labetalol/nifedipine/ methyldopa are recommended in the Bangladeshi national guidelines (31).

Aspirin is recommended preventive measure for pre-eclampsia and eclampsia by WHO. WHO recommends a low dose of aspirin (75 mg) for women at high risk of developing pre-eclampsia (29). Guideline from WHO recommend calcium supplementation as a preventive strategy especially in areas with low calcium intake (72). This has also been highlighted in the Maternal Health Strategy of Bangladesh (63). (Table 2.2)

Magnesium sulphate is the recommended and preferred anticonvulsant for women with severe pre-eclampsia and for prevention and treatment of eclampsia (29). In Bangladesh, loading dose of magnesium sulphate and referral to secondary or tertiary level facilities is recommended for women with severe pre-eclampsia (31, 70).

For diabetes in pregnancy, counselling on diet and exercise is recommended in all three sources of guidelines. Metformin is recommended if there is no improvement after diet and exercise and if still unchanged, insulin is recommended to be added (33). The national guideline corresponds with the

WHO and NICE guideline in terms of diet and exercise counselling (31). It directly recommends introduction of insulin instead of metformin in case blood glucose remains uncontrolled.- (Table 2.3)

ii) Birth

Expectant management is preferred for women in WHO guidelines. Guidelines around the mode of birth indicate case-by-case decision-making considering all medical conditions of mother and foetus. An expectant management includes intra-hospital care that ensures administration of steroids to ensure lung maturation, antihypertensive if necessary, and continuous monitoring for indication of birth. Availability of special care facilities for newborns needs to be taken into account for this. Gestational age of the foetus needs to be considered for decisions related to expectant management (66).

In case of eclampsia, full intravenous or intramuscular magnesium sulphate regimen has been prescribed in the guidelines for the prevention and treatment. As per the national guidelines, women with severe pre-eclampsia or eclampsia are to be administered the full magnesium sulphate regimen. The loading dose must be followed by immediate transfer to a higher-level health care facility (31, 63). The expectant management is recommended in the absence of uncontrolled maternal hypertension, organ dysfunction or foetal distress (66). Early births are recommended for women with severe preeclampsia at term. Induction of labour is recommended for women with mild gestational hypertension or mild pre-eclampsia at term in WHO guideline (29). (Table 2.2)

Induction of labour is also not recommended for women with gestational diabetes if it is well controlled (10). Mode of birth and decision related to cases of HDP and DMP are not discussed in the national-level guideline. (Table 2.3)

Treatment of severe pre-eclampsia and eclampsia around the time of birth follows the same treatment guideline mentioned under ANC.

iii) Postnatal care (PNC)

Women who continue to have high blood pressure post-birth are recommended to continue taking antihypertensive drugs by WHO (29).

After the pregnancy ends, women should be re–classified as having either diabetes mellitus, Impaired Glucose Tolerance or normal glucose tolerance based on the results of a 75 g OGTT six weeks or more after delivery (32, 33). (Table 2.3)

Treatment of severe pre-eclampsia and eclampsia around the time of birth follows the same treatment guideline mentioned under ANC and birth.

2.4.2.4 Interaction between hypertensive disorder in pregnancy and diabetes in pregnancy

Interaction and linkage between the two conditions have also been identified through the review. Pre-existing diabetes mellitus or gestational diabetes are risk factors for pre-eclampsia/eclampsia. This however has not been explicitly mentioned in the Bangladesh based guidelines. While women with diabetes in pregnancy can be prevented from developing conditions like pre-eclampsia/ eclampsia, if they have developed the conditions, the treatment guidelines related to hypertensive disorder of pregnancy are to be followed.

Table 2.2 is a summary of all conditions related to HDP; gestational or chronic hypertension, moderate or severe pre-eclampsia and eclampsia. The table lists down the risk factors and symptoms and treatment regime for HDP related conditions based on the two sets of guidelines. Detailed tables for individual conditions have been added in appendix 1. Risk factors in the tables have been summarised from WHO guidelines. The symptoms have been reported following those used in the national guidelines. The recommended treatment includes interventions from the WHO and the national guidelines.

Table 2.2: Guideline summary for Bangladesh – Hypertensive Disorders of Pregnancy

Risk factors	• **Nulliparity** • **age (40+)** • **history of pre-eclampsia or Gestational hypertension** • **Family history of pre-eclampsia** • **multi-fetal** • **BMI** • **family history of pre-eclampsia** • **Hypertensive disease during previous pregnancy** • **Chronic kidney disease** • **autoimmune disease** • **Type 1 or 2 diabetes** • **Chronic hypertension**

Symptoms	• Gestational hypertension: Two readings of systolic blood pressure (SBP) four hours apart 140 mmHg or higher but lower than 160 mmHg and/or DBP 90 mmHg or higher but lower than 110 mmHg after 20 weeks of gestation , no proteinuria , no features of preeclampsia. Admit, if BP falls over 160/110 mmHg
	• Pre-eclampsia:
	  ◦ SBP 140 mmHg or higher and/or DBP 90 mmHg or higher before 20 weeks of gestation
	  ◦ After 20 weeks: – Proteinuria 2+ on dipstick –
	  ◦ Presence of any preeclampsia features below:
	  ▪ Severe headache,
	  ▪ blurry vision,
	  ▪ Severe pain just below the ribs
	  ◦ Vomiting, swelling of hands, feet or face
	• Eclampsia:

	● Convulsion, seizure
Treatment	
Antenatal care	● Increased surveillance (BP monitoring, renal function testing, ultrasound assessment) ● Calcium supplementation ● Low-dose aspirin ● Pharmacological treatment (labetalol, nifedipine or methyldopa as indicated), if BP remains above 140/90 mmHg. Aim for BP of 135/85 mmHg or less ● Start anticonvulsant (magnesium sulphate) for prevention and treatment of severe pre-eclampsia/eclampsia
Birth	● Planned early birth before 37 weeks not to be offerred to women whose blood pressure is lower than 160/110 mmHg, unless there are other medical indications ● Expectant management is recommended by ensuring intra-hospital care ● If planned early birth is necessary, offer a course of antenatal corticosteroids and magnesium sulfateph if indicated ● During labour, measure blood pressure hourly and monitor vital signs ● Start anticonvulsant (magnesium sulphate) for prevention and treatment of pre-eclampsia/eclampsia
Postnatal	● Increased monitoring of blood pressure ● Continue antihypertensive drug if there is severe hypertension during antenatal period ● For women with gestational hypertension who did not take antihypertensive treatment, start treatment if their blood pressure is 150/100mmHg or higher ● Start anticonvulsant (magnesium sulphate) for prevention and treatment of pre-eclampsia/eclampsia

A summary table with the list of risk factors, symptoms and treatment regime for diabetes in pregnancy (Table 2.3) is provided below. All components of the table have been described in section 2.4. Summary was done following the same process detailed for table 2.3.

Table 2.3: Guideline summary for Bangladesh – Gestational Diabetes Mellitus

Risk factors	• BMI above 30 kg/m2 • Previous macrosomic baby weighing 4.5 kg or above • Previous gestational diabetes • Family history of diabetes (first-degree relative with diabetes)
Symptoms	• fasting plasma glucose 5.1-6.9 mmol/l (92 -125 mg/dl) • 1-hour plasma glucose ≥ 10.0 mmol/l (180 mg/dl) following a 75g oral glucose load* • 2-hour plasma glucose 8.5-11.0 mmol/l (153 -199 mg/dl) following a 75g oral glucose load
Treatment	
Antenatal care	• At every antenatal visit, if capillary blood glucose is ≥ 6.7 mmol/l two hours after 75gm oral glucose challenge, refer to specialist/higher-level facilities • Plan for all antenatal visits • Refer to higher-level facilities for expert consultation • Counsel of diet and exercise
Delivery	• Induction of labour not recommended for women with an uncomplicated pregnancy and gestational age of less than 41 weeks • For controlled GDM, induction of labour before 41 weeks of gestation not recommended
Postnatal	• Women to be re–classified based on the results of a 75 g OGTT six weeks or more after delivery • Women who were on low dose insulin stop and monitor. Otherwise, women with insulin>1 unit reduce the dose to 50% while the rest should be decided based on expert consultation

Appendix 1: Table 1- Table 8 contains the summary tables from the clinical guidelines for hypertension, severe hypertension, pre-eclampsia, severe pre-eclampsia, eclampsia, chronic hypertension, gestational diabetes mellitus and diabetes during pregnancy respectively.

2.5 Implications for my thesis

The review of clinical guidelines developed by WHO and national programmes provided some very useful information that will help in the development of the economic evaluation model. First, it helped to define the health conditions related to hypertension and diabetes in pregnancy, which was necessary to understand the level of severity of each disease conditions and the treatment that are relevant for each. The definitions also suggested the specific gestational age at which hypertensive disorders develop. Comparison across the three sources of guidelines assured that the national guidelines were largely in line with the WHO recommendations with certain adaptations to country context . For example, although screening of GDM is usually done in the second trimester of pregnancy between 24 and 28 weeks, it was deemed appropriate to screen GDM or DMP as early as possible

considering the context of Bangladesh. Since the Bangladesh specific guidelines did not specify a gestational age for diagnosis of hyperglycaemia and subsequent allocation between GDM or chronic diabetes mellitus, additional literature review and discussion with experts may be required. It also indicated that simplifications of the disease classification may be required to limit the number and the type conditions to be included in the analysis. The definitions also pointed out that while HDP includes both chronic and gestational hypertension, pregnancy specific diabetes mellitus is referred as gestational diabetes mellitus. GDM and pre-existing chronic diabetes mellitus together has been referred as diabetes mellitus in pregnancy or DMP throughout the thesis.

Second, the review identified a set of both common and distinct risk factors among women associated with the development of hypertensive disorder or diabetes in pregnancy. The risk factors provide important information on attributes of population that could be considered when initiating the model and the type of data that will be required. The risk factors also underscored the linkage between chronic diabetes mellitus and GDM as contributors to the risk factors for pre-eclampsia. The list also highlighted the possible link between the two pre-existing conditions. Interaction between the two diseases can play a pivotal role in determining patient pathways and highlight the complexity it adds to the model. It also emphasizes that an intervention targeting one condition may have indirect impact on the other.

Finally, the recommended treatment pathway along the pregnancy continuum of care highlighted the importance of the antenatal, intra-partum and post-natal period in regard to what can be done to prevent, treat or manage the two conditions or complications related to them. The antenatal care recommendations revealed the type of preventive measures are available alongside the treatment and management options throughout pregnancy. Antenatal period is the longest window and the appropriate time during pregnancy to provide preventive interventions. As a result, majority of interventions are recommended for the antenatal time period and preventive interventions dominated the list of interventions. These include nutritional supplements as well as generic intervention like diet and exercise counselling. The screening and assessment related interventions would also fall within preventive interventions through identification of high-risk women and their subsequent allocation to a treatment pathway that can prevent the onset of pre-eclampsia and eclampsia.

The WHO recommendations covered some crosscutting issues related to the health system, which are related to service delivery, especially in the context of LMICs. Findings from the review will feed into the development of the model. Comparison across the different sources of guidelines will help in explaining the differences and reassure consistency of recommendations and treatment pathways.

What the national-level guidelines added compared to the other two sets of guidelines are the various tiers of the health system through which treatment is provided. For conditions like HDP and GDM and their associated complications, women are usually referred to secondary or tertiary-level facilities for treatment. These are the key government health facilities that play a crucial role in delivering interventions as and when needed. The tiers in health care facilities stretch from the grassroots level in the communities up to the medical college hospitals and are the service delivery points for interventions depending on their type, need for clinical interventions and appropriateness of intervention delivery. The health system related recommendations from the WHO guidelines can help shape the issues related service delivery and quality assurance.

2.6 Conclusion

The two sets of guidelines were generally consistent in terms of using risk stratification and diagnosis to inform care and treatment decisions. There is a little variation in diagnosis of pre-eclampsia where Bangladesh uses a lower level of protein urea. Overall, the findings are reassuring as it suggests that the Bangladesh specific guidelines do not represent an 'outlier' that could be subject to dramatic changes. The main differences are in relation to available resources, which lead to different recommendations for specific types of monitoring and treatment.

3. Economic evaluation models of hypertensive disorder of pregnancy and diabetes mellitus in pregnancy: a systematic review of model population, structure, interventions and outcomes

3.1 Introduction

This review intended to explore modelling methods and attributes that have been published in the field of economic evaluation pertaining to screening, management and treatment of pregnancy-related hypertension and its associated complications, and of diabetes mellitus during pregnancy. There is a paucity of research focusing on economic evaluations related to pregnancy-related hypertension and diabetes in the context of low and middle-income countries and with a specific focus on Bangladesh. A review would help uncover insights into how economic evaluation models have been formulated for developed or less developed countries, the outcome measures these studies considered, the type of interventions taken into account for the economic evaluation and the pathways they followed in the models. The review is expected to feed into the broader research agenda and aid in selection of a suitable model structure and methodology in addition to identifying potentially useful parameter values which can later be applied in the modelling process. In addition to model structure, the review would also help lay a foundation for the model based on the population, intervention, comparator and outcomes (PICO) format and formulate the research question for the thesis (73).

The primary research question for this review is what economic modelling methods and model attributes have been used in existing published literature on interventions addressing hypertensive disorder in pregnancy (HDP) and diabetes mellitus in pregnancy (DMP)?

3.2 Objectives

Based on the research question, the objectives of the review are as follows:

1. To conduct a systematic review of economic evaluation models focusing on interventions related to hypertensive disorders and diabetes mellitus in pregnancy which will help
    - To identify relevant literature utilising economic modelling for HDP and DMP and review the methodological approach taken
    - To identify key structural characteristics associated with the models, including:
        i. The population covered
        ii. The interventions evaluated
        iii. The outcomes used
        iv. The time horizon used

v. The health states and events included

vi. The method by which effectiveness was incorporated (e.g use of absolute or relative effects) and the inclusion of confounding factorsTo identify how the two conditions has been combined within a single model

2. To conduct a narrative review to identify and extract information on model structure, time horizon, health states, outcomes and perspectives from additional models related to ANC

3.3 Methods

The following approach was taken for the systematic review of economic models related to HDP, DMP and ANC. Whilst the methods for the three searches are described together in order to avoid repetition in section 3.3, the results in section 3.4 have been reported separately for the three searches. Whilst the first two are the most important and are expected to identify all relevant information, the additional review was still thought useful in order to add wider context, guard against the disease-specific models being too narrow and supplement the first two review findings.

3.3.1 Data sources

Medline (OvidSP) and CINAHL databases were searched in March 2020, with searches restricted to studies published after the year 2000. Medline has strong coverage of health technology evaluations. It is a bibliographic database. CINAHL is rich in obstetrics and gynaecology-related journal articles covering topics related to nursing, biomedicine, health sciences, and other related health disciplines. Grey literature searches used the National Institute for Health and Care Excellence (NICE) website and Google. The first 10 pages of Google search results were reviewed and filtered. The search for the narrative review of the antenatal care model was conducted using Medline alone. The DART European e-thesis portal was also searched for grey literature.

3.3.2 Search terms

Search strategies applied to each database included variations of the words “hypertension”, “pre-eclampsia” and similar/ “gestational diabetes”, “hyperglycaemia” and similar/”antenatal care”, “prenatal care” combined with the search terms for pregnancy and economic evaluations. Validated sets of search strategies were used for the two search engines. These were accessed through the Inter-TASC Information Specialists' Sub-Group (ISSG). The Boolean operators “OR” and “AND” were used to combine these terms. Further details have been provided in Appendix tables 3.1 – 3.6. For grey literature, the NICE website was searched to look for additional published documents on economic evaluation of HDP, DMP and antenatal care. Google searching was done using generic terms like ‘Economic evaluation on hypertension or diabetes during pregnancy’ to look for additional relevant grey literature.

The third part of the work was more of a narrative review to capture general antenatal care models including relevant model structures for pregnant women that can be utilised for the research. Since antenatal care covers a vast range of complications and interventions, the sifting was done by title initially.

3.3.3 Inclusion/exclusion criteria

Articles that were included cover:

- Economic evaluations based on formal decision analytic models (i.e. for which the structure is explicitly described, as opposed to being implied by a series of calculations).
- Economic evaluation protocols with clear model descriptions and outcome measures (which did not include results)
- Studies that focused on HDP/DMP/ANC and their related conditions or outcomes
- Studies published since 2000
- Studies written in English

Articles excluded were:

- Systematic reviews of economic evaluations

3.3.4 Study selection

All literature identified through electronic searches of the two databases were transferred to EndNote version 9. The titles and abstracts of each publication were then assessed for whether they met inclusion criteria. A full text review was done for all papers meeting inclusion criteria. Reference lists for the selected full-text articles were reviewed in order to identify additional publications published prior to the particular paper. For each full-text article included in the review, a citation search was also done using Google Scholar to identify relevant literature published after the publication of the respective papers. The references and citations were selected based on title review and included in the Endnote library. Duplicates were then removed to obtain the final set of literature.

No citation search or grey literature search was done for the review of antenatal care models. Only one round of sifting was done based on titles.

3.3.5 Data Extraction

The data to be extracted provide general information on the studies plus specific information that aligns with the three objectives of the review. For objective 1,general information including author and year of publication were extracted. In order to attain objectives 2 and 3,specific aspects of model

design, including outcomes, model type, time horizon, perspective of the analysis, and model structure were extracted and summarised (Annex 1). Model structures were summarised in terms of health events and health states. For decision trees, key decision nodes were summarised and presented as a list of 'events', which were defined as the number of sequential chance nodes, while the final outcomes were presented as terminal nodes. For Markov and other models, health states or events were listed. Under objective 4, the narrative review ensured any relevant models that cover general pregnancy related interventions are identified and supplemented the systematic review findings.

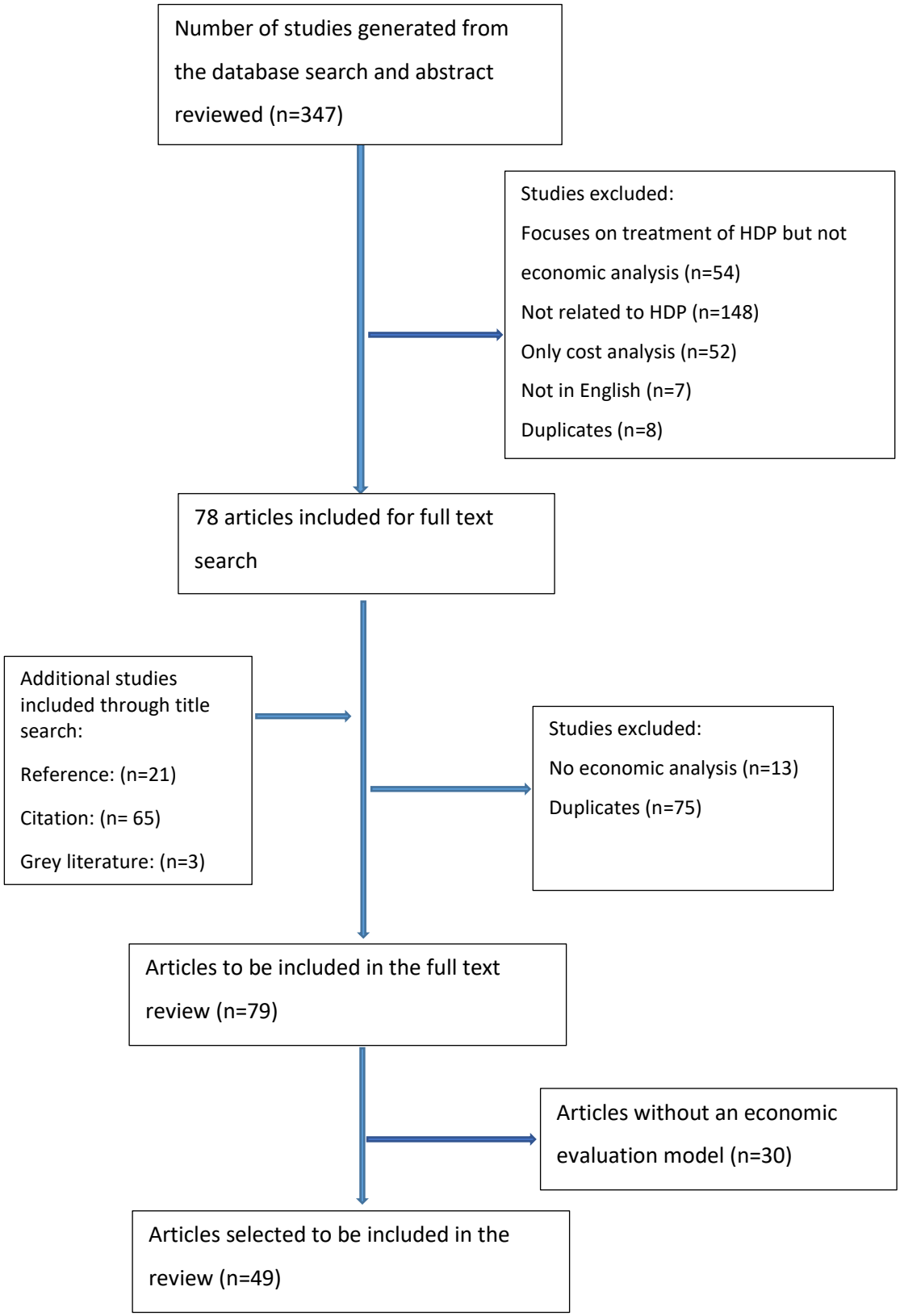
3.4 Results

3.4.1 Hypertensive Disorder in Pregnancy (HDP)

3.4.1.1 Systematic search

The HDP-related search identified 347 references after applying the search strategies in the two selected databases (164 from CINAHL and 183 from Medline). All the articles were downloaded for abstract review and were screened for relevance. The initial exclusion covered 54 studies without any economic analysis, 148 that were not related, 52 that were only costing studies, 7 written in a language other than English, and 8 that were duplicates from the two databases. A total of 78 studies matched the inclusion criteria after the initial abstract screening. An additional 86 papers were added through reference and citation searches of the selected papers. Three relevant studies were found from the Google search. From these, 13 studies identified did not include any economic analysis, while 75 studies were duplicates identified during the primary search. In total, that left 79 articles for full text review. Thirty studies did not include a structured economic evaluation model. Finally, 49 studies were selected to be included in the review (Figure 3.1).

Figure 3.1 PRISMA diagram for economic evaluation models related to Hypertensive Disorder in Pregnancy



3.4.1.2 Data extracted

Data extraction and summary of the full text article was done in the following order: study population, intervention type, outcomes, model structure, time horizon, model perspective, health states and source of data for intervention effectiveness. Detailed tables with these summaries are presented in Appendix 3 (Table 1 to 8).

3.4.1.3 Summary of included studies

Among the HDP-related models, 28 focused on screening, diagnosis or treatment of pre-eclampsia (74-101), four studies were on induction of labour (102-105), and seven of them focused on antenatal care related interventions, safe motherhood promotion, community level triage and referral and improving quality of care (106-112). Six studies were developed around supplements, diet and lifestyle-related interventions (113-118). The remaining four studies were on adherence to guidelines and health financing (119-122). (Figure 3.2)

i) Screening, diagnosis and treatment of pre-eclampsia

The population in the 28 studies that focused on screening, diagnosis and treatment of pre-eclampsia were mostly pregnant women. Some of the studies had a narrower focus in terms of selecting study participants, which included nulliparous women, women over 20 weeks of gestation with new hypertension, women with history of hypertension, women presenting risk factors of hypertension and women with signs and symptoms of pre-eclampsia.

The interventions included multiple screening strategies looking at Placental Growth Factor (PlGF)-based test ratios to detect pre-eclampsia, screening of pre-eclampsia at an early stage of pregnancy, screening using the spot protein-creatinine ratio (SPCR) tests, new medical device usage and other novel tests for pre-eclampsia (PE). Twenty four out of the 28 studies related to screening and diagnosis focused on early diagnosis of pre-eclampsia or risk of developing pre-eclampsia and the resultant increased surveillance or treatment. Among these, 12 studies used screening of pre-eclampsia using the PlGF ratio test (75, 78-81, 87, 91, 96, 99, 123-125). Six studies covered evaluation of aspirin for women assessed as high risk of developing pre-eclampsia (83, 85, 86, 95, 98, 100). Four were on early screening of pre-eclampsia through risk assessment (101, 126), screening pre-eclampsia using a novel medical device (127) and screening women for pre-eclampsia using the SPCR test (92). Two studies were focused on screening women for long-term outcome of pre-eclampsia (74). Among the final two, one study evaluated a community level intervention programme including treatment with MgSO4 (128) and one assessed cost-effectiveness of treatment of pre-eclampsia using MgSO4 in 33 countries (89). Comparators of the studies were more commonly regular care or placebo.

The studies used a wide range of outcomes, most commonly pre-eclampsia diagnosis or identification of high-risk women, onset of pre-eclampsia, adverse maternal outcome, costs, QALYs, life years, hospital admission, mode of delivery, hospital stay, and birth outcome for mothers and babies.

Only two were Markov state transition models (74, 129) and one was developed alongside a trial (89), while the rest were decision trees (75, 76, 78-83, 85-87, 91, 92, 94-101, 124-127). The decision trees had a minimum of two to a maximum of seven levels of events while the markov model used 4/5 health states. The health events in the decision trees included the following: test results (PlGF level, Doppler test, negative or positive test outcome), level or intensity of management and development of pre-eclampsia. The terminal nodes included development of pre-eclampsia, severe pre-eclampsia or eclampsia, preterm and term eclampsia and survival. Markov health states included hypertensive disorder of pregnancy, development of cardiovascular diseases, myocardial infarction (MI)/stroke and death. Two were budget impact analysis.

The time horizon of the models ranged between the pregnancy period to the lifetime of women. Twenty two studies covered the time horizon throughout pregnancy until childbirth or discharge from hospital or 6 weeks postpartum or until 1 year (75, 76, 78-81, 85, 86, 91, 94-101, 124-126, 130). Another six studies covered a longer period. Within these, four studies covered lifetime horizon of mothers and/or babies (74, 92, 127, 128) and two studies covered 20 and 32 years of time each (92, 125) in their respective models.

Twenty three models have conducted the economic analysis from a healthcare system perspective and three from the healthcare payer's perspective. Two studies were based on societal perspective. (Appendix 3: Table 1)

The PlGF-based studies utilised effectiveness data focusing on the reduced risk of onset of pre-eclampsia from trial finding and observational studies. Reduced relative risk of pre-eclampsia was the most commonly used data for screening and treatment in pre-eclampsia-related studies, followed by reduced risk of adverse events like death. Data on diagnostic accuracy in terms of sensitivity and specificity were applied commonly in the screening based studies. The effectiveness of interventions like screening followed by treatment using aspirin or magnesium sulphate on women at risk of pre-eclampsia/eclampsia was applied in the relevant studies. Use of effectiveness data has gone beyond the onset of pre-eclampsia in some of the models, taking into account of outcomes like stillbirth, preterm birth and newborn deaths as a result of reduced risk of pre-eclampsia. The relative risks of pre-eclampsia and other outcomes were derived from direct observations of experimental or observational study data, literature review and expert elicitation methods. (Appendix 3: Table 6)

ii) Induction of labour

Among the four studies, the study population covered low-risk nulliparous women with singleton pregnancy, nulliparous term births, pregnant women at term, women with HDP between 36 and 41 weeks of gestation (102-105).

The outcomes of interest were mode of birth, maternal complications, neonatal survival, neonatal complications and need for specialised care, costs and QALYs. Three studies followed decision trees and one was an individual-based markov microsimulation model.

Health events in the decision trees covered labour induction and expectant management, mode of birth and development of HDP, while the terminal nodes included mode of birth, shoulder dystocia, maternal and neonatal survival. Two studies were done from a health system perspective, while the other two were from a societal perspective. (Appendix 3: Table 2)

Odds Ratios and relative risks of c-section after induction or expectant monitoring as well as proportions were used for estimating effectiveness. Risks of events like c-section upon induction, need for specialised care for newborns, development of HDP post induction, neonatal injury and deaths were applied. All of the studies derived effectiveness using data from observational studies. (Appendix 3: Table 7)

iii) Antenatal care, safe motherhood and quality of care

A total of seven studies fell under this group (106-111). The Global Maternal Health (GMatH)-based models took into account women of reproductive age, while the other studies covered pregnant women .

All of the studies assessed a package of intervention. Three studies were on delivering interventions for promoting safe motherhood, while one focused on improving quality of care and one was on community level triage and referral. The other two studies focused on intensity of the ANC visit schedule and ANC attendance.

Outcomes covered pregnancy-related mortality, maternal morbidity and mortality, stillbirths, ANC coverage, mode of birth, institutional delivery rate, costs, life years saved, DALYs and QALYs.

Two of the studies followed the individual-based microsimulation model using GMatH model for estimating intervention effects, followed by a cost-effectiveness analysis. One was a cohort-based markov state transition model, and two models were developed alongside observational studies. Two studies followed decision tree structure.

Health states in the markov model included place of birth, maternal health, postnatal morbidity and mortality. For babies, the states were live birth, postnatal morbidity or healthy state. The GMatH-based models reported abortion, uptake of antenatal care, complications during labour and delivery, maternal complications and death. The decision tree health events covered regular vs reduced ANC visits, mode of birth, complications while the terminal node was maternal or foetal death or survival. Five of the studies were based on a health systems perspective, and one was based on societal perspective. (Appendix 3: Table 3)

Baseline and up-scaled coverage levels and secondary source-based intervention effectiveness data were applied in the GMatH models. Reduction in the risk of perinatal and maternal mortality were estimated based on expert elicitation in one of the studies. Odds ratios for mode of birth, complications and maternal and foetal deaths were used in one study. One study utilised probabilities based on primary data. Most of the data were obtained through direct observation from existing research. (Appendix 3: Table 8)

iv) Supplements, diet and lifestyle

Six studies were included in this group. All the models targeted pregnant women.

Three of the studies evaluated interventions related to diet and physical exercise (116, 118, 131), and one focused on weight management in pregnancy (115). The other two evaluated effect of calcium supplements on pregnant women. One had intervention arm with or without MgSO4 while the other one compared universal calcium supplementation to only those at high risk of pre-eclampsia and those with low calcium intake.

The model outcomes covered pre-eclampsia, gestational diabetes, c-section, stillbirth, perinatal outcomes, costs and DALYs.

All of the models followed decision tree structures, while one of the decision trees was developed alongside a trial. The health events in the models included development of GDM, HDP, hospitalisation, c-section, induction of labour and normal vaginal birth. The terminal nodes included maternal and newborn death and survival, stillbirth and perinatal death. Four were developed from a health systems perspective, while one took a societal perspective. (Appendix 3: Table 4)

Two of the studies used direct observational data. Relative risks of GDM, HDP and c-section were used from a trial and an observational study. Two studies conducted meta-analysis to estimate relative risk of GDM, HDP and maternal deaths for diet and physical exercise-related interventions. Two of the studies extracted relative risks through a secondary literature search. Increased risk of pre-eclampsia,

c-section and macrosomia due to weight gain was utilised in the study related to weight management in pregnancy. (Appendix 3: Table 9)

v) Adherence to guidelines and health financing

Four studies falling in this category targeted pregnant women in their models. The interventions were about adherence to clinical guidelines (121, 122) and introduction of a health financing scheme (119, 120) compared to regular care.

Health events in the models covered institutional birth, type of assistance during birth, referral care, mode of birth and maternal complications. The terminal nodes included development of pre-eclampsia, maternal death or survival, newborn death and morbidity. Events in one study were not clearly stated. Two of the studies were done from a healthcare system perspective, and two others followed a societal perspective. All four models followed decision tree structures. One used a lifetime horizon while the rest covered the period till childbirth. (Appendix 3: Table 5)

For effectiveness data, two studies used direct observations while the other two used secondary sources. Baseline risks and relative risks of development of pre-eclampsia, hypertensive disorders and mortality were extracted from literature and applied in the models. The study protocol described the plan to use descriptive statistics and regression analysis for primary observation data for parameters including mode of birth, hypertension-related complications, foetal death rates, maternal and newborn mortality rates. (Appendix 3: Table 10)

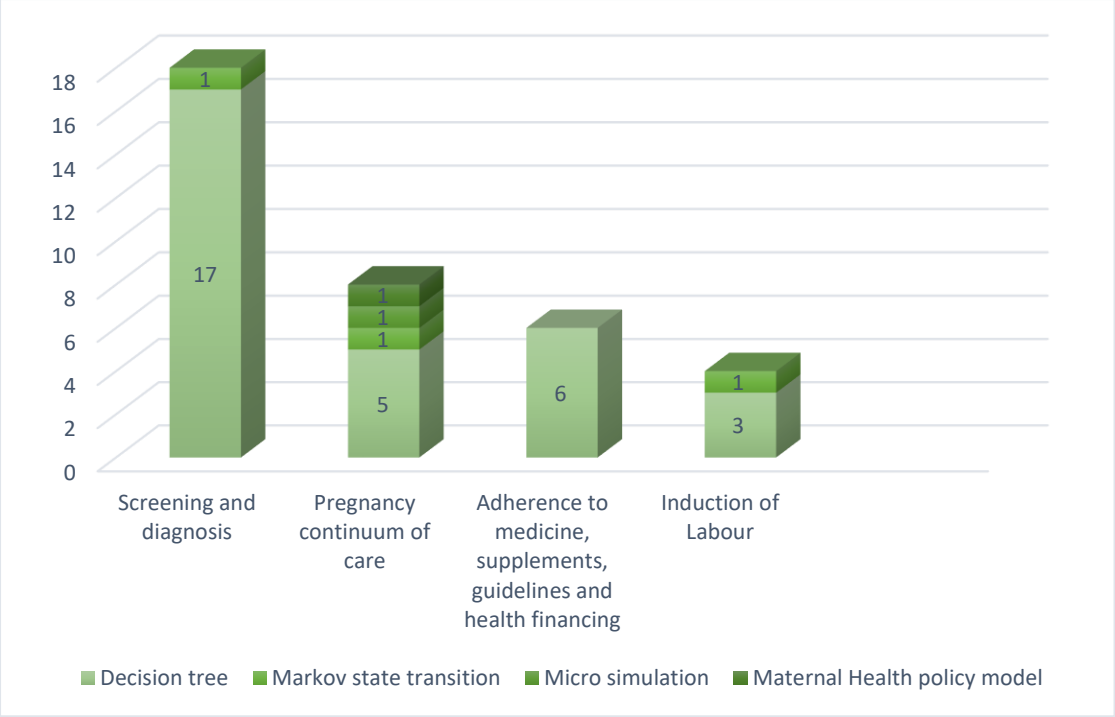


Figure 3.2 Distribution of model types by type of intervention – Hypertensive disorder of pregnancy

3.4.2 Diabetes Mellitus in Pregnancy (DMP)

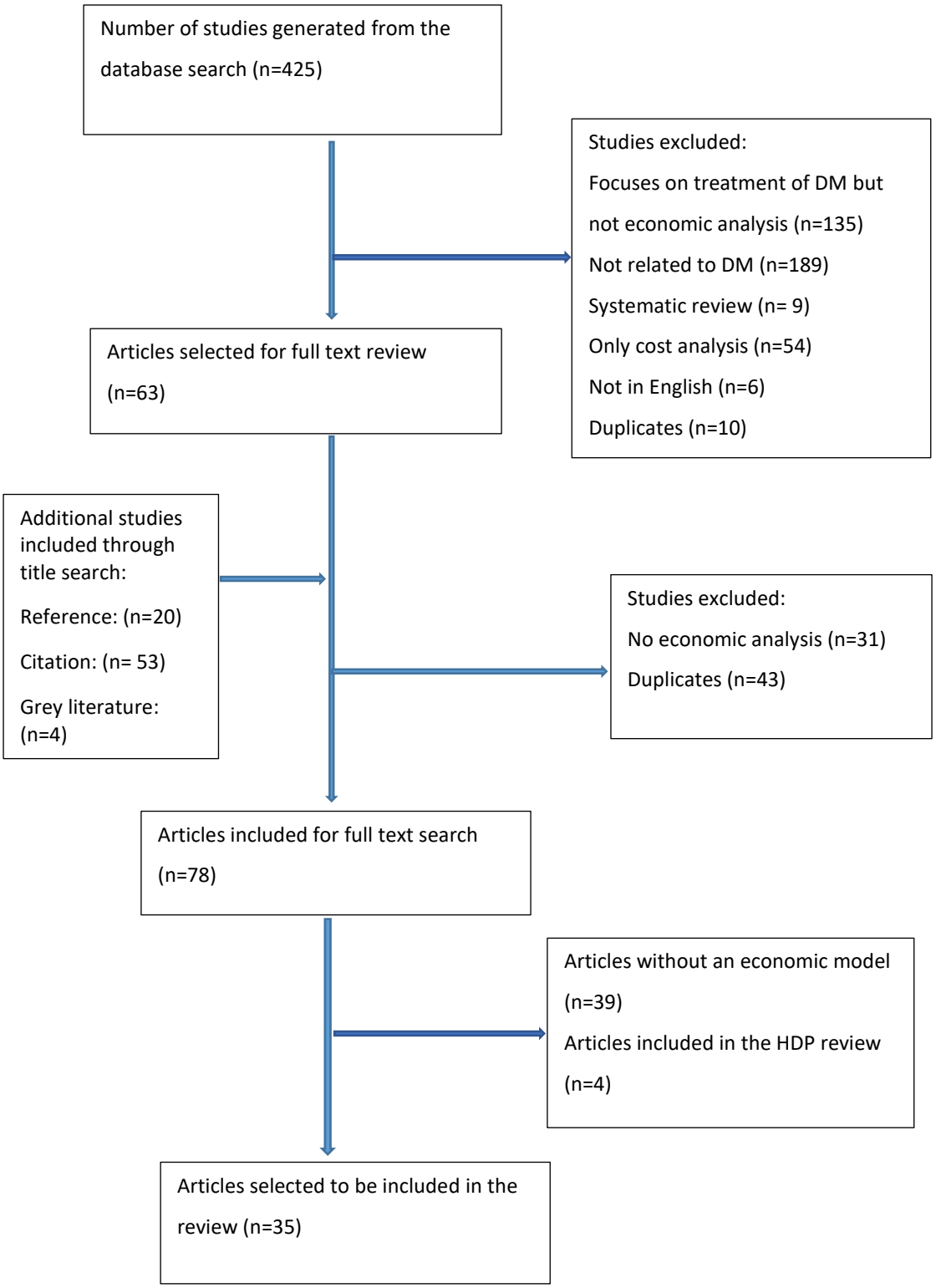
3.4.2.1 Systematic search

The diabetes mellitus model search identified 425 references after applying the search strategies in the two selected databases (259 from CINAHL and 156 from Medline). All the articles were included for abstract review and were screened for relevance. A total of 350 studies were excluded, 106 were not economic analysis studies, 165 were not related to DMP, 54 had only cost analysis, 9 were systematic reviews, 10 were duplicates and 6 were not in English. Seventy-eight articles remained after abstracts were screened. Additional 73 papers from reference and citation searches from the selected. Four grey pieces of literature were identified. When all sources were brought together, 43 studies were duplicates and 31 studies had no economic analysis (figure 2). Seventy-eight papers were included in the full text review. Thirty-nine of these did not have a model and 4 were included in the HDP model review. In total 35 studies were finally selected. (Figure 3.3).

3.4.2.2 Data extracted

As with the HDP model review, data extraction and summary of the full-text article was done in the following order: study population, intervention type, outcomes, model structure, time horizon, model perspective, health states and source of data for intervention effectiveness. Detailed tables with these summaries are presented in Appendix 3 (Table 11-15).

Figure 3.3 PRISMA diagram for economic evaluation models related to diabetes mellitus during pregnancy



3.4.2.3 Summary of included studies

The review identified 29 studies that followed decision trees as a method for the economic evaluation model. Three of the studies used the Markov state transition model. One study used a decision tree that followed a Markov state transition to capture long-term impact. Two of the analysis were done alongside trials. Among the selected literature, 17 studies focused on screening and diagnosis of diabetes in pregnancy (132-147) and 9 were on diet and lifestyle related interventions (148-156). Four of them focused on treatment of diabetes while one was on an antenatal-care related intervention (103, 157-159). One was on induction of labour (160), two on continuous glucose monitoring (161, 162) and two focused on economic burden of GDM (163, 164). (Figure 3.4)

i) Screening and diagnosis

All studies considered pregnant women as their study population, with some narrowing it down further to primi-gravidas at 24-28 weeks of gestation without pre-existing diabetes, women with GDM, diabetic pregnant women and women with GDM risk factors at 36 weeks of gestation.

The screening strategies primarily focused on various methods for screening GDM including comparing WHO screening methods, use of ultrasounds etc. In total, 15 studies developed models based on decision trees while one used a Markov state transition model.

The decision trees cover events related to diagnosis of women having GDM or no GDM, development of maternal complications like HDP, hospitalisation, mode of birth, preterm birth, macrosomia, stillbirth, newborn complications, NICU admission, maternal and newborn deaths, costs and QALYs. The Markov model used three maternal health states: perfect health, perfect health following hysterectomy, and maternal death. There were three neonatal health states: none/mild morbidity, moderate morbidity and severe morbidity/neonatal death.

Eleven models were developed from the health systems perspective, four were from the societal perspective and one from the payer's perspective. (Appendix 3: Table 11)

Absolute and relative risks of events and outcomes listed above were most commonly used in the models. Reduced risk of development of HDP, hospitalisation, mode of birth, preterm birth, macrosomia, stillbirth, newborn complications, NICU admission and maternal and newborn deaths were applied in the models. Effects of early screening or different screening mechanisms of GDM on the various outcomes mentioned above were sourced through direct observation from randomised controlled trials (RCTs) and observational studies. Literature reviews were also a common way to obtain data on intervention effectiveness. (Appendix 3: Table 15)

ii) Diet and lifestyle

There were nine studies that focused on interventions related to healthy dietary practice, physical exercise with or without counselling or overall lifestyle counselling. The outcome measures used a variety of indicators covering gestational weight gain, fasting glucose, insulin resistance, BMI, physical activity level, birth weight, adverse neonatal outcome, induction of labour, c-section, miscarriage, death, stillbirth, cost and QALY.

Except for two models developed alongside an RCT and a Markov model, the rest of the models were developed based on decision trees. The health events in the decision trees included GDM diagnosis status, gestational weight gain, type of treatment received, development of HDP, maternal complications and mode of birth. The terminal nodes were maternal morbidity and mortality.

Four of the studies used health system perspectives, three used the societal perspective while one followed both societal and health system perspectives. Five of the models covered a time horizon till birth, one till hospital discharge, one was between 28 weeks of gestation till birth and one for 12 months. (Appendix 3 Table 12)

Average risks of events and outcomes for baseline or comparators and relative risks for intervention effects were primarily extracted from secondary data sources for the above list. All studies used published literature as data sources except for one using direct observation. (Appendix 3 Table 15)

iii) Treatment

Five studies covered treatment of GDM. Three of the models targeted pregnant women with GDM, while one focused on all pregnant women and one focuses on women with Type 1 diabetes. The intervention evaluated included continuous glucose monitoring and in-patient treatment with insulin compared to regular care.

Primary outcome measures were morbidities like pre-eclampsia, thrombosis, macrosomia, neonatal complications, permanent brachial plexus injury, NICU admission, costs and QALYs.

All studies related to the treatment of GDM utilised decision trees for developing the models. Three of the models were developed from the health system perspective and one from the societal perspective. (Appendix 3 Table 13)

Average risk of events and relative risks for intervention effects were primarily extracted from secondary data sources for the above-mentioned events. All studies used published literature as data sources except for one that used direct observation. (Appendix 3 Table 15)

iv) Others

Among the five remaining studies included in this group, model population covered nulliparous women, women with GDM, women of reproductive age, women who are overweight or obese prior to conception.

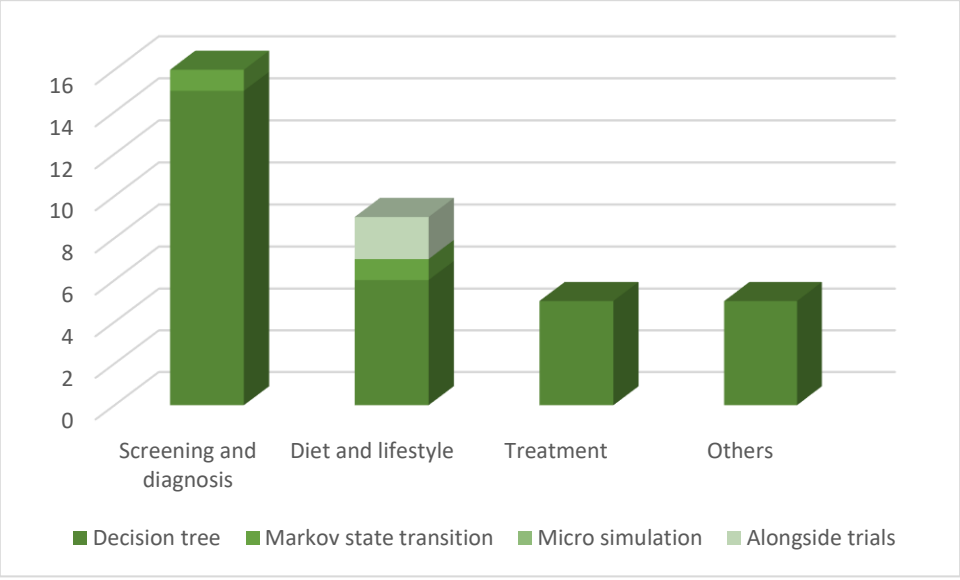
One of the studies was focused on induction of labour and two modelled economic burden of GDM, while one was on antenatal care. The outcomes covered mode of birth, HDP, macrosomia, stillbirth, preterm birth, birth defects, newborn and perinatal mortality.

While all models used decision trees, one used multiple decision trees to address short and long-term consequences. Another one utilised Markov state transition in addition to decision trees to incorporate long-term effects. Two models were from the health system perspective and two from the societal perspective. (Appendix 3 Table 14).

Health events covered labour management, development of HDP, mode of delivery/ foetal condition, maternal survival, macrosomia status, shoulder dystocia status, complications of mother and newborn, infant survival status and neonatal outcome.

The effectiveness data were used in the form of probabilities and relative and absolute risks. Studies modelling economic burden used increased risks of events depending on women's health status. One study used direct observation from trial data, while the rest used data from published literature. (Appendix 3 Table 15).

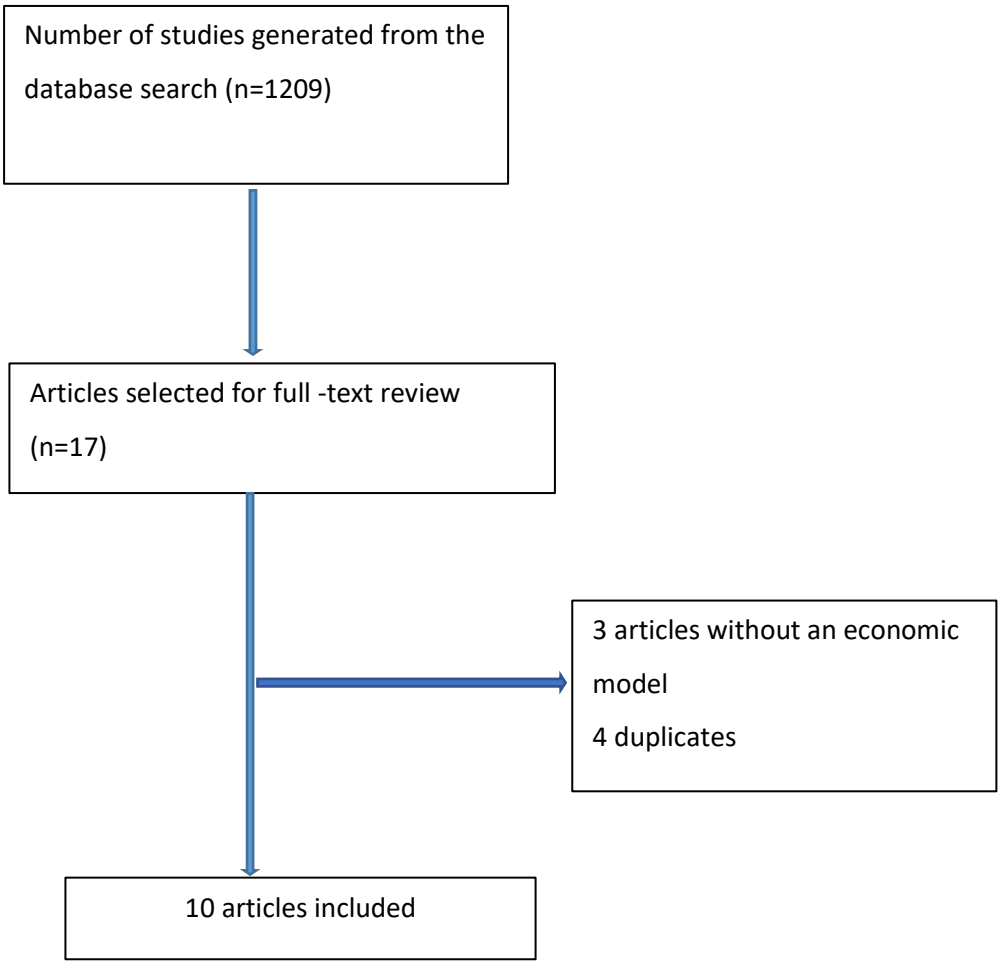
Figure 3.4 Distribution of model types by type of intervention for DMP



3.4.3 Narrative review for antenatal care

A total number of 1209 related articles were identified through the search engines (Medline: 484 and CINAHL: 725). Seventeen relevant economic evaluations were shortlisted based on relevance of title. Three of these did not have an economic model while four were captured in the systematic reviews. Ten of them were included in the review (Figure 3.5).

Figure 3.5 PRISMA diagram for antenatal care



The population of interest was mostly pregnant women, while one publication covered women of reproductive age. The models covered a variety of interventions including introduction of a clinical decision support system, package of maternal and newborn health interventions, m-health initiative, quality improvement initiatives, ensuring safe motherhood and prenatal nutritional supplementation. The outcomes included in the analysis covered antenatal visits, maternal complications, birth outcome

and morbidity, maternal and newborn mortality, stillbirths, preterm births, and babies with low birth weight. The time horizon covered varied from birth to one year to whole lifetime.

Five of the studies used decision tree-based models, while four were done alongside observational studies, and another model was developed based on the Lives Saved Tools (LiST). Models following decision trees used several health events. These included intervention allocation and outcomes, risk assessment results, ANC status, type of provider used for delivery and birth outcome. For newborns, neonatal health status, care-seeking pattern and final health outcome were used. One of the studies also included mortality of newborn and women and status of childhood stunting. The LiST-based model evaluated multiple interventions some of which covered interventions directly targeting HDP. (Appendix 3: Table 16)

Effectiveness data were used in the form of probabilities, intervention coverage and relative risks of interventions. GMatH and LiST has built-in effectiveness data and projects the impact of increased coverage of interventions. These were sourced through direct observations, meta-analysis, review of published literature and analysis of national databases. Three of the models were developed from the societal perspective, while one was from the third party payer's perspective. The rest were done from the health care perspective. Most of these models did not explicitly mention pre-eclampsia or GDM as complications or health events or outcomes except for the GMatH and LiST-based model. Both these models measure the effectiveness of the intervention on pre-eclampsia and subsequently on maternal deaths due to that. Both models, however, are limited in their capacity in estimating intermediate outcomes. GMatH is solely focused on estimated maternal mortality while the LiST produces outputs on maternal, child and newborn mortality, stillbirths and childhood undernutrition. (Appendix 3: Table 17)

3.4.4 Inclusion of interaction between hypertension and diabetes in pregnancy in the models

Three of the modelling studies identified in the review of models related to HDP considered women with GDM in their models. Bailey et al (2020) developed a decision tree-based model for a diet and lifestyle-related intervention (131). Interaction between the two conditions was taken into account in the decision tree-based model in the form of health events: development of gestational diabetes and hypertensive disease in pregnancy. Higher relative risk of HDP among women with GDM was incorporated. Madan and Chilcott (2012) undertook an economic analysis of a weight management programme and took into account both GDM and pre-eclampsia and their related complications (115). The decision tree-based model did not take into account the increased risk of pre-eclampsia among women with GDM. The main outcome of interest was to look at macrosomia among newborns and a

reduction in HDP and related complications. Neither of the two models incorporated pre-existing diabetes mellitus, which is also a risk factor for HDP. Rogozinska (2017)(116) evaluated a diet and lifestyle intervention including both GDM and preeclampsia as separate events in the decision tree. The model has not taken into account interaction between the two events.

Unlike the hypertensive disorder related models, a much larger number of models identified through the review of GDM-related models included the interaction between the two conditions, primarily through the increased risk of HDP among women with GDM. In total, 10 models that were related to GDM have recognised hypertensive disorders or pre-eclampsia as an important intermediate adverse outcome for women with GDM (103, 116, 132, 133, 139, 158, 159, 162, 164-166). All of the 11 models followed a decision tree structure where pre-eclampsia was led by GDM.

Review of the antenatal care-related models did not identify events or outcomes that take into account interaction between GDM/DMP and HDP.

3.5 Discussion

This review aimed to identify and explore the economic evaluation models related to HDP and DMP, extract information pertaining to the structural issues of the model and type of data applied to assess effectiveness, and explore interaction between the two disease conditions. As an added objective, the review also aimed to look at general antenatal care-related economic evaluation models in order to supplement what has been achieved through the two primary reviews.

The majority of the model population were pregnant women, with some narrowed down to specific risks, gestational age or disease prevalence, while some models expanded the population to women of reproductive age. The varying range of population provides insight into how the model population can be selected and the possible attributes that can be considered for inclusion in the model.

The choice of type of population for the model will essentially depend on the type of intervention selected for the model and the problem is question. In case of preventive measures, all pregnant women would cover a larger share of the population rather than focusing on those with some risk factors. Data on women with risk factors may not always be available. Covering reproductive age women would enable incorporating a wider set of interventions that can be introduced before conception, however, will again depend on the problem in question.

Interventions that the models evaluated could broadly be categorised as screening, diagnosis and treatment, diet and lifestyle, induction of labour, safe motherhood, antenatal care, quality of care, nutritional supplements, guideline adherence and health financing. Interventions covered by the models suggest antenatal care period provides the longest window to intervene in pregnancy. More

importantly, the interventions during this period indicate a need to focus on preventive measures. Prevention of HDP developed during pregnancy could happen through early screening and treatment, diet and exercise, ensuring a certain number of antenatal care visits, improving quality of care and nutritional supplements. Preventive interventions for GDM relates to counselling, diet and lifestyle related interventions. Regular monitoring, diagnosis and treatment related interventions were used to prevent more severe form of HDP such as pre-eclampsia.

Decision trees were the commonly adopted structure of the models, while few models were markov state transition models, cohort and individual based markov microsimulation models or models based on existing epidemiological software like the GMatH and LiST (following a microsimulation and cohort structure). A number of models were developed alongside randomised control trials or observational studies. The decision on the type of model will again depend on the research questions, risk factors included, the model intervention and the disease type, whether there is any interaction between patients and the outcomes of interest. Pregnancy outcomes would often involve outcome for both mothers and newborns. Adding pre-existing conditions of mothers may add an additional layer of complexity to the model. To supplement the findings from this systematic review, some additional literature reviews may be required to be finally able to decide the structure for the model to be developed.

While the review took note of the time horizon, type of outcome, intervention and effectiveness data used in developing the models, one focus was to extract the type of effectiveness data and the source of these data. Additional modelling studies identified through a narrative review for antenatal care economic models did not add a lot of new information to the systematic reviews. It was still useful to conduct the review to cover as much literature as possible.

The database searches were done separately for each condition. A predominant number of studies focused on economic modelling focusing on interventions related to identification, treatment and management of HDP and DMP. These can be useful in providing information on how the screening or diagnostic accuracy can be incorporated within a model. The other models evaluating impact of diet and lifestyle, induction of labour, nutritional supplements or treatment of diseases also focused on economic evaluation of single interventions and can feed information to the model to be developed for Bangladesh depending on what intervention is selected. Few of the studies modelled a package of interventions targeting safe motherhood, quality of care or insurance schemes for pregnant women. These models either depended on direct observational data or used the global maternal health policy model or the lives saved tools, which are epidemiological modelling software that uses its own built-in equations (83-85). These two software-based models that depend on coverage data and use a pre-

defined set of effectiveness parameters and relative risks associated with them. Additional search on methodologies followed by GMatH and LiST can provide guidance on ways to combine multiple interventions throughout the pregnancy continuum of care.

The models covered different time horizons. While the majority of the models where limited within pregnancy, childbirth and the post-partum period, a total of 20 studies have assessed far-reaching impacts on the long-term health of women, while three of these took into account lifetime horizon for the offspring too. This suggests that although a lifetime horizon is not always considered, there are available models that can guide ways to incorporate outcomes for mothers as well as their newborns for a lifetime.

There were no specific types of intervention that determined the time horizon or model type. Decision trees with limited number of health states with short time horizons were the most common structure. Models also utilised a combination of a decision tree for the short term and Markov state transition for lifetime effect or used multiple decision trees for short and long-term models. Two studies used the Markov state transition model and considered lifetime as the time horizon for both women and newborns. Some assessed long-term impact using decision trees.

The decision trees have been used for all sorts of interventions. Markov state transition models were also utilised for screening, lifestyle-related and safe motherhood promotion interventions. Two of the studies used micro-simulation and evaluated WHO ANC recommendations and induction of labour until discharge. There are plenty of options and issues that need to be taken into account when deciding the model design. It will depend on what intervention is selected for the model, the population characteristics and other model attributes to be included in the model.

Generally, the studies utilised a common set of outcomes that stretch from screening for the conditions, complications during pregnancy or at birth, birth outcome and long-term morbidity and survival. Outcome at birth including preterm birth, stillbirth, maternal and newborn death were the most commonly reported by the models. Further review and consultations may be required to decide on a set of the most important outcome for the thesis. The majority of the literature conducted the cost analysis from a health care system perspective while some used societal and third party payer perspectives. The perspective for the proposed research will rather rely upon what is most useful for decision makers.

Health states used in the decision trees varied depending on the intervention types, outcome and time horizon. Models related to GDM involved two to eight health states. The HDP-related decision trees included up to nine health states. The ANC models used two to five health states: the Markov states,

mild and severe morbidity for women and newborns and eventually death. The global maternal health policy model considered abortion, complications in labour and delivery, maternal and newborn morbidity and survival. Within each health state, there are a wide array of built-in conditions. For example, maternal complications vary widely and so do newborn complications. It will require further research and consultation to understand what are the most prevalent and relevant complications for both women and newborns in Bangladesh. Chapter one highlighted primary causes of maternal and newborn mortality and morbidity nationally. Additional consultation with experts and further literature review may be required to understand resultant newborn complications due to HDP and DMP.

In addition to the model structure, the review also covered the type of effectiveness data used in the models and how they were derived. Studies used average and relative risks of subsequent pregnancy and birth outcomes to describe the effectiveness of interventions. Some applied the risks to intermediate outcomes (e.g. pre-eclampsia upon better diagnostic accuracy), while some applied them directly to the final outcomes (e.g. mortality). Models have assessed both direct and indirect outcomes of an intervention. While some only focused on the number of HDP or GDM cases prevented, others have gone beyond these complications and estimated indirect impact on additional maternal and newborn health outcomes including mortality. For example, early screening and diagnosis of risk factors related to hypertensive disorder would lead to early treatment and eventually lead to an aversion of downstream outcomes like c-section or death. The way effectiveness data is applied to a model depends on the type of intervention, its related outcomes, and the availability of evidence regarding the effectiveness and causal pathway. In addition to revealing the various sources of effectiveness data, the reviews revealed important information on the possibility of modelling multiple interventions when required. Further exploration on detailed methodologies on incorporating multiple intervention effects together can add important information for model development.

The reviewed models predominantly used effectiveness data in terms of risk reduction through observed changes in outcomes. Both primary data from experimental or observational studies and secondary data on effectiveness from literature have been used to populate the models. One other important takeaway from the review would be the availability of a risk equation that takes into account, for example, both HDP and GDM and their consequences on downstream pregnancy and birth outcomes. The review did not find any studies that used risk equations based on patient characteristics (e.g. pre-existing chronic hypertension or diabetes mellitus) to determine the risk of subsequent events and outcomes in pregnancy. Basing effectiveness on observed changes in outcomes, rather than modelling changes via risk equations, has advantages and disadvantages. The

main disadvantage is that the effectiveness of some care improvements may be difficult to attribute to the different diseases; so, if increased access to ANC reduces stillbirths by 20%, is this due to improvements in HDP or GDM or both? This attribution has implications for determining what input data to include in the model and how comorbidities can be taken into account. Additional literature searches might be required in order to be able to populate the model with the most relevant data on effectiveness.

The review also revealed useful information on ways HDP and GDM interacted within a model. For interventions targeting HDP, there is no downstream effect on GDM. When risk factors of HDP are being taken into account in selecting population, women with GDM will be at a high risk of developing HDP. Pre-eclampsia on the other hand can be included as a downstream event of GDM. If the model is about an intervention that effects the risk of GDM or reduces risk of downstream events followed by GDM, it will reduce the risk of pre-eclampsia and its subsequent outcomes. This is very crucial for a model that intends to consider the two conditions together. None of the models, however, have taken into account pre-existing chronic diabetes mellitus which is also a risk factor for developing HDP.

3.5.1 Strengths and weaknesses

The systematic review utilised a robust search method and covered two important databases. All articles were included in the abstract review and upon shortlisting of abstracts, all references and citations were checked for relevant published documents. Grey literature was searched using the DART Europe e-thesis portal, the Google search engine and the NICE website.

One limitation is that the review used only two databases, but it has been confirmed by information experts that the two databases were large and comprehensive enough to cover most literature in the topic area. It should also be noted that the two reviews were supplemented by citation searches, reference searching, grey literature searches and a narrative review of the wider ANC literature. One other limitation would be that data were extracted by a single reviewer. However, whilst this would be a major drawback for critical appraisals (which by their nature incorporate subjective assessments), for this descriptive review it is less problematic. However, it should be recognised that one of the main purposes of the review was to inform the development of a model for Bangladesh. As that process is multifaceted, the need for a completely comprehensive review is diminished.

Another drawback is that the review did not involve any critical appraisal. However, given that the overall purpose of the review was to build understanding of the model structures and associated attributes, critical appraisal was deemed not necessary. It would not bring much added value for the purpose of this review, although it could potentially help in identifying high quality models with good

reporting. This could be useful if a model was to be rebuilt or adopted but was not the purpose of this review.

The narrative review of the antenatal care model did not add substantially to what the review specific to the two conditions has picked up. However, it is still reassuring that the review has been comprehensive and tried to explore all possible types of models that can be useful and informative for developing a model for Bangladesh.

3.6 Conclusion

This chapter provided useful insights about the various types of economic evaluation models that are available, related to hypertensive disorders and diabetes mellitus in pregnancy. The models were generally simple decision tree-based models with some exceptions. The review mostly identified cohort models, but individual-based models for pregnancy were also available. The interventions covered in the review were mostly focused on preventive care. The review identified how models have incorporated effectiveness data both on direct and indirect outcomes. The key mode of interaction between the two conditions is to consider GDM as a risk factor for HDP, particularly pre-eclampsia. Most models are focused on single intervention effects. Multiple intervention effects are usually incorporated through estimates based on direct observation or based on existing software. Modelled effects of multiple interventions are generally assumed to be independent but will need further exploration.

4. Understanding perspectives of stakeholders in addressing the two NCDs during pregnancy in Bangladesh

This chapter is divided into three sections. Section 4.1 describes the process of identification and preparing a list of interventions addressing the two NCDs in pregnancy. Section 4.2 discusses the process of developing the conceptual modelling framework. Whilst the two have their distinct methods described in the respective sections, stakeholders' perspective contributed to both.. The generic method of the stakeholder interview process is provided in section 4.1, while methods specific to the components of the two sections are detailed out in the relevant sections. The final section describes a set of useful interventions for the model that would ideally be implemented. Considering feasibility of inclusion in the model, a single intervention was selected to show how the model would work.

4.1 Identification of interventions

Interventions can be broadly defined as measures with the aim of improving health outcomes (167). These can be either preventive measures that stop disease onset or curative measures by treating or reducing severity or duration if a disease has already occurred. Interventions can focus on individuals or communities or target overall health system improvement. Interventions can cover a wide spectrum of measures such as clinical care that includes drugs and invasive care, vaccines, health education and behaviour change at individual or community level. Identifying a set of useful interventions and then evaluating their costs and effects covering outcomes during pregnancy, childbirth, postpartum as well as lifetime of women and children can add substantially to the existing evidence base.

Decisions around which intervention(s) to include in the model were made following an iterative process of literature review and incorporation of stakeholder views. The process can be divided into three components: a list of interventions identified through the two previous reviews done in chapters two and three, supplemented by an ad hoc review of documents, informal discussion with stakeholders to expand the list and finally, stakeholder interviews to inform the model and understand their views in the intervention selection and model development process. Figure 4.1 shows the detailed process of selecting the set of useful interventions.

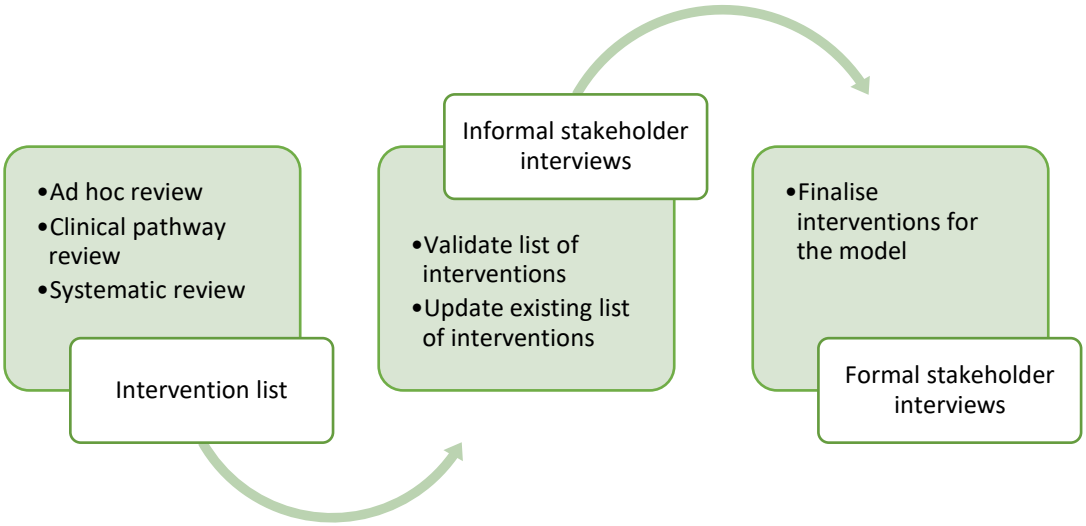


Figure 4.1 Process of intervention selection

Identifying a list of interventions based on document review and prior reviews would help in planning the discussion with stakeholders and aide in identifying priority interventions.

4.1.1 List of interventions

In order to develop a model for cost-effectiveness analysis of selected interventions addressing HDP and DMP, one crucial step was to list down a set of proven and recommended interventions that could be modelled. This section describes the objectives, detailed methodology and the list of identified interventions from the different sources.

4.1.1.1 Objective

The objective of this section is to develop a list of interventions based on clinical guideline review, systematic reviews and additional desk review.

4.1.1.2 Methods

Type of interventions

The list included interventions related to prevention, diagnosis and management of the conditions. Interventions that are feasible for Bangladesh and targeted pregnant women have been included.

Clinical pathway review and systematic reviews for preparing a list of interventions

The two reviews done in chapter 2 and 3 were the primary source of interventions. The national and global clinical guidelines provided a comprehensive list of possible ways to prevent, treat and manage the two conditions. The systematic review helped include additional interventions not covered in the

clinical pathway review. Interventions that are included in national strategy and planning documents, global recommendations and other published literature were listed.

Supplemental literature review for the list of interventions

The initial list of interventions was supplemented through an ad hoc review of documents. The selection of documents for the review was done following three mechanisms: a Google search, use of documents retrieved in the literature search done for chapters two and three, use of prior knowledge and informal discussion with colleagues working in the field of maternal and newborn health. Since global and country-level policy documents are more widely available through Google, it was the preferred means to get hold of these documents. Generic search terms such as maternal health, gestational diabetes, diabetes in pregnancy, hypertensive disorder in pregnancy, pre-eclampsia, eclampsia, intervention, programme and strategy were used in different combinations. Strategy documents that were known from before were directly searched by title or obtained through communication with colleagues. A large number of the documents were already covered in the clinical pathway review in chapter two.

The interventions were divided across the different stages of pregnancy, childbirth and the postpartum period. Interventions with their sources were documented in a Microsoft Excel worksheet.

4.1.1.3 Results

List of documents

The review of documents included World Health Organisation (WHO) recommendations, the Lancet series on maternal health and nutrition, the Bangladesh maternal health strategy, the Bangladesh national action plan for maternal health, Postpartum Haemorrhage (PPH) and Eclampsia Action Plan Bangladesh, National Plan of Action on Nutrition (NPAN) Bangladesh. Table 4.1 lists the documents included for identifying the interventions.

Table 4.1: List of documents included in the ad hoc review

	Global strategies and recommendations: publications
1	The Global Strategy for Women's, Children's and Adolescent's Health (168)
2	Managing Complications in Pregnancy and Childbirth: a guide for midwives and doctors (10)
3	WHO Recommendations for Management of Pre-Eclampsia and Eclampsia (29)
4	WHO Recommendation on the Diagnosis of Gestational Diabetes in Pregnancy (71)
5	WHO Recommendations on Antenatal Care for Positive Pregnancy Experience (65)
6	WHO Recommendation on Community Mobilization through Facilitated Participatory Learning and Action Cycles with Women's Groups for Maternal and Newborn Health (169)
7	WHO recommendation: Calcium supplementation during pregnancy for prevention of pre-eclampsia and its complications (170)
	Bangladesh specific national strategies and action plans: publications
8	Bangladesh National Strategy for Maternal Health 2019-2030 (63)
9	PPH and Eclampsia Action Plan Bangladesh 2017-2022 (70)
10	Maternal Health Action Plan Bangladesh (69)
11	Second National Plan of Action for Nutrition (171)

List of interventions

Below are the details of the interventions including the activities under each throughout the pregnancy continuum of care: antenatal care, delivery and postnatal care, management of HDP and DMP. Appendix 4.1 lists all interventions and also indicates the source documents and possible source of evidence related to the interventions. Interventions related to management of pre-eclampsia/eclampsia can take place during pregnancy, childbirth or postpartum.

i) Interventions during pregnancy

The WHO recommendations on antenatal care are set out in five groups of interventions: ensuring maternal nutrition, maternal and foetal assessment, preventive measures, common physiological symptoms and improving utilization and quality of ANC by strengthening the health system.

In general, antenatal care related interventions documented from all sources could be divided across these five broad categories. Taking into account of the five groups mentioned above, the nutrition-related intervention directly affecting HDP would be calcium supplementation. Identification, screening and diagnosis of HDP and DMP would be done through maternal assessment for both of the conditions. The assessment is expected to lead to allocating to women to a treatment pathway, which

can include introducing low dose aspirin (universal or high risk), drugs treatment for women with pre-existing or gestational hypertension and drug or insulin for women with DMP.

A number of these interventions fall under prevention. Diet and lifestyle counselling and awareness building among husbands or partners are part of preventive measures. Improving women's nutritional status through calcium supplementation would also fall under the preventive interventions for gestational hypertension, pre-eclampsia and eclampsia. Maternal and foetal assessment leading to early identification of high risk women and treatment could also prevent the occurrence of pregnancy induced hypertension, pre-eclampsia and eclampsia as well as GDM. Health system level interventions can be both preventive or curative depending on the type of intervention and how they aide in improving care.

The health system interventions are cross cutting and able to improve overall uptake and quality of care. They cover ensuring a minimum number of contacts for ANC, women-held case notes during ANC visits, midwife-led care, group antenatal care, community-based interventions to improve communication and support and having a set ANC contact schedule in place (Table 4.2, Appendix 4.1). Although generic, these interventions are also able to address the burden of HDP and DMP.

Some of the interventions listed during ANC can be curative. Once screened as hypertensive, weekly blood pressure monitoring and referral to higher-level facilities in case BP rises above 90 are recommended. Antihypertensive drugs are recommended for women reaching DBP >95. Counselling on possible danger signs of pre-eclampsia/eclampsia for women and families is a recommended intervention to increase awareness and knowledge to ensure timely referral to a healthcare facility. (Appendix 4.1)

For women at risk of developing pre-eclampsia or eclampsia and at gestational age of less than 37 weeks, intervention ensuring regular check-up covering monitoring of blood pressure, urine, reflexes and foetal conditions is recommended. Ensuring referral to secondary or tertiary-level facilities for further management depending on their blood pressure and urine test reports is another intervention. (Appendix 4.1). In case of severe pre-eclampsia or eclampsia, a loading dose of $MgSO_4$ and referral is required upon rapid assessment of vital signs. In case of convulsion, $MgSO_4$ needs to start after convulsion. Oxygen administration is essential during convulsion.

Women with diabetes are recommended an increased number of ANC visits. Women with diabetes or at risk of developing GDM should be referred to secondary or tertiary-level facilities in Bangladesh. Those receiving oral tablets for controlling blood glucose level are recommended to switch to insulin.

Advice on diet and exercise to maintain weight and control blood glucose levels should also be given. (Appendix 4.1)

Among the crosscutting interventions, health worker training for detecting preeclampsia and eclampsia and availability of equipment of drugs for such management were identified and listed.

There is no evidence available on the number of ANC visits that is optimal. One study covered by the systematic review looked at a reduced number of visits to increase ANC uptake. Studies have reported effectiveness of insulin in controlling blood glucose and subsequent positive pregnancy outcomes. WHO recommendations reported effectiveness of diet and exercise counselling on pre-eclampsia, c-section, weight gain, preterm birth, macrosomia, low birth weight, induction of labour, shoulder dystocia and neonatal hypoglycaemia (172). Cochrane reviews have reported the effectiveness of low dose aspirin in preventing pre-eclampsia . WHO also has specific recommendations with evidence of effectiveness of calcium supplementation among pregnant women on gestational hypertension, pre-eclampsia, eclampsia, pre-term birth, stillbirth, newborn and maternal deaths (170). A more recent WHO recommendation discussed the importance of pre-pregnancy calcium supplementation for addressing gestational hypertension, pre-eclampsia, eclampsia and their related complications (72).

The WHO recommendations on treatment of pre-eclampsia and eclampsia included evidence of antihypertensive drugs for moderate and severe hypertension in pregnancy. The outcomes were mild and severe pre-eclampsia, eclampsia, HELLP syndrome, shoulder dystocia and maternal death (29). Evidence on the effect of low-dose aspirin on HDP is available in the WHO recommendations based on a Cochrane systematic review. Effectiveness on gestational hypertension, pre-eclampsia, preterm birth, newborns who are small for gestational age and newborn deaths are available (29, 173). Evidence of interventions related to treatment of diabetes mellitus are available in WHO recommendations, NICE clinical guidelines and articles identified in the systematic reviews.

ii) Delivery or care around the time of birth

For delivery care, induction of labour or early birth have been recommended depending on the severity of the women's condition. Expectant management is recommended in case of absence of several severe symptoms of HDP and DMP as detailed out in table 4.2. Recommendations related to labour and delivery are from NICE guidelines and WHO recommendations. The national guideline and WHO recommendation calls for ensuring skilled care at birth, be it at home or in a facility. Interventions in this groups are related to clinical management of mode of birth.

Few studies retrieved from the systematic review related to induction of labour vs expectant monitoring had effectiveness data on resultant type of births, which can be useful in case such interventions are prioritised. (Appendix 4.1)

iii) Postnatal period

Continued treatment with antihypertensive drugs in the postnatal period is recommended for those on medication before conception or those with severe hypertension in the postnatal period. Among women with GDM, glucose tests after giving birth and 6-12 weeks postpartum are recommended to check if women developed type 2 diabetes. Interventions during postnatal care are related to management of the conditions and identifying the occurrence of long-term chronic conditions.

As described earlier, evidence on the effectiveness of antihypertensive drugs is available for certain maternal health indicators, such as pre-eclampsia, eclampsia, and maternal death post birth. (Appendix 4.1)

iv) Cross- cutting

Among the crosscutting interventions are the health system improvements like ensuring a skilled birth attendant[7], health worker training and health financing-related interventions. (Appendix 4.1)

Effectiveness data for these interventions were not readily available in the clinical guidelines or national or global strategy documents. Review of economic evaluation models covered health financing but were limited to mortality and estimated through the LiST. Interventions in this category will need additional review of literature to extract effectiveness data.

Table 4.2: Interventions during antenatal period

Interventions during antenatal period	Preventive	Curative, treatment or management related
Early uptake ANC (<12 weeks)	√	√
ANC attendance (Scheduled ANCs: 1 in <12 weeks, then 20,26,30,34,36, 38, 40 weeks of gestation)	√	√
History of women for assessment of risk of HDP or DMP ***- LMP and EDD Calculation*** ***- Past obstetric history (if any)*** ***- Family history*** ***- Medical history*** ***- History of TT immunization***	√	

[7] Health professional like midwife, doctor and nurse

- Ask about risk factors and refer women needing additional ANC		
Physical examination for identification and treatment: ***- Blood Pressure, pulse, weight, height, BMI*** ***- Anaemia, jaundice, oedema***		√
Investigation to diagnose presence of HDP or DMP **- urine R/M/E (ASB, protein, glucose)** **- USG to exclude congenital anomalies and multiple pregnancy** **- 2 hrs after 75gm glucose**		√
Nutritional supplementation **-Calcium**	√	
Counselling **-Danger signs** **- Rest** **-Diet and exercise** **-Birth planning and emergency preparedness**	√	√
Management of high risk pregnancies **-Low-dose aspirin (75mg) to begin as early as 12 weeks for women at high risk of pre-eclampsia** **-Frequent follow up for monitoring of PE development** **-Additional counselling to family members about the danger signs** **-Referral for women with DBP 90+ and proteinurea 2+ refer to secondary or tertiary level facility for further management**	√	√
Management of pre-eclampsia/eclampsia **-Antihypertensive drugs** **-Referral**		√
Management of diabetes mellitus **-Referral to higher level facilities** **-Insulin administration**		√
Health system level interventions **-Raising awareness through community mobilization** **- Women held case-notes or antenatal care cards** **-Pregnancy registration** **-Group antenatal care**	√	√

4.1.2 Informal Stakeholder consultation

Informal discussion with the stakeholders fed additional information to the list of interventions prepared, based on the clinical pathway review, systematic review and review of strategies and action plans. This step was important to build a rapport with stakeholders before the formal interviews and validate the list of interventions produced through the exercise described in section 4.1.1. The section describes the objectives, methodology used in identifying who the stakeholders are and how the informal consultations were held and what were the findings.

The objective of this exercise was to identify stakeholders and validate and expand the existing list of interventions based on stakeholder opinion.

4.1.2.2 Methods

Identifying stakeholders

A simple literature search was done to identify a list of agencies or organizations who are the stakeholders. Stakeholders were identified based on an existing known pool of experts that included funding agencies who often advocates policies through the government, researchers, implementing agencies and government bodies in Bangladesh working in the area of maternal and newborn health.

Validating the list of interventions

The informal stakeholder consultation was utilised to update the list of interventions generated, based on the reviews, and identify priority areas. In addition to the informal discussion, notes from group meetings organised for developing the national action plan for maternal health were reviewed. I personally attended the group meeting on pre-eclampsia and eclampsia. I reviewed meeting notes from the antenatal care group to identify and add any interventions not included to the original list. At this stage, the discussions were informal and did not include any structured data collection or analysis. As such, the discussions did not require research ethics approval.

Formal stakeholder involvement was built into the final two years of the thesis. This followed protocol development and ethics committee approval and has been explained in the next section.

4.1.2.3 Results

Identifying stakeholders

Stakeholders are a group of people or organizations directly or indirectly interested in, involved in or invested in the topic area (174). There are multiple ways to identify who should be included as a stakeholder for economic evaluation model development. Some suggest stakeholders be subject experts, while others recommend the inclusion of modellers, decision-makers, and health professionals (175). Patients/clients are also often considered as stakeholders.

For identifying decision problems, decision-makers, funders, and implementers are essential. The World Health Organization (WHO) prescribe a detailed methodology for identifying stakeholder characteristics through an analysis covering position/organization, knowledge on policy, position on the policy matter, interest, alliances, available resources, power and leadership (174) . The WHO has a detailed list of who can be the stakeholders was followed for selecting stakeholders. Consequently, this part of the thesis included government bodies, practitioners at the central and local level (physicians, field-level service providers), development partners, professional bodies and researchers who work on the specific or broader topic, and programme implementers like Non-Government Organizations (NGOs).

Informal consultation

It was almost unanimously agreed that the antenatal period was critical for handling women with HDP or DMP. Identification and screening of high-risk women was emphasised by stakeholders. Early uptake of ANC along with all components of care was mentioned by all. Pregnancy identification and registration was identified as an important by one of the experts and was added to the existing list of interventions. Timing of first ANC contact was also crucial to ensure women are in touch with the health system as soon as possible.

In addition to that, it was emphasised that the health workforce needed to be trained in identification and screening of these complications. Awareness building at community level was deemed important in order to increase utilisation. Raising awareness on NCDs and adopting a life-course approach for treatment and management of women with HDP and GDM was also highlighted by one expert. Continuity of care throughout pregnancy, especially for women detected with HDP or DMP, and follow-up post birth were highlighted as important steps to address long term chronic conditions.

4.1.3 Stakeholder interviews for selection of interventions for the model

4.1.3.1 Introduction

The formal stakeholder interviews can be broadly divided into two sections. The first part of the consultation focused on selecting interventions for the economic evaluation model. The second part focuses on understanding their views pertaining to the finalisation of the conceptual modelling framework. Whilst this section focuses solely on the interventions that the stakeholders thought were important, the conceptual modelling framework has been described in a later section of this chapter.

The final step for selecting interventions for the model was the formal stakeholder interviews. The large number of interventions obtained through the list needed to be narrowed down to a limited number of interventions that could plausibly be evaluated in an economic model. The clinical pathway review and the systematic review highlighted the need for interventions throughout the pregnancy

continuum of care with antenatal care having the longest window for interventions. Within the antenatal care interventions, preventive interventions dominated the existing health economic modelling studies identified in the systematic review. The overarching goal of incorporating stakeholder views was to have them on board in the process of developing an economic evaluation model that would be useful to them and informative for programme and policy making. Having stakeholders on board during the model development process can also enhance its usage and implementation in future. This part of the exercise did not follow the formal methods of intervention prioritisation but a step-by-step approach was taken to incorporate stakeholder views in identifying interventions for the model. The list of interventions was first expanded based on stakeholder interview while it was narrowed down eventually to select the intervention for the model.

4.1.3.2 Objectives

Objectives of the stakeholder interviews were to:

1. To inform and understand stakeholder views on the interventions by
   - Asking stakeholders whether the existing list of interventions is complete, or whether there are other things, to enable development of a complete list of interventions.
   - Getting some idea from stakeholders which interventions would be most useful to include and evaluate in the model.

2. To develop a conceptual modelling framework based on the reviews and incorporating views of stakeholders in Bangladesh

4.1.3.3 Methods

Sample size and sampling

As the purpose of the stakeholder interviews was to understand their opinion on various aspects of the economic evaluation model, the qualitative interviews did not have to reach a saturation point. The number of stakeholders was chosen purposively and through snowballing to cover a range of experts in the field of maternal health and non-communicable diseases in Bangladesh.

Ethical approval

A protocol was developed and ethical approval was received from the Internal Review Board of icddr,b in Bangladesh (PR20123) (Appendix 4.2). The protocol was later uploaded to the University of Sheffield's online ethics application system and approved. Further extension of the ethics approval was sought, and the protocol has been approved until February 2024. (Appendix 4.2)

Identifying and mapping stakeholders

The first step for identifying stakeholders was done through desk reviews. National strategies, five-year plans and programme-related operational plans were reviewed to prepare an exhaustive list of the agencies within the government, donor community and professional bodies involved in the field. An initial list of development partners and relevant bodies who are potential stakeholders for this research was available from the informal interviews. Both were compared, and an extensive list of relevant experts was prepared. Service providers from different tiers of the government health system were also included to capture the viewpoint of those working in the frontline and directly providing services.

The second step was to conduct interviews with the initial list of identified stakeholders and snowball for possible additional relevant stakeholders.

Stakeholder interviews

In-depth interviews were held with the stakeholders individually. All interviews were one-to-one and conducted through Google Meet as per the University of Sheffield's guidelines. Consent forms were sent with an invitation to be sent back with an electronic signature. Each participant was verbally asked if they agreed to the interview being recorded. A presentation was given during the first 10 minutes of the interviews and the objectives and research questions were described. The duration of the interviews ranged between 40-60 minutes.

Discussion on interventions addressing HDP and DMP

Stakeholders were presented with a list of interventions and asked to select key interventions in terms of their importance in addressing HDP and DMP in Bangladesh. There were 24 interventions selected in total through document reviews, and these were included in the presentation. Also, there were some overlaps between the interventions, and they were not mutually exclusive. The interventions were divided into four segments; antenatal care, continuum of care, management of diabetes mellitus, and hypertensive disorder. A single slide containing all the interventions was shown to participants during the interview. Stakeholders were asked if the list of complete or if they wanted to add any intervention to the list. Were any additional interventions recommended, the list was updated.

The stakeholders were then asked to choose the five key interventions that in their view would help address HDP and DMP. Once the top five were chosen, they were asked to select the top three and at the final stage to select a single intervention.

4.1.3.4 Results

Stakeholder identification

An initial list of stakeholders was prepared and included in the protocol. Additional stakeholders were included through snowballing based on suggestions coming from each IDI. A total of 15 interviews were conducted. Among the participants were government programme managers/ deputy programme managers, health economists, researchers, funders, non-government implementing agencies and practitioners. The table below includes a list of the type of stakeholders involved in the consultations. (Table 4.3)

Table 4.3 Type of stakeholders interviewed

Type of stakeholder	Number
Government bodies	6
Medical practitioners	3
Academia	2
Implementing agencies	1
Funding agencies	3

Stakeholder views on the list of interventions

A total of 24 interventions were included in the list obtained through the reviews and informal stakeholder consultations and were presented to stakeholders.

When asked about the completeness of the list of 24 interventions, a few additions were made by some of the participants. The most common intervention suggested outside of the list was pre-conception counselling about the two conditions . The other newly suggested interventions were community-level screening programmes for hypertension and diabetes mellitus, community-level distribution of calcium to protect against hypertensive disorder, and community-level distribution of MgSO4 for pre-eclampsia and eclampsia. One stakeholder also suggested post-partum family planning as a measure to prevent future HDP episodes. Three experts mentioned pre-conception counselling as an important intervention.

Eight of the experts noted that antenatal care visits were essential. Most of them also said it would only be effective if high-quality service was received ensuring service providers covered all components of antenatal care. Within the antenatal package of interventions, four experts highlighted the importance of identification of high-risk women separately. Three experts considered the importance of increased awareness through counselling as important. One emphasised developing a

model for screening and diagnosis of the two conditions and preparing facilities for providing quality ANC. Making a standard protocol for patient management available for all, increased number of ANC visits for high-risk women and ensuring calcium supplementation were also highlighted as key interventions to address HDP and GDM.

Interventions related to management of pre-eclampsia and eclampsia through pre-referral management/loading dose of MgSO4, stabilisation, and referral to higher-level facilities were cited as crucial interventions by six of the experts. Three of the experts mentioned ensuring availability of basic/comprehensive emergency obstetric care facilities round the clock. Few experts pointed out that improved screening through the ANC check-ups would increase the number of patients visiting higher-level facilities, and the assumption that 24/7 emergency obstetric care (EmOC) was available would need to be incorporated into the model. Promotion of facility delivery and community-level screening and distribution of MgSO4, each were selected twice. Insulin for diabetic mothers, hypertension treatment with labetalol/nifedipine/methyldopa and encouraging mothers to have personal device for monitoring BP and glucose were the interventions, each of which were selected once by an expert.

Table 4.4 below presents the interventions based on stakeholder interviews, identified as the most important interventions. ANC along with all necessary components was identified as the single intervention to be implemented. Management of pre-eclampsia/eclampsia emerged among the most important intervention. The third intervention was identification and screening of high-risk pregnancies, which is also a component of ANC. Identification and screening can be done in two ways, the screening can be home-based through community-level domiciliary workers or done at facilities by health service providers. The number of ANC visits, increased awareness through counselling during antenatal care and calcium supplements were also among the interventions chosen by experts as the most important interventions. These are also part of the components of antenatal care.

The interventions listed through reviews and added later by experts but not identified as important include pregnancy registration/couple registration, dietary restrictions, physical exercise, induction of labour or emergency c-section and postnatal screening and diagnosis of hypertension or diabetes mellitus. The rest were covered by the selected interventions directly or indirectly.

Table 4.4 List of interventions after stakeholder interviews by stakeholders by group

Group	Interventions
Pre-conception care	Pre-conception counselling
Antenatal care	Four antenatal visits with all components (nutrition, assessment, counselling)
	Identification and screening/diagnosis of high-risk pregnancy
	Increased awareness through antenatal counselling
	Antenatal care visits (4 or 8)
	Women-held case notes/antenatal care cards
	Increased number of ANC visits for high-risk women
	Calcium supplements
Management and treatment of conditions	Community-level screening and distribution of MgSO4
	Management of pre-eclampsia/eclampsia
	Screening and diagnosis at community level
	Insulin for diabetic mothers
	Hypertension treatment with labetalol/nifedipine/methyldopa
	Encourage mothers to have personal device for monitoring BP and glucose
	Availability of drugs free of cost
	Increase facility birth
Postnatal care	Postnatal diagnosis and management
	Postpartum family planning
Health system interventions	Demand-side financing scheme
	24/7 availability of EmOC facilities
	Ensure availability of standard treatment protocol

The interventions can also be divided into four groups: pre-conception care, antenatal care, management of complications at facility and community levels and health systems interventions. Table 4.5 below categorised the interventions by these groups. The majority of interventions fell under two groups: antenatal care and management and treatment of conditions.

The antenatal care interventions were overlapping. While the nutrition supplements, assessment and counselling aspects all fall within ensuring four ANC visits with all components, these have also been selected as standalone interventions. Identification and screening/diagnosis of high-risk pregnancies, calcium supplements and ensuring four or eight antenatal care visits are also part of the package of antenatal care. Some stakeholders have selected four ANC visits with all components as the most important to emphasise the need for each of the components. Like ANC, management and treatment of conditions also have a few overlapping interventions. These include screening and management at community level, primarily focused on management of pre-eclampsia/eclampsia in the community, and introducing MgSO4.

Six interventions were highlighted by the stakeholders the maximum number of times. These fall under three broad interventions, antenatal care with all essential components and required number of visits, management of pre-eclampsia/eclampsia and ensuring availability of EmOC services (Table 4.5). Antenatal care dominated the interventions identified through stakeholder interviews. This re-emphasised on the need of developing economic evaluation model on the antenatal care package.

Table 4.5 List of interventions selected as most important by stakeholders by group

Group	Interventions	Components
Antenatal	Antenatal care with all components	- At least 4 antenatal care visits - Assessment of mothers for identification and screening of high risk pregnancies - Nutritional supplement (calcium) - Counselling for increased awareness
Antenatal/birth/postnatal	Management of pre-eclampsia/eclampsia	-
Health system	Availability of 24/7 EmOC services	-

4.2 Developing the conceptual modelling framework

Developing an economic evaluation model is an iterative process. Modellers have to make several decisions to finalise the model structure. Questions on what to choose arise at each stage of model development. These include decisions regarding what interventions or comparators should be included, the possible health states and sequence of events, population to model, and the modelling methods to be followed. Stakeholder involvement adds a new dimension of understanding of the decision problem, thereby assisting in developing a valid and relevant set of parameters for the model (176, 177). The stakeholder interviews can help inform and understand their views on the model's focus, answering questions like what should be included, if the current care pathway or sequence of events is logical, and how the selected parameters should be included using existing evidence.

A conceptual modelling framework represents understanding the complexity of the decision problem and available choices for a specific problem identified by the modeller (177). It has been defined it as "The abstraction and representation of complex phenomena of interest in some readily expressible form" (Tappenden et al, 2012, Page 9) (176). The conceptual framework provides a full picture of the possible model attributes and parameters that need to be incorporated. The initial draft framework can get very complex, covering a comprehensive set of risk factors, interventions, and outcomes (176, 177).

The good practice of developing a conceptual model suggested by Squires et al (2016) includes the following (177):

i) Developing an understanding of the dynamic complex systems of public health economic modelling taking into account history, lack of a clear boundary, heterogeneity and possible externalities
ii) Developing understanding of the problem for a valid, credible and feasible model
iii) Incorporating views of stakeholders throughout the model development process
iv) Considering the determinants of health including individual, community, environmental and social factors

This section draws from the reviews done in chapters two and three and incorporates stakeholders' view into the model. There are several stages of a conceptual modelling framework: understanding the problem, choosing model options, determining the model's scope, deciding on the level of details, setting the premises, and finally, deciding on the type of model to be implemented (177). To highlight all the stages, a draft conceptual modelling framework was developed based on what has been learnt about the two conditions through the literature reviews (Appendix 4.3). It included the disease

conditions, definitions of the conditions, events, immediate and long-term outcomes, possible perspectives, time horizon, and sub-groups.

4.2.1 Objectives

The objective of this part of the stakeholder consultation was to receive inputs from stakeholders on setting the model scope in order to develop the final conceptual modelling framework.

Specific objectives of this part of the consultation were:

- To share and discuss the draft conceptual framework with stakeholders in terms of the following:
    a. The decision problem
    b. The sequence of clinical events and pathways
    c. Immediate , long-term and aggregate outcomes
    d. Aggregate outcome measures
    e. Model perspective, and
    f. The time horizon
    g. Selection of sub-groups for the model (if any)
- To summarise the model attributes based on the stakeholder consultation
- To gather insights on possible model structure
- To identify sources of relevant cost data
- To develop the final conceptual modelling framework for the thesis

4.2.2 Methods

Generic methodology related to sample size, sampling and ethical approval for the stakeholder consultation has been described in section 4.1.3.3. This section focuses on how the conceptual modelling framework has been developed.

The draft conceptual model was developed with inputs based on the reviews undertaken in chapters two and three and the preceding sections of this chapter. As suggested in literature, the process followed reviews to develop understanding of the problem, to learn about the clinical pathways of the conditions and to identify recommended interventions that can help mitigate the problem and are feasible in the context of Bangladesh. The first draft conceptual framework was developed including all available information on risks, events, outcomes and interventions. (Appendix 4.3)

The draft conceptual framework was presented to the stakeholders in the form of several Powerpoint slides to simplify the components and make it easier to understand and receive feedback.

Each stakeholder was given a description of the disease conditions, events and outcomes for mothers and newborns. They were asked to share their thoughts about the target population, model time horizon, perspective and preferred unit for aggregate outcome (DALY/ QALY). Finally, discussion of possible model structure was held. This part, however, was only limited among those familiar with economic evaluation models.

Figure 4.2 summarises the steps followed to develop and finalise the conceptual modelling framework. The white boxes depict the steps followed in finalising the model scope or specifications while the green boxes contain details of what was involved in each step. Hence these are often overlapping.

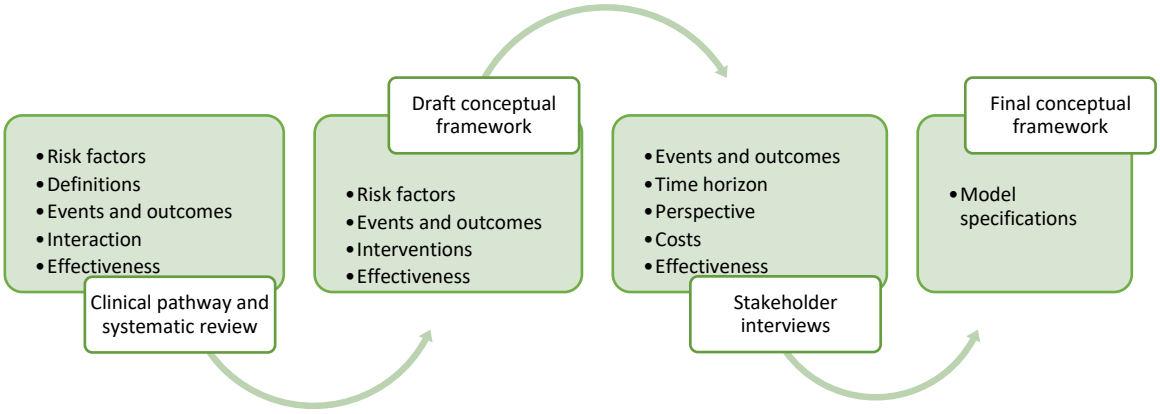


Figure 4.2 Process of developing the conceptual modelling framework

4.2.3 Results

4.2.3.1 Model scope

The model, based on reviews and stakeholder views would focus on a package of antenatal care interventions. This would mean pregnant women were going to be the model population. The key pathway to be identified would be around antenatal care. Interventions prior to pregnancy hence were not considered for the model.

4.2.3.2 Outcomes for mothers and newborns

The consensus from all interviews was that outcomes around the time of birth, both for mother and babies, needed to be included in the model. Table 4.6 lists possible outcomes among mothers and babies after childbirth and long-term health events that can occur among mothers and their babies.

In terms of pregnancy or birth outcomes, experts asked to include mode of birth, maternal death, and morbidity around the time of delivery. Only one expert suggested including renal failure or Chronic Kidney Disease as an outcome for pre-eclampsia/eclampsia. One expert indicated including infection for mothers with diabetes mellitus during pregnancy, who are more likely to develop an infection in the post-partum period. For babies, the outcomes to be included covered abortion/miscarriage, stillbirth, preterm birth, newborn death, newborn morbidity, and disability.

In terms of the long-term outcomes, the experts suggested focusing more on long-term morbidities among mothers. Since the model was going to focus on hypertension and diabetes, they emphasized the development of chronic hypertension and chronic diabetes mellitus among women later in their lives.

The majority of the stakeholders suggested looking at the impact on babies until the time of birth. One expert suggested including the development of chronic conditions in the long-term.

Table 4.6 List of possible outcomes for mothers and newborns

Women	**Newborn**

Mode of birth	Birth outcome
	• Abortion/miscarriage
	• Stillbirth
	• Preterm birth
	  ○ Low birth weight
	• Newborn death
	• Macrosomia
	  ○ Shoulder dystocia
	• Intra Uterine Growth Restriction (IUGR) + birth defect
	• Serious diseases or infection

Maternal mortality	
Long-term morbidity • **Impact of pre-eclampsia/eclampsia** • **Development of chronic hypertension/cardiovascular disease (CVD)** • **Development of chronic diabetes mellitus**	Long-term morbidity • Cognitive impairment

4.2.3.3 Aggregate outcome measure

The majority of the stakeholders were familiar with Disability Adjusted Life Years (DALYs) and thought this was more applicable for Bangladesh.

4.2.3.4 Model perspective

The most preferred perspective was the publicly funded health system perspective, as the government needs to understand the resource need for delivering interventions through the public health system. One stakeholder suggested using a societal perspective. A few of them suggested including both public and private-sector perspectives as a large number of women get treated and give birth in private sector facilities. Most emphasised that high out-of-pocket payment is a challenge. However, in their opinion the model should focus on reducing out-of-pocket payment through improved service delivery of the public-sector facilities.

4.2.3.5 Time horizon

All stakeholders preferred to cover the long term, beyond the point of birth, for the model. Most of them mentioned including the lifetime of women and limiting the time horizon to a shorter term for babies. While most suggested finishing the model at the postpartum period for babies, one suggested capturing the lives of children until five years of age, subject to evidence.

4.2.3.6 Sub-group

Most of the stakeholders thought sub-groups were important in terms of disparities in wealth. Some identified that age as a sub-group would be essential to add to the model. Some of the experts did think residence (urban/rural) was not necessary while others thought it was. One expert suggested adding parity within the model.

4.2.3.7 Model structure

Most stakeholders were not familiar with the details of economic evaluation models. They were not explicitly asked about model structures. Two health economists within the stakeholder panel suggested the type of model that could be used. Both of them recommended Markov state transition models. They also suggested that a hypothetical cohort of women could be modelled through individual-based simulation for this work.

Table 4.7 below lists some key points related to model specification based on the stakeholder consultation described in sections 4.1.4 and 4.1.5.

Table 4.7 Summary of model specifications based on the consultation

Components	Details
Interventions	1. Antenatal care ensuring women receive all components 2. Management of pre-eclampsia/eclampsia

	3. Identification and screening/diagnosis of high-risk pregnancy
Outcomes	1. Pregnancy and birth outcome for women and off-spring 2. Chronic hypertension and chronic diabetes melli-tus among women with HDP and DMP
Time horizon	1. Birth outcome for baby can include impact till 5 years of age 2. Pregnancy, birth outcome and long-term outcome for mother
Aggregate outcome measure	DALY
Model perspective	Health system
Sub-group	Wealth, type of residency (urban/rural), parity
Model structure	Markov state transition/microsimulation

4.2.3.8 Risk factors

The stakeholder interviews did not include a discussion on risk factors for the two diseases. The risk factors were extracted based on the clinical pathway reviews. The conceptual modelling framework included the risk factors for the two disease conditions and have been listed in the following section.

4.2.3.9 Final conceptual modelling framework

Figure 4.3 below is the conceptual model developed after discussing possible interventions and model boundaries with the stakeholders. Risk factors for HDP included nulliparity, age above 40, BMI greater than 35, twin pregnancy, history of gestational hypertension or pre-eclampsia, family history of pre-eclampsia/eclampsia, pre-existing conditions life chronic hypertension or diabetes mellitus, and gestational diabetes mellitus. Risk factors of GDM covers BMI greater than 30, previous gestational diabetes, family history of diabetes, and a previous macrosomic baby.

The antenatal care components covered ensuring at least four ANC visits, including one received from a medically trained provider, screening and identification of pregnancies at risk of HDP or GDM, and counselling on danger signs and calcium supplementation. All of the components have been included in the conceptual framework, given that they will all share the similar pathway for impact.

The health conditions during pregnancy, around birth and postnatal period, were hypertension (chronic or gestational), mild pre-eclampsia, severe pre-eclampsia, eclampsia and diabetes mellitus (chronic or gestational) or healthy. The birth could happen at or after or before term (37 weeks) through normal vaginal birth or c-section. Birth outcomes for women included morbidity, death or healthy. For babies, they included healthy newborn, stillbirth, low birth weight and newborn death. Postnatal health conditions for women were the same as those during antenatal care and birth, while for babies they included newborn morbidity, mortality or healthy newborn. Long-term health conditions for women included healthy women and chronic hypertension, diabetes mellitus or both, and the model ends with women's death.

4.3 Selection of model intervention

The package of antenatal care interventions were identified to be a key intervention in addressing the two conditions. Models identified through the systematic review that estimated the effect of a bundle of interventions obtained effectiveness data based on direct observations. Another two studies incorporated the effectiveness of a package of interventions using the global maternal health microsimulation model (GMatH) and the Lives Saved Tools (LiST) (178, 179). Methods for incorporating the multiple interventions prescribed in LiST are similar to methods of estimating disability weights for comorbidities (180). The total impact of interventions was considered to be the product of the impact of each intervention on the remaining pregnant women with a specific condition, for example, the risk of pre-eclampsia when screening and calcium is being given to all women:

$$R_{all} = 1 - (1 - R_1)*(1 - R_2)* (1 - R_3)* (1 - R_4) \quad (178)$$

It is however, still unclear how joint effectiveness would be modelled and attributable fractions can be decided for each component of the package. The software-based models result in final outcomes for single as well as bundle of interventions. Consequently, before directly incorporating the equation in the model, a step-by-step approach would probably be needed to validate the model and enable it to produce the impact of a single intervention. This would also add further complexities in terms of how the various events and outcomes would be affected through the different interventions. It was therefore decided to focus on a single intervention as an exemplar in the first instance but to structure the model in a way that would allow the other interventions to be incorporated into future work.

As each component of this bundle is an intervention in itself, a decision on what intervention should be modelled was taken following two conditions: the feasibility of including the intervention in terms of availability of evidence and readiness of the health system.

Calcium supplementation and diet and exercise counselling are the two interventions that can directly prevent onset of HDP or DMP within the antenatal care package. Early screening can help prevent preeclampsia. It was also among the most common interventions identified in the systematic review of economic evaluations in preventing pre-eclampsia. However, the particular diagnosis test evaluated in these models is not available in Bangladesh yet. Diet and exercise counselling is only recommended for women with DMP through specialised care in the national guidelines.

Calcium supplementation was also identified in the reviews and mentioned by the stakeholders as important standalone interventions. Women in Bangladesh have been classified as calcium deficient (181). It is both a part of the Bangladesh national policy and the distribution channels are already determined. Although the intervention is recommended for all pregnant women in Bangladesh, yet it is not implemented at scale.

Globally, calcium supplementation for pregnant women as an intervention has a solid evidence base as a standalone intervention and can impact women at risk of HDP. Apart from its recommended use as a nutrition supplementation during antenatal care, WHO also has a distinct recommendation specifically for calcium supplementation. The WHO recommendation also highlighted the absence of availability of evidence of cos-effectiveness of calcium supplementation. It was recommended by stakeholders among the top three single interventions outside of the ANC package. While three studies in the systematic review and one from the narrative review included calcium supplementation as a means to reduce pre-eclampsia, country-specific effectiveness data was also available for Calcium[8](182-184). Also, from the health system's perspective, distribution of calcium would not be restricted by low level of facility readiness. As one stakeholder recommended, community level distribution of calcium can help avoid the complexities of low level of system readiness. Since the intervention is not being newly introduced, the baseline or current care coverage needs to be considered and effect of a scale-up or increased uptake/coverage would be appropriate for the economic evaluation model.

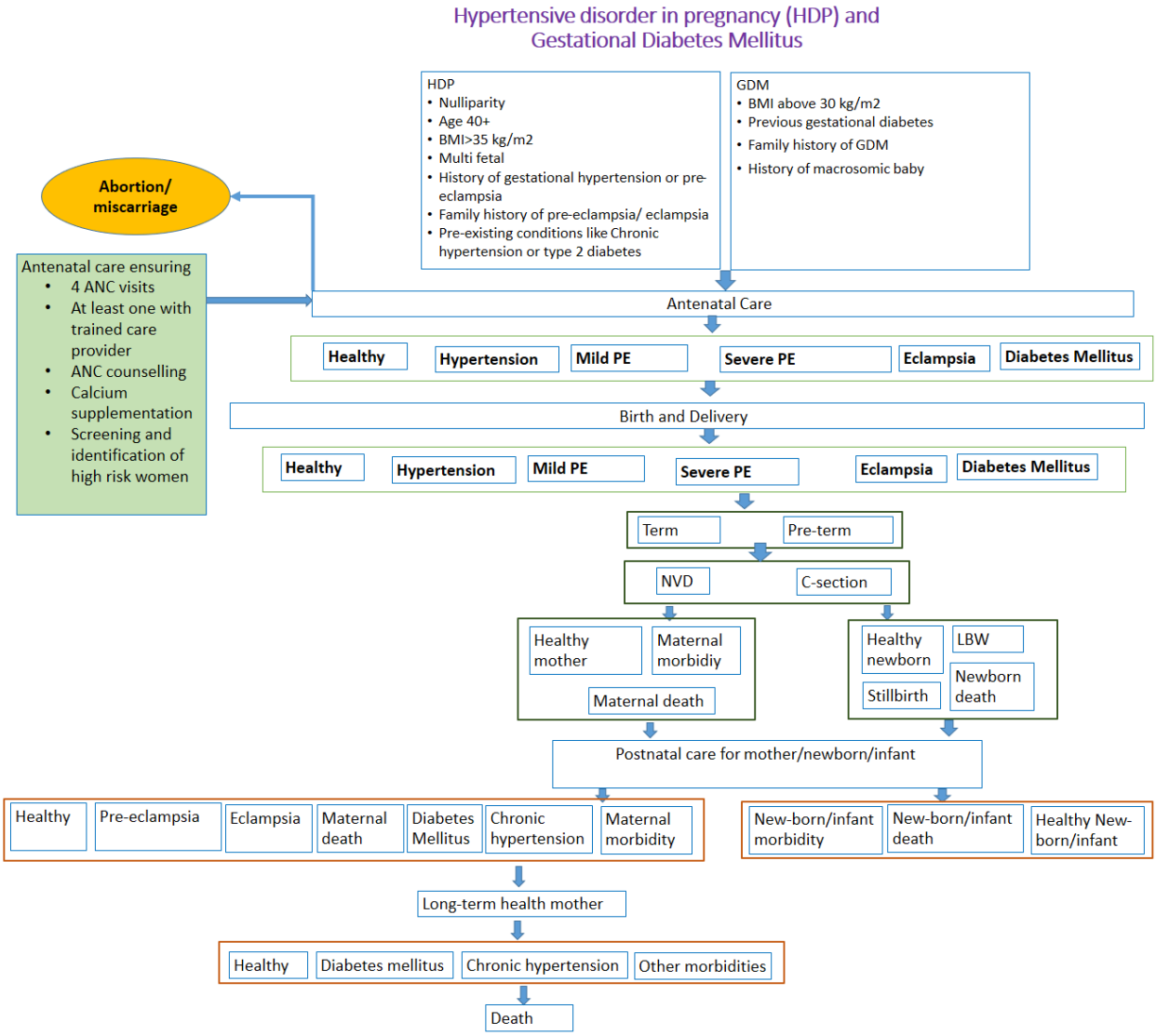
Calcium supplementation is hence the exemplar intervention within the ANC package chosen for the model as it had a strong evidence base and could overcome the health system-related barriers through community-level initiatives. It is a possible "low hanging fruit" which may be implemented at scale with minimal resource utilisation. It is also a preventive intervention targeting one of the two NCDs that this thesis focuses on. Given the limited capacity and readiness of the public health system in

[8] Details of all evidence are provided in chapter 5

ensuring care for those who are in need, such preventive measurement can offload some burden from the health system, help save lives and make better use of existing resources.

There is, however, a lack of availability of data regarding the status of women receiving calcium in pregnancy. Over 46% women receive four antenatal care visits in the country, while over 18% receive all components of antenatal care. Further review of evidence will be required to set the current care coverage level of calcium. When point of care is taken into account, over 35% of the care is received at home and the rest is done in facilities. Considering the low level of ANC coverage, it might be an option to distribute calcium through home visits by existing health and family planning domiciliary workers.

Figure 4.3 Conceptual modelling framework



4.4 Discussion

4.4.1 Selection of a single intervention

Calcium supplementation was the exemplar intervention chosen for the model as it had a strong evidence base and can overcome the health system-related barriers through community-level initiatives. Calcium supplementation is also crucial for Bangladeshi women, especially those giving birth. A review synthesizing information on calcium deficiency in Bangladesh reported low intake of calcium among overall population. This was pertinent, especially among women of reproductive age (181). In a country like Bangladesh where most women are calcium deficient, universal supplement of calcium is desirable following WHO recommendations (65, 72). Calcium is also a preventive measure, a highly recommended way for tackling NCDs.

4.4.2 Provision for a flexible model structure

Given that the methodology for modelling multiple intervention effect has been explored and identified and there is an interest in looking at the effect of a package of intervention for antenatal care, it may be helpful to consider a flexible model structure. This will allow for additional interventions to be incorporated for future use which also has direct impact on women with DMP. A flexible model will be able to accommodate additional interventions as and when demanded by policymakers. Each intervention effect size can be modified between relative risk of 0 if not being accounted for to its actual relative risk when accounted for. Both single and multiple intervention effects can be incorporated in the model following this method. It will also enable to look at cost-effectiveness of different combination of interventions.

This is expected allow to manipulate the input data of the modelled intervention. Such a model will enable incorporating interventions related to the two NCDs in pregnancy during antenatal period and throughout the continuum of care in the future. Decision makers will be able to adjust and change the coverage levels of the interventions as required which will aide in national programme and planning. The interventions incorporated will be able to address a single or both NCDs and produce results that are useful for policymaking.

4.4.3 Final conceptual framework and model attributes

The draft conceptual framework covered multiple interventions as part of the pregnancy continuum of care, their associated health states, immediate and long-term outcomes. The immediate outcome measures prioritised by experts included in the conceptual framework covered the key outcomes listed based on the literature reviews. For babies, preterm birth, stillbirth and neonatal deaths were

the key outcomes. For mothers, immediate outcomes including mode of birth and maternal mortality and long-term morbidities like chronic hypertension and diabetes mellitus were identified as priorities for inclusion in the model. Given the choice of the outcomes, the model will cover a time horizon between pregnancy and long-term outcome of women for their lifetime. For offspring, birth outcomes and the long-term outcome covering a period of 5 years after birth will be included.

The stakeholder interviews revealed that the cost to the publicly funded health care system was the key for implementing the interventions. The Essential Service Package (ESP), which is one key pathway for ensuring Universal Health Coverage (UHC) in the country, is planned to be delivered through the public health care system, so is the pilot social health protection scheme (185). However, it may be important to further explore how out-of-pocket payment can be incorporated within the model as it is suggested to be of critical importance in the context of Bangladesh.

As suggested by the stakeholders, any urban-rural difference was unlikely to exist. There is a possible impact on different age categories and wealth quintiles, and inclusion of that will depend on the availability of data. Age will be incorporated within the model through life tables. Nevertheless, analysis by specific age groups will require age to be divided into specific sub-groups and will be determined based on risk of developing the disease conditions.

The final conceptual framework was narrowed down to the ANC related package of interventions and the outcomes and time horizon selected and finalised through discussion with stakeholders. The risk factors to be included are age, pre-existing conditions, BMI and more but may need further review and discussion to be finalised depending on data availability.

4.4.4 Limitation

One limitation of the stakeholder interview exercise was that the interventions did not follow a formal priority setting method like the Child Health Nutrition Initiative (CHNRI) or the Delphi technique (186, 187). However, the objective was to understand the views of stakeholders and incorporate their views in the process of selecting an intervention which would be the starting point of developing a flexible economic evaluation model.

A second limitation would be that the selected interventions were overlapping each other. However, this is not unique to the stakeholder consultation done for this thesis alone. Research following the CHNRI method has also reported overlap between the priorities identified (188).

4.5 Conclusion

Findings from this work was helpful for the finalisation of population, intervention, comparator and outcome (PICO) of the economic evaluation model. In this section, I have described the findings and their implications for the model in generic terms. The PICO was finalised based on the reviews, stakeholder interviews and through conducting reviews to identify effectiveness data from existing databases and literature.

Based on stakeholder consultation, a number of interventions identified to be important for improving maternal and newborn health outcomes for women with HDP or DMP have been selected to be included in the model. Where a broad intervention category was recommended by stakeholders, it was eventually narrowed down into one specific intervention taking into account stakeholder opinion and the available evidence base of interventions and its relevance to the two disease conditions.

The stakeholder consultation aided in informing then incorporating their views in setting the model boundaries. The consultation helped to shortlist the outcomes and the model's time horizon for mothers and babies. It also helped gather opinions about the model perspectives. This information was used to update and prepare the final conceptual modelling framework. The general decision problem for this piece of research relates to publicly funded mother and child services in Bangladesh. The services relating to this span tertiary, secondary, primary, community-level and informal care. Given the structure of the Bangladeshi health system, the funding decision is taken by the Ministry of Health and Family Welfare.

Calcium supplementation has been chosen as the exemplar intervention for this economic evaluation model for Bangladesh as it is a preventive measure, it has a clear evidence base, and its implementation will not be restricted by limited capacity of the public health care facilities in Bangladesh. The cost-effectiveness model will be developed for a scaled-up of coverage of calcium supplements in Bangladesh with the potential for extension to additional preventive or curative interventions covering the full antenatal care package and both the NCDs.

5. Model development methods

This chapter describes the detailed methodologies followed for the development of the cost-effectiveness model. The intervention modelled, as described in Chapter 4, is universal calcium supplementation among pregnant women in Bangladesh. This is modelled in terms of scaling up the current level of provision to higher levels of provision. Such a formulation has been chosen as it generates national estimates of total costs and DALYs, which was favoured by stakeholders. The model has been divided into two parts. The first part covers the pregnancy and childbirth period and the second part covers the long-term outcomes. The model was built in the statistical software R.

The chapter begins with a description of the chosen model structure and the justifications behind it in section 5.1. Next, detailed description of how the baseline population has been selected and set up in the model is provided in section 5.2. Section 5.3 describes how risks of events and outcomes were assigned to individuals through simulation. Once the baseline scenario was produced, intervention effects were added. These methods have been elaborated in section 5.4. Section 5.5 discusses how the long-term outcomes have been incorporated within the model. This was followed by section 5.6, which added details on how and when the various model inputs were analysed. The chapter then moves onto explaining the methods followed to estimate the aggregate outcome or DALYs in section 5.6, and costs in section 5.7. Next, section 5.8 describes the methods used for validating the model, and section 5.9 explains the type of model analysis that has been undertaken. The final section highlights approach taken for model verification. All input data along with their sources and assumptions have been discussed in their relevant sections.

5.1 Model Structure

An individual-based Markov microsimulation model was developed for the pregnancy and childbirth period with weekly cycles. This model structure was deemed most suitable based on several points. First, the health states in the model are not mutually exclusive. There are two pre-existing disease conditions included in the model along with their interaction and multiple downstream events and outcomes. An individual-level model can take into account transition between health states that are mutually not exclusive depending upon individual-level characteristics. Fitting these into a markov state transition model would lead to a very large number of health states. The micro-simulation structure enabled incorporating the risks and outcomes for individuals based on their pre-existing diseases and comorbidities and additional downstream events as they progress through pregnancy. Applying the weekly time intervals by gestation was also easier to incorporate using cycles for the pregnancy phase, following this model structure. (189)

The second part of the model or the long-term outcome model is also an individual-based model that follows a decision tree structure. This selection of the model structure was done for several reasons. The objective of the long-term model was to project the impact of the intervention on development of chronic hypertension and diabetes mellitus during the lifetime of women. The pathway through which the intervention would have an effect in the long term is linked to pregnancy-specific conditions: HDP and GDM. Adding the chronic disease progression and reaching end of life would not add much to the evidence base. Rather, the priority was to estimate the impact as an extension of costs and benefits per woman in the long term. The simple long-term model would help attain the purpose of the overall modelling exercise and keep the focus on maternal health outcomes while highlighting the linkage between maternal health and NCDs.

As discussed in the previous chapter, the model will be programmed in a way that allows flexibility in terms of manipulating input data, coverage of the intervention. It will also allow to add additional intervention effects, both individual and combined following the methods described in chapter 4, section 4.3. It is important to note here that the model focuses on scaled up provision of calcium from its current care coverage as this is not a new intervention for the context of Bangladesh.

Figure 5.1 shows the risk factors, conditions, events and outcomes as finalised based on the model specifications detailed in the previous chapter.

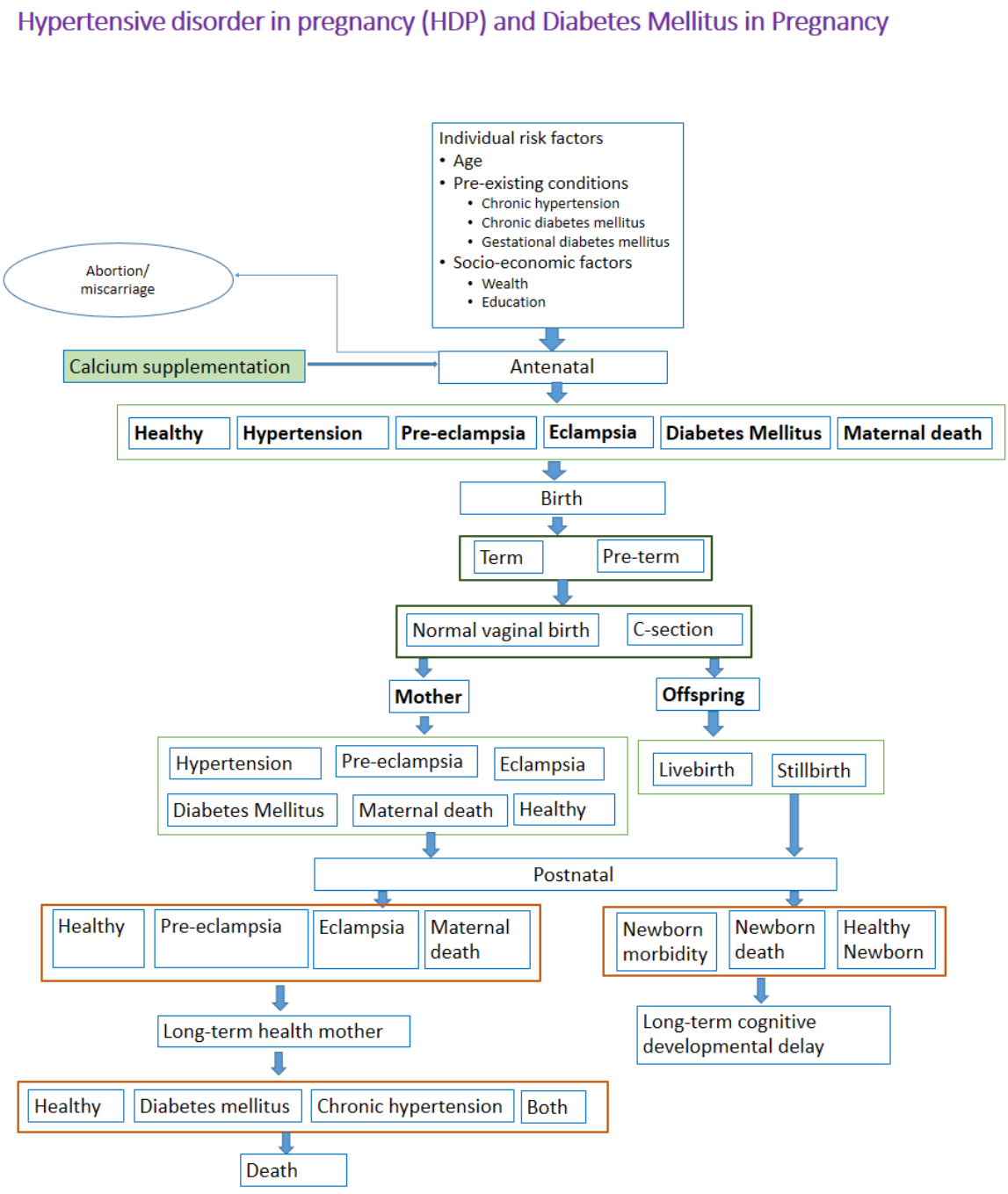


Figure 5.1 Final conceptual modelling framework

5.2 Baseline population and birth outcomes methods

5.2.1 Setting up the baseline population

5.2.1.1 Input data

The model population is pregnant women. The baseline population draws heavily on two important, high-quality national surveys: Bangladesh Maternal Mortality and Health Care Survey (BMMS) 2016 and Bangladesh Demographic and Health Survey (BDHS) 2017-18 (45, 52).

The baseline population for the model was sampled from the Bangladesh Maternal Mortality and Health Care Survey 2016 (BMMS) (45). The BMMS is a cross-sectional survey and covers a nationally representative sample of pregnant women. The sampling frame was constructed covering urban and rural areas across the eight administrative divisions in the country. The data collection period was between 2014 and 2016 covering a total number of 111,688 women who gave birth in the three years preceding the survey.

The BDHS is a cross-sectional survey that covers 20,160 households and provides nationally representative prevalence estimates on two non-communicable diseases: chronic hypertension and chronic diabetes mellitus in the overall population (52). Age-specific disaggregated data on these conditions are available in the survey report. The section on blood pressure and diabetes mellitus covered around 7,000 women in total, of which more than 5,000 fell within the reproductive age group (18-49). Both the surveys have publicly available data and can be downloaded directly from the website (190, 191).

5.2.1.2 Population characteristics

For setting up the baseline population, three variables from the BMMS data on socio-demographic characteristics of women, age, educational attainment and wealth quintile were included. The entire population of BMMS was used for analysing the population characteristics. Age was included as a continuous variable while educational attainment was divided into six categories: no education, primary incomplete, primary complete, secondary incomplete, secondary complete and higher. Wealth quintile was generated using household assets in the survey dataset and divided into five groups: lowest, second, middle, fourth and highest. The variables were directly derived from the survey dataset and did not have any missing data as these were women directly interviewed about their birth in the three years preceding the survey period. Table 5.1 below presents baseline characteristics of women included in the BMMS.

According to BMMS 2016, women's mean age was around 32 years. The majority of women who gave birth were between 20 and 29 years of age (36%). Around 10% of women belong to the age group between 13 and 19 years while the rest were over 30 years of age. Nearly two thirds of women had

at least primary-level education complete and the rest attained no or less than primary-level education (Table 5.1).

Table 5.1 Baseline population characteristics

Category	Mean	SD
Age	31.53	9.35
	%	n
Total	100	111,688
Age group		
13-19	9.91	11,075
20-29	35.9	40,099
30-39	30.4	33,950
40-49	23.8	26,564
Educational attainment		
No education	20.2	22,518
Primary incomplete	17.8	19,865
Primary complete	14.2	15,816
Secondary incomplete	30.9	34,577
Secondary complete or higher	16.9	18,912
Household wealth quintile		
Lowest	19.3	21,540
Fourth	20.3	22,704
Medium	20.3	22,682
Second	20.1	22,459
Highest	20.0	22,303

Source: Estimated based on Bangladesh Maternal Mortality and Health Care Survey 2016 (45, 192)

5.3 Additional characteristics in the baseline population: assigning two additional risk factors

5.3.1 Assigning risk of pre-existing diabetes mellitus to the baseline population

Women in the BMMS cohort selected for the model were assigned a risk of pre-existing diabetes and gestational diabetes based on age (Table 5.2). The prevalence of diabetes mellitus ranged between 2.9% among women aged 18-19 and 14.9% among women aged 45-49 years. Age-specific risk of diabetes mellitus was assigned to the baseline population, and women who had chronic diabetes mellitus prior to pregnancy were randomly selected through probabilistic sampling.

Table 5.2 Underlying prevalence of pre-existing hypertension, diabetes mellitus and gestational diabetes mellitus

Parameter detail	Average	Source
Hypertension (18-19)	0.046	NIPORT (2020) (45)
Hypertension (20-24)	0.079	
Hypertension (25-29)	0.141	
Hypertension (30-34)	0.210	
Hypertension (35-39)	0.313	
Hypertension (40-44)	0.373	
Hypertension (45-49)	0.437	
Diabetes (18-19)	0.029	
Diabetes (20-24)	0.036	
Diabetes (25-29)	0.059	
Diabetes (30-34)	0.082	
Diabetes (35-39)	0.112	
Diabetes (40-44)	0.12	
Diabetes (45-49)	0.149	
Gestational diabetes- (< 20)	0.099	Jesmin et al (2014) (50)
Gestational diabetes (20-24)	0.068	
Gestational diabetes (25-29)	0.119	
Gestational diabetes (>30)	0.097	

5.3.2 Assigning risk of pre-existing hypertension to the baseline population

Table 5.3 shows there is an increasing prevalence of hypertension as women's age increases (52). Prevalence of hypertension ranged from as low as 4.6% between the ages 18 and 19, to 43.7% among women aged 45-49 years.

The probability of women having hypertension and pre-existing diabetes mellitus was estimated based on a logistic regression using the BDHS data (Table 5.3). Age, education and wealth quintiles were used as covariates in the regression analysis. The coefficients from this regression were then used to assign women with risk of having pre-existing hypertension with or without diabetes mellitus, after controlling for the effects of age and education. When the coefficients were converted to odds ratios, the odds of women with pre-existing chronic diabetes mellitus having chronic hypertension was 2.74 compared to those without chronic diabetes mellitus. Age was included as a continuous predictor variable, and the OR suggests that a unit increase in age would lead to a 7% increase in the odds of having chronic hypertension. A shift from a lower to higher educational attainment would lead to a 1% decline in the odds of developing chronic hypertension. Shift from the lowest wealth quintile to the higher quintiles would lead to a 14% increase in the odds of developing chronic hypertension.

Table 5.3 Results of logistic regression analysis to estimate correlation between pre-existing diabetes and hypertension among pregnant women in Bangladesh from BDHS 2017-18 data

Coefficients:	Estimate	Std. Error	z value	Pr(>|z|)
Intercept	-4.367	0.210	-20.768	<2e-16***
Pre-existing Diabetes Mellitus	1.007	0.104	9.659	<2e-16***
Age	0.074	0.005	14.592	<2e-16***
Education	-0.008	0.125	-0.645	0.792
Wealth	0.132	0.033	3.933	0.000***

Source: Analysis based on BDHS 2017-18 data (190)

5.3.3 Pregnancy and childbirth events and outcomes

All women started at a gestational age of 12 weeks. The median age of pregnancy at which women in Bangladesh have their first ANC visit is 4.7 months (52). However, it is recommended for women to be in touch with the health system as soon as pregnancy is detected and preferably in the first trimester which is between 8 and 12 weeks. The model assumes that all women enter at 12 weeks or 3 months of gestation. The model takes into account only one pregnancy and moves onto possible long-term effects based on outcomes of the single pregnancy. Twin pregnancies were not taken into account considering that they were low in numbers and would add further complexities to the model.

Once all the baseline characteristics were added to the population, GDM was assigned to women based on age through probabilistic sampling. Data one age specific risk of developing GDM was available from literature based in Bangladesh. (Table 5.2)

The rest of the events and outcomes related to pregnancy were simulated depending on gestational age. The outcomes occur in sequence throughout the pregnancy period and until six weeks after birth. The sequence of events were determined based on stage of gestation and how each event relates to the occurrence of a subsequent set of events.

The first level or the intermediate outcomes relate to women who develop gestational hypertension, pre-eclampsia or eclampsia from 20 weeks of gestation. The risks of developing gestational hypertension, pre-eclampsia and eclampsia depends on women's characteristics at baseline. The risks of adverse outcomes increased if women had pre-existing hypertension, diabetes mellitus or gestational diabetes.

All women were assigned with one of the three birth outcomes: abortion/miscarriage, stillbirth or a livebirth. The pregnancy outcomes occur in two levels. Abortion or miscarriage happen before women reach 28 weeks of gestation. Babies can be born at term or preterm. Women who did not have an abortion or miscarriage would end up having a stillbirth or a livebirth. There were two possibilities of mode of birth. It was divided between normal vaginal birth and c-section.

The final set of outcomes for the pregnancy and childbirth model included maternal and newborn death. Newborn deaths can occur between zero and four weeks after birth and maternal deaths could occur anytime from entering the model till six weeks after birth.

Figure 5.2 below depicts the flow of events from the beginning of the model. Deaths in the model were linked to direct causes. For example, maternal death was linked to pre-eclampsia and eclampsia, as they are a direct cause of death among mothers. No direct link was established between diabetes and maternal death. Deaths due to diabetes mellitus in the model hence happened through increased risk of pre-eclampsia/eclampsia or other indirect causes. For newborns, preterm birth was the direct cause of death. Term newborns were assigned with a lower risk of death due to other causes.

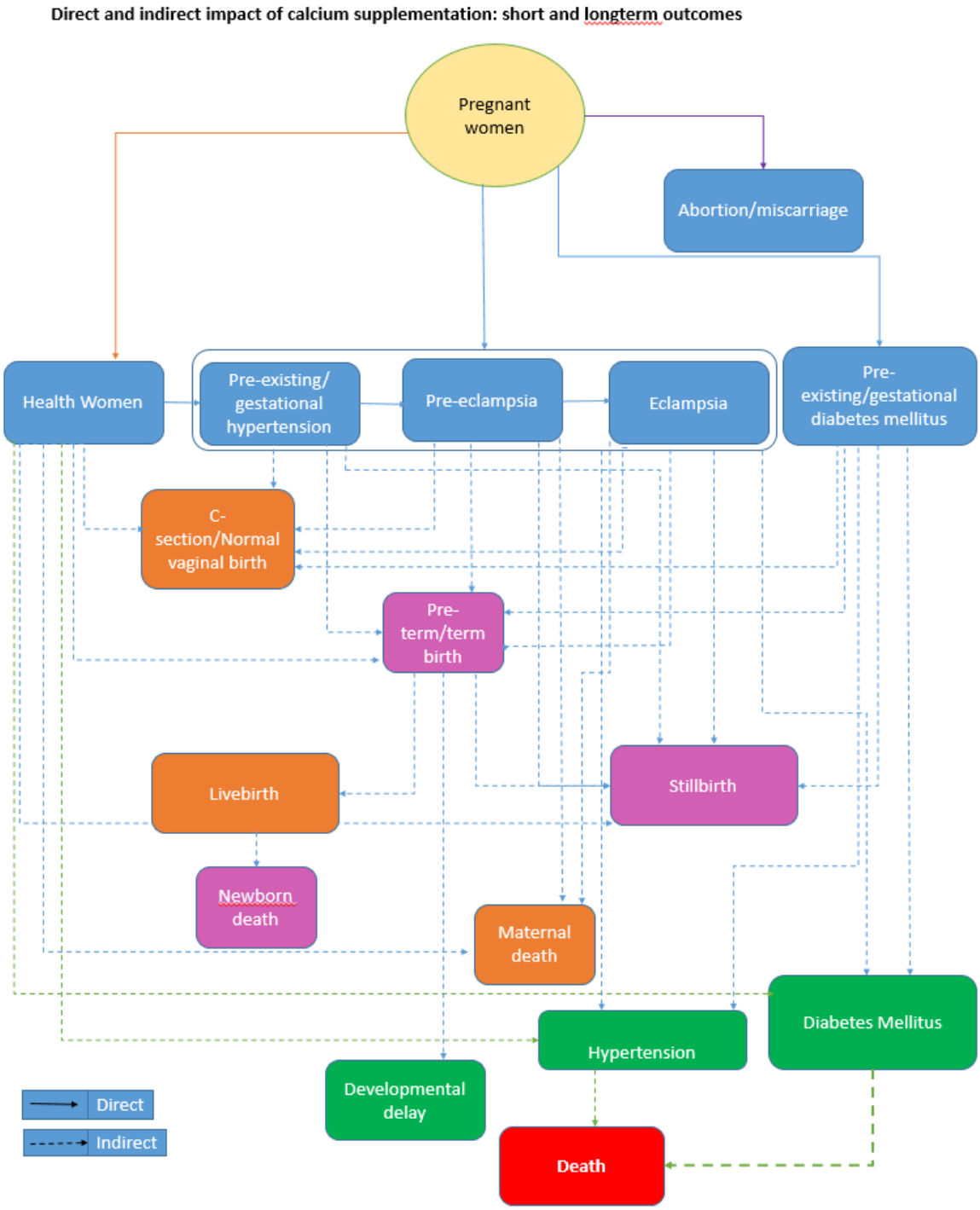


Figure 5.2 Flow of events and outcomes in the model

5.3.4 Converting odds ratios and relative risks

All ORs were converted into relative risks, and relative risks into absolute risk. Risks were multiplied for multiple conditions assuming independence (hypertension and diabetes together). Those who did not have any conditions were assigned a lower than population-level risk based on estimates. This was required for the model to be able to assign risks to people who have a condition like diabetes or hypertensive disorder during pregnancy and subsequent pregnancy and birth outcomes. Relative risks were directly assigned to all women with and without the conditions and a base-case scenario portraying current country situation was generated.

The following formula was used to convert the odds ratios into relative risks:

RR = OR / (1 – p + (p x OR)), where p is the risk in the control group (193).

National averages were considered to be the risks among those in the control group. This is a limitation of the method as the control group should have a lower risk. However, this was the best available data to be used for the conversion. This helped produce risks that were more relevant and close to the national average.

Once the odds ratios were converted into relative risks, it was necessary to make sure that the geometric mean of all relative risks for a given outcome equals one. The relative risks were thus adjusted for each risk factor using the equation below:

Adjusted RR of having a condition = Original RR ^ (Individual Value Risk Factor - Population Average Value Risk Factor)

Original RR = relative risk for a particular outcome, given a particular risk factor

Individual Value Risk Factor = whether or not the person has the risk factor (1 or 0 depending on if they have the condition or not)

Population Average Value Risk Factor = underlying population prevalence of the risk factor

The relative risk of an event or outcome or no event was calculated compared to the average person. It was then multiplied by the absolute risk for all people overall or the population prevalence, which resulted in the individual absolute risk of an outcome.

Initially the relative risks were extracted or estimated for diabetes and hypertension and related complications and outcomes separately. There is a paucity of published literature reporting the effects of comorbidities. As the model also took into account women having both conditions, it was assumed that risks of any downstream events or outcomes depending upon the two diseases were independent.

For example, for those having both hypertensive disorder and diabetes at the same time, the two relative risks were multiplied together and then converted into absolute risks.

Average weekly risks were assigned to women based on risks in overall pregnancy. The conversion to weekly instantaneous event rates assuming a fixed rate with respect to time were estimated based on the total pregnancy period risks derived following methodologies prescribed in Briggs et al (194).

Rate = -[ln(1-overall average risk)]/total number of weeks

5.4 Assigning risks of events using simulation

All risks were assigned based on Odds Ratios, relative or absolute risks reported in literature. The gestational age of onset of conditions based on their definition were considered. The model assumed that women entered at a gestational age of 12 weeks and the maximum duration of pregnancy was restricted to 39 weeks.

5.4.1 Hypertensive disorders of pregnancy

The first level of events included hypertensive disorders of pregnancy that cover gestational hypertension, pre-eclampsia and eclampsia. As shown in figure 5.1, there are four health events associated with HDP, chronic or gestational hypertension, pre-eclampsia and eclampsia. While chronic hypertension was a pre-existing condition, for the rest, women were assigned with the risk of each of the events depending on their pre-existing health conditions. These pregnancy induced hypertensive disorders develop after 20 weeks of gestation.

5.4.1.1 Gestational hypertension

The risk of developing gestational hypertension in the model relied on whether women have previous diabetes or have developed gestational diabetes during any stage after 20 weeks until childbirth. Healthy women could also develop gestational hypertension but would have a lower risk than average.

Prevalence of gestational hypertension in Bangladesh has been reported in two country-specific studies based in facilities in two different sub-districts. Both studies reported the same underlying prevalence of around 9% and this was applied in the model (195, 196).

Risks based on women's status of diabetes were included in the model based on the literature review. The only study reporting this was found through a PubMed search and was published in 2003. Bryson et al (2003) conducted a case control study including over 9000 cases of hypertensive disorders of pregnancy (197). The article reported that women with gestational diabetes were more likely to develop gestational hypertension compared to those without diabetes [OR=1.4 (95% CI: 1.2 - 1.6)]. The estimated average risk of gestational hypertension among women with diabetes was 0.115 while

it was 0.085 for non-diabetic women. It was assumed that the same relative risk would be applicable for women with both chronic or gestational diabetes as no other data was found that associated gestational hypertension and gestational diabetes. (Table 6.4)

Table 5.4: Risk of gestational hypertension

Type of parameter	Parameter description	Average	RR	LB	UB	Source of data
Underlying population prevalence	Gestational hypertension	0.088	-	0.026	0.123	Haque et al (2020), Bhuiyan et al (2019) (195, 196)
Risk of event	Gestational hypertension among women with diabetes	0.115	1.352	1.179	1.520	Bryson et al (2003) (197)
Risk of event	Gestational hypertension among women without diabetes	0.085	1.352	1.179	1.520	Estimate

5.4.1.2 Pre-eclampsia

The risks of pre-eclampsia are higher among women with pre-existing diabetes, gestational diabetes and pre-existing or gestational hypertension.

The prevalence of hypertensive disorders, especially pre-eclampsia and eclampsia is difficult to estimate as there are varied definitions and the conditions develop at different stages of pregnancy. The global burden of disease studies provided detailed methodology and the epidemiological region-specific burden of pre-eclampsia (198). However, no estimates of prevalence were given for Bangladesh or the region it belongs to. Mou et al (2021) conducted a cross-sectional study in one of the largest tertiary medical college hospitals with Sylhet Osmani Medical College, Sylhet Diabetic Hospital, and another private hospital in the Sylhet city area and provided estimate of prevalence of pre-eclampsia (48). Only 220 women were identified and women enrolled were those who came for regular check-ups and not only those with a complication. The study reported the country-specific estimated average risk of pre-eclampsia was around 14%.

Studies assessing progression of gestational hypertension to pre-eclampsia are rare. A literature search identified one study by Saudan et al (1998) who conducted a retrospective and prospective study of more than 800 women in Australia (199). The study found between 15% and 25% of women with gestational hypertension would eventually develop pre-eclampsia (199). Mou et al reported the odds of pre-eclampsia among women with pre-existing hypertension [OR 1.93 (CI 0.57-5.56)]

compared to those without (48). This was assumed to be relevant for gestational hypertension too and the same data was applied both for pre-existing and gestational hypertension.

A systematic review on gestational diabetes mellitus and its adverse outcomes reported several relevant outcomes that were relevant and included in the model. The review reported risks disaggregated by developed and developing countries. The odds of pre-eclampsia among those with gestational diabetes compared to those without in developing countries was [OR 1.48 (CI 0.64 – 3.39)]. The estimated average risks based on prevailing risk factors have been reported in table 5.5 below.

Table 5.5: Risk of pre-eclampsia

Type of parameter	Parameter description	Average	RR	LB	UB	Source of data
Underlying population prevalence	Pre-eclampsia	0.144	-	0.079	0.209	Mou et al (2021)
Risk of event	Pre-eclampsia - with pre-existing/gestational hypertension	0.227	1.70	0.600	3.640	Mou et al (2021)
Risk of event	Preeclampsia with pre-existing/gestational diabetes	0.190	1.38	0.670	2.520	Lai et al (2016) (200)
Risk of event	Preeclampsia with both conditions	0.299	-	-	-	Estimated
Risk of event	Preeclampsia with none	0.127	-	-	-	Estimated

5.4.1.3 Eclampsia

By definition, women developing eclampsia and have convulsion or fit along with all symptoms of pre-eclampsia. Like gestational hypertension and pre-eclampsia, this condition also develops after 20 weeks of gestation and can occur until 6 weeks after birth.

One Bangladesh-specific study conducted in hospitals covering 32,999 patients reported that 9% women developed eclampsia (49). This rate is rather high. A large RCT following up a cohort of over 36,000 women throughout pregnancy was analysed and revealed 2% of women reported convulsion during pregnancy, childbirth and postpartum (201). This finding also falls within the range of prevalence of eclampsia reported in other studies (47). Although it is stated by definition that eclamptic patients would have all symptoms of pre-eclampsia and have seizures or convulsion, the pathological relationship is still unknown. Therefore, the model estimate of eclampsia is done based on the average population prevalence of 2%. The increased risk due to progression from pre-eclampsia could not be taken into account in the model due to lack of data (202).

5.4.2 Pregnancy outcome

Abortion/miscarriage, stillbirth and livebirths were considered as birth outcomes in the model. At any point of abortion/miscarriage, women stopped moving forward in the model. At the point of a livebirth or stillbirth, women moved into the six weekly cycles of postpartum period.

5.4.2.1 Abortion/ miscarriage

Abortion/miscarriages are foetal loss prior to 28 weeks of gestation (203). The Child Health and Mortality Prevention Surveillance (CHAMPS) study in Bangladesh maintains a Health and Demographic Surveillance System (HDSS) that collects individual-level data from Baliakandi sub-district of Rajbari district in Bangladesh. The area is located in the southwest region of the country (53). The surveillance collects data on women's pregnancy and outcomes. Although the region is comparatively under-developed, it is a reliable source of information for pregnancy outcomes such as miscarriages and stillbirths, as the national-level pregnancy registers do not report these indicators. Due to substantial error in recall of gestational age by women, the national surveys are not able to report outcomes that are time dependent.

Gestational age-specific prevalence of abortion/miscarriage was available from the surveillance dataset and included in the model. The population average risk estimated from the dataset was 8.7% (53). By definition, abortion/miscarriage can occur from the beginning of pregnancy until 28 weeks of gestation. Literature reporting estimate of the higher risk of abortion/miscarriage in women with diabetes mellitus is scarce. One study reported an 18% increase in risk of pregnancy loss per 10 mm Hg increase in diastolic blood pressure (204). Although studies suggest an increased risk of miscarriage among women with diabetes, relevant data was not found through a pub-med and google search. Since the rate of abortion/miscarriage would remain the same before and after scale-up of the intervention, population average risk was assigned to all women.

As mentioned previously, the model assumed abortion/miscarriage as an outcome of pregnancy and occurrence of such events stopped women from progressing further in the pregnancy and childbirth section of the model. Unless there was a maternal death, they were taken into account in the long-term model.

5.4.2.2 Stillbirth

Stillbirths are defined as a loss of foetus after 28 weeks of gestation (205). Each woman was assigned a risk of stillbirth depending on their pre-existing health condition and pregnancy-related health events. Women with hypertension, diabetes or both, or pre-eclampsia and eclampsia were assigned relative risks estimated from ORs based on available literature. Healthy women were assigned risks estimated for those not having any of the two conditions.

Like abortion/miscarriages, population-average risk of stillbirth was estimated from the Baliakandi Health and Demographic Surveillance System (HDSS) dataset (53). Although the BDHS 2017-18 did not report stillbirth rates directly, estimates based on the perinatal deaths reported was similar to that of Baliakandi HDSS (52). No Bangladesh-specific studies have yet reported the association between diabetes and stillbirth. Mackin et al (2019) conducted a study based on routine data in Scotland and reported risk of stillbirth among women with HbA1c (206). The same level of risk was applied to women with gestational diabetes as the literature review found no other study that reported this parameter. The odds of stillbirth among women with diabetes were 1.05 (CI 1.02-1.08) compared to those without diabetes. One facility-based study conducted in China analysed 6,970,032 births that included 66,496 stillbirths and reported the relative risks of stillbirth among women with pre-existing hypertension [RR 2.32 (CI 1.87-2.88)], gestational hypertension [RR 1.21 (CI 1.08-1.36)] and pre-eclampsia [RR 4.15 (CI 3.81 -4.52)] (207). All risks related to stillbirth depending on health conditions are listed in table 5.6.

Table 5.6: Risk of stillbirth

Type of parameter	Parameter description	Average	RR	LB	UB	Source of data
Underlying prevalence	Stillbirth	0.024	-	0.022	0.026	Estimated from Baliakandi HDSS data (53)
Risk of event	Stillbirth with diabetes mellitus	0.025	1.05	1.02	1.08	Macintosh et al (2006) (206)
Risk of event	Stillbirth with Pre-existing Hypertension	0.055	2.32	1.87	2.88	Xiong et al (2018) (207)
Risk of event	Stillbirth with Gestational Hypertension	0.029	1.21	1.08	1.36	Xiong et al (2018) (207)
Risk of event	Stillbirth with pre-eclampsia	0.096	4.15	3.81	4.52	Xiong et al (2018) (207)
Risk of event	Stillbirth with both conditions	0.101	4.35	3.88	4.87	Estimated
Risk of event	Stillbirth with none	0.023	-	-	-	Estimated

5.4.3 Maternal and newborn health outcomes

5.4.3.1 Preterm birth

Women who had a livebirth or stillbirth outcome were assigned into term and preterm birth. Babies born before 37 weeks of gestation are considered preterm (208). The risks were assigned based on

pre-existing health conditions and complications. Women with hypertensive disorder or diabetes are more likely to have a preterm birth, and those risks were assigned based on the literature review.

The population average risk for country-specific preterm birth was taken from a systematic review and modelling analysis by Chawanpaiboon et al (2019) (55). The study estimated country-specific risks based on modelling using global and country-level data. Baqui et al (2013) estimated preterm birth in a rural Bangladeshi cohort and reported similar rate of preterm births (208). The likelihood of events specific to risks were primarily taken from global literature as no national level data was available. Shen et al (2017) reported preterm birth among women with hypertension compared to those without [OR 1.8 (CI 1.2 – 2.7)] (209). Bilano et al (2014) analysed the WHO Global Survey on Maternal and Perinatal Health that covered 276,388 mothers and infants (210). The study reported odds of preterm among women with pre-eclampsia and eclampsia [OR 2.86, CI: 2.7-3.1] in Low and Middle Income Countries (LMICs). In a more recent study Ye et al (2022) conducted a systematic review and meta-analysis covering 156 studies (211). The analysis reported the odds ratio of preterm birth among women with gestational diabetes [OR 1.51 (CI 1.26-1.80)]. Table 5.7 reports the converted relative risks and average risks.

Table 5.7: Risk of preterm birth

Type of parameter	Parameter description	Average	RR	LB	UB	Source of data
Underlying population prevalence	Preterm birth	0.194	-	0.132	0.262	Chawanpaiboon et al (2019) & Baqui et al (2013) (55, 208)
Risk of event	Preterm birth in women with pre-eclampsia/eclampsia	0.353	2.10	2.02	2.18	Estimated from Bilano et al (2014) (210)
Risk of event	Preterm birth in women with hypertension	0.273	1.56	1.15	2.04	Estimated from Shen et al (2017) (209)
Risk of event	Preterm birth in women with diabetes	0.247	1.37	1.19	1.56	Estimated from Ye et al (2020) (211)
Risk of event	Preterm birth in women with hypertensive disorder and diabetes	0.313	1.81	1.36	2.38	Estimated from Shen et al (2017) (209) and Ye et al (2022) (211)
Risk of event	Preterm birth in women with none	0.173	-	-	-	Estimated

5.4.3.2 Mode of birth

Diabetes and hypertensive disorders can increase the risk of caesarean section birth. Prevalence of c-section was taken from a BMMS 2016 survey report. Like other outcomes, risks were extracted from literature and assigned based on the existing health condition of women. When odds ratios were extracted from literature, they were converted into relative risks. Women were sampled for a c-section. The rest were assumed to have a vaginal birth including normal vaginal/vacuum extraction and forceps. Similar approach has been followed in other published literature based in Bangladesh (212).

No country-specific paper reported the risk of c-section for women with hypertensive disorder or diabetes/gestational diabetes. ORs were extracted from Shen et al (2017) that reported association between c-section and hypertensive disorders of pregnancy [hypertension: OR 1.1; CI 0.8-1.4, pre-eclampsia: OR 2.2; CI 1.7 – 3.0] (209). A systematic review done by Ye et al (2022) reported higher odds of c-section among women with gestational diabetes (OR 1.09 [CI 0.48-2.51]) (211). Relative and average risks of having a c-section depending on women's conditions were estimated from the ORs as listed in table 5.8 below.

Table 5.8: Risk of caesarean section

Type of parameter	Parameter description	Average	RR	RR LB	RR UB	Source of data
Population prevalence proportion	C-section rate	0.327	-	0.31	0.34	NIPORT 2020 (45)
Risk of event	C-section among women with hypertension	0.341	1.06	0.85	1.23	Estimated from Shen et al (2017) (209)
Risk of event	C-section among women with pre-eclampsia/eclampsia	0.446	1.58	1.39	1.78	Estimated from Shen et al (2017) (209)
Risk of event	C-section among women with diabetes	0.340	1.06	0.58	1.68	Estimated from Ye et al (2022) (211)
Risk of event	C-section among women with hypertension and diabetes	0.355	1.13	0.49	2.07	Estimated from Shen et al (2017) (209) & Ye et al (2022) (211)
Risk of event	C-section among women with none	0.314	-	-	-	Estimate

5.4.3.3 Maternal death

Maternal death is defined as a death during pregnancy or within six weeks after childbirth due to causes other than accidents (45). Risk of maternal death was assigned to women throughout pregnancy and until six weeks after birth. Pre-eclampsia/eclampsia is the second leading cause of maternal deaths both globally and in Bangladesh (45). Odds ratios of maternal death from pre-eclampsia/eclampsia were reported in Bilano et al [OR 4.48 (CI 3.0-6.7)] (150). Diabetes mellitus is not a direct cause of maternal death. Studies have found no association between mortality and diabetes among pregnant women (213). Diabetes indirectly causes maternal mortality through haemorrhage, obstructed labour and pre-eclampsia/eclampsia (214). Thus, in the model, diabetes-related deaths were mediated through the increased risk of developing pre-eclampsia or eclampsia.

Table 5.9: Risk of Maternal death

Type of parameter	Parameter description	Average	RR	LB	UB	Source of data
Underlying population prevalence	Maternal mortality rate	0.000149	-	0.000126	0.000174	NIPORT (2016) (45)
Risk of event	Maternal death with pre-eclampsia/eclampsia	0.008690	4.48	2.99	6.69	Estimated from Bilano et al (2014) (210)
Risk of event	Maternal death without pre-eclampsia/eclampsia	0.000148	-	-	-	Estimated

5.4.3.4 Newborn death

The risks of a newborn death vary between preterm and term babies. In the model, all births transit through the state of preterm or term birth which were assigned based on individual health conditions and their associated risks. The population average risk of newborn death came from BDHS 2017-18 (52) . Preterm birth is one major cause of death among newborns both globally and in Bangladesh and accounts for 11.4% of overall newborn deaths nationally (54). Analysis of preterm birth and neonatal mortality in a rural Bangladeshi cohort reported risk of death among preterm newborns by gestational age (208). Relative risk of death among preterm newborns compared to those born at term was 3.6 (CI 2.1 -6.1) at the gestational age of 34 weeks. Since majority of preterm births occur around that gestational age, this was assumed to represent risk for all preterm births.

Table 5.10: Risk of neonatal death

Type of parameter	Parameter description	Average	RR	LB	UB	Source of data
Underlying prevalence proportions	Neonatal mortality	0.030	-	0.026	0.034	NIPORT 2020 (41)
Risk of event	Newborn death - preterm	0.104	3.6	2.1	6.1	Baqui et al (2013) (208)

5.5 Modelling intervention effects

This section describes how the selected intervention and the scale-up effect have been measured and how they affected the various events and outcomes.

Figure 5.3 shows the pathways through which the intervention effects various events and outcomes directly and indirectly. The intervention has both direct and indirect effects on the events and outcomes. Calcium directly reduces gestational hypertension, pre-eclampsia and eclampsia. Calcium has a direct effect on gestational hypertension, which through the parameterisation of the model described up to this point, will have an indirect effect on the rates of pre-eclampsia, as hypertension is a risk factor for pre-eclampsia. Calcium also has a direct effect on pre-eclampsia that is not captured by its reduction of hypertension. Since the model applied a flat rate for eclampsia, only the direct effect of calcium has been taken into account for eclamptic women. The direct effect of calcium on pre-eclampsia and eclampsia will reduce the risk of the two events among all women including those with pre-existing conditions, gestational hypertension or diabetes mellitus.

For mode of birth, no significant impact on c-section has been reported in the literature. As a result, no direct risk reduction is expected. However, there may be some indirect effects through gestational hypertension, pre-eclampsia and eclampsia through model parameterisation. The effect on preterm birth and stillbirth can also be both direct and through reduction in HDP for the same reasons. Reduction in maternal death is through HDP, and some of it may happen directly as an effect of calcium. Change in newborn deaths occurs indirectly through reduction in preterm births.

5.5.1 Intervention effectiveness

Although calcium supplementation is proven to protect women from gestational hypertension and pre-eclampsia/eclampsia in pregnancy, it has no direct effect in preventing GDM. However, some indirect effect on women with GDM through reduction in pre-eclampsia will be secured. Recently updated recommendations on calcium supplementation by WHO re-emphasise on the benefits of a daily dose of calcium supplements (1500–2000 mg oral elemental calcium). The recommendation targets all women in areas with low consumption of calcium. Research suggests that women at high risk of developing pre-eclampsia can benefit more from intake of calcium. However, it was suggested to treat such data with caution. As a result, the effect on women with low calcium supplements was considered the most appropriate one for use in the model. Homogeneity in treatment effect may not hold. However, no such information is revealed yet. The model also assumed differences in dose level would not translate into differences in outcomes. Reviews do suggest positive findings where low dose of supplements were used but this is subject to further research (183).

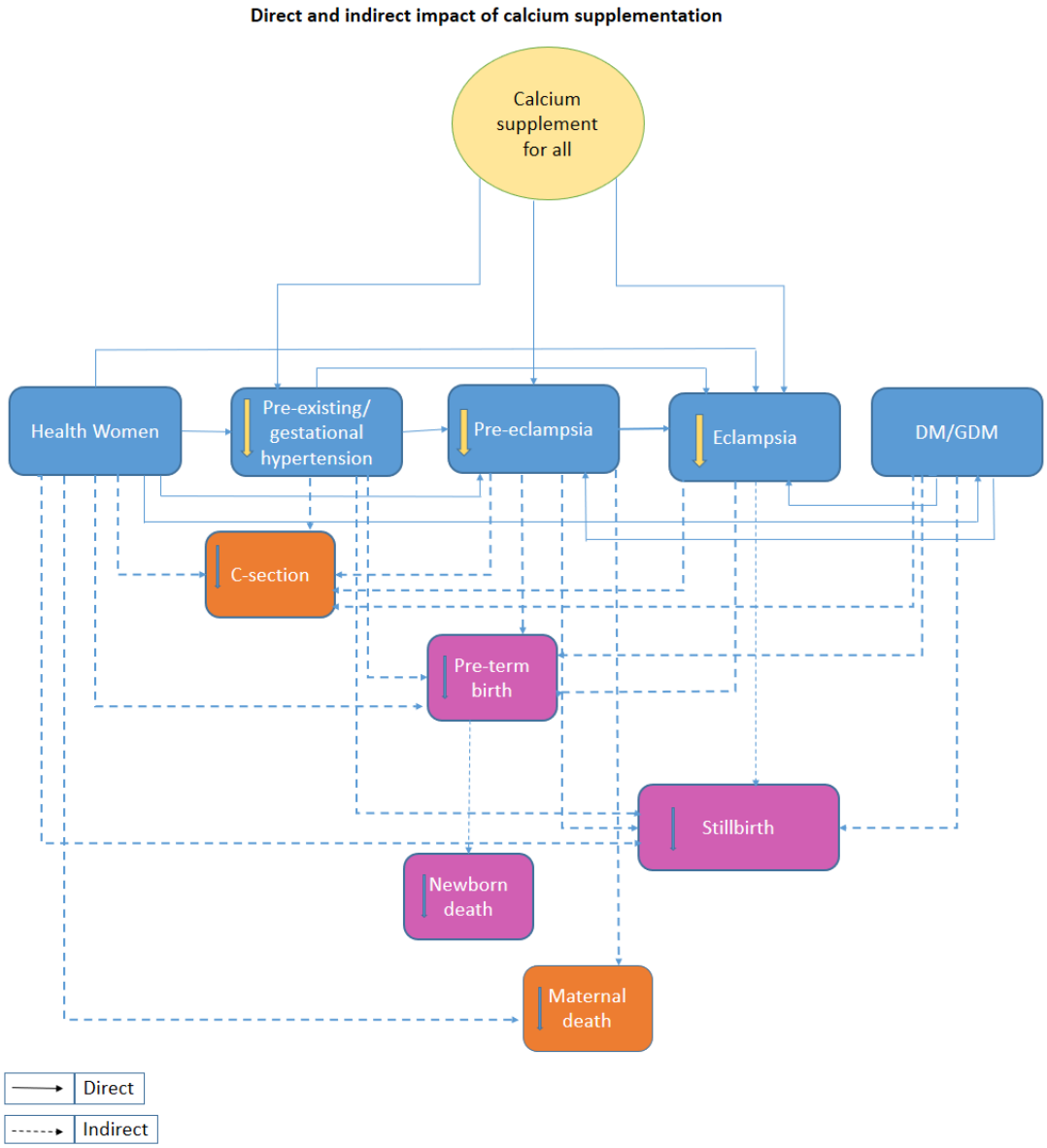


Figure 5.3: Schematic of model intervention effect

5.5.1.1 Direct and indirect effects of calcium supplementation

Calcium supplementation is a proven intervention in preventing hypertension in pregnancy and pre-eclampsia , especially among women with low calcium intake (183). It is the mineral that ensures several vital functions of the body, including maintenance of skeletal, cardiovascular, neurological, muscular, hormonal and enzymatic functions (215). Studies found better biochemical markers among pregnancies complicated by pre-eclampsia when calcium supplement is given, through preservation of the maternal skeleton (216). A Cochrane systematic review reported that daily calcium supplement among pregnant women can reduce the risks of pre-eclampsia, c-section birth, stillbirth, preterm birth and maternal and newborn death (184). The exact mechanism in which calcium supplementation reduces the risk of gestational hypertension, pre-eclampsia/eclampsia and subsequent events is not clear. One possible pathway as suggested in literature could be through reduced level of parathyroid release and intracellular calcium. Calcium supplementation through this mechanism can reduce smoothen muscle contractility and reduce adverse birth outcomes (216).

Details of all the data sources along with the mechanism in which calcium works, its effectiveness and the way it has been incorporated in the model for each parameter is described below.

Gestational hypertension: calcium can help relax blood vessels, promote better blood flow and reduce the risk of hypertension (216). Systematic reviews revealed that calcium supplements can significantly reduce the risk of gestational hypertension among pregnant women [RR 0.65 (CI 0.53 - 0.81)] (Table 2.1) (183). This was directly included in the model as an effect of the intervention.

Pre-eclampsia: calcium also directly reduces the risk of pre-eclampsia. Majority of literature related to the effect of calcium supplementation on hypertensive disorders focuses on the reduction in pre-eclampsia. Calcium can reduce endothelial dysfunction associated with pre-eclampsia (216). It may also help by mediating immune system balance and reducing inflammation and mitigate the risk of pre-eclampsia. Improved placental blood flow is another possible explanation for reduction in risk of pre-eclampsia. In addition, calcium supports cellular and hormonal signalling pathways which may play a role in regulation of hormone release, and other processes leading to controlled blood pressure and resultant reduction in pre-eclampsia.

There are few sources of evidence that report the impact of calcium on reduction in risk of pre-eclampsia. The Cochrane review suggests calcium reduces the risk of pre-eclampsia by a significant proportion [RR 0.45 (CI 0.31 to 0.65)] (183). The effect of calcium also varies depending on maternal risk level. It is higher among women with low calcium intake [RR 0.36 (0.20-0.65)]. It is also higher among women at high risk of developing pre-eclampsia [RR 0.22 (CI 0.12-0.42)] but might be biased due to small study effect (183). The latest update on evidence related to calcium supplementation by

Keats et al (2021) reported the effect of calcium supplements on pre-eclampsia and eclampsia combined. The final RR applied for all women was taken from an updated review-based result [RR 0.45 (CI 0.19-1.06)] (217).

Effect of calcium supplementation in the model has been estimated through applying both indirect and direct effects. Some indirect effects in the model were attained through the reduction in gestational hypertension. The additional risk has been applied as a direct effect of calcium on reducing pre-eclampsia in the model.

Eclampsia: as mentioned before, recent literature reported the combined effect of calcium on pre-eclampsia and eclampsia. The same RR was used in the model. Since there were no additional reductions in eclampsia due to reduction in pre-eclampsia, no adjustment was made to account for indirect effects.

Evidence suggests that there is an increased risk of adverse maternal and newborn birth outcomes like c-section birth, preterm birth, stillbirth, maternal death and newborn death among women with HDP (183). The reduction in hypertension and pre-eclampsia are expected to lead to reductions in c-section, preterm birth, stillbirth and maternal death (Figure 5.3).

C-section: Calcium can smoothen muscle contractility, improving the chances of a normal vaginal birth (218). Reviews found a very small reduction in c-section [RR 0.99 (CI 0.89-1.02)] among women receiving calcium in pregnancy (183). Effects on c-section in the model have been attained through a reduction in hypertensive disorders in pregnancy.

Preterm birth: In addition to reduction in preterm birth through reduction in risk of pre-eclampsia, calcium can also directly reduce the risk of preterm birth. There are multiple possible mechanisms through which this can happen. Calcium can support improvement in hormonal balance, help reduce inflammation, improve blood vessel function, strengthen cervical tissue and improve uterine muscle function, eventually reducing the chances of a preterm birth (216).

Review results found moderate level of evidence in favour of calcium supplement among pregnant women for reducing preterm birth compared to placebo (RR 0.76, [95% CI 0.60 to 0.97]) (Table 5.11) (219).

The effect of calcium on preterm birth was incorporated within the model both directly and indirectly. First, an indirect effect through a reduction in pre-eclampsia was estimated and in the second step, the remaining reduced risk was directly applied.

Stillbirth: stillbirth reduction takes place through reduction in pre-eclampsia. Other direct mechanisms include ensuring proper development of the heart and circulatory system of the foetus and ensuring proper uterine muscle contraction (216). Cochrane systematic review reported the effect of stillbirth among women receiving calcium compared to placebo [RR 0.90 (CI 0.74-1.09)] (183). Similarly, to preterm birth, effect on stillbirth was estimated through both indirect and direct effect.

Maternal death: reduction in maternal death is expected to take place through reduction in pre-eclampsia and eclampsia. However, evidence in favour of reduction in maternal death [RR 0.17 (CI; 0.02 – 1.39)] is weak due to the low number of cases (183). Reduction in maternal deaths in the model were attained through reduction in pre-eclampsia/eclampsia in the model in the first step. Adjusted relative risk was applied directly to maternal deaths to attain the expected reduction.

Newborn death: An indirect effect on newborn death would primarily be achieved through a reduction in preterm birth. Evidence suggests a protective effect of calcium on newborns [RR 0.90 (CI 0.74-1.09)] (183). This is same as the one reported for stillbirths. Effect on newborn deaths was attained only through indirect effect.

To summarise, the direct effect of calcium on women was through a reduction in gestational hypertension and pre-eclampsia/eclampsia in the model. The effect on c-section was attained indirectly. The effects on offspring was attained through reduction in preterm birth and stillbirth. While a proportion of the reductions in these two outcomes were attained through reduction in HDP among women, additional direct effects were applied to attain the full estimated impact. The model was first run with effects applied only on the two direct outcomes of calcium supplements. The results were checked for all downstream outcomes, relative risks were adjusted and the ratio between the output RR and input RR was then applied back to respective outcomes. Table 5.11 lists the relative risks based on literature and direct risks applied in the model.

5.5.1.2 Converting intervention effects for scaling up of coverage

The base case model produces the current scenario of Bangladesh in terms of the pregnancy and childbirth outcomes as discussed above. The increased coverage of interventions thus required adjusting the relative risks for the intervention outcomes in a manner that accommodates individuals who have already received the intervention.

The relative risks were hence adjusted using the formula below:

Risk to whole population at current coverage = RR/((Current population coverage x RR with intervention) + ((1- current coverage) x RR without intervention))

Risk to whole population at target coverage = RR/((Target population coverage x RR with intervention) + ((1- target coverage) x RR without intervention))

Where, RR = relative risk; current coverage = proportion of population already receiving the intervention; target coverage = proportion of population to receive intervention; RR without intervention = 1.

Risk across whole population = Risk to whole population at current intervention coverage/ Risk to whole population at target intervention coverage

Table 5.11: Relative risks from literature and adjusted relative risks for scaling up of calcium supplementation

Event/Outcome	Relative Risk (Applied to the whole population at 80% coverage)			Relative risk with intervention (Literature)			Source
	Mean	LB	UB	Mean	LB	UB	
Gestational hypertension	0.768	0.838	0.967	0.65	0.53	0.81	Hofmeyr et al (2018) (183)
Pre-eclampsia	0.621	0.511	0.768	0.45	0.19	1.06	
Eclampsia	0.668	0.550	0.826	0.45	0.19	1.06	
C-section	1.000	-	-	0.95	0.89	1.02	
Maternal death	0.395	0.262	1.226	0.29	0.06	1.39	
Stillbirth	0.936	0.831	1.055	0.87	0.70	1.07	
Preterm	0.844	0.733	0.981	0.86	0.70	1.05	
Newborn death	1.000	-	-	0.90	0.74	1.09	

5.6 Long-term outcome methods

Health conditions like gestational hypertension and gestational diabetes mellitus occur during pregnancy, and most women will reach their pre-pregnancy state after their babies are born. Most women with GDM are likely to go back to normal blood sugar level (220). Hypertensive disorders like gestational hypertension and pre-eclampsia are also expected to correct within 12 weeks post birth for most women (221). However, a proportion of women exposed to hypertensive disorders or gestational diabetes during pregnancy are also at a higher risk of developing chronic diseases like type 2 diabetes mellitus, chronic hypertension and ischaemic heart disease later in their lives (220-225). Evidence suggests an increased risk of developing chronic hypertension among women who had gestational hypertension/pre-eclampsia/eclampsia (226). Increased risk of type 2 diabetes mellitus has also been reported in literature among women who had gestational diabetes mellitus. In addition to specific conditions developed during pregnancy turning into chronic illnesses, the risk of hypertension has been reported to be higher among women who had gestational diabetes and vice versa (227, 228).

Babies born to mothers with hypertensive disorder or diabetes mellitus are also at a higher risk of developing these diseases later in their lives. Babies who are born preterm can be exposed to a higher risk of delayed development in the first few years of their lives (229, 230). Reviews suggest cerebral palsy, intellectual disability and visual and hearing impairments as some of the developmental disorders among preterm-born infants (231).

This part of the model focuses on the long-term outcomes of HDP and GDM on women and their offspring.

5.6.1 Model structure

The post-birth long-term model focused on the increased risk of hypertension and diabetes in later life among women who had hypertensive disorder or gestational diabetes during pregnancy. The reduction in gestational hypertension and pre-eclampsia through a scale-up in calcium supplementation intervention were expected to reduce the prevalence of chronic hypertension and type 2 diabetes mellitus among women included in the model.

The long-term model for women followed an individual-based structure similar to the pregnancy model. However, it has been structured as a decision tree, estimating the number of women who would develop either or both of the diseases at some point in their lives. Individual risk of developing the diseases was assigned depending on women's condition before and during pregnancy (figure 5.4). Women who would eventually develop one or both of the conditions were then selected through probabilistic sampling.

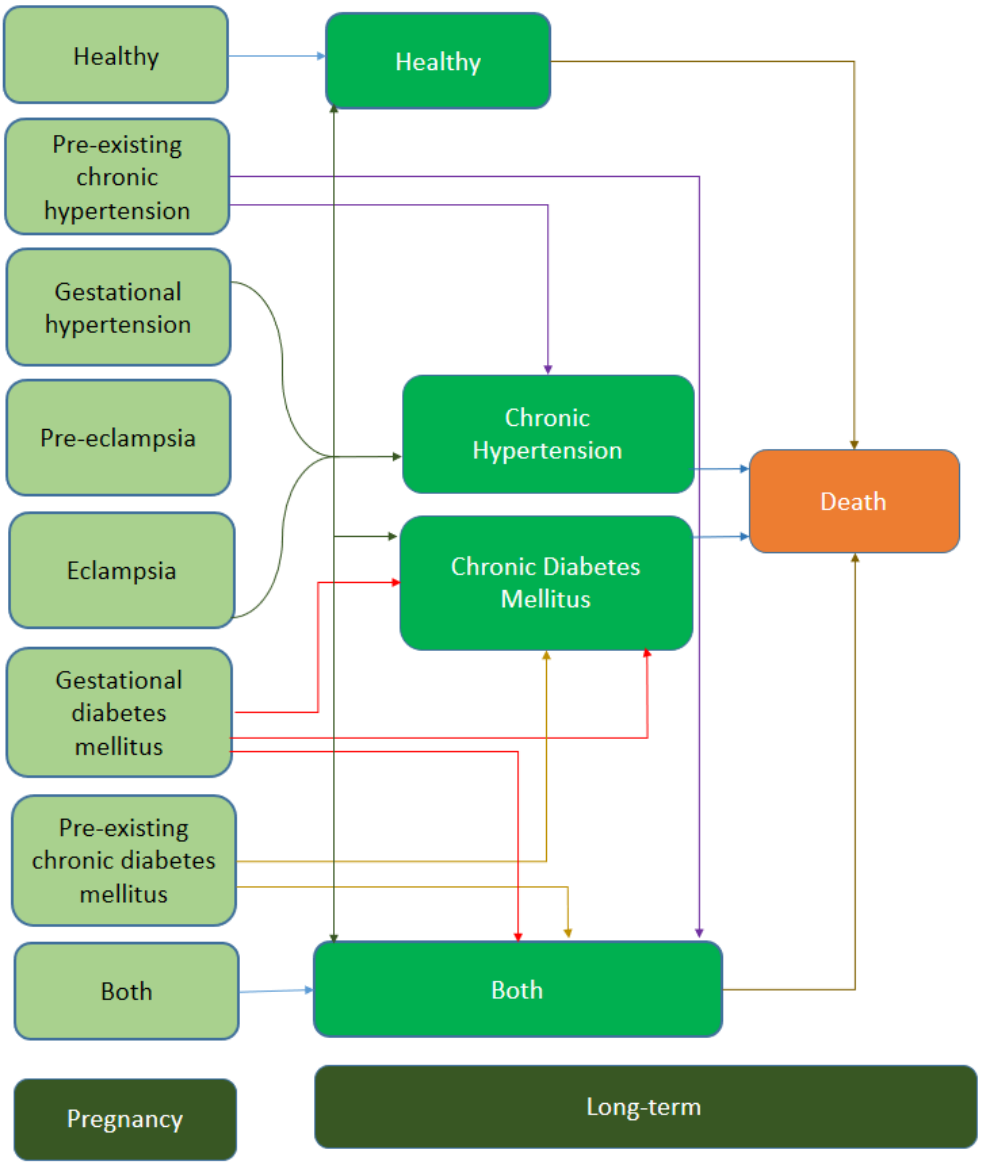


Figure 5.4: Long-term Model Schematic

For babies, a simple estimation using the model was done to report the reduced number of children facing a developmental delay during the first five years of their lives (Figure 5.5). The outcomes and duration of the long-term model was decided based on the stakeholders' recommendation. The number of preterm born babies at risk of facing a developmental delay was estimated for the current and scaled up provision of care. (Figure 5.5).

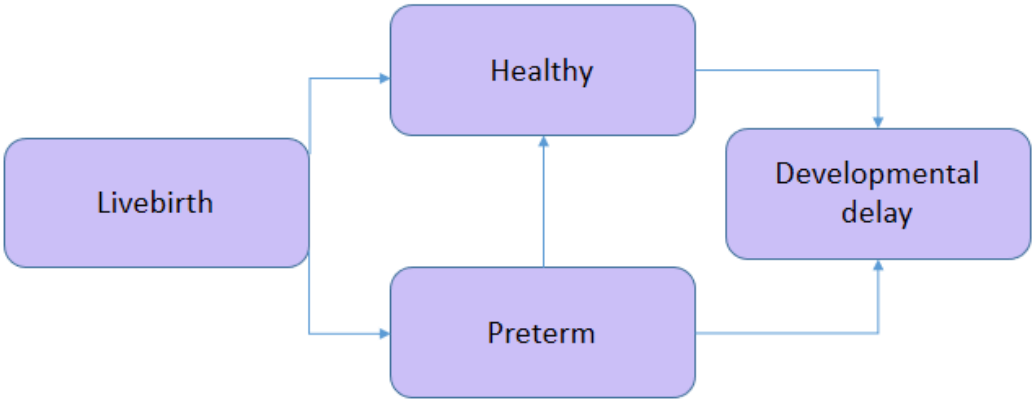


Figure 5.5: Model schematic for offspring

5.6.2 Input data: long-term outcome for women

5.6.2.1 Hypertension

Lifetime risk of developing hypertension was not available at the national level. The age-specific proportion of women with hypertension was available from BDHS (2018) (52). For the model, it was assumed that the prevalence among women aged over 70 was the lifetime risk of developing chronic hypertension. Lifetime risk of a disease would be the cumulative risk of developing a disease at different ages. As women in Bangladesh have an average life expectancy of 74 years, it would be logical to assume that one or both of the chronic conditions can develop by the age of 70.

Mean age of onset of the chronic conditions was assumed to be 40. Not many studies have reported the age of onset of chronic diabetes and chronic hypertension after encountering HDP or GDM. Heida et al (2015) reported mean age at onset of hypertension to be 43.5 years among a cohort of Dutch women (232). The same study reported age at onset of chronic diabetes mellitus among women with GDM to be 52.8 years. Another study reported 35-60% of women with GDM to development type 2 diabetes mellitus within 10 years after pregnancy (233). Considering the mean age of the modelled women to be around 32 years, assuming the age of onset to be 40 would therefore closely comply

with the literature. The model reports two scenarios: women developing the chronic conditions immediately after birth and at age 40.

In order to attain the correct national prevalence, prevalence of pre-existing hypertension was deducted from lifetime prevalence. While prevalence for women aged 70+ was 61.0%, and 20.5% women had pre-existing hypertension before pregnancy, the long-term model took into account the additional 40.5% women who would develop hypertension at some point in their lifetime after giving birth (52).

Multiple studies reported the impact of hypertensive disorder of pregnancy and its relation to cardiovascular disease with a focus on pre-eclampsia and eclampsia. Garovic et al reported the risk of developing chronic hypertension after gestational hypertension separately. The article revealed that women with gestational hypertension have a relative risk of 1.88 [CI 1.49 – 2.39] of developing chronic hypertension later in life compared to those who did not have hypertension in pregnancy (225). The article did not distinguish between hypertension only and other hypertensive disorders of pregnancy. A systematic review and meta-analysis by Bellamy et al reported that women with pre-eclampsia during pregnancy were 3.7 times more likely to develop chronic hypertension later in life compared to those who completed pregnancy without developing pre-eclampsia (226). Tobias et al reported that women who had gestational diabetes mellitus were also at a higher risk of developing hypertension compared to those without GDM in the long term (RR 1.26 [CI 1.11-1.43]) (227). Table 5.12 below lists the average risks estimated from the relative risks extracted from the literature.

Table 5.12: Long-term risks of chronic hypertension among women with gestational diabetes or hypertensive disorder of pregnancy

Parameter	Overall average risk (estimated from RR)	Relative risks	LB	UB	Source of data
Lifetime hypertension	0.40	-	0.36	0.44	NIPORT (2020)(52)
Hypertension among women with gestational hypertension compared to those without	0.55	1.88	1.49	2.39	Garovic et al (2010)
Hypertension among women having pre-eclampsia or eclampsia compared to those without	0.84	3.7	2.7	5.05	Bellamy et al (2007) (226)
Hypertension among women with gestational diabetes mellitus compared to those without	0.43	1.26	1.11	1.43	Tobias et al (2011) (227)

5.6.2.2 Diabetes Mellitus

Similarly to hypertension, the risk of developing diabetes mellitus after age 70 was assumed to be the lifetime risk. Nearly 8.5% of women had pre-existing diabetes in the model while the prevalence among women aged over 70 was 13.7%. An additional 5.3% of women would develop diabetes post-pregnancy at some point in their lives in order to obtain the average lifetime prevalence (52).

Those who developed gestational hypertension, pre-eclampsia or eclampsia were assigned with a higher risk of developing type 2 diabetes mellitus (T2DM) in their lifetime after their pregnancy ended. Table 5.13 details the risk of diabetes mellitus among modelled women who did or did not have gestational diabetes mellitus.

A systematic review studying T2DM after gestational diabetes between 1960 and 2009 conducted a pooled analysis of 20 studies. Among women who had gestational diabetes, the relative risk of developing type 2 diabetes mellitus is 7.43 [CI: 4.79 – 11.51] compared to women who maintained normal blood sugar level during pregnancy (223). A second systematic review reported that women with gestational hypertension had 2.19 times the risk of developing diabetes mellitus [CI: 1.69-2.84] while women who had pre-eclampsia or eclampsia were at 2.56 times the risk of developing the T2DM compared to those without [CI: 2.02 – 3.24] (228).

Table 5.13: Long-term risks of diabetes mellitus among women with gestational diabetes or hypertensive disorder of pregnancy

Parameter	Overall average risk (estimated from RR)	Relative risks	LB	UB	Source of data
Diabetes mellitus	0.053	-	0.033	0.092	NIPORT (2020)(52)
Diabetes mellitus among women who had GDM	0.395	7.43	4.79	11.51	Bellamy et al (2009) (223)
Diabetes mellitus among women who had gestational hypertension	0.125	2.19	1.69	2.84	Zhao, Grace et al (2021)(228)
Diabetes mellitus among women who had hypertensive disorder of pregnancy	0.145	2.56	2.02	3.24	Zhao, Grace et al (2021) (228)
Diabetes mellitus among healthy women	0.047	-	-	-	Estimated

5.6.2.3 Hypertension & Diabetes Mellitus

Apart from individual disease conditions, the model also took into account those having both conditions during pregnancy. First, women with two conditions – gestational hypertension and gestational diabetes mellitus – were assigned a higher risk of developing chronic hypertension and/or chronic diabetes mellitus. These risks were generated based on published literature. HWU et al (2016) (234) studied a cohort of pregnant women between 15 and 44 years of age in Taiwan. The study reported risk of hypertension and diabetes mellitus in women with hypertensive disorder and gestational diabetes during pregnancy. Adjusted hazard ratio of hypertension was reported to be 16.8 (95% CI, 11.8-24.1), while for diabetes mellitus it was 16.2 (95% CI, 13.2-19.9) (234). (Table 5.14)

Table 5.14: Long-term risks of hypertension and diabetes mellitus among women with both conditions in pregnancy

Parameter	Overall average risk (estimated from RR)	Relative risks	LB	UB	Source of data
Hypertensive disorder and gestational diabetes	0.021	-	-	-	Modelled estimate
Diabetes Mellitus among women with hypertensive disorder of pregnancy and gestational diabetes	0.74	16.2	13.2	19.9	Hwu et al (2016) (176)
Hypertension among women with hypertensive disorder of pregnancy and gestational diabetes	2.17	16.8	11.8	24.1	Hwu et al (2016) (176)

5.6.3 Input data: long-term outcome for offspring

5.6.3.1 Developmental delay

The Bangladesh Multiple Indicator Cluster Survey (MICS) 2019 reported 25% children to have delayed early childhood development (235, 236). Johnson et al (2015) compared 1130 preterm and 1255 term babies at two years in a prospective population-based study (237). The study suggests late and moderate preterm-born babies to have a 1.28 [CI: 1.04-1.58] times higher risk of developmental delay. Considering social competency as a marker of development, an estimated 30% of preterm babies would end up with delayed social competency. (Table 5.15)

Table 5.15: Long-term risks of developmental delay among preterm babies

Parameter	Overall average risk (estimated from RR)	Relative risks	LB	UB	Source of data
Developmental delay	0.250	-	-	-	MICS (2019) (235)
Delayed social competency among children born preterm (used as a proxy for developmental delay)	0.300	1.28	1.04	1.58	Johnson (2015) (237)

5.7 Incorporating aggregate outcome measure

5.7.1 Methods of DALY estimation

Disability Adjusted Life Years (DALY) is a measure that captures both mortality in terms of time lost due to premature death and morbidity in terms of time lost due to disability. DALY started being used in the early 90s by WHO as a standard 'universally applicable' measure of burden of disease with the aim of aiding in designing and prioritising health policy and planning as well as identifying vulnerable groups of people. It is a common measure that helps in programme evaluation and comparison across different disease conditions (238, 239). DALYs over time became more of an evaluative effort that added to a simple count of number of deaths (240). The objective of this section is to describe DALY estimation methods in general and how it has been adopted for the model and sources of country-level data for estimating DALYs for women in the model.

The DALYs have two distinct segments of measurement, Years of Life Lost (YLLs) and Years Lived with Disability (YLDs). YLL is measured by calculating the difference between a reference life expectancy and age at death. The loss function is expected to represent the maximum life span of an individual if he/she were in perfect health. In the Global Burden of Disease (GBD) studies, global DALY estimates are made based on life expectancy using the lowest age-specific mortality rates projected for a population (180). National level DALY and their YLL and YLDs are available from the Institute of Health Metrics Evaluation (IHME) database (241).

DALY is the summation of YLL and YLDs and calculated for a specified cause of death (240).

DALY(c,s,a,t) = YLL(c,s,a,t) + YLD(c,s,a,t) for given cause c, age a, sex s and year t (180) (a)

Measurement of DALYs has evolved over time since its beginning during the early 90s. At the initial stage, the different weights were decided completely through expert opinion (180). Since GBD 2020, there have been surveys to include public opinion in the disability weights (DWs). Also in the initial phase of DALY measurements, DALYs were discounted at a rate of 3% per year considering future uncertainties, possibility of improvement in health care interventions in future and preference over current goods than those in the future (180, 239, 240). Amid criticisms, since 2010, GBD estimates are done without discounting the YLL, counting every life year equally (239, 240). The first phase of DALYs also used age weighting which was removed since 2010, putting equal weight to every life year of people of all age groups.

Basic formula for YLLs is the following for a given cause c, age a, sex s and year t:

$YLL(c,s,a,t) = N(c,s,a,t) \times L(s,a)$ (180, 239) (b)

YLDs on the other hand are assigned with a disability weight (DW) between 0 and 1 where 0 represents full health and 1 represents a loss equivalent to death (240). Disability weights are a common unit of measurement to value time lived in a non-fatal health state. Disability is captured by complicating causes that lead to the cause of death. YLD is estimated as a product of time span spent with a condition and the disability weight. The disability weight reflects how severe the impact of the disease has been over a certain time period.

The formula for YLDs is the following for a given cause c, age a, sex s and year t:

$YLD(c,s,a,t) = I(c,s,a,t) \times DW(c,s,a) \times L(c,s,a,t)$ (180, 239) (c)

YLD calculations were simplified and estimated by multiplying prevalence by the relevant weights and adjusted for comorbidities. Co-morbidities are calculated following the multiplicative formula below.

$DW1+2 = 1 - (1 - DW1) \times (1 - DW2)$ (180) (d)

Prevalence YLDs for individual:

$YLD_i = DW_i \times p_i$ (180) (e)

Combining the two equations:

$YLD_{1+2} = 1 - (1\text{-}YLD_1) \times (1 - YLD_2)$ (180) (f)

The GBD studies contain hierarchical causes and sequelae lists to be used by a wide range of users. Sequelae are “distinct, mutually exclusive categories of health consequences that can be directly attributed to a cause”(242). The report used type 2 diabetes mellitus as an example. Diabetes Mellitus type 2 in GBD is included as a level 3 cause of death under the level 1 category of communicable, maternal, neonatal, and nutritional diseases and the level 2 category of diabetes and kidney diseases.

While neuropathy and blindness are sequelae of diabetes, Chronic Kidney Disease (CKD) is not. Disability for CKD due to type 2 diabetes mellitus was included as a covariate within CKD and no direct attribution was made (242). Similarly, hypertensive heart disease was included as a level 3 cause within level 2 of causes of cardiovascular diseases under the level 1 category 'Communicable, maternal, neonatal and nutritional diseases' and as a covariate in CKD. Disability weights were available for hypertensive heart disease, stroke and CKD due to hypertension (242).

The systematic review (chapter 3) of economic evaluations included a number of studies that used DALY as an outcome. However, methodologies about how the DALY weights were used lacked sufficient detail to fully understand what was done. One paper that evaluated a diabetes screening technology for pregnant women used disability weights from existing literature, primarily the weights available through global burden of disease studies (138). A study focusing on a quality improvement initiative used project-specific data and assumed that for every maternal death, between 5 and 20 women were disabled due to complications. This ratio was used as a disability multiplier (107). A similar ratio was used in a study evaluating a maternal health voucher scheme in Uganda (119). Another study based in Pakistan evaluated cost-effectiveness of community engagement, HDP-oriented ANC and use of oral antihypertensive therapy or IV based MgSO4. The authors used only YLL as disability and ignored YLD as disability weights were not available (82). An evaluation of a calcium supplementation programme mentioned using national surveys and secondary literature for DALY weights (114). The most recent GBD studies produced DALY weight for maternal hypertensive disorders and was used by at one study identified in the review (114). In all the exercises, DALY has been applied in an aggregate level to the whole population and not to individual patients/participants. It should be noted that there are only one set of global level disability weights available in the GBD reports.

5.7.2 Estimating DALYs for the model

DALYs for this model have been estimated following the latest methodology described by the WHO (180). The updated methods and estimates emphasise DALY to be a measure for "quantifying loss of health, rather than the social value of loss of health" (180). No age weighting or discounting has therefore been applied in these calculations. Scenario analysis and deterministic sensitivity analysis, however, has been conducted and presented using 3% and 5% discount rate to generate total DALYs over the model time horizon. The discounting rates have been applied as is standard in other economic evaluations (243). Individual YLL and YLD has been assigned depending on women's health states following the methodology described below.

5.7.2.1. DALY for pregnancy and childbirth

Maternal disorders in GBD covers: 1) abortion and miscarriage; 2) ectopic pregnancy; 3) obstructed labour and uterine rupture; 4) maternal haemorrhage; 5) maternal sepsis and other maternal infections; 6) maternal hypertensive disorders; and 7) other (direct) maternal disorders. Although abortion and miscarriage were incorporated in the model, it was a flat rate applied throughout the model as calcium supplementation does not have any effect on this (180). As a result, DALY for this outcome was not included in estimating the aggregate outcome measure.

Neonatal morbidity covers five individual causes: i) neonatal preterm birth complications, ii) neonatal encephalopathy due to birth asphyxia and trauma, iii) neonatal sepsis and other neonatal infections, iii) hemolytic disease and other neonatal jaundice, and iv) other neonatal disorders (180).

In this model, individual-level mean DALY has been estimated and assigned to each woman. Summation of the DALYs provided an estimate of overall loss of DALY within the modelled population for current care and scale-up of intervention. For the pregnancy and childbirth section of model, the outcomes were gestational hypertension, pre-eclampsia, eclampsia, c-section birth, preterm birth, stillbirth and maternal and neonatal deaths. The direct causes of maternal deaths in the model included pre-eclampsia and eclampsia, while for neonatal death the direct cause was preterm birth.

YLL for this part of the model was calculated based on the difference between age-specific average life expectancy of women in Bangladesh and their age at death (244). It was assigned to maternal deaths due to pre-eclampsia/eclampsia both for current care and scaled up provision of the intervention. YLL for the model also included newborn deaths due to preterm birth. For newborns, average national life expectancy at birth was assigned to each newborn death.

The YLD following the most recent method of DALY estimation was estimated by assigning disability weights to individuals for the current care and scaled up provision of the intervention (gestational hypertension, pre-eclampsia, eclampsia and preterm birth). (Table 5.16).

Disability weights for maternal hypertensive disorders specific to pre-eclampsia and eclampsia were available in the GBD estimates, while the overall weight for maternal hypertensive disorder was used for gestational hypertension. Duration of the disability was assumed to be seven days following severe pre-eclampsia and eclampsia. Post pregnancy disability weights for lifetime impact of severe pre-eclampsia and eclampsia were directly available from the GBD report and included in the model. The disability weights assigned to women are listed in table 5.16 below.

Finally, total DALY was estimated by adding up the YLL and YLD for current care and intervention for all women for the pregnancy and childbirth period.

Disability weight for c-section is not available in the latest GBD estimate. It was estimated following the expert elicitation method previously followed for measurement of DALYs while the latest weights for all other health states are estimated using survey-based data (180). The weight for C-section was around 0.349 in GBD 2004 (245). No weights are available for GDM. Disability among women due to GDM were limited to pre-eclampsia among women with GDM.

Table 5.16: Disability weights for maternal health states associated with pregnancy

Health state	Disability weight (95% confidence interval)	Duration (days)	Source
Other hypertensive disorders of pregnancy	0.049 (0.031 – 0.072)	7	World Health Organisation (2020) (180)
Severe pre-eclampsia	0.174 (0.427 – 0.753)	7	World Health Organisation (2020) (180)
Eclampsia	0.602 (0.427 – 0.753)	1	World Health Organisation (2020) (180)
C-section	0.349	7	World Health Organisation (2004) (245)

5.7.2.2 DALY for long-term outcomes

The long-term outcomes for women were chronic hypertension and diabetes mellitus. For estimating YLL for each or both conditions, reduced years of life expectancy due to each of the two diseases were extracted from literature and deducted from the age specific life expectancy of women. Years of life lost due to both conditions were assumed to be the higher of the two conditions. Table 5.17 below summarises the reduced life expectancy depending on women's condition.

Table 5.17: Life expectancy with morbidity for YLL estimation

	Years lost	Source
Reduced life expectancy with diabetes mellitus	6.0	Franco et al (2005) (246)
Reduced life expectancy with hypertension	4.9	Rao et al (2011) (247)
Reduced life expectancy with both conditions	6.0	Assumption

For the disability part, diabetes mellitus had a number of health states as its sequelae with disability weights assigned to each. Mean weight was estimated based on Bangladesh-specific prevalence of each health state and assigned to all women with chronic diabetes mellitus. It was then multiplied by the reduced life expectancy of women due to the disease/s. The data extracted from literature on prevalence of the disease sequelae in Bangladesh are reported in table 5.18.

Table 5.18: Country-specific proportion of population in health states related to diabetes mellitus and hypertension

Health state	Prorportion of women with diabetes in different health states	Source
Uncomplicated diabetes mellitus	0.473	Estimate
Diabetic neuropathy	0.197	Mørkrid et al (2010) (248)
Moderate vision loss	0.122	Muqit M et al (2019) (249)
Severe vision loss	0.183	Muqit M et al (2019) (249)
Blindness	0.025	Muqit M et al (2019) (249)
CKD due to diabetes mellitus	0.195	Islam et al (2021) (250)
CKD due to hypertension	0.384	Feng et al (2019) (251)
Hypertensive heart disease	0.105	Chowdhury et al (2018) (252)
Stroke	0.797	Mondal et al (2022) (253)

For chronic hypertension, weights were not directly available as hypertension is not a direct cause of death but leads to complications associated to CVD like heart disease, stroke and renal diseases that are direct causes of death (254). It has been included as a sequelae in conditions like chronic kidney diseases (239, 242). Stroke and cardiovascular disease are two most common consequences of hypertension and were included in the model. For simplification, the model assumed moderate consequences and included disability weights assigned for the moderate health states for each. For example, direct weight was available for heart failure due to hypertensive heart disease and was included to estimate YLD due to hypertension. It had four stages: mild, moderate, severe and controlled. The weight for moderate heart failure was used for everyone who had a hypertensive heart disease.

For women having both diseases, DW adjustments were made following the methods published by WHO (2020) (equation f) (180). All the relevant disability weights for sequelae related to diabetes mellitus and hypertension are listed in table 5.19. Disability weights estimated for comorbidities are also reported in the table.

Table 5.19: Disability weights associated with diabetes mellitus and hypertensive heart disease

Health state	Disability weight (95% CI)	Source
Uncomplicated type 2 diabetes mellitus (T2DM)	0.049 (0.031-0.072)	Vos et al (2020) (242)
Diabetic neuropathy	0.133 (0.089 – 0.187)	Vos et al (2020) (242)
Moderate vision loss	0.031 (0.019 – 0.049)	Vos et al (2020) (242)
Severe vision loss	0.184 (0.125 – 0.259)	Vos et al (2020) (242)
Blindness	0.187 (0.124 – 0.260)	Vos et al (2020) (242)
Chronic Kidney Disease due to T2DM	0.104 (0.07 – 0.149)	Vos et al (2020) (242)
Moderate heart failure due to hypertensive heart disease	0.041 (0.047 – 0.103)	Vos et al (2020) (242)
Controlled, medically managed heart failure due to hypertensive heart disease	0.049	Vos et al (2020) (242)
Chronic Kidney Disease due to hypertension	0.104 (0.07 – 0.149)	Vos et al (2020) (242)
Stroke – moderate consequences	0.07 (0.046 – 0.099)	Vos et al (2020) (242)
Mean disability weight – T2DM	0.163	Estimated
Mean disability weight – hypertension	0.108	Estimated
Mean disability weight – hypertension and T2DM	0.254	Estimated

While age of onset for women developing chronic conditions was set at 40, those with pre-existing morbidity were assigned a duration based on their age-specific life expectancy. Finally, the pregnancy and childbirth and the long-term DALY were summed up to report a total DALY for the model. Differences between the current care and scaled-up provision of care in DALY produced the total DALYs averted through the intervention.

Long-term outcome for babies was not included in the model as suggested by stakeholders. The effect on preterm birth was estimated as a standalone measure. To complement that, DALY for preterm births was also calculated and presented as a standalone measure. YLL equivalent to average life expectancy at birth for newborn deaths due to preterm-related causes was included in the pregnancy and childbirth model. For long-term YLD, disability weight for moderate motor impairment was used for all preterm births [DW 0.203 (CI 0.134-0.290)]. This will provide a very gross estimate of the possible loss of DALY due to preterm birth. The time duration of this was set at the national average life expectancy.

5.8 Costs

Costs were estimated based on the key components of the model at different stages of antenatal, delivery and postnatal care for the pregnancy and childbirth section of the model. Treatment costs for long-term consequences were also included. The objective of this section is to describe the methods and source of data for costing the care pathway for individual women during pregnancy and through their life course.

5.8.1 Perspective

Costing for the model has been done from a public health care system perspective. This was recommended by the majority of experts during consultation.

5.8.2 Discounting

A standard 3% discounting rate was applied to lifetime costs following other CEA analysis done based on Bangladesh (255).

5.8.3 Inflation, currency and exchange rate

Inflation adjustments and currency exchange have been done following two methods depending on data availability (256). All costs for the pregnancy and childbirth section of the model have been estimated in Bangladeshi taka. Inflation adjustment was done using gross domestic product (GDP) deflator as health-specific inflation was not available for Bangladesh (256). The inflated value then was converted into US dollars using purchasing power parity (PPP) exchange rate. Costs for the long-term model were available in US dollars. USD was converted into local currency using PPP exchange rate and then inflated using the GDP deflator in Bangladesh. Both exchange rates and inflation were adjusted using 2021 values as they were the latest available values published and were assumed to remain the same till 2023.

5.8.4 Literature search

For the pregnancy and childbirth section of the model, all costs were extracted from available literature and nationally conducted costing exercises. The first priority was given to country-specific published and unpublished costing exercises of health services related to maternal health, newborn health and non-communicable diseases, diabetes mellitus and chronic hypertension. This search was done primarily through discussion with relevant people working in the field. Next, a PubMed search was done to identify published articles relevant to costing of relevant health services when government documents were not available. Priority was given to costing done based on a health systems perspective. Where not available, patient fees were used as a proxy for the health system's costs. Online searches were supplemented by discussion with experts and colleagues in the field to

identify unpublished and most recent sources of data. Personal experience also helped to gather data on costing exercises.

For the long-term model, a simple review using PubMed was conducted for the two diseases. Simple search terms such as diabetes AND Bangladesh AND cost or hypertension AND Bangladesh AND cost were used for conducting the two searches. The Google search engine was used to identify available grey literature. As with the pregnancy and childbirth section of the model, published literature reporting costs based on the health system's perspective was preferred. Information on unpublished costing done at the country level were sought through discussion with experts.

5.8.5 Cost components

Costs were estimated based on the key components of the current care pathway at different stages of antenatal, delivery and postnatal care for the pregnancy and childbirth section of the model. Cost components included capital costs and recurrent costs. Capital costs primarily covered establishment of specialised units in facilities and equipment, while recurrent costs included drugs and supplies, staff time and ongoing staff training. Apportioning for staff time was done based on assumptions regarding time allocated for maternal and newborn health services through expert consultations. Average costs per case, when not available directly, were estimated based on caseload of facilities per annum.

Costs have been estimated per case for newborns and the lifetime of women after giving birth. Costs were summed up for all women and babies receiving certain health care services to get total cost. The percentage of women receiving calcium supplements during antenatal care was taken from current national coverage, and the target coverage. Women were allocated with costs related to modes of birth and care for pre-eclampsia or eclampsia based on the model results. All costs were taken to the 2021 price level after adjusting for inflation following the latest available GDP deflator (257).

Details of costing methods for the pregnancy and childbirth and long-term outcome sections of the model have been explained separately in the following sections.

5.8.6 Pregnancy and childbirth model costs

The costs for the pregnancy and childbirth section of the model comprise costs for maternal health care and antenatal, delivery and postnatal care. Here the postnatal care costs have been included with delivery costs. An additional cost component is the cost of treatment of hypertensive disorder of pregnancy among women with severe pre-eclampsia or eclampsia. For newborn health care costs, it was assumed that the major cost would be driven by preterm birth complications, and hence the cost of care for preterm newborn with complication has been included in the model.

5.8.6.1 Antenatal care costs

The Bangladesh Every Newborn Action Plan (BENAP) was costed in 2016 in order to provide the government with information on resource needs regarding the implementation of a comprehensive newborn care package (258). The costing exercise included a set of maternal and newborn health-related interventions, which were prioritised by relevant stakeholders and approved by the National Newborn Technical Committee.

The costing exercise included detailed costs of components of antenatal care, drugs and supplies like iron, folic acid, calcium, diagnostics tests for blood and urine and ultrasonography. Staff involvement in antenatal care was not costed. Staff costs were excluded as they are paid from the government's revenue budget and the purpose of the exercise was to feed into the programme implementation budget.

In order to include a complete cost of ANC, staff time and cost have been included with the components of ANC. The government's gadget on pay scale has been used to acquire salary rates of relevant staff (259). As the country is moving towards midwifery-led care, it was assumed that ANC was primarily done by midwives with some proportion of the care provided by medical officers and obstetric consultants as suggested by experts. Time involvement of the specialised staff was decided based on discussion with obstetricians and relevant programme personnel. Five percent of the time of consultants for the ANC visits has been included in the model to cover either the consultant's or medical officer's time during ANC.

The baseline antenatal care coverage for four visits including all ANC components are listed in table 5.20 below. Column (b) represents the number of times a medicine or supplement would be taken, while column (c) is the total number of days for each of the components of care. Columns (e) to (h) represent the costs per unit, total cost, inflation adjustment and costs converted into USD (Table 5.20).

Table 5.20 Cost of antenatal care

Cost components	(a) Percentage receiving this aspect of the treatment	(b) Times per day	(c) Days per case	(d) Units per case	(e) Unit cost (BDT)	(f) Cost per average case (BDT)	(g) Cost per average case (BDT 2021 price)	(h) Cost per average case (USD 2021 PPP)
Iron and folic acid tablets	100	1	238	238	0.2	47	63	1.96
Calcium, tablet, 600 mg	100	1	210	210	4	840	1113	34.67
Blood test for pregnancy	100	1	1	4	67	268	355	11.06
Urine test: test for urine albumin and albumin to creatinine ratio	100	1	1	4	300	1200	1590	49.53
Ultrasonography	100	1	1	2	233	466	617	19.23
HR cost for ANC - midwife	100	1	0.042	4	43121	7187	9521	296.61
HR cost for ANC - consultant	100	1	0.020	4	91414	7313	9689	301.82

Source: Report on Costing of the Bangladesh Every Newborn Action Plan (unpublished data) (258)

5.8.6.2 Cost of calcium distribution through domiciliary workers

Cost of calcium per woman per pregnancy was extracted from the BENAP report. The add-on was the distribution of calcium. The model assumed community-level distribution of calcium and took into account time of domiciliary health and family planning workers. A fixed cost per case for promotional materials was added to the cost.

Table 5.21: Cost of calcium supplementation

Cost component	(a) Percentage receiving this aspect of the treat-ment	(b) Times per day	(c) Days per case	(d) Units per case	(e) Unit cost (BDT)	(f) Cost per average case (BDT)	(g) Cost per average case (BDT 2021 price)	(h) Cost per average case (USD 2021 PPP)
Calcium, tablet, 600 mg	100	1	210	210	4	840	840	26.17
Domiciliary worker salary	100	1	4	4	12	49	49	1.52
Job aid/ promo-tional material	100	1	1	1	40	40	40	1.25

Source: Report on Costing of the Bangladesh Every Newborn Action Plan

5.8.6.3 Cost of treatment of pre-eclampsia/eclampsia

According to the maternal health Standard Operating Procedure (SOP) and the action plan, women coming with pre-eclampsia or eclampsia are managed by providing magnesium sulphate (31, 69). The cost for this component for the model has been estimated based on price of drugs and supplies, hospitalisation and human resource utilisation. The model assumed all women received MgSO4 with the loading dose given in the emergency department where a medical officer will attend the patient. The rest of the treatment would take place in the inpatient department, and women would need five days of hospitalisation on average. The model also assumed that this treatment would be provided to all women with eclampsia and those with severe pre-eclampsia (50% of pre-eclampsia) (Table 5.19). The rest received usual treatment for hypertension and increased monitoring. All assumptions were made and verified through consultation with practitioners.

Table 5.22: Treatment of maternal complications of pre-eclampsia/eclampsia

Items	(a) Percentage receiving this aspect of the treatment	(b) Number of units	(c) Times per day	(d) Days per case	(e) Units per case	(f) Unit cost (BDT)	(g) Cost per average case (BDT 2021 price)	(h) Cost per average case (USD 2021 PPP)
Loading dose of MgSO4	100	1	1		1	250	250.00	7.79
Full dose of MgSO4	100	1	4		1	250	1000.00	31.15
Hospitalisation	100	1	1		5	2500	12500.00	389.41
Blood bag (if needed)	100	1	2	1	2	1200	4800.00	149.53
Gloves, exam, latex, disposable, pair	100	2	1	1	2	10	20.00	0.62
Gloves, surgeon's latex, disposable, sterile, pair	100	2	3	1	6	11	198.00	6.17
Syringe, 10 cc with needle	100	5	3	5	5	10	150.00	4.67
Consultation	100	3	1		5	1000	5000.00	155.76

Source: Estimated from pricing exercise of Shashtho Shurokkha Kormoshuchi Bangladesh 2023 and expert consultation

Column (b) represents the number of times supplies have been used, while column (c) represents the total number of days for each of the components of care. Column (e) provides details of the number of units of each supply used. Columns (f) to (h) represent the costs per unit, inflation-adjusted cost per case and costs converted into USD (Table 5.23).

Table 5.23: Cost of treatment of gestational hypertension and gestational diabetes mellitus

Items	(a) Percentage receiving this aspect of the treat-ment	(b) Times per day	(c) Days per case	(d) Units per case	(e) Unit cost (BDT)	(f) Cost per average case (BDT 2021 price)	(g) Cost per average case (USD 2021 PPP)
Gestational hypertension							
Losartan	100	1		210	8.0	1680.00	52.33
Aspirin	100	1		210	0.5	113.00	3.53
Staff cost - consultant	100	0.02	4	91414	7313	12533.00	390.44
Gestational Diabetes Mellitus							
Insulin	100	1		4	400	1600.00	49.84
Staff cost - consultant	100	0.02	4	91414	7313	12533.00	390.44

Source: Price list from NCD operational plan

Costs of recommended treatment for hypertension and gestational diabetes during pregnancy have also been taken into account. Women with gestational hypertension would be prescribed with antihypertensive drugs, while recommended practice from GDM is to use insulin (34).

5.8.6.4 Cost of birth

The model has simplified the mode of births into two: normal vaginal birth and c-section birth. All the rest of the delivery types would fall within the category of Normal Vaginal Birth (NVBs).

A detailed costing of normal vaginal birth has been conducted for costing the piloting of the national insurance programme Shasthyo Shurokkha Kormoshuchi (SSK), which will be implemented at scale by the government (260). The costing provides detailed estimates considering cost categories such as labour room, diagnostic tests, drugs and supplies, blood bag if needed, hospitalisation and staff costs (Table 5.21).

The model assumes all women having NVB receive all aspects of care with 25% requiring blood transfusion (column (a)). Column (b) represents the number of times supplies have been used or tests were done, while column (c) represents the total number of days for each of the components of care. Column (d) provides details of the number of units of each supply used. Columns (e), (f) and (g) represent the costs per unit, inflation adjusted cost per case and costs converted into USD (Table 5.24).

Table 5.24: Cost of normal vaginal birth

Items	(a) Percentage receiving this aspect of the treatment	(b) Times per day	(c) Days per case	(d) Units per case	(e) Unit cost (BDT)	(f) Cost per average case (BDT 2021 price)	(g) Cost per average case (USD 2021 PPP)
Diagnostic tests	100	1	1	1	3681.00	3681.00	114.67
Drugs/supplies	100	1	1	1	9008.77	9008.77	280.65
Staff costs	100	1	1	3	1500.00	4500.00	140.19
Hospitalisation	100	1	1	1	1500.00	1500.00	46.73
Blood bag	25	1	1	2	1200.00	600.00	18.69
Labour room charge	100	1	1	1	5200.00	5200.00	161.99

Source: Pricing exercise of Shashtho Shurokkha Kormoshuchi Bangladesh 2023

The cost of c-section was also taken from the costing done for the Shastho Shurokkha Kormoshuchi (SSK) costing exercise (260). The costs were estimated as part of a benefit package women are expected to receive under the insurance programme. The cost components included cost of consultation, hospitalisation, laboratory tests and medicine costs. (Table 5.25)

Table 5.25: Cost of c-section

Items	(a) Percentage receiving this aspect of the treatment	(b) Times per day	(c) Days per case	(d) Units per case	(e) Unit cost (BDT)	(f) Cost per average case (BDT 2021 price)	(g) Cost per average case (USD 2021 PPP)
Diagnostic tests	100	1	1	1	1620	1620.00	50.47
Drugs/supplies	100	1	1	1	4000	4000.00	124.61
Staff cost	100	1	6	6	1000	6000.00	186.92
Hospitalisation	100	1	4	4	1500	6000.00	186.92
Blood bag (if needed)	100	2	1	2	1200	4800.00	149.53
Surgical costs	100	1	1	1	1	5000.00	155.76

Source: Pricing exercise of pilot Shashtho Shurokkha Kormoshuchi Bangladesh 2016

5.8.6.5 Cost of treatment of preterm newborns

Among the babies born in the model, the outcome that was impacted indirectly by the intervention and contributed a difference in terms of cost would be the number of preterm babies and the resources needed for care of preterm babies with complications. The model assumed that a proportion of preterm babies would require stabilisation and support after birth. Usually, such care is provided in neonatal stabilisation units (NSU) or Special Care Newborn Units (SCANU) in Bangladesh. Evidence suggests that preterm babies are more prone to infection and are hence more in need for specialised care. While around 6% of newborns develop complications during the first few weeks of life, this rate is almost threefold for preterm babies (261). The model considered 25% of preterm babies to need specialised care as 75% of preterm deaths are said to be preventable without intensive care (262). The model assumed 70% of preterm babies in need of specialised care could be treated in NSU and the rest in SCANU.

Data on the cost of NSU and SCANU has been extracted from the national newborn health Standard Operating Procedure (SOP) at primary and secondary care facilities (263). The capital cost for establishing the specialised newborn care units along with recurrent costs like maintenance has been detailed out in the SOP. For the establishment cost of each of the units, it was assumed that each facility would have a lifespan of 20 years and the costs were annuitized using a standard discount rate of 3% following other studies done in Bangladesh (255, 264). Staff costs which were not directly included in the document have been estimated based on the details provided in the SOP and discussion with relevant experts.

As mentioned in the SOP, the SCANU would have one dedicated nurse round the clock and one medical officer or paediatrician for clinical care and oversight. Considering eight-hour shifts for nurses, holidays and illness, the model included 100% salary of four nurses for each type of facility. Time apportioning of medical officers/consultants was done based on discussion with paediatricians in a facility with SCANU/NSU facilities. Salaries were estimated based on the national pay scale. Caseload per NSU was around 500, while for SCANU this was 2788 (265).

Like the other sections of the costing, Table 4.5 column (a) represents the percentage of preterm babies receiving the care. Column b represents the number of health care providers required in each. For specialised doctors, time apportioning was done through consultation with an expert paediatrician. The total cost of each of the two units was then divided by throughput. The same has been followed for estimating staff time in NSU (column c). Column d shows the unit costs per item, while column f estimates the annual cost where the cost of establishing the units has been annuitized. Based on discussion with a member of the national newborn technical committee, the model assumed BDT

5000 as the medicine cost per patient. The average duration of stay was assumed to be three days for NSU and five days for SCANU. (Table 5.26)

Table 5.26: Cost of treatment for preterm newborn

	Percentage receiving treatment (a)	Number of units (b)	FTE (c)	Unit cost (BDT) (2016) (d)	Annual cost (e)	Cost per average case (BDT 2021) (f)	Cost per average case (USD 2021) (g)
NSU							
Establishment cost (renovation and civil works, equipment and furniture, trainings)	100	1	1	2025000	1121193	3161.77	98.50
Recurrent cost	100	1	1	69000	38204	107.73	3.36
HR cost							
Nurse	100	4	100%	708680	2834720	7993.91	249.03
Doctor	100	1	50%	1094570	547285	1543.34	48.08
Medicine	100	3		5000		15000.00	467.29
Total					4541402	27806.75	866.25
SCANU							
Establishment cost (renovation and civil works, equipment and furniture, trainings)	100			7350000	4069517	2412.96	75.17
Recurrent cost	100			100000	55367.58	32.83	1.02
HR cost							
Nurse	100	8	100%	708680	5669440	3361.61	104.72
Medical officer	100	3	80%	844910	2027784	1202.34	37.46
Consultant	100	1	50%	1094570	547285	324.50	10.11
Medicine		5			5000	25000.00	778.82

Source: Estimated based on expert consultation, DHIS-2 and newborn health SOP (263, 266)

5.9 Long-term outcome model costs

A simplified cost analysis has been done for the long-term model, and all cost-related data were extracted from existing literature. Priority was given to country-specific cost information. Articles reporting patient level costs were included when health system-specific costing studies were not available. Where direct costing of services related to a disease condition was not available, costs of implementing new or existing interventions were considered.

Given the structure of the long-term model, the unit costs relate to the lifetime costs of hypertension and diabetes mellitus, over the remaining life of women. Total lifespan of individuals was estimated using mortality rates from the Bangladesh Sample Vital Statistics 2020 and BMMS 2016 (45, 267). Lifetime cost was then estimated for the years women were expected to live post pregnancy.

5.9.1 Chronic hypertension

Average cost of hypertension across all women was estimated in two parts: primary care management for all and care for management of complications like cardiovascular disease. One Bangladesh-based study revealed 30% of hypertensive adults over the age of 35 to develop CVD.

No literature reported direct costs to the public health system in Bangladesh. However, a few primary care intervention trials tested health service delivery through the government system and conducted studies that involved costing, budget impact and cost-effectiveness analysis (264, 268).

It is widely recognised that hypertension can be significantly brought under control through primary care interventions (269). Therefore, these costing studies provided sufficient information to be used for estimating annual cost of treatment of hypertension. The studies, however, did not take into account costs associated with complications related to hypertension. With a high lifetime burden of hypertension as reported in BDHS at 61%, it was important to take into account lifetime costs (52). Detailed description of the sources and how complications were taken into account is given below.

Studies reporting the cost of treatment of hypertension patients were mostly intervention trials. The Control of Blood Pressure and Risk Attenuation-Bangladesh, Pakistan, Sri Lanka (COBRA-BPS) trial conducted a cost-effectiveness analysis and reported the annual per-patient cost to be USD 10.65 (264). The intervention is relevant for the public sector as it included monitoring and counselling for controlling blood pressure using government community-level health workers. It also trained the physicians and ensured coordination within the public health system. The only additional expense the project covered for delivering the intervention would be the compensation to community health workers, which was equivalent to 20% of their salaries. Given that the government's non-communicable disease control programme (NCDC) has recently conducted a pilot following similar

methods and established NCD corners in public facilities, the costs of COBRA-BPS are likely to be relevant for a scale-up. The second study reports costing on delivering primary care for scaling up the Technical package for cardiovascular disease management in primary health care: Risk-based CVD management (HEARTS) pilot project. The project aimed at hypertension management and risk-based cardiovascular disease (CVD) prevention including integrated hypertension, diabetes and cholesterol management. The intervention was delivered through sub-district level facilities and estimated only hypertension management cost to be USD 8.9 per patient, while the integrated programme would cost USD 18 per patient (268). The cost categories included average price of drugs, supplies, provider time and salaries (268). USD 18 was used in the model as the cost of managing hypertension at primary care level.

As the country-specific costs associated with complications due to hypertension were not available, the costs were assumed to be the same as management of diabetes mellitus in Bangladesh. A systematic review based on South Asia identified treatment of cardiovascular disease and diabetes mellitus to be similar and identified that the costs substantially increase with complications (270). Although hypertension is not same as CVD, it is a cause of CVD. One study based in Bangladesh found 30% of CVD patients to be hypertensive. Considering that, the model assumed 70% of women to receive treatment for hypertension in primary care, while the remaining 30% would require treatment for complications like CVD. Average annual cost of treatment for patients with complications of hypertension were assumed to be USD 766, as discussed in detail in section 6.9.2. The average cost estimated based on this assumption was applied to women with chronic hypertension based on their age at disease onset and life expectancy. The estimated average annual cost for hypertension management was USD 237. (Table 5.27)

5.9.2 Diabetes Mellitus

A PubMed search identified a number of studies that costed treatment of diabetes mellitus. A global study modelling and projecting the total cost to over 180 countries estimated USD 4.74 billion of costs of diabetes for the population from age 20 in Bangladesh, indicating an increasing economic burden to the country (271). One study based in a tertiary-level hospital reported average annual cost of diabetes treatment to be USD 314 per patient (272). Another study based on a tertiary hospital in Dhaka reported the total annual cost of care to be USD 635 (273, 274). However, the Bangladesh-specific studies focused on the patient's perspective rather than the health system's perspective (272-275). As this was the best alternative, patients' costs were used as the cost to the public sector for treatment of diabetes mellitus. Cost of transportation is not usually borne by the public sector and hence has been excluded from the total annual treatment cost per patient.

The most recently published paper covered data from six hospitals under the Bangladesh Diabetic Association that included primary to tertiary levels and reported mean annual cost of USD 864.7 per patient and USD 850.1 per female patient (275). The direct cost per female patient per year was almost USD 766, and this was considered to be the cost to the health system. The cost components included outpatient visits, hospitalisation if needed, medicine, laboratory tests and other services like blood glucose monitoring devices. The patients included covered those with or without any complications. Indirect costs included the opportunity cost to patients and their attendants and therefore were not included in the model. As this study covered the maximum number of facilities directly working under the Diabetic Association of Bangladesh and did a comprehensive costing considering treatment of complications, this data was found to be the most suitable for the model. The study however excluded patients with terminal conditions. (Table 5.27)

5.9.3 Comorbidity

The study used for cost related data on treatment of diabetes reported direct cost of chronic diabetes mellitus among patients with hypertension to be USD 854 (275). This was directly applied in the model. (Table 5.27)

Table 5.27: Cost of chronic hypertension, diabetes mellitus and both per women per year

	Total cost per annum	
	USD	BDT
Cost of diabetes mellitus management	749.20	24049.32
Cost of hypertension management without complications	18.00	577.80
Cost of hypertension management with complications	749.20	24049.32
Average cost of hypertension management	237.36	7619.25
Hypertension and diabetes mellitus	853.60	27400.56

5.10 Model validation

It was ensured that the model produces mean values corresponding to the latest reported national-level prevalence of each event and outcome. For this, the pregnancy and childbirth model for current care has undergone repeated internal validation. The expected values of all events and outcomes were reproduced to an acceptable level of variation.

5.10.1 Prediction of proportion of events – pregnancy and childbirth model

Proportion of events such as gestational hypertension, pre-eclampsia and eclampsia were close to those of the national level for the pregnancy and childbirth current care model. (Table 5.28)

5.10.2 Prediction of proportion of outcomes – pregnancy and childbirth model

The model was coded in such a way that made sure that each woman has a birth outcome between livebirth, stillbirth and miscarriage. A fourth category was for women who had a maternal death before any of these outcomes could take place, and these were taken into account to check that the number of outcomes equalled the total number of women.

Newborn death was estimated to be around 31 per 1000 live births as opposed to 30 per 1000 live births. Maternal Mortality Rate was estimated to be .0002 while the national rate was estimated to be .000149. Variation in MMR was also acceptable as it is a very rare event and difficult to reproduce without a large sample size. C-section rate estimated to be 31.8% in the model, while the national rate stands at 0.327 (CI 0.305-0.344). All values fell within the confidence intervals of the mean except for maternal mortality rate, which is likely due to the small number of cases. (Table 5.28)

As the increased risks were taken from global literature, it is expected that the model values would vary from those of the national rates.

No calibration was used in the pregnancy and childbirth care model as the primary objective was to model the changes attributable to the intervention; calibration was expected to change results for both current care and the intervention by similar amounts, thereby leaving the increment largely unchanged.

5.10.3 Prediction of proportion of outcomes – long-term model

The current care model included the proportion of women with one or both of chronic hypertension and chronic diabetes mellitus as pre-existing chronic conditions. Some model checking and verification was done to ensure expected values were attained.

The relative risks applied to the long-term model were adjusted to reach the expected values. The relative risks applied to the model included risks among women who had HDP or GDM or both during

pregnancy. Relative risks were increased/decreased by a factor of input RR and output RR after repeated deterministic model run until the predicted value reached close to the observed value. (Table 5.28)

Table 5.28: Maternal and newborn events and outcomes in the current care estimates

Events and outcome	Current care predicted values	Expected values	LB	UB
Miscarriages	0.087	0.087	0.835	0.091
Gestational hypertension	0.093	0.088	0.026	0.123
Pre-eclampsia	0.014	0.014	0.079	0.209
Eclampsia	0.019	0.020	0.018	0.026
Stillbirth	0.025	0.024	0.022	0.026
Preterm birth	0.185	0.194	0.132	0.262
C-section	0.333	0.327	0.305	0.344
Newborn death*	0.031	0.030	0.026	0.034
Maternal death	0.000180	0.000149	0.000126	0.000174
Chronic hypertension	0.405	0.40	0.36	0.44
Chronic diabetes mellitus	0.060	0.053	0.033	0.092

5.11 Model verification

In order to reduce error and improve the model's credibility, the model was verified following a selected list of components from the technical verification checklist summarised by Buyukkaramikli (2019) (276). Although it is ideal for a second person to verify the model, I have done the work in order to ensure that good practice has been followed in developing the model. The checklist does not cover all points related to verification but rather focused on some relevant parts of the technical verification checklist for economic evaluation models.

Model structure: the model structure was informed by literature reviews and discussion with experts in economic evaluation modelling. Model specifications were narrowed down by the stakeholders.

Data: the model inputs involved data based on large surveys specific to Bangladesh, while data on relative risks and intervention effectiveness were extracted through literature reviews. The reviews included systematic, scoping and ad hoc reviews. A hierarchy was maintained for selection of sources based on literature.

Assumptions: all model assumptions were documented in their relevant sections with justifications on how they were relevant and realistic for use in the model.

Mathematical formulas: all mathematical formulas were based on published literature, which has been referenced. Some were added based on advice from supervisors and reviewed by them.

Software: R studio is a widely used software program for economic modelling and was selected based on its relevance to model structure. Existing models based in R were reviewed and expert consultations were done to ensure efficient and correct choice of packages for the model.

Sensitivity analysis: both deterministic and probabilistic sensitivity analysis were undertaken, observed and estimated values were compared to ensure robustness and validity of its results.

Validation: the model findings were compared and validated against the observed values extracted from literature. In case the results did not match the exact observed mean values, they were checked to ensure that they fell within the reported confidence intervals.

Documentation: the modelling methods have been documented in detail. The codes for the model, however, are not yet publicly accessible.

Peer review: some aspects of the model such as its structure and face validity have been peer reviewed. Parts of the code have been reviewed by fellow PhD students and the R support group from the department of computer science, University of Sheffield.

User friendliness: modification of the model needs advanced knowledge in R for the model to be adjusted or reproduced. A user-friendly interface could help but has not yet been developed.

Scenario analysis: several scenario analyses have been undertaken in the form of both deterministic (DSA) and probabilistic sensitivity analysis (PSA) for the model. The analyses highlighted the areas where there are methodological divides or possible impact on results due to changes in certain parameters. Some sub-group-level analyses were also included.

Consistency check: the model was checked for consistency at every step from developing the current care scenario, incorporating intervention effect and, finally, modelling the long-term outcomes. The model was built following a step-by-step process, and inputs and outputs were verified for addressing internal contradictions or errors at every stage.

5.12 Model analysis

5.12.1 Sensitivity analysis

5.12.1.1 Probabilistic Sensitivity Analysis (PSA)

The model used a large number of parameters in assigning the diseases, health states, relative risks based on health state, costs and DALYs. Each type of parameter was estimated accounting for uncertainty. To account for parameter uncertainty in the model, Probabilistic Sensitivity Analysis (PSA) was done on all parameters relating to probabilities, relative risks, costs and DALYs following standard mechanisms.

Assigning distribution to parameters

All PSA samples for the parameter uncertainty were chosen following published methodologies (194).

Beta distribution was used to account for uncertainty underlying the data on probabilities and for assigning age-specific pre-existing diabetes mellitus and gestational diabetes mellitus. The variance covariance matrix from the logistic regression model was used for generating random samples for each coefficient. Lognormal distribution was applied for generating random samples from the relative risks.

Uncertainly around costs were not reported in the sources, and 20% variation was assumed. A gamma distribution was applied to generate samples for the PSA. For disability weights, beta distributions were applied to the PSA samples. A total number of 1000 random values were drawn for each parameter and the simulation was run for the PSA samples.

Secondary analysis

In addition to reporting the results of the main model outcomes, the PSA was also used to report cost-effectiveness of delivering calcium supplementation as part of a complete ANC package. This included costs of all other ANC components along with calcium. As BDHS reports that around 18% of women received all ANC components, this was taken as a baseline coverage and increased to 80%. This analysis assumes all ANC component coverage to be at 18%, which may not be the case.

Lifetime DALY aversion through reduction in preterm birth has also been estimated and presented. The second analysis was presented based on the DALY weight for c-section. Since there were methodological differences in DALY weights reported for c-section and other health states, it was included as part of a DSA and reported.

The final scenario analysis was done assuming a 0% coverage of calcium supplementation at current care. The scaled up provision remained the same at 80%.

5.12.1.2 Deterministic Sensitivity Analysis (DSA)

Deterministic analysis reported applying a 3% discount rate to DALYs, 5% discount rate to both costs and DALYs and 5% discount rate only to costs.

5.12.2 Analysis of outcomes

Once the model validation and PSA run was complete, the mean values of each outcome, gestational hypertension, pre-eclampsia, eclampsia, birth outcomes and maternal and newborn outcomes were estimated. Mean costs and DALYs for the overall model, pregnancy and childbirth model and the long-term models were estimated. They were disaggregated by outcomes to understand the parameters that act as the drivers behind the costs and the benefits.

Cost consequences

Mean costs saved and DALY averted per woman covered by the intervention were estimated. This would help decision-makers to get a sense of the overall per capita cost in the population as well as marginal cost and benefit for the additional coverage per woman.

The costs and DALYs were disaggregated by several subgroups, pre-existing diseases, age, education and wealth quintiles. These helped to identify whether the intervention was particularly beneficial for any group of women who can be prioritised in the scaling-up process.

5.12.3 Incremental analysis

Cost saved per DALY averted

The incremental cost effectiveness ratio was estimated by diving the cost saved per women by DALY averted per woman. Here, the intervention was the increased coverage of calcium supplementation and the comparator was the current care coverage. Unlike QALY, the gain in DALY is measured in terms of DALY averted as it represents the loss of life years. In the case of the incremental analysis per woman, cost saved and DALY averted per additional woman covered by the intervention were reported.

Willingness to pay (WTP)

Bangladesh does not have a country-specific willingness to pay threshold. The WHO-CHOICE based on the Commission of Macroeconomics and Health recommends three times per-capita GDP as the willingness to pay threshold. This thesis reports two scenarios, the 1xGDP per capita and 3xGDP per capita (277). Other country-specific thresholds are available but have not been used as this is the more widely used threshold and preferred by stakeholders (278, 279).

Cost-effectiveness plane

A cost-effectiveness plane was plotted with each combination of cost saved and DALY averted per additional woman. The willingness-to-pay line was set at GDP per capita of BDT 78,899. The CE plane would help understand the uncertainty surrounding the decision-making regarding the scale-up.

Net monetary benefit (NMB)

Net monetary benefit was estimated by the difference between the monetised value of DALYs per woman multiplied by the willingness to pay threshold and the cost saved per woman. This was estimated for each WTP threshold.

Incremental Net monetary benefit (INMB)

INMB was estimated by the difference between the NMBs estimated for the scaled-up provision of care and the current care.

Cost-effectiveness acceptability curve (CEAC)

The cost-effectiveness acceptability curve was drawn to plot the probabilities of the scale-up of intervention being cost-effective at different levels of WTP ranging from zero to three times per-capita GDP.

Value of information (VOI)

The value of information analysis was done in two steps. First, the overall expected value of perfect information was estimated using the following formula:

EVPI = Expected Value with Perfect Information - Expected Value under Uncertainty (194)

This would help decision-makers by providing information on the need for additional research and reduce uncertainty around decision.

This was done using the Sheffield Accelerated Value of Information tool (SAVI) (280).

6. Model results

This section presents the outcomes derived from the cost-effectiveness model, focused on scaling up of calcium coverage among pregnant women. Initially, the chapter outlines the impact of the intervention on maternal health events and outcomes. Subsequently, it details the expenses tied to current care, the escalated provision of calcium and the associated healthcare costs. Following this, the section explores the aggregate effects associated with health conditions and their downstream outcomes. The incremental net monetary benefit, cost-effectiveness plane and cost-effectiveness acceptability curves are then introduced. Next, the results of the value of information analysis are presented. Finally, the chapter outlines the incremental costs and benefits based on selected subgroups.

6.1 Numbers of events and outcomes associated with current and scaled-up provision of intervention

Table 6.1 below shows the number of events per 1000 pregnancies. Between the current care coverage and scale-up coverage, there was a direct impact of the intervention through reduction of around 21 cases of gestational hypertension leading to 23% reduction. As expected given the direct impact of calcium on pre-eclampsia, 56 cases of pre-eclampsia and 7 cases of eclampsia would be expected to be averted per 1000 pregnancies. Through the intervention scale-up, over 40% and 36% reduction in pre-eclampsia and eclampsia respectively were attained.

Among the outcomes where both direct and indirect effects were applied, nearly two cases of stillbirths were reduced per 1000 women. A total of 7% reduction in stillbirths was attained through direct and indirect impact. The model predicted that 13 preterm births per 1000 women were avoided, which indicates a 7% reduction combining both direct and indirect effect. The expected reduction of preterm births was 12% [CI: 0.73 – 0.98], higher than what was estimated from the model. The Cochrane review suggested interpreting the effects on preterm birth with caution due to the small study effect. The reported relative risks for stillbirth were also unclear (183, 281).

The modelled estimate suggests a close to 45% decrease in maternal deaths. Estimated per 100,000 live births. This corresponds to the reported effectiveness of calcium on maternal deaths. This reduction however needs to be interpreted with caution as the reported change in literature was not significant but possibly due to small number maternal deaths (183).

Among the outcomes influenced by indirect effects of the intervention scale-up, C-section rates saw a reduction of 7% in the model (22 per 1000 women) [CI: 0.93 -1.00]. Newborn deaths were estimated

per 1000 live births, and around 8% reduction was attained by the intervention, which equates to the aversion of over 2 deaths.

The intervention led to a reduction of around 32 cases of chronic hypertension per 1000 woman, which is equivalent to an 8% risk reduction. There was not a notable change in the number of cases of chronic diabetes mellitus per 1000 women (less than 1 case averted per 1000 woman). Both rates in pre and post scale-up provision of calcium falls within the estimated confidence interval of prevalence of chronic diabetes mellitus developed among women post-pregnancy based on BDHS 2017-18 data (52, 190).

Table 6.1: Maternal and newborn events and outcomes with current and scaled-up provision estimated by the model

Reduction in adverse outcome	Current numbers per 1000	Scaled-up numbers per 1000	Difference	Percentage change
Gestational hypertension	92.30	70.96	21.34	0.23
Pre-eclampsia	139.86	83.94	55.92	0.40
Eclampsia	19.66	12.63	7.02	0.36
Stillbirth	24.79	23.14	1.65	0.07
Preterm birth	185.53	172.42	13.11	0.07
C-section	318.99	297.45	21.53	0.07
Newborn death*	31.40	28.86	2.48	0.08
Maternal death**	26.41	14.51	11.91	0.45
Chronic hypertension	415.06	383.22	31.84	0.08
Chronic diabetes mellitus	62.97	62.28	0.68	0.01

*per 1000 live births, **per 100,000 live births

6.2 Cost of current and scaled-up provision of intervention

The model estimated an incremental cost of scaling up provision of calcium supplements. An additional BDT 576 per woman would be required to ensure calcium supplements reach an 80% coverage level. The increase in uptake would lead to nearly a 3.5-fold increase in direct intervention costs compared to current care costs.

The model estimated that treatment of maternal complications including gestational hypertension, GDM, pre-eclampsia and eclampsia would see a reduction in cost per woman by BDT 1467. This is

equivalent to a 31% decline in costs accrued by the public health system for treatment of complications.

Delivery care included the costs of a normal vaginal birth and c-section birth. The difference between costs at the current coverage level and after scale-up was estimated to be BDT 259 per woman. This would lead to around a 1% cost saving.

Newborn care costs covered the costs for treatment of preterm newborns who required specialised care. The model estimated BDT 96 could be saved per live birth after the scale-up, which is equivalent to a 7% reduction.

Finally, the cost saving from management of chronic hypertension and chronic diabetes mellitus was estimated at BDT 3,875 per woman, equivalent to a 3% decline in costs.

Overall, when all costs are added up, the intervention scale-up is cost-saving. Within the aggregate costs, the largest portion of savings were accrued from the reduction in management and treatment of chronic diseases in the long-term. This was followed by the cost savings from treatment of gestational hypertension, pre-eclampsia, eclampsia, GDM and, subsequently, costs associated with the mode of birth and neonatal care. (Table 6.2)

Table 6.2: Costs with current and scaled-up provision

Type of care	Current cost per woman		Scaled-up cost per woman		Incremental cost		Percentage change
	BDT	USD	BDT	USD	BDT	USD	
Calcium and associated costs of distribution	167	5	743	23	576	18	344
Maternal complications	4,788	149	3,321	103	- 1,467	- 46	- 31
Mode of birth	28,465	887	28,205	879	- 259	- 8	- 1
Neonatal care	1,357	42	1,261	39	- 96	- 3	- 7
Chronic disease manage-ment	123,808	3,857	119,933	3,736	- 3,875	- 121	- 3
Total cost (calcium)	158,585	4,940	153,463	4,781	- 5,122	- 160	- 3

6.3 DALYs associated with current and scaled-up provision of intervention

Table 6.3 below presents the estimated DALYs by events with current care and scaled-up coverage of the intervention per woman. Total DALYs of around 0.29 were lost due to hypertensive disorders of pregnancy at current care coverage, which went down to nearly 0.18 DALYs with the intervention. This led to the aversion of almost 0.11 DALYs due to intervention, a reduction of over 38%.

DALYs around preterm birth were estimated for newborn deaths due to preterm-related complications. The model estimated the loss of a total 0.38 DALYs at current care coverage as opposed to 0.35 DALYs post scale-up coverage. DALYs averted due to reduction in newborn deaths related to preterm births was estimated at 0.04, leading to a reduction of 10%.

A major contributor of aversion of DALYs was the chronic conditions and, to be more specific, hypertension. The lifetime segment of the model estimated approximately 5.78 DALYs to be lost at the current coverage level, which would decline to a loss of almost 5.54 DALYs per woman after scale-up. This led to the aversion of almost 0.24 DALYs per woman equivalent to a 4% reduction.

The total DALY loss at current coverage level was estimated to be around 6.45 per woman, which would decrease to 6.07 DALYs post scale-up of coverage, leading to an overall aversion of 0.38 DALYs per woman, which was equivalent to almost 6% reduction in DALYs.

Table 6.3: DALYs with current and scaled-up provision

Event	Current DALYs per woman	Scaled-up DALYs per woman	Incremental DALYs averted	Percentage change
Hypertensive disorder of pregnancy	0.287	0.177	0.109	38.17
Preterm birth	0.382	0.345	0.040	10.46
Chronic conditions	5.781	5.544	0.237	4.09
Total DALYs	6.450	6.067	0.382	5.93

6.4 Net monetary benefit of scaled-up provision

Net monetary benefit (NMB) was estimated using two threshold levels, GDP per capita and three times GDP per capita. Table 6.4 presents the monetary values of health and NMB related to current and scaled-up provision of care per woman. The final column presents incremental net monetary benefit (INMB) for the pregnancy and childbirth model, chronic conditions in the long-term model and both

combined. INMB was positive at the two levels of willingness to pay, for both parts of the model as well as the two combined.

At per capita GDP (BDT 78,899), INMB was BDT 12,747 for the pregnancy and childbirth model and BDT 22,537 for the long-term model. Overall, INMB was estimated to be BDT 35,284. At 3 times per-capita GDP (BDT 236,697), INMB was BDT 35,747 for the pregnancy and childbirth section of the model. INMB was estimated to be higher for the long-term model at BDT 59,862. Overall, the INMB was estimated to be BDT 95,609.

Table 6.4: Net monetary benefit of scaled-up provision

Type of care	Monetary value of health relating to current care per woman	Monetary value of health relating to scaled-up care per woman	NMB of current care per woman	NMB of scaled-up care per woman	INMB of scaled-up care per woman
1 x GDP per capita (BDT 78,899)					
Pregnancy and childbirth	- 52,780	- 41,280	- 87,557	- 74,810	12,747
Chronic conditions	- 456,116	- 437,454	- 579,924	- 557,387	22,537
Total	- 508,896	- 478,734	- 667,481	- 632,197	35,284
3 x GDP per capita (BDT 236,697)					
Pregnancy and childbirth	- 158,340	- 123,839	- 193,117	- 157,370	35,747
Chronic conditions	- 1,368,348	- 1,312,361	- 1,492,156	- 1,432,294	59,862
Total	- 1,526,688	- 1,436,201	- 1,685,273	- 1,589,664	95,609

6.5 Cost-effectiveness plane

Figure 6.1 shows the standardised cost-effectiveness plane per person for the 1000 model runs based on uncertain model parameters that simultaneously varied in the probabilistic sensitivity analysis (PSA). The cost-effectiveness plane in figure 6.1 presents the difference in DALY averted per woman in comparison with the difference in cost per woman.

The incremental cost per woman is BDT -5122 which shows a cost saving for the scaled-up provision of care. The 97.5% credible interval for the incremental cost is (BDT -8264.23 , BDT -2245.85). The mean incremental benefit of scaled-up provision as opposed to current care is 0.38 DALYs averted. The 95% credible interval for the incremental benefit was (0.22 DALY, 0.54 DALYs averted). The probability that scaled-up provision is more beneficial than current care was 1.00.

All of the 1000 points fall in the South-East (SE) quadrant of the cost-effectiveness(CE) plane, suggesting lower cost and increased benefit (lower DALYs) of the intervention (Figure 6.1). The probability of the intervention being cost effective is one with all the points falling below the willingness-to-pay threshold set at the GDP-per-capita threshold level. This essentially suggests that the intervention will be cost-effective at three times GDP per capita as well (BDT 236,697). The scaled-up provision dominated the current care coverage of the intervention in this model. Based on the model results, the probability that the intervention will be cost saving is 1. There is 0 probability that the intervention might cost additional money.

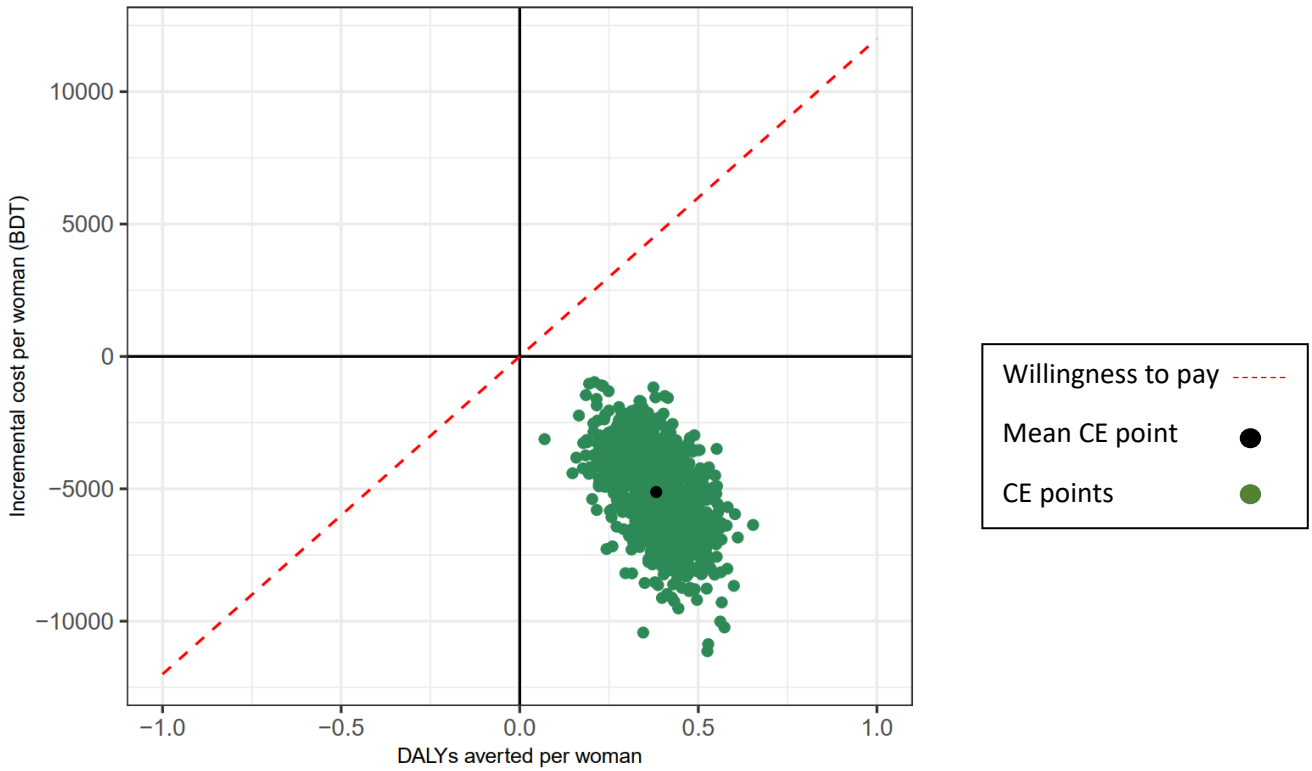


Figure 6.1: Cost-effectiveness plane for scaled-up provision of care compared to current care

6.6 Cost-Effectiveness Acceptability Curve

The cost effectiveness acceptability curve (CEAC) illustrates the uncertainty around the intervention being cost-effective for a willingness-to-pay threshold between 0 to 250,000 (194).

The CEAC in figure 6.2 suggests that the intervention is cost-effective even at a zero willingness-to-pay threshold compared to the current care level, indicating that the intervention is cost saving for all parameter values randomly generated through the Probabilistic Sensitivity Analysis (PSA). The 1000 PSA runs of the model, based on which the CEAC has been drawn, show that at a threshold value for cost-effectiveness of BDT 78,899 per DALY, the strategy with the highest probability of being cost-effective is the scaled-up care with a probability of one. The scaled-up provision is cost saving at the threshold levels of both GDP per capita and three times GDP per capita.

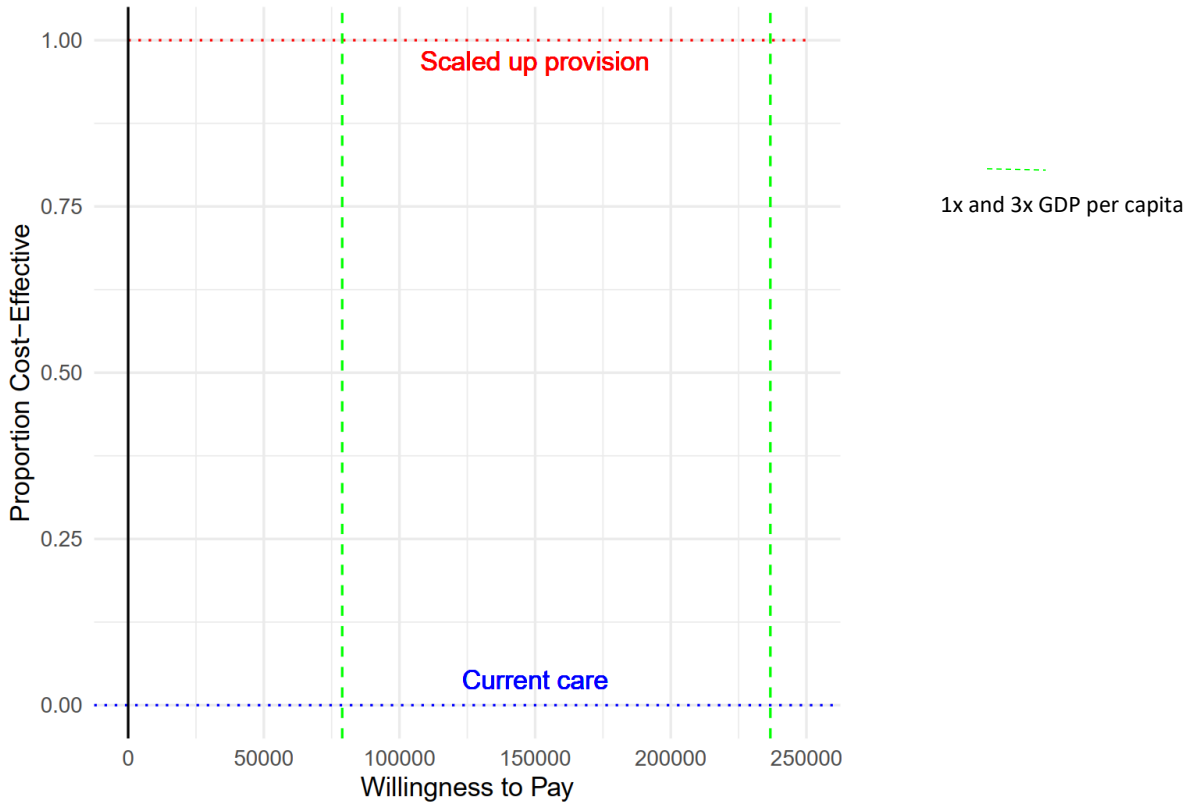


Figure 6.2: Cost-effectiveness acceptability curve (CEAC)

6.7 Overall expected value of perfect information

The overall expected value of perfect information (EVPI) per woman affected by the decision was estimated to be BDT 0. Therefore, no further investment in research based on the DALY averted and cost savings to further reduce decision uncertainty is recommended. Since all points of the CE plane fell into the SE quadrant, additional analysis related to EVPI was not undertaken.

6.8 Secondary analysis

6.8.1 Long-term impact on babies: preterm birth

The long-term impact on newborns was estimated as a standalone analysis. Around 1.22 children per 1000 live births will be able to avoid developmental delay due to preterm birth. The result suggests that over 214 DALYs would be averted per 1000 live births over the lifetime of babies. Overall, there was a 7% estimated reduction in children with developmental delay through a reduction in preterm birth.

6.8.2 All ANC components included as direct cost of intervention

According to BDHS 2017-18, coverage of all quality components of ANC was around 18%. Considering this as the current care coverage, the incremental cost for the scaled-up provision of the whole ANC package was estimated to be BDT 8052 per woman. When all downstream costs are included, the incremental cost would be BDT 2,354 per woman. The incremental NMB for including the direct cost of all ANC components at GDP per capita was BDT 27,808.

6.8.3 DALY averted: C-section

As mentioned in the methods section, disability weights for c-section were not available in the latest Global Burden of Disease (GBD) reports. DW was available in GBD 1990. Due to substantial differences in methodologies, it was not included in the main model, so it was estimated alongside the PSA as a standalone measurement. The estimates suggest an aversion of almost 5 DALYs per 1000 additional women receiving the intervention. This also ensures that there would be no substantial difference to the model even if the weight was included in the base case analysis.

6.8.4 Setting baseline calcium coverage at 0

Since calcium coverage is not directly available for Bangladesh, this scenario presents the intervention effect assuming zero coverage level at current care. The estimated cost for implementing the intervention at 80% coverage level was estimated to be BDT 743 per woman. When all downstream costs were added, this led to a cost saving of BDT 3052 per woman. The incremental NMB at 1xGDP per capita threshold was BDT 28,475. At 3xGDP per capita threshold, it was BDT 77,860.

6.9 Sub-group analysis

Table 6.5 presents the NMBs and INMBs at the threshold level of 1xGDP per capita in BDT by sub-groups: pre-existing conditions, age, level of education and wealth quintiles. Both NMBs and INMBs are presented per woman in their respective sub-groups.

INMB was positive for women with pre-existing chronic hypertension, diabetes mellitus or both as well as for those without any conditions. Women with chronic conditions prior to pregnancy were at high risk of developing pre-eclampsia/eclampsia and their subsequent adverse outcomes. Some of these adverse effects were reduced through the scaled-up intervention, leading to cost saving and DALY aversion. The INMB was higher among women with both pre-existing chronic hypertension and diabetes compared to other women. Women with pre-existing chronic diabetes mellitus gained more compared to those with pre-existing hypertension. Women without any conditions were prevented from developing pregnancy-related conditions and the resultant long-term chronic conditions. Overall prevalence of pre-existing chronic hypertension was higher compared to chronic diabetes, however, average costs and DALYs were lower compared to diabetes mellitus, which may have led to the lower INMB compared to the other groups.

In general, women below the age of 30 gained more from the scale-up compared to women between the age of 30-49. The maximum benefit, of BDT 40,441 was accrued by those in the age group of 13-19. This went down to BDT 30,133 among those in the age group of 40-49. Baseline risks were assigned based on age for chronic diabetes mellitus, chronic hypertension and gestational diabetes mellitus. Older women were at higher risk of having pre-existing conditions and the subsequent pregnancy-related complications like GDM and HDP. Older women also had a lower age-specific life expectancy, contributing to the lower level of INMB.

INMB was positive across all levels of educational attainment of women. There were differences in the level of benefit accrued. Women with education below primary level were found to have lower INMB compared to women who had attained an education of at least primary level. Among women with no education, INMB was estimated to be BDT 32,149, which increased to around BDT 36,000 among women who at least completed primary-level education. Women with no education were more likely to be hypertensive and diabetic compared to those with a secondary education or higher according to the BDHS 2017-2018 report (52). The only way the model took into account educational attainment was while assigning the risk of pre-existing hypertension. Further analysis may be needed to be able see visible differences.

Cost and estimated DALY followed no particular pattern in terms of wealth quintiles. Overall, INMBs were positive across all quintiles. Women belonging to the middle wealth quintile, however, gained

more benefit compared to the rest. Like education, the only way wealth was accounted for was while assigning the risk of pre-existing chronic hypertension to women. The BDHS reported no notable variation in prevalence of hypertension among women across the wealth quintiles, except some differences between the highest and lowest quintiles (26% vs 32%) (52). The observed pattern also supports that with the lowest quintile attaining an INMB of BDT 34,643 as opposed to over BDT 35,000 for each of the two top quintiles.

Table 6.5 Net Monetary Benefit (NMB) by population sub-groups at the threshold level of 1xGDP per capita in BDT per woman

Sub-group	Monetary value of health relating to current care per woman	Monetary value of health relating to scaled-up care per woman	NMB of current care per woman	NMB of scaled-up care per woman	Incremental net monetary benefit of scaled-up care per woman
Pre-existing chronic conditions					
Diabetes Mellitus	- 1,004,116	- 976,919	- 1,470,883	- 1,439,455	31,428
Hypertension	- 724,266	- 703,075	- 952,978	- 929,707	23,271
Both	- 1,032,411	- 994,086	- 1,508,721	- 1,467,461	41,260
None	- 425,643	- 392,482	- 548,952	- 509,871	39,081
Age					
"13-19"	- 455,898	- 421,142	- 589,852	- 549,411	40,441
"20-29"	- 472,391	- 439,476	- 614,445	- 575,909	38,536
"30-39"	- 535,292	- 506,373	- 702,317	- 668,525	33,792
"40-49"	- 552,346	- 526,665	- 735,363	- 705,231	30,133
Education					
No education	- 533,311	- 505,891	- 704,905	- 672,757	32,149

Sub-group	Monetary value of health relating to current care per woman	Monetary value of health relating to scaled-up care per woman	NMB of current care per woman	NMB of scaled-up care per woman	Incremental net monetary benefit of scaled-up care per woman
Primary incomplete	- 515,846	- 486,070	- 677,978	- 643,200	34,778
Primary complete	- 506,265	- 475,456	- 663,699	- 627,680	36,019
Secondary incomplete	- 494,520	- 462,975	- 645,859	- 608,997	36,862
Secondary and above	- 501,056	- 470,297	- 654,663	- 618,621	36,042
Wealth					
Lowest	- 510,535	- 481,000	- 669,180	- 634,537	34,643
Second	- 520,037	- 490,682	- 681,872	- 647,600	34,272
Middle	- 501,518	- 470,655	- 658,403	- 622,303	36,100
Fourth	- 507,993	- 477,600	- 666,356	- 630,771	35,585
Highest	- 504,157	- 473,463	- 661,309	- 625,458	35,851

6.10 Deterministic sensitivity analysis

Table 6.6 below shows the results of deterministic sensitivity analysis (DSA) done for the model. The table shows that with a 5% discount rate applied to cost, discount rate of 3% to DALY, and 5% discount rate applied to both cost and DALY, the intervention would still be beneficial at the threshold of 1xper capita GDP.

Table 6.6: Results of deterministic sensitivity analysis (DSA) (1xGDP per capita, in BDT)

Sensitivity analysis	Monetary value of health relating to current care per woman	Monetary value of health relating to scaled-up care per woman	NMB of current care per woman	NMB of scaled-up care per woman	Incremental net monetary benefit of scaled-up care per woman
1xGDP per capita (BDT 78,899)					
Discounted cost (5%)	541,375	525,059	385,826	365,017	13,285
Discounted DALY (3%)	481,713	457,763	385,826	365,017	20,808
Discounted cost and DALY (5%)	318,910	313,509	197,472	195,101	2,371

6.11 Discussion

Overall, the results suggest a cost saving, a reduction in DALY and positive incremental net monetary benefits, which assures the scale-up provision to be highly cost-effective. Sub-group analysis identified specific age groups and disease conditions for which the intervention will be most beneficial. Deterministic sensitivity analysis suggests the intervention is likely to be cost-effective even if discount rates were applied to DALY.

The intervention has both a direct and an indirect impact on health outcomes and resulted in a lower number of adverse intermediate and final outcomes during pregnancy and childbirth and in the long term. Most of these effects aligned with what was expected based on literature and what was actually put in the model, except for the impact of the intervention on c-section, which was noted to have a very low level of impact of around 1% according to the available evidence base but has reduced by 7% in the model through reductions in hypertensive disorders in pregnancy. However, the modelled effect was still within the confidence interval [CI: 0.93 – 1.00].

The model predicted that change in preterm births was lower than expected (0.07 vs 0.13). Still, it was within the CI of reduction in risk of preterm births.

The model predicted a 45% reduction in maternal deaths as an indirect effect of the intervention. Estimated relative risk based on published literature was 0.39 [CI: 0.26-1.22]. The reduction in maternal deaths took place through a reduction in pre-eclampsia and eclampsia as well as direct effect on maternal deaths. It is possible that published trials had no significant results due to small number of maternal deaths. Effect on maternal death is likely as pre-eclampsia/eclampsia is a direct cause of maternal death.

The model predicted that one case of chronic diabetes mellitus per 1000 woman would be averted in the long term, which indicates no change. The only pathway to reduction in chronic diabetes mellitus would be through the reduction in HDP. There are no direct effects of calcium on preventing GDM and, hence, the long-term risk of developing chronic diabetes mellitus. The number of women with GDM would not be affected by the intervention. There is a reduction in the number of women developing HDP.

The model was found to be beneficial both at the threshold level of 1xGDP and 3xGDP per capita. The scaled-up provision dominated the current level of care. The sub-group level analysis suggests no notable difference across the wealth quintiles. Women with pre-existing diabetes or hypertension benefited through the intervention in terms of reduction in adverse pregnancy outcome. Women with comorbidities also accrued a positive benefit from the intervention in terms of reduction in pre-eclampsia and eclampsia although this proportion was very low, ranging between 3 and 5% of the population. Younger women would benefit more due to higher life expectancy compared to older women. Hypertension and diabetes were more prevalent among women with a lower level of education and the maximum benefit of the intervention in the model went to those with an education of primary level complete and above. INMB was a little higher in the highest three wealth quintiles compared to the lowest two. The middle and fourth quintile has the maximum prevalence of hypertension in the country, while chronic diabetes is more prevalent in the highest two quintiles. Benefit was higher among young women compared to older women. Additional analysis looking at relationship between age and wealth quintile may provide deeper understanding and help identify any possible pattern.

6.12 Conclusion

This chapter presented and summarised the model findings in terms of the reduction in adverse health outcomes, cost savings and the reduction in the aggregate outcome measure, DALYs through PSA runs. Overall model results, the pregnancy and childbirth section and long-term outcome section alongside

selected sub-group-level analysis has been summarised through estimated INMBs. The INMBs were positive for the main analysis as well as specific scenarios and subgroups, suggesting the scaled-up provision to be beneficial compared to the current coverage level. Selected DSA results were also presented, showing that the model would likely be cost-effective even if discounting was applied to DALYs and costs at varying rates.

7. Discussion

7.1 Main findings

This thesis aimed to develop an economic evaluation model for preventive interventions addressing two NCDs: hypertensive disorder and diabetes mellitus during pregnancy. A comprehensive understanding of both disease conditions was cultivated through a review of relevant clinical guidelines. Systematic reviews were conducted to identify existing economic evaluation models shedding light on potential model structure, population, interventions, perspective, outcomes and time horizon. The thesis identified key interventions to address HDP and DMP interventions through desk reviews while interviews with selected stakeholders in Bangladesh helped to further narrow down the interventions for the model. The reviews and stakeholder interviews revealed that antenatal care was the key to address the two diseases. It was also the ideal window to deliver preventive interventions that comprised of nutritional supplements, diet and exercise counselling and some level of screening and identification of women with HDP and DMP. The interventions were already part of the ANC package offered through the public health system in Bangladesh but their coverage was low. A single intervention, scaling up of provision of calcium supplements among pregnant women in Bangladesh, was selected for developing the cost-effectiveness model.

Finally, an individual-level Markov Microsimulation model for pregnant women in Bangladesh was developed, considering pre-existing chronic hypertension and diabetes mellitus for the pregnancy and childbirth period. An individual-based model following a decision tree structure was developed for estimating the long-term effects. The outcomes for women were the development of hypertensive disorder, gestational diabetes mellitus, maternal death, long-term development of chronic hypertension and diabetes mellitus. The pregnancy outcomes were abortion/miscarriage, stillbirth and live birth. Outcomes for the offspring were preterm birth, newborn death and developmental delay in the long term.

My thesis has estimated that expanding coverage of calcium supplementation among pregnant women from 18% to 80% through the public health infrastructure of Bangladesh will save BDT 5,122 per woman and avert 0.38 DALYs throughout pregnancy, childbirth, the postpartum period and the lifetime of women. The scaled-up provision dominated the current care provision of calcium supplements in Bangladesh. A larger share of the impact was attained through reduction in DALYs during the long-term phase, while an additional positive gain was estimated for the pregnancy period too. Women with pre-existing conditions would benefit by averting complications like pre-eclampsia and eclampsia during pregnancy. Healthy women or women with other risk factors such as being

above the age 35 would attain additional benefit through diminished risk of developing hypertensive disorder in pregnancy and a decreased likelihood of long-term chronic hypertension.

7.2 Contribution to evidence base

My research produced an estimate of the cost and aggregate impact of scaling up the coverage of calcium supplements among pregnant women in Bangladesh. In addition, the events and outcomes of impact included aversion of fatal complications like pre-eclampsia and eclampsia, lowering the number of required c-section births and averting preterm birth, stillbirths, newborn and maternal deaths, long-term chronic hypertension and chronic diabetes mellitus. This adds important knowledge for national-level programme and planning and helps identify a cost-saving solution for addressing the second largest cause of maternal deaths and its resultant adverse outcomes of pregnancy. This work contributes as the first study in Bangladesh that builds a microsimulation model for pregnant women targeting a single nutrition-specific intervention. It is also the first of its kind that brings the two most common cardio-metabolic disorders of pregnancy together for a cohort of pregnant Bangladeshi women. The model is the first for Bangladesh that links chronic diseases like hypertension and diabetes mellitus to maternal health. My thesis also illustrates how a single preventive intervention can help in achieving positive pregnancy outcomes, avoid maternal complications and subsequent loss of life of women and their babies and have a possible long-term impact in terms of reducing chronic diseases.

When economic evaluation models at global level are considered, the systematic review revealed that models focusing on GDM often utilised pre-eclampsia as an outcome of GDM. A systematic review recently published by Li et al (2022) also identified no economic models that considered the two diseases together (282). In addition to incorporating the interaction between GDM and HDP, pre-existing chronic diabetes and hypertension and the increased risk of subsequent complications have been accounted for in my model. Few studies have looked at the lifetime impact on women in terms of developing chronic hypertension or diabetes mellitus as a result of GDM and HDP together. The systematic review identified two such models that evaluated lifestyle interventions for women with HDP and looked at impact on long-term chronic hypertension. Drost et al (2015) and Van Baaren et al (2014) assessed screening for hypertension or cardio vascular diseases among women with history of pre-eclampsia (129, 283). Whilst my model looked at the risk of developing chronic hypertension after HDP and chronic diabetes mellitus after GDM, it also took into account the increased risk of chronic hypertension post GDM and chronic diabetes mellitus after events of HDP. My model may not be unique globally in combining the two diseases, but it is one of only a small number of models that focused on the interaction between the two different diseases, with overlapping risk factors and outcomes.

The WHO recommendations on calcium supplementation in pregnancy 2018 highlighted cost-effectiveness of calcium to be absent and the cost of calcium to be relatively high compared to other nutritional supplements such as iron and folic acid (170). In addition to combining the two diseases, my research generated evidence of cost-effectiveness of calcium supplements for pregnant women in Bangladesh. The findings re-emphasised the need for calcium supplementation for pregnant women globally, especially for LMICs.

My model also has the potential to incorporate multiple interventions pertaining to the two diseases. Two existing software-based epidemiological models are able to assess the impact of multiple maternal health interventions on maternal/newborn mortality. The first one is the Global Maternal Health (GMath) Model (179). The GMath is a simulation-based model that includes individual women from 200 countries and covers 11 clinical interventions. The model targets women of reproductive age and incorporates heterogeneity in women's background and characteristics related to pregnancy history. A model with increased coverage of interventions to 90% using GMath estimated the reduction in maternal mortality in 200 countries. However, the outcome of the GMath model has been limited to maternal deaths. The second model is the Lives Saved Tools (LiST) which is also a software-based tool to assess the impact of change in coverage of interventions related to maternal, newborn and child health and the impact on maternal, newborn, child mortality, stillbirths and childhood nutritional status (284). It is a cohort-based tool that follows a decision-tree structure. LiST generates both global and country-specific maternal, child and newborn mortalities. Neither of the models however are economic evaluation models. The intervention effectiveness and costing information needs to be extracted and analysed separately for assessing cost-effectiveness. Since the models are not designed to do cost-effectiveness analysis, sensitivity analysis involving all parameters can be difficult to do. Deterministic Sensitivity Analysis may be performed by manipulating the coverage levels alone.

Both of the tools are useful in terms of planning an expansion, prioritising intervention and producing rapid estimates for tracking progress. GMath or the LiST are used more for tracking progress of countries towards the SDG targets on reducing maternal or newborn mortality. These tools can be very useful for rapid analysis of the impact of single or multiple interventions and feed quick information to the implementers. For example, a global analysis of the impact of Covid-19 on maternal, newborn and child mortality due to service disruption was published during the pandemic using an assumed reduction in coverage (285). Such analysis can help to develop new plans or strategies for unexpected events and to revise country-specific targets for reaching the national plans or SDGs.

My model corresponds to both models in terms of using risk data for individual women based on available literature. Among the interventions targeting women with pre-eclampsia, both models incorporate calcium supplementation and have used the same level of risk reductions from the Cochrane reviews. My model, however, is Bangladesh-specific, focused on increasing coverage of a single intervention and estimating both costs and aggregate impacts of the intervention. It also extends beyond survival of the mother and child and looks at the long-term effect. The results present multiple intermediate events and outcomes in addition to maternal and newborn deaths. Adopting an individual-level model has enabled me to account for the impact of combined risk factors (albeit with some assumptions on how they interact) and incorporate sub-group analysis based on individual characteristics. The model is also bespoke for Bangladesh, and programming in R enabled me to conduct PSA simultaneously for all input parameters taking into account of uncertainty in the model.

Multiple cost-effectiveness models assessing calcium was found. While three of them were captured in the systematic review, one was not. Calcium supplementation as part of the intervention package in the LiST has been evaluated in two of the studies. The first one is an analysis covering 37 interventions for Eastern Sub-Saharan Africa and South-East Asia (286). The study reported an average cost-effectiveness ratio (ACER) for calcium supplements separately compared to a no-calcium scenario and found it to be cost-effective. The analysis covered a period from adolescence to pregnancy and childbirth. For babies, the model covered the first five years of life. The model estimated the cost per million population to be I$364,785 and Healthy Life Expectancy[9] to be 44 (286). ACER for calcium supplements for the South-East Asia region was estimated to be I$8353 (cost estimated at I$[10]). Comparison of the results were difficult since this covers the whole south-east Asian region, and the unit of aggregate outcomes are different too.

A similar analysis based in Ethiopia was identified in the narrative review of antenatal care models (243). The model used the LiST to assess the impact of 13 maternal and newborn health interventions for pregnancy, childbirth and the newborn period. The study found calcium supplements not to be cost-effective when implemented in Ethiopia following a 20% target coverage. This may be due to introduction of calcium as a completely new intervention with coverage increasing from 0 to 20%.It is also noteworthy that the objective of the study was to evaluate multiple interventions and it used a software-based model that estimates the impact on mortality alone. The limited time horizon may have led to more conservative estimates of the benefits of the interventions. Overall scenarios of maternal and newborn health and their outcomes in the two countries are also not comparable.

[10] An international dollar comparable to amount of goods and services a U.S. dollar would buy in the United States

The systematic review that I undertook identified two other economic evaluation focused on calcium supplementation. The first one was based in Nepal (114). Published alongside the results of a pilot study, the results found calcium to be a cost-effective solution when introduced alongside existing regular treatment of MgSO4. The intervention effectiveness on pre-eclampsia onset in the study was the same as that in my model. Like my model, the Nepal-based model included both years of life lost and disability weights for hypertensive disorder in pregnancy. The incremental DALY per woman was estimated to be 0.08, which closely corresponds to the incremental DALY of 0.11 estimated for hypertensive disorders of pregnancy by my model. The second study by Merteens et al (2017) was based in a high income country and compared effect of advising calcium intake for all pregnant women, high risk women and women with low dietary intake of calcium and found them to be cost-effective (117). Results however were not comparable to my model as the study was based on a hypothetical cohort of Dutch population and used Quality Adjusted Life Years as an aggregate outcome measure.

Rose and Hoque (2016) reported the benefit-cost ratio of calcium supplements along with two other nutritional supplements and their impact on maternal mortality related to HDP among pregnant women in Bangladesh (287). The study utilised global-level evidence for prevalence, risks and costs. Understandably, the evidence was based on literature published post 2016. The combined Net Present Value of calcium supplements for maternal mortality related to hypertensive disorder (BDT 130) and low birth weight was BDT 52,813 per pregnant woman at the 3% discount rate, while the cost per woman was BDT 1881. Overall, the benefit-cost ratio at the 3% discount rate was estimated at 28.07. The results were not comparable to my model. However, it is useful to note that the Net Present Values of the benefit were positive for calcium at different discount rates.

My model also assigned baseline risks depending on age category from the country-specific disease burden. Socio-economic variables such as wealth and education were adjusted using a logistic regression to assign the risk of pre-existing hypertension. This was also adjusted for pre-existing diabetes mellitus, taking into account comorbidities. This led the way to some meaningful sub-group analysis, which can be very useful for policymakers in programme planning and implementation and aide in additional sun-group level analysis if needed.

Calcium is an under-studied area both globally and in Bangladesh in several ways despite being a proven intervention and an intervention strongly recommended by the WHO for pregnant women, particularly in LMICs. My model, using the gold standard of evidence – systematic reviews and national level data adds an LMIC-specific cost-effectiveness study, which can be adopted for other countries as well as being used for evaluating additional interventions addressing HDP and diabetes in pregnancy.

7.3 Strengths

7.3.1 Microsimulation model for two NCDs among pregnant women in an LMIC

The individual-based microsimulation model has helped to accommodate individual-level risk factors, the overlapping risks and outcomes among both women and babies and pre-existing conditions. The model addressed two disease conditions and looked at the impact of interventions on those with one or both conditions. Each of the outcomes was assigned to risks based on the women's condition. The model incorporated both women and babies and went beyond pregnancy and postpartum. The long-term model has been simplified to cater for what is needed to reach the objective of this thesis.

My model is the first individual-level microsimulation model for assessing cost-effectiveness of calcium on maternal and newborn outcomes. It also analyses the impact of cardio-metabolic disorders of pregnancy in the long term for women and babies. It allowed for interaction between the two CMDs. Existing studies conducting cost-effectiveness analysis related to maternal health in LMICs were more commonly done alongside trials or observational studies and followed decision-tree-based models. Some studies using software like the GMath or the LiST are tailored for primarily assessing the impact of interventions on mortality. While some models have added cost-effectiveness, they lack the flexibility of conducting PSAs and, as a result, are limited in their capacity to analyse scenarios accounting for parameter uncertainty (15, 16). The individual-based structure enabled my model to incorporate pre-existing conditions based on women's socio-demographic characteristics.

7.3.2 Use of multiple sets of reviews

My model underwent a comprehensive and well-informed process of developing understanding of the problem and model attributes utilised in existing economic evaluation models of the two diseases, through multiple sets of reviews. This ensured thorough understanding of the disease attributes, the content of existing economic evaluation models and available interventions. The model involved reviews of clinical guidelines that are developed in accordance with global standards and compared them to country-specific guidelines. This allowed my model to precisely define and identify population characteristics and risk factors to improve its relevance and validity.

To enrich the model further, I have undertaken two systematic reviews of economic evaluations related to both diseases supplemented by a narrative review on antenatal care models. This approach further enriched the model development process and refinement of the model in terms of selection of intervention, use of effectiveness data and other model specifications. The systematic review also provided information on how review-based effectiveness data were incorporated within the model in comparison to the use of trial-based data. The models identified in the systematic review covered both direct and indirect effects of the interventions. Some of the models applied relative risks to

intermediate outcomes or events like pre-eclampsia/eclampsia, while others applied relative risk data to final outcomes like mortality.

In addition to informing the model attributes from clinical pathway and existing economic evaluation models, my research delved into global and national strategy documents and action plans to identify available interventions addressing the two conditions. The comprehensive reviews helped identify an exhaustive list of interventions that effectively address both the CMDs and pre-existing conditions of hypertension and diabetes during pregnancy.

7.3.3 Stakeholder engagement

An inclusive approach of involving stakeholders was integral to my thesis from its inception. It leveraged local knowledge, contextual sensitivity and data validation to establish a meaningful and sustainable impact on healthcare planning in Bangladesh.

I was in communication with a wide spectrum of experts including maternal health researchers, health economists, funding organizations, healthcare practitioners, gynaecologists, obstetricians, and program implementers. By involving the diverse set of experts, my research tapped into local expertise.

The interviews and informal discussions with the stakeholders helped me consider factors of local relevance that are crucial in the context of Bangladesh. Health system and health care practices and, most importantly, resource allocation and availability vary significantly across countries. Engaging local experts ensured these were taken into account and that potential interventions were locally relevant.

On top of the formal stakeholder interviews, contacting relevant individual experts for data sources and data validation was a crucial step. Local experts familiar with the healthcare infrastructure, resource need and data sources in Bangladesh verified the accuracy and reliability of the data and sometimes were able to direct me to unpublished data sources. This process enhanced my model's validity, its relevance to Bangladesh and trustworthiness.

Engaging local stakeholders helped align the model outcomes with local priorities and strategies. This enhanced the likelihood of my thesis informing policy decisions and being relevant to the maternal and newborn health programme in Bangladesh. Involving the stakeholders also helped build awareness and a sense of ownership of the research among those working at the policy level. This further increases the model's validity and the chance of the findings being utilised to improve maternal and newborn health outcomes in Bangladesh.

7.3.4 Use of Bangladesh-specific data

My thesis was able to utilise a wealth of parameter values derived from national sources. This process significantly underpinned the model's reliability and relevance to the Bangladeshi context.

Over 100,000 women who experienced a pregnancy within three years prior to the survey were drawn from the extensive dataset of the BMMS (17). Detailed information on women with pre-existing hypertension and diabetes mellitus were derived from the BDHS 2017-2018 for over 5000 women (18).

The decision to use national-level data was not limited to the individual level risk for pre-existing conditions alone. I also incorporated national-level prevalence data extracted based on a comprehensive review of literature for each event and outcome. For collecting cost data, I utilised both published and unpublished costing exercises conducted for the government of Bangladesh. Long-term costs were extracted from country-specific published literature. In this way, it was ensured that the model's cost components were firmly rooted in national-level data. This was further enhanced by engaging health economists who possess expertise in national-level costing, thereby further validating the model outputs.

Intervention effectiveness data for Bangladesh was available from a retrospective study based in Bangladesh (19). The study, however, estimated the impact on pregnancy-induced hypertension, which is expected to cover gestational hypertension, pre-eclampsia and eclampsia together. Although the data was not directly integrated into my model, it played an important role in validating the use of global-level evidence in my model. Generally, the values extracted and incorporated for gestational hypertension and pre-eclampsia/eclampsia in my model based on global evidence were close to what was obtained from country-specific evidence. It underscored that the insights from the global evidence base holds relevance when applied to the national context.

7.3.5 Policy relevance

7.3.5.1 Implications for programme and planning

My thesis unveiled several key issues related to addressing HDP and DMP and their associated complications among women in Bangladesh. Despite calcium being a proven intervention, it has not received much attention by programme implementers as a means of reducing HDP. As Bangladesh is a country identified as having low calcium intake, universal calcium supplementation for pregnant women remains a neglected intervention. Despite Bangladesh having a National Plan of Action for Nutrition (NPAN) in place and despite a strong recommendation by WHO, there is no mention of calcium other than one strategy document. Through the reviews and model development, my thesis has highlighted how essential this micronutrient is to reduce some of the adverse maternal and newborn outcomes and how simple a solution it can be in terms of resource allocation and attaining

long-term health. This has implications in reaching the SDG-related maternal mortality goal for Bangladesh as calcium can directly impact the second leading cause of death among mothers.

Widespread use of national data and early engagement of stakeholders have positioned the model results for adoption by the government. The adoption can take place in the form of implementation of the intervention directly, through an antenatal care platform or through other means. The research generated outputs related to cost savings and benefits attained nationally and at sub-group levels. This work can have far-reaching implications through its relevance to four distinct operational plans and programmes for maternal health, newborn health, nutrition and non-communicable disease control.

The National Maternal Health Action Plan has been developed in recent years. While a draft costed action plan has been produced that provides costing for a selected set of activities, the model can complement the action plan by adding a critical component of cost-effectiveness analysis of critical interventions. Detailed costing was not available and hence could not be compared to what has been used as inputs to the model. A game changer for evidence-based decision-making for Bangladesh will be to turn to cost-effectiveness analysis for setting priorities. At present, interventions are selected based on clinical effectiveness of interventions, which sometimes is accompanied with an overall costing for implementing interventions. Most costing does not go into detailed analysis of cost effectiveness. Incorporating modelling exercises will represent a leap forward, adding a robust quantitative dimension to the decision-making process. A focus on maternal nutrition-related interventions, more specifically calcium supplementation, can unlock the potential for better resource mobilisation and address a large untapped area within maternal healthcare.

7.3.5.2 Resource allocation for scale-up

One of the caveats in implementation is the low level of public health spending in Bangladesh. The total health expenditure as reported in the Bangladesh National Health Accounts (BNHA) is only 2.7% of GDP (288). Public spending on health in 2020 was less than BDT 180 billion. This amount covered only 23% of the total health expenditure and represented 0.66% of GDP. The rest were out-of-pocket payments. While expenditure information by programme is not available, there is a question of how much of the costs can be borne by the government as there will be some extra cost for the expansion of calcium supplementation.

The scale-up process can be time-consuming due to limited resources although it is mostly cost-saving from the perspective of the public health system. In the meantime, the model can be modified for a lower level of interim coverage or phased implementation, targeting improved coverage for specific population groups (e.g. age/region/residence type). Costs and effects can be disaggregated at more

granular levels, which means specific population groups can be targeted if a phased expansion of the intervention is planned.

The model can also be used as a foundation for improving HDP or GDM-related interventions overall. Once the single intervention, calcium supplementation, is in the process of a scale-up, additional interventions can also be included to assess the impact of multiple interventions scaled up at the same rate or at different coverage levels. Use of such robust analysis will equip policy makers with the tools to make choices for maximising health outcomes for a given level of resources. This is even more crucial as the country is embarking on implementing a national health insurance programme, the "Shastho Shurokkha Kormoshuchi"(SSK) (289).

7.3.5.3 Exploring an alternative service delivery channel

The thesis also lays the foundation for further research within government settings to understand the optimum intervention delivery mechanism for ensuring maximum outreach. The model presents two scenarios for distributing calcium through the domiciliary health and family planning workers and the facility-based antenatal care platform. A single delivery channel or combination of the two platforms complementing each other can help reach targets of improved ANC to women. There is a new cadre included at the community level, the multi-purpose volunteers who can also complement the distribution of nutritional supplements (290). This may lead to even additional cost saving. Providing support in increasing coverage of maternal health-related interventions falls within the job description of community health workers. Alongside counselling, it can be an easy solution for improving coverage of nutritional supplements among pregnant women.

Another interesting way would be to explore possible ways of food fortification, which may be able to fulfil the need for calcium partially. The rest can be addressed through low dose supplements during pregnancy. The impact of food fortification, however, will need additional understanding of the overall situation of food security as well as intra-household food distribution.

7.3.5.4 Improving measurement for tracking coverage and progress in scale up

There were some challenges in incorporating baseline coverage data for calcium supplementation in Bangladesh. Although published data related to effective coverage of the nutrition component of antenatal care was used, coverage of calcium alone may be different. Considering the role of calcium in reducing pre-eclampsia and associated complications, more attention needs to be paid to where and how this information can be collected.

One key source could be the routine health information data that is accessible through the District Health Information System 2. Incorporation of information relating to women's use of calcium supplementation onto that system would be the best ways to get up-to-date information.

Other potential data sources include the national-level health surveys like the BDHS or, BMMS or the Multiple Indicator Cluster Survey (MICS). Alongside reporting overall antenatal care coverage, BDHS and BMMS report on the components of antenatal care. Although the components cover iron and folic acid supplementation, calcium is so far not included. This is crucial to monitor national-level progress if a scale-up of calcium supplementation is to be undertaken. Nevertheless, it is worth noting that these surveys are only undertaken periodically and so are not as useful as routinely collected antenatal information .

7.3.6 Preventive intervention in addressing NCDs

The model re-emphasised the need to focus on preventive measures for tackling NCDs in pregnancy. While generally, promotion of healthy diet is a key intervention for NCD prevention, nutritional supplements like calcium can help prevent hypertensive disorders in pregnancy. The model while establishing the linkage between NCDs and maternal health indicated the need to focus on preventive nutritional interventions for pregnant women which has not yet been explicitly included in the NCD related policy documents (291).

7.3.7 Flexible model structure

The model was built keeping in mind a package of intervention rather than a single intervention and that can cover interventions beyond prevention alone. Thus the programming includes intervention effects in a manner that can be manipulated to accommodate both single and multiple intervention effects. Although my thesis currently report cost-effectiveness of a single preventive intervention, the model has the capacity to go beyond that single intervention. This will be a very helpful tool for policymakers when it comes to evidence informed decision making. While at present use of evidence is usually limited to intervention effectiveness, my model will help to generate evidence of cost-effectiveness for multiple interventions in different combinations simultaneously.

7.4 Limitations

7.4.1 Data

Whilst a strength of the thesis is that most of the data are directly relevant to Bangladesh, there were some limitations too. Although extensive national data has been used in the model, most of the intervention effectiveness data has been taken from findings of experimental studies around the globe. It is, however, impossible to obtain trial-based national data for each parameter for such a complex

model. Utilising data from other countries for generating parameter values is not unusual either. A similar method has been followed in software-based models like the LiST where for some indicators assumptions are also made for baseline prevalence values. Other microsimulation models including the GMaTH model depends upon diversified source of data for analysing intervention effects. As described in chapter 6, the relative risks or odds ratios when extracted followed a methodological process of selection and a hierarchy of evidence for using the most relevant data as model inputs. Systematic reviews were the gold standards, followed by national and LMIC-specific global studies. In the event of no such studies being available, data from high-income countries were sought. The method followed does recognise the trade-off between quality and relevance. It is also aligned with the recommended checklist prescribed by Kaltenthaler et al (2013) (292).

Not all risk factors for HDP and GDM could be taken into account in the model. Age, pre-existing hypertension and pre-existing diabetes mellitus were covered when sampling women for complications. While the risk of these two diseases was assigned based on probabilities and coefficients from a logistic regression run on the BDHS data and assigned to women in BMMS database, there were gaps in terms of women's age in the two datasets.

Other risk factors such as history of events in previous pregnancy, family history of morbidity, parity and BMI were not covered due to the unavailability of data. Although BDHS 2017-18 contains information on BMI for samples covered in estimating prevalence of diabetes mellitus and hypertension, the sample size was small. Imputing such data was not possible as other biomarkers were not available in either of the datasets. The model, however, was still able to produce the national-level prevalence estimates. Since the intervention considered in the model was not related to change in lifestyle that would have an impact on women's BMI and its consequences in pregnancy, there would perhaps not be much impact on the results. There is also the issue of the reliability of family history through women's reports in surveys. As almost half of the diabetic and hypertensive population were unaware of having the disease, it is unlikely they would be aware of its prevalence among their parents (52). Parity data, however, was available in the BMMS cohort but was not available in the BDHS data on hypertension and diabetes mellitus. Inclusion of this risk factor would require the subsequent events and outcome risks to be drawn from literature that took into account parity, which is uncommon and may require adding more assumptions to the risks. This would add further complexity to the model. Neither the GMath nor the LiST-based models take into account parity and still produced reliable projections on maternal, child and newborn health outcomes (179, 284). My model, however, is able to incorporate additional risk factors upon the availability of data.

National prevalence estimates for conditions like pre-eclampsia and eclampsia were available from a limited number of facility-based studies. These are likely to have biased estimates, as hospitals tend to attract more severe patients. The study reporting pre-eclampsia prevalence sampled women from an antenatal care clinic, which reduces the bias. Still, there are other socio-economic factors that may influence the patient characteristics. Eclampsia prevalence was estimated from a large RCT dataset which followed over 35,000 pregnant women throughout pregnancy (201). Although data was sourced from a questionnaire of women at several visits during and after pregnancy, it can be assumed that convulsions are significant events and are less likely to remain unnoticed and hence underreported. In addition, literature related to pre-eclampsia and severe pre-eclampsia is scarce and did not always have available risk data that could be incorporated within the model. No data were found regarding the proportion of pre-eclampsia cases transitioning into eclampsia, and thus a flat rate had to be applied for risk of eclampsia. This, however, did not have much impact on the downstream outcomes as for all outcomes the risks applied were the same for pre-eclampsia and eclampsia. Assumptions were made regarding the proportion of pre-eclamptic women requiring stabilization and referral and preterm babies requiring specialised care when estimating costs and DALYs. Some of the assumptions were made based on partially available data such as the proportion of preterm babies having complications or were verified through experts for data related to pre-eclampsia.

The cost of attendance at emergency departments was not accounted for when estimating staff costs for treatment of pre-eclampsia/eclampsia. Such costs will need to consider patient flow from different facilities. Women might arrive at higher-level referral facilities through primary care facilities or directly from their home. However, the time spent on the loading dose of MgSO4 should not be long and therefore is likely to add a very minimal amount to the overall cost.

7.4.2 Modelling lifetime impact on newborn

Based on stakeholder suggestions, the model did not take into account the long-term impact of the two cardio-metabolic diseases among babies born. This is likely to underestimate the overall benefits of the intervention as babies born to mothers with CMDs are at higher risk of developing chronic diseases late in their lives (18). Only delayed social competency as a measure of developmental delay was presented as a standalone measure for five years after birth, and a secondary analysis was presented estimating disability for the lifetime of preterm newborns. Incorporating long-term outcomes among babies in the form of chronic diseases can provide important information to policymakers, especially to those involved in the NCD programme implementation. Maternal hyperglycaemia has been proven to be associated with obesity and overweight among offspring when they reach the age of 10-14 (293, 294). There are also neuro-cognitive impacts on children who are

born to mothers with hyperglycaemia. Studies found offspring securing a lower cognitive score and greater attention deficiency (295, 296).

Babies born to mothers with hypertensive disorders of pregnancy also suffer from several long-term effects. These offspring have almost 60% higher incidence rates of endocrine, nutritional and metabolic diseases (297). Children born to mothers with pre-eclampsia had a higher risk of developing neurodevelopmental disorders. Babies born to mothers with pre-eclampsia had a two-to-nine-fold higher risk of developing cerebral palsy (297). Pre-eclampsia and gestational hypertension increase the risk of autism spectrum disorder, schizophrenia and attention deficit hyperactivity disorder.

7.4.5 Possible supply side constraints

Although the model took into account time and staff costs related to distribution of calcium using the domiciliary health and family planning workers, it may be important to look at their overall workload, as they are the service contacts for many community-level interventions. These staff already have their time allocated between household visits, services at the community clinics and immunisation days throughout the week. Many of them do not manage to complete their round of household visits within the assigned time period. However, as they already provide services related to maternal health and family planning, it might be fairly simple to add this component of distributing supplements and counselling. It is also worth thinking about bringing more women to the facilities for ANC visits and ensuring they receive all components of care including the necessary nutritional supplements. The model's additional scenario analysis using overall ANC at the facilities was estimated to be a cost-saving solution too. A phased transition between the two modes of service delivery may be helpful in ensuring maximum utilisation.

It is not unusual for cost effectiveness analyses (CEAs) to assume no constraints on the supply side, leaving the decision to be made by the providers. One way to address the supply-side constraints would be to conduct budget impact analysis. In some ways, this makes the issue of supply-side constraints more transparent. There are other ways of incorporating resource constraints in CEAs. Some cost-effectiveness analysis also took into account resource constraints. In a systematic review, Salleh et al (2017) reviewed resource modelling based on Discrete Event Simulation (DES) models, considering both direct and indirect methods of incorporating resource constraint (298). The direct methods incorporated the limited resource, while other models adjusted the throughput of patients in order to reflect the supply side constraints. Despite all the supply-side obstacles, the model findings remain relevant and useful as it has taken into account all possible downstream costs including annuitized costs of establishing certain newborn care facilities. Findings from my model add value to the current evidence base on cost savings through scaling up an intervention and help mobilise

resources in other important areas. More importantly, with the current plan of expanding the SSK, a national health insurance scheme by the government, applicability of decision analysis will become increasingly important for efficient distribution of the limited public resources channelled into the health sector.

7.4.6 Estimating DALY for stillbirths

Disability weight for stillbirths was not available in the Global Burden of Disease (GBD) studies. There is a limited amount of research available that estimated DALY for stillbirths. One economic evaluation identified in the systematic review incorporated stillbirths for DALY estimation using the same methods as for newborn deaths. The years of life lost (YLL) was estimated by considering the average national life expectancy for a livebirth (128). Very few published papers have suggested how the DALY for stillbirths should be estimated. Kant et al (2019) estimated the DALY for stillbirth using a stillbirth adjusted life expectancy approach (299). The paper also mentioned that the effect on parents would not be easy to measure, especially for developing countries, due to a lack of data. My model did not incorporate the DALYs for stillbirths for two reasons: a lack of data on the effects on women and second the lack of clarity on recommended methods.

7.4.7 Incorporating low birth weight as an outcome

Preterm birth is one of the two main causes of low birth weight, the second being intrauterine growth restrictions. The model has taken into account preterm births only. Incorporating both low birth weight and preterm would be difficult as it would largely depend upon gestational age. Data availability on low birth weight is also limited due to the difficulties in measurement and flaws in recording birth weight.

7.4.8 Gestational age

The timing or gestational age of events in the model were not tracked as time-bound data on risks were not available. However, the window of gestational age at which the events can occur has been accounted for in the model.

7.5 Further Research

From the viewpoint of decision uncertainty in relation to calcium supplementation, the Expected Value of Perfect Information (EVPI) suggests there is no need for further research relating to the estimation of the cost-effectiveness of calcium supplementation in this population. There are still several pending issues beyond the distributions used in my model. , however, other aspects of research that are beyond the scope of EVPI that are worthy of consideration.

First, the development of a user-friendly interface for my model will enable relevant programme and policy-level people to explore alternative scenarios, for example, region-by-region implementation. At present, the model can only be used by a researcher with good knowledge of programming in R. For more general use, a user-friendly interface needs to be developed. For example, other models related to CVD prevention have developed Return on Investment Tool and the NHS Diabetes Prevention Programme Return on Investment Tool (27, 28). These tools offer the flexibility to generate model results tailored to the national or regional level. Some packages in R like R Shiny support development of user-friendly interfaces for economic evaluation models without users having to learn or know coding in RStudio (29).

Secondly, evaluating other interventions for improving outcomes associated with HDP and GDM. Whilst calcium supplementation appears highly cost-effective, other interventions offer the potential for yet further improvements in outcomes, and could be even more cost-effective. This will require information on the effectiveness of those interventions and the costs of implementing them, but all other information is already present within the existing model.

Thirdly, the model can be adopted to examine more sub-groups, such as, different geographic areas. This could be important due to regional variation in mortality and nutrition. The sub-group analysis can further be extended by adding the equity lenses to it. A distributional cost-effectiveness analysis, if applied, will help understand equity aspect of the scaled-up provision in terms of the administrative divisions.

It is also possible to develop an extended cost-effectiveness analysis taking into account issues like financial risk protection. As mentioned in previous chapters, there is an ongoing second phase implementation of pilot of the SSK, a national financial protection scheme for health covering the costs of essential care related to maternal health. Considering that the model has included downstream healthcare costs associated with the intervention, it has created an opportunity for further analysis. It may be possible to add the financial protection aspect to the model, which can feed information to the existing pilot and help in national scale-up of the insurance programme (300).

The model assumed the same compliance and dose level as is available in the existing evidence base. The issue of compliance for Bangladesh may need further exploration. A study assessing the effectiveness of calcium supplements in pregnancy assessed compliance by counting strips of tablets (184). It revealed that over 66% of women continued to take calcium tablets for 3-6 months during pregnancy and consumed between 90-179 tablets. Only around 14% consumed more than 180 tablets. This should be interpreted bearing in mind a study setting where women were regularly followed up in relation to calcium intake. Interestingly, the study still found positive effects, a little lower compared

to that of global evidence. The compliance level suggested by the paper also emphasised the importance of repeated follow-up and counselling on nutrition supplements. This can happen during home visits by community health workers or during ANC check-ups. One possible area of research would be the level of compliance attained with and without counselling. Repeated counselling through physical visits may be more resource consuming. Alternative sources of counselling using the government's existing call centre set-up needs to be explored (301).

The optimum dose of calcium for Bangladeshi women also needs to be determined. Whilst the model assumed the dose level to be that reported in literature (> 1g a day), the effectiveness study based in Bangladesh used a lower dose of 500 mg compared to the WHO recommended dose (184). Although low dose calcium has also been reported to be effective through Cochrane reviews, its applicability in Bangladeshi women is unknown (183). The WHO recommendation highlighted that the optimum dose of calcium supplement needs further research and analysis to be determined (170). It also highlighted research gaps related to the most effective, acceptable and feasible regimen of the supplement. Country-specific research to determine the correct dose and the modality through which it can be delivered (single or multiple tablets a day) to women in Bangladesh or other countries can add a very important dimension of knowledge to existing literature. This will have implications for the model results too.

While the current recommendation is to start calcium at 20 weeks of gestation, a new recommendation covers pre-pregnancy or early pregnancy calcium supplementation for women (72). There is lack of evidence in this area. Cost-effectiveness of this is also unknown. The model has the flexibility to be extended to incorporate additional gestational weeks to add to the limited evidence that is available through a small amount of literature.

Finally, any further research will depend on what is needed for the country. As the final aspect of the research, I plan to disseminate my research findings among the stakeholders as part of a fellowship I will be undertaking. The dissemination can lead to the use of the research findings by policymakers. It will also help to identify and prioritise the need for additional research related to the thesis, which can be undertaken in future.

7.6 Conclusion

Calcium supplementation during pregnancy has been identified as an essential nutrition action that targets the first 1000 days of life (302). Despite its potential to mitigate a multitude of adverse pregnancy outcomes, it has remained under-researched both in Bangladesh and other LMICs. Cost-effectiveness studies around this intervention are also limited. My thesis adds important knowledge to this domain, highlighting the far-reaching implications of the knowledge for the well-being of both

mothers and newborns. It also highlights the need for preventive interventions in order to save and redirect resources for better health of the overall population.

My thesis is novel in multiple ways. My model adopted an individual-based Markov microsimulation model structure to assess cost-effectiveness of calcium supplements, which is rare in the context of LMICs. The thesis added a new dimension compared to other economic evaluations done globally, modelling multiple conditions together and considering the common risk factors, their interaction and the impact of the combined risk factors of the two conditions on events and outcomes. This thesis reiterated the importance of calcium as a nutritional supplement and as a simple solution for preventing the complications arising from two key NCDs in pregnancy, HDP and DMP, and their long-term impact on women and babies. As an added attribute, the thesis is informed by stakeholders who are national experts in the field of maternal and newborn health.

Finally, my research serves as a catalyst for informed decision-making and underscores the urgent need for a fresh perspective on calcium supplementation in the context of maternal, newborn and women's health in Bangladesh and LMICs at large. It has shown that the "low hanging fruits" are not essentially exhausted as claimed by recently published literature (47) and there are still potential low investment interventions that remains untapped. It adds timely and important information to the existing evidence base, which can enable policy makers and implementers to mobilise resources more efficiently, have a greater impact on maternal health at the same time and be on track to reach the SDGs for maternal and newborn health.

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Appendices

Appendix 1: Guideline summaries

Table 1: Guideline summary for HDP

Risk factors	• Nulliparous women • age over 40 • history of pre-eclampsia or GH • Family history of pre-eclampsia • multi-fetal pregnancys • High BMI • pre-existing conditions like CVD or Kidney disease
Symptoms	• Two readings of SBP four hours apart 140 mmHg or higher but lower than 160 mmHg and/or DBP 90 mmHg or higher but lower than 110 mmHg after 20 weeks of gestation • No proteinuria • No features of preeclampsia
Antenatal care	• Increased surveillance (BP monitoring, FBC, LFT, renal function testing, ultra-sound assessment, PlGF-based testing if there is suspicion of preeclampsia • Calcium supplementation • Low-dose aspirin • Pharmacological treatment (labetalol, nifedipine or methyldopa as indi-cated), if BP remains above 140/90 mmHg. Aim for BP of 135/85 mmHg or less • Consider cardiotocography (CTG)

	• Consider fetal heart auscultation at every antenatal appointment
Delivery	• Do not offer planned early birth before 37 weeks to women whose blood pressure is lower than 160/110 mmHg, unless there are other medical indications • If planned early birth is necessary offer a course of antenatal corticosteroids and magnesium sulfate if indicated • During labour, measure blood pressure hourly
Postnatal	• Increased monitoring of blood pressure • Continue antihypertensive drug if severe hypertension during antenatal period • For women with gestational hypertension who did not take antihypertensive treatment, start treatment if their blood pressure is 150/100mmHg or higher • Medical review at 2 weeks for women on pharmacological treatment and 6–8 weeks otherwise

Table 2: Guideline summary for severe HDP

Risk factors	• Nulliparous women • Age over 40 • History of pre-eclampsia or gestational hypertension • Family history of pre-eclampsia • Multi-fetal pregnancy • High BMI • Pre-existing conditions like CVD or CKD
Symptoms	Blood pressure of 160/110mmHg or more
Antenatal care	• Admit, but if BP falls below 160/110 mmHg then manage as for Hypertension • Offer pharmacological treatment to all women • Aim for BP of 135/85 mmHg or less • Measure BP Every 15–30 minutes until BP is less than 160/110 mmHg • Dipstick proteinurea daily while admitted • Measure full blood count, liver • function and renal function at • presentation and then weekly • Carry out PlGF-based testing on 1 occasion if there is suspicion of preeclampsia
Delivery	Measure blood pressure every 15–30 minutes until blood pressure is less than 160/110 mmHg in women with • severe hypertension. • Continue use of antenatal antihypertensive treatment during labour • If a woman in a critical care setting who has severe hypertension or severe preeclampsia has or previously had an eclamptic fit, give intravenous magnesium sulfate.

Postnatal	NA

Table	3.1
Medline	Search terms for economic evaluation of hypertensive disorders during pregnancy
1	Pregnancy, High-Risk/ or Pregnancy Trimester, First/ or Pregnancy/ or Pregnancy Complications/ or Pregnancy Proteins/ or Hypertension, Pregnancy-Induced/ or Pregnancy Trimester, Third/ or Pregnancy Outcome/ or Pregnancy in Diabetics/ or Pregnancy Trimester, Second/
2	exp hypertension, pregnancy-induced/ or pre-eclampsia/
3	(pre-eclampsia or preeclampsia).ab,ti.
4	exp Hypertension/
5	exp Pregnancy/
6	4 and 5
7	hypertension.mp. and pregnancy.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8	2 or 3
9	1 and 8
10	6 or 7 or 9
11	*economics/
12	exp *"costs and cost analysis"/
13	(economic adj2 model*).mp.
14	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab,kf,kw.
15	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,kf,kw.
16	(life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab,kf,kw.
17	(cost or economic*).ti,kf,kw. and (costs or cost-effectiveness or markov).ab.
18	or/11-17
19	10 and 18

Table	3.2
CINAHL	Search terms for economic evaluation of hypertensive disorders during pregnancy
21	s10 and s20
20	s11 or s12 or s13 or s14 or s15 or s16 or s19
19	s17 and s18
18	AB costs or cost-effectiveness or markov
17	TI (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR MW (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR SU (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s)
16	AB (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR MW (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR SU (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s)
15	TI (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs) OR MW (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs) OR SU (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs)
14	TI (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s) OR AB (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s) OR MW (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or econ ...
13	economic N2 model*
12	(MH "Costs and Cost Analysis+")
11	(MM "Economics")
10	s6 or s7 or s9
9	s1 and s8
8	s2 OR s3
7	s4 AND s5
6	TI (hypertension AND pregnancy) OR AB (hypertension AND pregnancy)
5	(MH "Pregnancy+")
4	(MH "Hypertension+")
3	TI (pre-eclampsia or preeclampsia) OR AB (pre-eclampsia or preeclampsia)
2	(MH "Pre-Eclampsia+") OR (MH "Pregnancy-Induced Hypertension+")

1	(MH "Pregnancy") OR (MH "Pregnancy, High Risk") OR (MH "Pregnancy Trimesters+") OR (MH "Childbirth")

Table	3.3
Medline	Search terms for economic evaluation on diabetes mellitus during pregnancy
1	exp diabetes, gestational/ or pregnancy in diabetics/
2	gestational diabetes.mp. or (pregnan* adj2 diabet*).ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3	1 or 2
4	Pregnancy, High-Risk/ or Pregnancy Trimester, First/ or Pregnancy/ or Pregnancy Complications/ or Pregnancy Proteins/ or Hypertension, Pregnancy-Induced/ or Pregnancy Trimester, Third/ or Pregnancy Outcome/ or Pregnancy in Diabetics/ or Pregnancy Trimester, Second/
5	*economics/
6	exp *"costs and cost analysis"/
7	(economic adj2 model*).mp.
8	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab,kf,kw.
9	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,kf,kw.
10	(life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab,kf,kw.
11	(cost or economic*).ti,kf,kw. and (costs or cost-effectiveness or markov).ab.
12	or/5-11
13	3 and 4 and 12

Table	3.4
CINAHL	Search terms for economic evaluation of hypertensive disorders during pregnancy
21	s10 and s20
20	s11 or s12 or s13 or s14 or s15 or s16 or s19
19	s17 and s18
18	AB costs or cost-effectiveness or markov
17	TI (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR MW (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR SU (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s)
16	AB (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR MW (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR SU (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s)
15	TI (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs) OR MW (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs) OR SU (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs)
14	TI (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s) OR AB (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s) OR MW (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or econ ...
13	economic N2 model*
12	(MH "Costs and Cost Analysis+")
11	(MM "Economics")
10	s6 or s7 or s9
9	s1 and s8
8	s2 OR s3
7	s4 AND s5
6	TI (diabetes AND pregnancy) OR AB (diabetes AND pregnancy)
5	(MH "Pregnancy+")
4	(MH "Diabetes+")
3	(MH "gestational diabetes+")
2	TI ("Gestational diabetes") OR AB ("Gestational diabetes")
1	(MH "Pregnancy") OR (MH "Pregnancy, High Risk") OR (MH "Pregnancy Trimesters+") OR (MH "Childbirth")

Table	3.5

Medline	Economic evaluation on antenatal care
23	Pregnancy, High-Risk/ or Pregnancy Trimester, First/ or Pregnancy/ or Pregnancy Complications/ or Pregnancy Proteins/ or Hypertension, Pregnancy-Induced/ or Pregnancy Trimester, Third/ or Pregnancy Outcome/ or Pregnancy in Diabetics/ or Pregnancy Trimester, Second/
24	*economics/
25	exp *"costs and cost analysis"/
26	(economic adj2 model*).mp.
27	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab,kf,kw.
28	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,kf,kw.
29	(life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab,kf,kw.
30	(cost or economic*).ti,kf,kw. and (costs or cost-effectiveness or markov).ab.
31	or/24-30
32	22 and 23 and 31
33	Prenatal Care/ or Pregnancy/
34	antenatal care.mp. or exp Prenatal Care/
35	33 or 34
36	5 and 18 and 35
37	31 and 33 and 34

Table	3.6
CINAHL	Economic evaluation on antenatal care
S101	S99 and S100
S100	AB costs or cost-effectiveness or markov
S99	TI (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR MW (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR SU (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s)
S98	AB (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR MW (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR SU (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s)

S96	TI (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s) OR AB (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s) OR MW (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or econ ...
S95	economic N2 model*
S94	(MH "Costs and Cost Analysis+")
S93	S88 and S92
S92	S89 or S90 or S91
S91	TI prenatal care OR AB prenatal care
S90	TI antenatal care OR AB antenatal care
S89	(MH "Prenatal Care")
S88	S87 or S94 or S95 or S96 or S97 or S98 or S101
S87	(MM "Economics")

Table 3: Guideline summary for pre-eclampsia

Risk factors	• Nulliparous women • Age over 40 • history of pre-eclampsia or gestational hypertension • Family history of pre-eclampsia • Multi-fetal pregnancy • High BMI • Pre-existing conditions like CVD or CKD
Symptoms	• SBP 140 mmHg or higher and/or DBP 90 mmHg or higher before 20 weeks of gestation • After 20 weeks: – Proteinuria 2+ on dipstick – • Presence of any preeclampsia features below: • Severe headache, • blurry vision, • Severe pain just below the ribs • Vomiting, swelling of hands, feet or face
Antenatal care	• Carry out a full clinical assessment at each antenatal appointment for women with pre-eclampsia, and offer admission to hospital for surveillance and any interventions needed if there are concerns for the wellbeing of the woman or baby. Concerns could include any of the following: • sustained systolic blood pressure of 160 mmHg or higher • any maternal biochemical or haematological investigations that cause con-cern, for • example, a new and persistent: • rise in creatinine (90micromol/litre or more, 1mg/100ml or more) or • rise in alanine transaminase (over 70 IU/litre, or twice upper limit of normal • range) or • fall in platelet count (under 150,000/microlitre) • signs of impending eclampsia • signs of impending pulmonary oedema • other signs of severe pre-eclampsia • suspected fetal compromise • BD guidelines: • Increased surveillance. Calcium supplementation • Low-dose aspirin, (75 mg) for the prevention of pre-eclampsia
Delivery	• Do not offer planned early birth before 37 weeks to women with gestational hypertension whose blood pressure is lower than 160/110 mmHg, unless there are other medical indications • If planned early birth is necessary offer a course of antenatal corticosteroids and magnesium sulfate if indicated
Postnatal	• Continue antihypertensive drug if severe hypertension during antenatal pe-riod • Those who did not take antihypertensive treatment and have given birth, measure blood pressure: • at least 4 times a day while the woman is an inpatient • at least once between day 3 and day 5 after birth • Continue treatment for those who took antihypertensive drugs; measure BP at least 4 times while in patient, measure BP 1-2 days for upto 2 weeks

Table 4: Guideline summary for moderate risk pre-eclampsia

Risk factors	• More than 1 symptom • First pregnancy, • 40 years or older, • More than 10 years birth interval • BMI 35 or more • family history of pre-eclampsia • multi-fetal pregnancy
Symptoms	• SBP 140 mmHg or higher and/or DBP 90 mmHg or higher before 20 weeks of gestation • After 20 weeks: – Proteinuria 2+ on dipstick – • Presence of any preeclampsia features
Antenatal care	• Increased surveillance • Calcium supplementation • Low-dose aspirin, (75 mg) for the prevention of pre-eclampsia • Antihypertensive drugs for pregnant women
Delivery	• Do not offer planned early birth before 37 weeks to women with gestational hypertension whose blood pressure is lower than 160/110 mmHg, unless there are other medical indications • If planned early birth is necessary offer a course of antenatal corticosteroids and magnesium sulfate if indicated
Postnatal	• Continue antihypertensive drug if severe hypertension during antenatal period or were treated with the drug during pregnancy

Table 5: Guideline summary for high risk pre-eclampsia

Risk factors	• Hypertensive disease during previous pregnancy • Chronic kidney disease, • Autoimmune disease, • type 1 or 2 diabetes • Chronic hypertension
Symptoms	• SBP 160 mmHg or higher and/or DBP 110 mmHg or higher after 20 weeks of gestation • Proteinuria 2+ on dipstick • Presence of any preeclampsia features
Antenatal care	• Increased surveillance • Monitor BP, urine and fetal condition weekly • Counsel women and their families about danger signals of pre-eclampsia or eclampsia • If all observations remain stable allow to proceed towards term; • If diastolic BP is more than 90 (BD), refer to higher level facilities. With labetalol/nifedipine/ methyldopa
Delivery	• At secondary and tertiary level facilities women can be allowed to proceed to normal labor and childbirth, • At secondary and tertiary level facilities if diastolic BP reaches 95, start treatment hypertension and aim for blood pressure is lower than 135/85 or less mmHg, unless there are other medical indications • If planned early birth is necessary offer a course of antenatal corticosteroids.

	• Record maternal and fetal thresholds for planned early birth before 37 weeks in women with pre-eclampsia. Thresholds for considering planned early birth could include (but are not limited to) any of the following known features of severe pre-eclampsia:
	  ○ Inability to control maternal blood pressure despite using 3 or more classes of
	  ○ Antihypertensives
	  ○ Maternal oxygen saturation less than 90%
	  ○ Progressive deterioration in liver function, renal function, haemolysis, or platelet count
	  ○ Ongoing neurological features
	  ○ Eclampsia
	  ○ Placental abruption
	  ○ Cardiotocograph, or stillbirth.
	• Consider giving intravenous magnesium sulfate to women with severe preeclampsia
	• who are in a critical care setting if birth is planned within 24 hours
	• Consider the need for magnesium sulfate treatment, if 1 or more of the following features of severe pre-eclampsia is present:
	  • ongoing or recurring severe headaches
	  • visual scotomata
	  • nausea or vomiting
	  • epigastric pain
	  • oliguria and severe hypertension
	• progressive deterioration in laboratory blood tests (such as rising creatinine or liver transaminases, or falling platelet count

Postnatal	• Treat women with antihypertensive drugs during the postpartum period if they: • Have severe postpartum hypertension; or (2) were treated with antihypertensive drugs during pregnancy

Table 6: Guideline summary for eclampsia

Risk factors	• More than 20 weeks of pregnancy: vomiting, epigastric pain, severe headache, blurred vision • Convulsions with signs of pre-eclampsia indicate eclampsia. • Can occur regardless of the severity of hypertension; • Are difficult to predict and typically occur in the absence of • headache or visual changes; • Occur after childbirth in about 25% of cases
Symptoms	Convulsion, seizure
Antenatal care	• Increased surveillance. Calcium supplementation • Low-dose aspirin, (75 mg) for the prevention of pre-eclampsia • Antihypertensive drugs for pregnant women
Delivery	• Monitor vital signs (pulse, blood pressure, respiration and pulse oximetry), reflexes and fetal heart rate hourly. • If systolic blood pressure remains at 160 mmHg or higher and/or if diastolic blood pressure remains at 110 mmHg or higher, give antihypertensive drugs. o Timely and adequate administration of anticonvulsive drugs Magnesium sulfate is the drug of choice for preventing and treating convulsions in severe preeclampsia and eclampsia. • Catheterize the bladder to monitor urine output. o Maintain a strict fluid balance chart (monitor the amount of fluids administered and urine output) to prevent fluid overload. o If urine output is less than 30 mL per hour: ▪ Withhold magnesium sulfate and infuse IV fluids (normal saline or Ringer's lactate) at 1 L in eight hours. • Monitor for the development of pulmonary oedema • Never leave the woman alone. A convulsion followed by aspiration of vomit may cause death of the woman and fetus. • Auscultate the lung bases hourly for rates indicating pulmonary oedem
Postnatal	• Treat women with antihypertensive drugs during the postpartum period if they: Have severe postpartum hypertension; or (2) were treated with antihypertensive drugs during pregnancy

Table 7: Guideline summary for chronic hypertension

Risk factors	• More than 20 weeks of pregnancy: vomiting, epigastric pain, severe headache, blurred vision • Convulsions with signs of pre-eclampsia indicate eclampsia. • Can occur regardless of the severity of hypertension; • Are difficult to predict and typically occur in the absence of • headache or visual changes; • Occur after childbirth in about 25% of cases
Symptoms	Hypertension before or after pregnancy
Antenatal care	

Delivery	• Treat women with severe hypertension who are in critical care during pregnancy or after birth immediately with 1 of the following:
	  • labetalol (oral or intravenous)
	  • oral nifedipine
	  • intravenous hydralazine
	• Consider using up to 500 ml crystalloid fluid before or at the same time as the first dose of intravenous hydralazine in the antenatal period
	• For women with hypertension in the postnatal period, if blood pressure is not controlled with a single medicine, consider a combination of nifedipine (oramlodipine) and enalapril[5]. If this combination is not tolerated or is ineffective, consider either: adding atenolol or labetalol to the combination treatment or swapping 1 of the medicines already being used for atenolol or labetalol

Postnatal	• Treat women with antihypertensive drugs during the postpartum period if they: Have severe postpartum hypertension; or (2) were treated with antihypertensive drugs during pregnancy

Table 8: Guideline summary for GDM

Risk factors	• BMI above 30 kg/m2 • Previous macrosomic baby weighing 4.5 kg or above • Previous gestational diabetes • Family history of diabetes (first-degree relative with diabetes) • Minority ethnic family origin with a high prevalence of diabetes.
Symptoms	• fasting plasma glucose 5.1-6.9 mmol/l (92 -125 mg/dl) • 1-hour plasma glucose ≥ 10.0 mmol/l (180 mg/dl) following a 75g oral glucose load* • 2-hour plasma glucose 8.5-11.0 mmol/l (153 -199 mg/dl) following a 75g oral glucose load
Antenatal care	• At every antenatal visit, if capillary blood glucose is ≥ 6.7 mmol/l two hours after 75gm oral glucose challenge • Refer to specialist/higher level facilities
Delivery	Induction of labour is not recommended for women with an uncomplicated pregnancy and gestational age of less than 41 weeks. If gestational diabetes is the only abnormality, but it is well controlled, do not induce labour before 41 weeks of gestation. If suspected fetal macrosomia at term is the only indication, do not induce labour.
Postnatal	After the pregnancy ends, the woman should be re–classified as having either diabetes mellitus, or IGT, or normal glucose tolerance based on the results of a 75 g OGTT six weeks or more after delivery

Appendix 2: Search strategies

Table	2a
Medline	Search terms for economic evaluation of hypertensive disorders during pregnancy
1	Pregnancy, High-Risk/ or Pregnancy Trimester, First/ or Pregnancy/ or Pregnancy Complications/ or Pregnancy Proteins/ or Hypertension, Pregnancy-Induced/ or Pregnancy Trimester, Third/ or Pregnancy Outcome/ or Pregnancy in Diabetics/ or Pregnancy Trimester, Second/
2	exp hypertension, pregnancy-induced/ or pre-eclampsia/
3	(pre-eclampsia or preeclampsia).ab,ti.
4	exp Hypertension/
5	exp Pregnancy/
6	4 and 5
7	hypertension.mp. and pregnancy.ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8	2 or 3
9	1 and 8
10	6 or 7 or 9
11	*economics/
12	exp *"costs and cost analysis"/
13	(economic adj2 model*).mp.
14	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab,kf,kw.
15	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,kf,kw.
16	(life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab,kf,kw.
17	(cost or economic*).ti,kf,kw. and (costs or cost-effectiveness or markov).ab.
18	or/11-17
19	10 and 18

Table	2b
CINAHL	Search terms for economic evaluation of hypertensive disorders during pregnancy
21	s10 and s20
20	s11 or s12 or s13 or s14 or s15 or s16 or s19
19	s17 and s18
18	AB costs or cost-effectiveness or markov
17	TI (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR MW (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR SU (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s)
16	AB (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR MW (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR SU (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s)
15	TI (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs) OR MW (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs) OR SU (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs)
14	TI (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s) OR AB (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s) OR MW (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or econ ...
13	economic N2 model*
12	(MH "Costs and Cost Analysis+")
11	(MM "Economics")
10	s6 or s7 or s9
9	s1 and s8
8	s2 OR s3
7	s4 AND s5
6	TI (hypertension AND pregnancy) OR AB (hypertension AND pregnancy)
5	(MH "Pregnancy+")
4	(MH "Hypertension+")
3	TI (pre-eclampsia or preeclampsia) OR AB (pre-eclampsia or preeclampsia)
2	(MH "Pre-Eclampsia+") OR (MH "Pregnancy-Induced Hypertension+")

1	(MH "Pregnancy") OR (MH "Pregnancy, High Risk") OR (MH "Pregnancy Trimesters+") OR (MH "Childbirth")

Table	2c
Medline	Search terms for economic evaluation on diabetes mellitus during pregnancy
1	exp diabetes, gestational/ or pregnancy in diabetics/
2	gestational diabetes.mp. or (pregnan* adj2 diabet*).ti,ab. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3	1 or 2
4	Pregnancy, High-Risk/ or Pregnancy Trimester, First/ or Pregnancy/ or Pregnancy Complications/ or Pregnancy Proteins/ or Hypertension, Pregnancy-Induced/ or Pregnancy Trimester, Third/ or Pregnancy Outcome/ or Pregnancy in Diabetics/ or Pregnancy Trimester, Second/
5	*economics/
6	exp *"costs and cost analysis"/
7	(economic adj2 model*).mp.
8	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab,kf,kw.
9	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,kf,kw.
10	(life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab,kf,kw.
11	(cost or economic*).ti,kf,kw. and (costs or cost-effectiveness or markov).ab.
12	or/5-11
13	3 and 4 and 12

Table	2d
CINAHL	Search terms for economic evaluation of hypertensive disorders during pregnancy
21	s10 and s20
20	s11 or s12 or s13 or s14 or s15 or s16 or s19
19	s17 and s18
18	AB costs or cost-effectiveness or markov
17	TI (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR MW (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR SU (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s)
16	AB (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR MW (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR SU (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s)
15	TI (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs) OR MW (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs) OR SU (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs)
14	TI (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s) OR AB (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s) OR MW (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or econ ...
13	economic N2 model*
12	(MH "Costs and Cost Analysis+")
11	(MM "Economics")
10	s6 or s7 or s9
9	s1 and s8
8	s2 OR s3
7	s4 AND s5
6	TI (diabetes AND pregnancy) OR AB (diabetes AND pregnancy)
5	(MH "Pregnancy+")
4	(MH "Diabetes+")
3	(MH "gestational diabetes+")
2	TI ("Gestational diabetes") OR AB ("Gestational diabetes")
1	(MH "Pregnancy") OR (MH "Pregnancy, High Risk") OR (MH "Pregnancy Trimesters+") OR (MH "Childbirth")

Table	2e
Medline	Economic evaluation on antenatal care
23	Pregnancy, High-Risk/ or Pregnancy Trimester, First/ or Pregnancy/ or Pregnancy Complications/ or Pregnancy Proteins/ or Hypertension, Pregnancy-Induced/ or Pregnancy Trimester, Third/ or Pregnancy Outcome/ or Pregnancy in Diabetics/ or Pregnancy Trimester, Second/
24	*economics/
25	exp *"costs and cost analysis"/
26	(economic adj2 model*).mp.
27	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab,kf,kw.
28	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,kf,kw.
29	(life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab,kf,kw.
30	(cost or economic*).ti,kf,kw. and (costs or cost-effectiveness or markov).ab.
31	or/24-30
32	22 and 23 and 31
33	Prenatal Care/ or Pregnancy/
34	antenatal care.mp. or exp Prenatal Care/
35	33 or 34
36	5 and 18 and 35
37	31 and 33 and 34

Table	2f
CINAHL	Economic evaluation on antenatal care
S101	S99 and S100
S100	AB costs or cost-effectiveness or markov
S99	TI (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR MW (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR SU (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s)
S98	AB (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR MW (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s) OR SU (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s)
S96	TI (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s) OR AB (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s) OR MW (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or econ ...
S95	economic N2 model*
S94	(MH "Costs and Cost Analysis+")
S93	S88 and S92
S92	S89 or S90 or S91
S91	TI prenatal care OR AB prenatal care
S90	TI antenatal care OR AB antenatal care
S89	(MH "Prenatal Care")
S88	S87 or S94 or S95 or S96 or S97 or S98 or S101
S87	(MM "Economics")

Appendix 3

Table 1: List of studies focused on screening, diagnosis and treatment of HDP

Sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
1	Duckworth et al (2016) (75)	Identification of women for risk of PE	Decision tree	Healthcare system	Introducing PlGF testing as a diagnostic adjunct	Signs and/or symptoms of suspected pre-eclampsia,	Pregnancy period	1. Test for PlGF level 2. Test outcome 3. PE status 4. Presence/severity of HDP
2	Drost et al (2015) (74)	Costs, QALY, life years	Decision analytic markov model	Healthcare system	Yearly hypertension screening for women with history of PE	Women with history of PE	20 years	Ischemic heart disease, stroke, heart failure, end-stage renal disease, CVD mortality
3	Duhig et al (2019) (76)	Time to PE diagnosis, Maternal adverse event prevented, cost saving	Decision tree	Health care system	PlGF testing alongside a clinical management algorithm	Pregnant women	Postnatal discharge	1. Test 2. PE status and adverse events

Sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
4	Figuera et al (2018) (77)	cost per patient per episode ofcare	Decision tree	Public and private healthcare payer	Introducing the soluble FMS-like tyrosine kinase (sFlt-to placental growth factor (PlGF) ratio test into clinical practice	Pregnant women	Child birth	1. Test results 2. Intensity of management 3. PE/HELLP syndrome status
5	Frusca et al (2017) (303)	High risk PE cases identified and treated, costs each arm, cost saving	Decision tree	Healthcare system	Introducing Elecsys sFlt-1/PlGF ratio test, in addition to standard practice, for the prediction of PE in women with suspected PE in the Italian National Health Service (INHS).	Pregnant women with suspected PE		Level 1: present or do not present risk factors related to PE, Level 2: high intermediate and low, Level 3: develop PE (depending on sensitivity/specificity)
6	Hadker et al (2010) (79)	PE diagnosis	Decision tree	UK healthcare payer	Novel PE diagnostic test (improving diagnostic accuracy then	Pregnant women	Pregnancy	1. PE risk factor assessment re-sults 2. PE diagnosis 3. Test results 4. PE status

Sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
					standard practice)			
7	Hadker N et al (2013) (304)	PE diagnosis	Decision tree	Payer	Novel PE diagnostic test (improving diagnostic accuracy then standard practice)	Pregnant women	Pregnancy	1. PE risk factor assessment results 2. PE diagnosis 3. Test results 4. PE status
8	Hodel et al (2019) (81)	Hospital admission, cost of diagnosis and management of PE	Decision tree	Healthcare system	PIGF based test for PE diagnosis	Pregnant women	Birth	1. Risk assessment 2. Level of follow up 3. Hospitalization status
9	Ortved et al (2019) (86)	Identification of women for risk of PE	Decision tree	Health care system	first-trimester screening program, based on the FMF algorithm, coupled with early use of aspirin	Pregnant women	Till birth	1. 1st trimester screening 2. PE risk assessment 3. PE status 4. PE onset time

Sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
10	McLaren et al (2017) (127)	DALYs, PE screening	Decision tree	Societal	Medical devices for diagnosis of PE	Pregnant women	Birth	1. Test for pre-ecampsia 2. Test outcome (x4) 3. Test for proteinuria 4. Test outcome (x4) 5. Normal recovery, Severe morbidity, Death
11	Simon et al (2006) (89)	Eclampsia reduction	Alongside trial	Payer's	MgSO4	Women with pre-eclampsia	six weeks after birth	Eclampsia and maternal death

Sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
12	Mone et al (2018) (85)	PE prevention, maternal death, perinatal death	Decision tree	Healthcare	Routine aspirin, no preventative testing or treatment offered and;	Pregnant women		1. Test result and screening 2. Vaginal bleeding status 3. PE status 4. Gestational age at birth 5. Perinatal outcome
13	Schlembach et al (2019) (87)	Hospitalization before developing preeclampsia, inpatient length of stay (LOS), the sFlt-1/PlGF test ratio, and diagnosis of preeclampsia, short term prediction of PE	Decision tree	Payer	Evaluated serum sFlt-1/PlGF ratio to detect PE	Pregnant women	Till discharge from hospital	1. Test retults 2. Treatment status 3. PE syndrome status 4. Retest allocation 5. Test results 6. Hospitalization status 7. PE status

Sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
14	Shmueli et al (2012) (88)	PE, mode of delivery, death of offspring, term or preterm delivery	Decision tree	Payer	Universal first-trimester screening for pre-eclampsia using two serum markers – PP13 and PIGF – together with uterine artery Doppler pulsatility index (PI)	Pregnant women	Offspring age 32	1. Screening 2. Test results 3. Intervention allocation 4. PE status 5. Delivery time status 6. Delivery outcome
15	Van Baaren et al (2014) (129)	Life expectancy, QALY, cost	Markov models	Health care	Post-partum screening on cardiovascular risk factors and subsequent treatment	Women with history of term hypertensive disorder	Life time	7 health states

Sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
16	Vatish et al (2016) (305)	Accuracy in the short-term prediction of pre-eclampsia, cost, duration of hospital stay, hospital admission	Decision tree	Health service payer	sFlt-1/PlGF test used in addition to current diagnostic procedures	Pregnant women presenting with a clinical suspicion of pre-eclampsia	Birth	1. Hospitalization status 2. Intensity of management 3. PE status

Sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
17	Waugh et al (2017) (92)	Adverse health outcomes for mother and newborns, hospital stay and admission	Decision tree	Health system	SPCR test using various assays, SACR test and urine concentration tests	women aged ≥ 16 years who were at > 20 weeks' gestation	Lifetime	1. Test results 2. Mode of delivery 3. Type of birth 4. Hospitalization status for mother and newborn 5. Death
18	Zakiyah et (2018) (93)	PE screening at early	Decision tree	Healthcare payer	New test for PE screening at	Healthy nulliparous women	Birth	1. Screening 2. Risk level

Sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
		pregnancy, birth outcome			early stage of pregnancy			3. PE status 4. Birth outcome
19	Khowaja (2018) (128)	Maternal and perinatal disabilities and deaths, DALY	Decision tree	Societal	Community engagement, HDP oriented ANC, use of oral antihypertensive therapy or IV based MgSO4	Pregnant women	Life time	1. Pregnancy care level 2. HDP status 3. Emergency transport and treatment 4. Pregnancy outcome 5. Maternal and perinatal outcome
20	Mallampati (2019) (83)	preeclampsia-related costs and number of cases per 100,000 pregnant women	Decision tree	Healthcare system	Aspirin prophalyxis based on study arm	Pregnant women	Delivery	1. Aspirin prophylaxis intake status 2. PE status 3. Birth outcome

Table 2: Studies with interventions relating to induction of labor

	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
1	Callander et al (2019) (102)	Rate of c-section delivery, QALY	Markov micro-simulation	Public health system	Induction of labor at 39 weeks of gestation, caseload midwifery (continuum of care) and chart audit (six monthly review)	Low risk nulliparous women with singleton pregnancy	Pregnancy until discharge	1. Pregnancy 2. Postnatal status of mother and baby 3. Hospital stay status 4. Survival status
2	Hersh et al (2019) (103)	C-section, HDP, stillbirth, neonatal death	Cohort based decision analytic model-decision tree	Societal	Induction of labor at 39 weeks of gestation	Nulliparous term births	Delivery	1. Type of labor 2. Mode of delivery 3. Birth outcome
3	Van Baaren et al (2013) (104)	c-section rate	Decision tree	Healthcare	Foley catheter induction	Pregnant women at term (37 weeks of gestation) scheduled for induction of labour with a vital singleton pregnancy in cephalic presentation, intact		1. Intervention allocation 2. Mode of birth

	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
						membranes and an unfavourable cervix (Bishop score <6)		
4	Vijgen et al (2010) (105)	maternal complications or progression to severe disease, cost	Decision tree!	Societal	labour induction compared with expectant monitoring	Women diagnosed with gestational hypertension or pre-eclampsia between 36+0 and 41+0 weeks of gestation	1 year postpartum	1. Type of labor 2. Mode of delivery 3. Birth outcome

Table 3: Studies covering ANC, safe motherhood and quality of care

sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
1	Goldie et al (2010) (106)	Reduction in pregnancy related mortality, life saved, cost saving	The computer-based Global Maternal Health Policy Model . A microsimulation model	Healthcare system	Package of intervention for reducing maternal death (family planning to safe delivery).	Women of reproductive age	Lifetime	Abortion, antenatal care, complication during labor,maternal and newborn death and complication
2	Henderson et al (2000) (108)	Maternal and fetal health and mortality	Decision tree	Healthcare system	Reduced number of antenatal care visit schedules	Pregnant women	Child birth, discharge	1. Schedule of ANC 2. Ante partum health status 3. Mode of delivery 4. Delivery outcome
3	Hitimana et al (2018) (109)	Perinatal and maternal mortallity, life years saved, cost, EQ-5D	Micro simulation model. Cohort based	Healthcare system	WHO antenatal care recommendations	Pregnant women	not mentioned	1. ANC attendance

sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
4	Goodman et al (2017) (107)	Maternal mortality, case fatality rates from HDP and haemorrhage, stillbirths, DALYs	Decision tree	Healthcare system	Quality improvement interventions in one hospital	Pregnant women	Birth	1. Quality of care intervention status 2. Quality of care and adherence to guideline 3. Maternal and fetal health status
5	Hu et al (2007) (110)	Reduction in pregnancy related mortality, life saved, cost saving	The Maternal Health Policy Model. Microsimulation model	Healthcare system	Package of intervention for reducing maternal death (family planning to safe delivery)	Women of child bearing age	a woman's lifetime	1. Pregnancy status 2. Pregnancy related complications 3. Birth outcome 4. Maternal outcome
6	Zhao et al (2011) (111)	Antenatal care coverage, insitutional delivery rate	Markov state transition	Societal	Safe motherhood interventions	Pregnant women	Lifetime of mother and child	1. ANC and place of delivery 2. Maternal outcome 3. Fetal outcome

Table 4: Studies covering supplements, diet and lifestyle

sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
1	Bailey et al (2020) (131)	gestational diabetes, pre-eclampsia and caesarean section, cost, ICER	Decision tree	Healthcare system	Lifestyle interventions (diet and physical activity)	pregnant women receiving routine antenatal care in secondary and tertiary care hospitals	Early pregnancy and the discharge of mother and infant from hospital after birth	1. Intervention allocation status 2. Complications during pregnancy
2	Madan et al (2012) (115)	Pre-eclampsia, GDM, Macrosomia, C-section, assisted delivery	Decision tree	Healthcare system	Weight management in pregnancy	Pregnant women	life time	1. Pregnancy complication status 2. Mode of delivery 3. Birth outcome 4. Long term health status
3	Rogozinska et al (2017) (116, 182)	Maternal and fetal outcome (miscarriage, death, stillbiirth), cost per case of PE aavoided	Decision tree	Healthcare system	Diet and physical exercise	Pregnant women	Till discharge from hospital	. 1. Diet and physicial activity status 2. Pregnancy complication status

sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
4	Feldhaus et al (2016)	DALYs averted for mothers and newborns, cost of introducing calcium	Decision tree	Program and societal	Calcium supplementation in addition to the existing standard of care (MgSO4)	Pregnant women	Child birth	1. Test result 2. Hospitalization and treatment status 3. Mode of delivery 4. Maternal and newborn outcome
5	Meertern et al (2018) (117)	Pre-eclampsia	Decision tree based simulation	Payer's	Calcium supplementation	Pregnant women	20 weeks to discharge from hospital	Level 1: current care, calcium for all pregnant women, high risk only, low calcium intake, user vs non-user, develop PE

Table 5: Studies covering interventions related to adherence to guidelines and health financing

sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
1	Luitjes et al (2010) (121)	Maternal complications (maternal death, organ specific complications of hypertension, HELLP syndrome, placental abruption). Secondary outcome measures for effectiveness are guidelines' adherence rates, fetal death rates, Caesarean delivery rates, and rates of neonatal mortality and morbidity. QALY and ICER	Decision Tree	Societal	Dutch Society of Obstetrics and Gynaecology (NVOG) guideline implementation strategies including a computerised decision support system	Pregnant women	Birth	1. Guideline adherence 2. Mode of delivery 3. Delivery outcome for mother and newborn

sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
2	Putra et al (2019) (122)	PE incidence	Decision tree		United States Preventive Service Task Force (USPSTF) with Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) hypertension guidelines, USPSTF with ACC/AHA hypertension guidelines, universal aspirin prophylaxis	Pregnant women		1. Aspirin allocation status 2. PE status
3	Alfonso et al (2015) (119)	Deaths averted, DALYs averted and cost per study arm	Decision tree	Societal and medical sector	Voucher scheme	Pregnant women	life time	1. Voucher scheme inclusion staus 2. Place of delivery 3. Type of delivery facility 4. Referral status
4	Gomez et al (2015) (120)	ICER, service delivery cost	Decision tree	Healthcare provider	Kwara State Health Insurance program (KSHI) in rural Nigeria	Pregnant women	Delivery	1. Pregnancy compli-cations 2. Survival status

Table 6: Effectiveness - PE screening, diagnosis and treatment

Author (Year)	Effectiveness of interventions		
	How included in the model	How it was derived	Source of data
Duckworth et al (2016)	Sensitivity, specificity, disease incidence, proportion of diagnosed women through the different measures	Direct observations	Trial
Drost (2015)	RR for each of the health states	Secondary data	
Duhig et al (2019)	Adverse events avoided per 1000 women, proportion of women at each stage	Observation data from PARROT trial	Trial
Figuera et al (2018)	Risk of PE onset; current practice vs current practice and PIGF test	Taken from findings of the PROGNOSIS study	Trial
Frusca (2017)	Risk of PE onset; impact of introducing sFlt-1/PlGF versus standard practice	Taken from findings of the PROGNOSIS study and literature review	
Hadker et al (2010)	Distributional probabilities based on sensitivity and specificity	Published literature and public databases of UK	Trial
Hadker N et al (2013)	Distributional probabilities based on sensitivity and specificity	Public database, expert inputs, test performance from literature	Secondary data
Hodel et al (2019)	Risk of PE onset; impact of introducing sFlt-1/PlGF versus standard practice	Taken from findings of the PROGNOSIS study and literature review	Trial
Ortved et al (2019)	Probability of each health state	Expert opinion	Experts
McLaren et al (2017)	proportions of pregnancy pre eclamptic, tested for PE, survival rate, rate of successful treatment	Other secondary sources	WHO global survey on maternal and perinatal health, Magpie trial etc
Simon et al(2003)	RR extracted from direct observations on PE reduction	Done using direct observation	Primary data

Mone (2018)	RR of death (neonatal, stillbirth), incidence rates for each intervention	Direct observation from other sources	Secondary literature review
Schlembach et al (2019)	Risk of PE onset; current practice vs current practice and PIGF test	Taken from findings of the PROGNOSIS study	
Shmueli (2012)	Base case probabilities and relative risks	Electronic database at the Bnai-Zion Medical Center and the Central Bureau of Statistics' reports for2005to2008	Secondary data
Van Baaren et al (2013)	Odds ratios	Observations	Primary data
Vatish et al (2016)	Proportion of women in each health state	Direct observation from PrOGNISIS study	Trial
Zakiyah et (2018)	Probability of PE among the risk groups, RR with aspirin for base case and intervention	Derived from IMPROvED data	Trial

Table 7: Intervention effectiveness- Induction of Labor

Author (Year)	Effectiveness of interventions		
	How included in the model	How it was derived	Source of data
Callander et al (2019)	Proportion of women needing induction, C-section, special care nursery, neonatal intensive care unit	Direct observation	Trial
Hersh et al (2019)	Used probabilities for each health states	From existing large cohort based studies	Secondary
Van Baaren et al (2013)	RR for c-section	Direct observation	Primary
Vijgen et al (2010)	RR for base case and interventions	Direct observation	Primary

Table 8: Effectiveness- ANC, safe motherhood and quality of care

Author (Year)	Effectiveness of interventions		
	How included in the model	How it was derived	Source of data
Goldie (2010)	Probability of each health state	Published literature	Secondary data
Goodman et al (2017)	Observed number of complications, death etc	Direct observation	Primary data
Henderson et al (2000)	OR for the various health states	Direct observation from trial	Primary data
Hitimana et al (2018)	Proportions	Direct observation, secondary data, Expert elicitation	Primary data
Hu et al et al (2007)	Probability of each health state	Secondary data, some regional data	Secondary data
Jingzhou et al (2011)	Age specific probability of dying, improvement in maternal, newborn and infant mortality rate	Directly observed data	Primary data

Table 9: Intervention effectiveness- Supplements, diet and lifestyle

-Author (Year)	Effectiveness of interventions		
	How included in the model	How it was derived	Source of data
Bailey et al (2020)	GDM, HDP, GDM and HDP and c-section risk ratios	Direct observation	Primary data
Madan et al (2012)	Increase in risk of PE, c-section, macrosomia due to weight gain, absolute rate of events in pregnancy/labor	Estimated using previous observational studies	Primary data
Rogozinska et al (2017)	Absolute Risk of PE, GDM, second trimester miscarriage, maternal death, LGA/SGA for women with PE for base case and deterministic analysis. RR for interventions	Meta analysis	Secondary analysis
Feldhaus et al (2016)	Baseline risk for current care and relative risk for each intervention	Peer-reviewed literature, Nepal Demographic and Health Survey 2011, the Nepal Maternal Mortality and Morbidity Study 2008/2009, and primary data collected by Jhpiego on the calcium supplementation program	Exisitng evidence and pilot findings
Meertern et al (2017)	Relative risks of events	Secondary literature	Cochrane reviews

Table 10: Intervention effectiveness- adherence to guidelines and health financing

-Author (Year)	Effectiveness of interventions		
	How included in the model	How it was derived	Source of data
Luitjes (2010)	NA	Direct observations	
Putra (2019)	Absolute and relative risk	Risk at current care and relative risk after intervention	Secondary data
Alfonso et al (2015)	Institutional delivery coverage, Maternal lives saved	Direct observations, Using the Lives saved tools	Observation
Gomes et al (2025)	RR for the health states for current scenario vs insurance programme	Direct obseervation	

Table 11: Intervention related to screening and diagnosis of GDM

Sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
1	Chen et al (2016) (132)	Cost and QALY	Decision tree	Payer's perspective	Screening for diabetes	Pregnant women	Delivery	1. Screening status 2. Test results 3. Primary outcome status
2	Coop et al (2015) (133)	Screening and treatment cost of GDM	Decision tree	Health system	Two step screening test	Pregnant women	9 months	1. GDM screening status 2. Screening results 3. Final outcomes
3	Culligan et al (2005) (306)	Number of brachial plexus injuries or cases of incontinence averted, incremental monetary cost per 100,000 deliveries, expected quality of life of the mother and her child, and QALY	Decision tree	Societal	Ultra sound at 39 weeks followed by c-section	Pregnant women (primigravidas)	Lifetime	1. Treatment status 2. Test results 3. Ultrasound result 4. Mode of delivery 5. Clinical outcomes
4	Danyliv et al (2016) (135)	Cost and QALY	Decision tree	Health care	Alternative screening strategy for GDM	Pregnant women	Lifetime	1. Screening status 2. Test results 3. Treatment status 4. Hypertension status 5. Delivery mode 6. Newborn delivery outcome 7. Gestation age status at birth 8. Newborn treatment status

Sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
5	Farrar et al (2016) (136)	GDM screened, cost	Decision tree	Healthcare system	Screening for diabetes	Pregnant women	Delivery	1. Screening status 2. Screening outcome 3. Diagnostic test status 5. Test outcome 6. Treatment status
6	Jacklin et al (2017) (137)	Cost and QALY, shoulder dystocia, c-section, NICU admission, jaundice therapy, PE, induction of labor	Decision tree	Health system	Screening for GDM using WHO	women of gestational age 24–28 weeks without pre-existing diabetes		1. GDM screening threshold 2. OGTT level and complication status 3. GDM status 4. Treatment/complication status 5. Complication status 6. Maternal or newborn health status
7	Marseille et al (2013) (138)	Cost, DALY	Decision tree	Health care	GDM screening	Women with GDM	Postpartum period	1. Initial screening 2. Test results 3. Postpartum tests 4. Health of mother and newborn
8	Mission et al (2012) (139)	Cost, QALY, maternal death, neonatal death, stillbirth	Decision tree	Societal perspective	Glucose tolerance test	Pregnant women	Delivery	1. Screening status 2. Screening outcome 3. Treatment status 5. PE status 6. Macrosomia status 7. Mode of delivery 8. Maternal survival status 9. Maternal and newborn health status

Sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
9	Nicholson et al (2005) (307)	Maternal and neonatal mortality and morbidity, test effectiveness, GDM, QALY, costs	Markov state transition	Societal perspective	GDM screening	Pregnant women (age 30)	24-28 weeks to postpartum	Three maternal health states: perfect health, perfect health following hysterec- tomy, and maternal death. There were three neonatal health states: none/mild morbidity, moderate morbidity, and severe rbidity/neonatal death .
10	Odibo et al (2006) (141)	Cost, fetal outcome	Decision tree	Societal	GDM screening	Diabetic pregnant women	NA	1. Screening type 2. Fetal condition
11	Poncet et al (2002) (142)	Macrosomia, prematuriry, perinatal mortality, hypertensive disorder	Decision tree	Health system	GDM screening with different levels of Oral glucose tolerance test	Pregnant women	Birth	1. GDM screening 2. Test results 3. Success rates of therapy

Sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
12	Round et al (2011) (143)	Cost, QALY	Decision tree	Health system	Different screening strategies for GDM	Pregnant women	Lifetime	1. GDM screening status 2. Screening results 3. Diet status 4. Hypoglycemia Status 5. Hospitalization status 6. Perinatal complication status
13	Wastlund et al (2019) (308)	Delivery mode, macrosomia	Decision tree		Universal ultrasound in the third trimester	Pregnant women	Long term	1. Screening strategy 2. Test results 3. Management strategies 4. Delivery outcome
14	Singweratham et al (2015) (144)	GDM screening, cost		Healthcare system	GDM screening	Pregnant women	1 year and lifetime	1. GDM/risk factor status, 2. Test results
15	Werner et al (2012) (147)	Maternal morbidity and mortality, c-section, preterm birth	Decision tree	Health care system	Screening strategies	Pregnant women	Lifetime	1. Screening status 2. Maternal morbidity 3. Mode of delivery 5. Delivery outcome
16	Sosa-Rubi et al (2019) (145)	GDM screened, treatment cost	Decision tree	Health care system	None	Pregnant women	Birth	1. GDM screening 2. Complication status 3. Mode of delivery

Table 12: Intervention related to Treatment of GDM

Sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
1	Goetzl (2002) (157)	GDM treatment, cost	Decision tree	Healthcare system	GDM treatment	Pregnant women with GDM	Delivery	Level 1. Treatment status, level 2. Health status after treatment (control of glucose), level 3. Development of hypoglycaemia, level 4. Hospitalization status
2	Murphy (2019) (162)	Cost, pregnancy and neonatal complications, hospital stay, NICU admission	Decision tree	Healthcare system	GDM screening	Pregnant women with GDM	10 weeks - postnatal	Level 1. Treatment allocation, Level 2. Delivery Complication status, level 3: pre-ecalmpsia, NICU admission, Postnatal ward
3	Ohno et al (2011) (158)	QALY, maternal and neonatal mortality and morbidity, cost	Decision tree	Societal	Mild GDM treatment	Women with mild GDM	Lifetime of women	Level 1. Treatment status, level 2. Pre-eclampsia status, level 3. Macrosomia status Level 4. Mode of delivery, level 5. Maternal survival status Level 6. Neonatal survival, neonatal morbidity
4	Todorova et al (2006) (159)	PE, Infections, thrombisis, macrosomia	Decision tree	Healthcare system	Screening strategies	Pregnant women	Lifetime of women	1. Diet/ insulin, level 2. Hypertensive disorder, infection, macrosomia

Table 13: Intervention related to diet and lifestyle

Sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
1	Broekhuizen et al (2018) (150)	Gestational weight gain, fasting glucose, insulin resistance (HOMA-IR), quality adjusted life years (QALYs), and societal costs	Decision tree	Societal and healthcare perspective	Healthy eating and/or physical activity	Pregnant women attending a clinic or hospital	Delivery	1. Intervention type 2. Intervention outcomes
2	Cavassini et al (2012) (151)	Cost	Decision tree	Healthcare system	2300- calorie diabetic diet	Pregnant women	Delivery	1. Final average cost 2. Treatment results
3	Kolu et al (2016) (309)	T2DM, QALY, BMI, physical activity	Decision tree	Societal perspective	Lifestyle counselling during pregnancy	Pregnant women	12 months	1. Intervention type 2. Intervention outcomes
4	Kolu et al (2013) (310)	Birth weight, QALY	Decision tree	Societal perspective	Lifestyle counselling on GDM during pregnancy	Pregnant women	Delivery	1. Intervention type 2. Intervention outcomes
5	Moss et al (2007) (154)	Adverse neonatal outcome, induction of labor, c-section birth	decision tree	Health system	Dietary advice, blood glucose monitoring and insulin therapy	Women with mild GDM	None	1. Antenatal service status 2. Delivery mode 3. Neonatal health status
6	Oostdam et al (2012) (311)	Maternal fasting blood glucose, insulin sensitivity, birth weight	Markov state transition	Societal	Exercise programme twice a week	Pregnant women at increased risk of GDM	NA	Not clear

Sl	Author (Year)	Outcomes	Study design	Perspective	Interventions	Population	Time horizon	Health events and health states each model used
7	Xu et al (2017) (156)	Maternal and fetal outcome, complications, mode of delivery	Decision tree	Health system	Lifestyle change	Women giving birth in China in 2015	28 weeks GA- birth	1. GDM diagnosis status 2. Treatment status 3. Maternal complication status 4. Delivery mode 5. Newborn complication status 6. Newborn complications and outcome

Table 14: Other interventions for GDM

Sl	Author (Year)	Outcomes	Study design	Interventions	Population	Time horizon	Health events and health states each model used
1	Meregaglia et al (2018) (163)	GDM, newborn death, macrosomia	Decision tree	None	Women with GDM	Last 3 months of pregnancy	Not clear
2	Niu et al (2014) (160)	Mode of delivery	Decision tree	Induction of labor between 39-41 weeks	Pregnant women with A1 GDM	Birth	1. Labor management 2. Mode of delivery/ fetal condition 3. Maternal survival 4. Macrosomia status 5. Shoulder dystocia status 7. Infant survival status 8. Neonatal outcome
3	Wijnkoop et al (2015) (164)	Macrosomia, complications for mother and newborn	Decision tree followed by markov state transition model	None	Women of childbearing age who are overweight or obese prior to pregnancy	Long term	1. GDM/overweight status 2. consequence on mother and child 3. complications for mother and child **For Markov states:** GDM, obesity, complications to mother and child
4	Peterson et al (2015) (312)	Preterm birth, birth defects, perinatal mortality	Decision tree	Societal perspective	Preconception care	Women of reproductive afe	Level 1. GDM/overweight status Level 2. consequence on mother and child (pre-eclampsia, hypertension, stillbirth, death) , Level 3. complications for mother and child For Markov states: GDM, obesity, complications to mother and child

Table 15: Effectiveness of economic evaluation models related to GDM

Sl	Author (Year)	Effectiveness of interventions		
		How included in the model	How it was derived	Source of data
1	Broekhuizen et al (2018)	Relative risks and average interventions costs	Direct observation	Primary data analysis
2	Cavassini et al (2012)	Absolute difference in rate compared to usual care	Direct observation	DALI trial
3	Chen et al (2016)	Probabilities and rates	Direct observation and literature review	Primary and secondary data analysis
4	Coop et al (2015)	Cost difference		
5	Culligan et al (2004)	Probability	Estimated from existing database	(Growing Up in Singapore Towards healthy Outcomes) GUTSO database
6	Danyliv et al (2015)	Probabilities	Estimated from existing database	National Women's Annual Clinical Reports.
7	Farrar et al (2016)	Probabilities	Systematic reviews	Medline
8	Goetzl et al (2002)	Proportions	Secondary literature and trial outputs	Secondary data sources
9	Herbst et al (2005)	Absolute risk at baseline vs RR for intervention	Systematic reviews	
10	Jacklin et al (2017)	Probability of events	Published literature	
11	Kolu et al (2016)	Probabilities	Published literature	
12	Kolu et al (2013)	Baseline absolute risk and RR for treatment effect	Existing database	HAPO study, Norwich, Atlantic diabetes in pregnanct
13	Marseille et al (2013)	Probabilities	Trial data	
14	Meregaglia et al (2018)	Probabilities	Trial data	

Sl	Author (Year)	Effectiveness of interventions		
		How included in the model	How it was derived	Source of data
15	Mission et al (2012)	Probabilities	HAPO study	Observation
16	Moss et al (2007)	Probabilities	Secondary data	
17	Murphy et al (2019)	Rates	Secondary analysis	UK pregnancy and diabetes audit, CONCEPT study and NICE
18	Nicholson et al (2005)	Proabilities	Secondary analysis	Literature
19	Niu et al (2014)	Probabilities	Published literature	
20	Odibo et al (2006)	Probabilities	Published literature, existing databse	HAPO study
21	Ohno et al (2011)	Absolute risk for base case and RR for intervention	Direct observation	ACHOIS trial
22	Oostdam et al (2012)	Proportions	Secondary data	
23	Peterson et al (2015)	Probabilities	Secondary datasets	
24	Poncet et al (2002)	Probabilities	Secondary datasets/literature	
25	Round et al (2010)	Probabilities, baseline absolute risk and relative risk for treatment	Direct observation from RCT	
26	Sosa-Rubi et al (2019)	Absolute baseline risk vs relative risks of treatment	Direct observation from RCT	
27	Todorova et al (2006)	RR for women with intervention	Published literature	
28	Wastlund et al (2019)	Probabilities	Published literature	Medline

Sl	Author (Year)	Effectiveness of interventions		
		How included in the model	How it was derived	Source of data
20	Werner et al (2012)	Absolute Risk of PE, GDM, second trimester miscarriage, maternal death, LGA/SGA for women with PE for base case and deterministic analysis. RR for interventions	Meta analysis	
30	Xu et al (2017)	Probabilities	Published literature	ACHOIS and London et al
31	Wijnkoop et al (2015)	Probabilities and RR	published literature	

Table 16: Interventions related to antenatal care

Sl	Author (Year)	Outcomes	Study design	Interventions	Population	Time horizon	Health events and health states each model used
1	Dalaba 2015 (313)	Number of complications during ANC or labor	Before-after	Clinical decision support system	Pregnant women	12 months	1. Diagnosis during ANC consultation and labor 2. Referral
2	Bowser 2018 (314)	Maternal, neonatal mortality and stillbirths	Matched case-control study	m-health initiative	Pregnant women	3 years	1. Intervention coverage 2. Change in mortality
3	Kashi 2019 (315)	DALY, icer, anaemia, preterm birth, LBW, stillbirth, maternal and neonatal death, infant mortality	Decision tree	Multiple Micronutrient supplements	Pregnant women	1 year-lifecourse	1. Intervention 2. Intervention outcomes
4	Kingkaew 2016 (316)	LBW, mortality	Decision tree	Maternal and child health voucher scheme	Pregnant women aged 25-29	Birth	1. Intervention 2. Risk status 3. ANC status 4. Delivery provider status 5. Birth outcome
5	Manzi 2019 (317)	Antenatal care visit with danger sign and vital sign assessment	Pre-post	Mentorship and quality improvement for ANC	pregnant women	12 months	1. Intervention status 2. ANC attendance

Sl	Author (Year)	Outcomes	Study design	Interventions	Population	Time horizon	Health events and health states each model used
6	Prinja 2016 (318)	ANC check-ups and institutional deliveries	Decision tree	m-health application to improve counselling services	Pregnant women	Birth-1 year	Birth cohort: 1. Intervention status 2. neonatal health status 3. Care-seeking status 4. Newborn and infant health status Pregnant women cohort 1. Intervention status 2. ANC status 3. Complication status 4. Careseeking status 5. Final outcome
7	Salihu 2014 (319)	Maternal and newborn morbidity and mortality	Decision tree	Paternal involvement during pregnancy	Singleton infants	1 year age of infant	1. father involvement status 2. Mode of delivery 3. Delivery outcome status 4. Morbidity status 5. Mortality status
8	Svefors 2018 (320)	Under-5 mortality and stunting, DALYs	Decision tree	Early prenatal food and micronutrient supplements	Pregnant women and infants	Lifetime	1. Intervention status 2. Birth outcome 3. Mortality and stunting
9	Saronga 2017 (321)	Quality of ANC and childbirth care	Pre-post	Clinical decision support system	Women undergoing antenatal consultation, women undergoing childbirth, newborns	Birth	

Sl	Author (Year)	Outcomes	Study design	Interventions	Population	Time horizon	Health events and health states each model used
10	Memiere 2019 (243)	MNH interventions	LiST based model	Package of intervention	Pregnant women	Childbirth	Intervention coverage, mortality

Table 17: Effectiveness of antenatal care interventions

		Effectiveness of interventions			
Sl	Author (Year)	How included in the model	How it was derived	Source of data	Perspective
1	Dalaba 2015	Number of complications detected during ANC consultations per 1,000 ANC consultations	Direct observation	Primary data	Health care
2	Bowser 2018	Coverage data in Lives Saved Tools	Direct observation	Primary data	Health care
3	Kashi 2019	Meta analysis	Published literature	Secondary data	Health care
4	Kingkaew 2016	Baseline probabilities, RR for output and outcomes	National statistics and published literature	Primary data	Societal
5	Manzi 2019	Probability of ANC visits	Direct observation	Primary data	Health care
6	Prinja 2016	Change in coverage	Direct observation	Primary data	Societal
7	Salihu 2014	Probabilities	Direct observation	Primary data	Third party payer
8	Svefors 2018	DALYs between intervention and comparison	Direct observation	Primary data	Health care
9	Saronga 2017	Quality indicator scores	Direct observation	Primary data	Health care
10	Memiere 2018	Relative risks	Published literature	Secondary data	Health system

Appendix 4

Appendix 4.1: List of interventions extracted from document review

Stage of pregnancy continuum of care	**Intervention**	**Source**	**Evidence base**
Community level interventions to improve communication and support	Community mobilization to increase ANC visits covering the following:	WHO recommendation on positive antenatal care National ANC guideline Bangladesh	Cochrane review and review of literature included in WHO recommendations
	Maternal health education		
	ANC attendance		
	Danger signs and care-seeking		
	Informing husbands or partners		
	Establish community-based emergency fund to arrange local vehicles		
	Home-based screening for identifying high-risk women		
	Train traditional birth attendants to recognise emergencies and refer		
	Pregnancy registration		
ANC contacts and components	Scheduled ANCs: 1 in <12 weeks, then 20,26,30,34,36, 38, 40 weeks of gestation		WHO recommendations on positive pregnancy experience, FANC WHO 2016, cochrane reviews, ANC card Bangladesh, WHO framework for quality of antenatal care, FIGO infograph, WHO guideline for diagnosis gestational diabetes
	Early-uptake ANC (first ANC <12 weeks of gestation)		
	History of women for assessment of risk of HDP or DMP *- LMP and EDD Calculation* *- Past obstetric history (if any)* *- Family history*		

	- Medical history *- History of TT immunization* *- Ask about risk factors and refer women needing additional ANC*		
	Physical examination to identify women at risk of HTN or GDM: *Blood Pressure, pulse,* *weight, height,BMI* *- Anaemia, jaundice,* *oedema*		
	Investigation to diagnose presence of HDP or DMP *- urine R/M/E (ASB, protein, glucose)* *- USG to exclude congenital anomalies and multiple pregnancy* *- 2 hrs after 75gm glucose*		
	Iron, calcium, folic acid supplementation		
	Importance of routine check up		
	Counselling on pregnancy, delivery and postpartum danger signs		
	Birth planning and emergency preparedness		
	Women held case notes during pregnancy		
	Monitor blood pressure weekly		
Treatment/management of hypertension	Counsel women and family about danger signs indicating pre-eclampsia/eclampsia	Maternal health strategy SOP	WHO recommendation for management of PE/E, WHO recommenda-

			tion drug treatment for severe hypertension during pregnancy, systematic review
	If diastolic pressure over 90, refer to higher-level facility for treatment		
	Otherwise proceed towards term		
	If diastolic pressure over 95, start antihypertensive tablet; labetalol as first line of drug/nifedipine/methyldopa		
Treatment/management of mild pre-eclampsia	Low-dose aspirin (75mg) to begin as early as 12 weeks for women at high risk of pre-eclampsia		
	Gestational age <37 weeks • If condition is stable, follow up twice a week • Monitor blood pressure, urine, reflexes and foetal conditions • Counsel family about danger signs indicating pre-eclampsia/eclampsia • Encourage additional rest • Encourage women to have normal diet (no restriction in salt intake) • If DBP 90+ and proteinurea 2+ refer to secondary or tertiary level facility for further management		
	Gestational age >37 weeks • *Conduct rapid assessment of vital signs* • If DBP 90+ and proteinurea 2+ refer to secondary or tertiary-level facility for further management		

Management of severe PE/E	Rapid assessment of vital signs		
	Give MgSO4 loading dose of 10 mg and refer to higher-level facility		
	After loading dose refer to higher-level facilities		
Management during convulsion	Gather equipment		
	Start MgSO4 after convulsion		
	Start oxygen during convulsion		
Treatment/management of diabetes	Recommended ANC schedule for diabetic mothers: >12, 16, 20, 25, 28, 32,34,36,38,39-41 weeks	Diabetes mellitus and pregnancy, consensus committee recommendation (Bangladesh, 2013)	
	Referral to higher-level facilities for women with diabetes or risk factors for diabetes		
	Dietary supplement of folic acid		
	Women under oral drug treatment to switch to insulin		
Birth	Induction of labour is recommended for women with severe pre-eclampsia at a gestational age when the foetus is not viable or unlikely to achieve viability within one or two weeks.	WHO recommendation on management of pre-eclampsia and eclampsia	Cochrane database systematic reviews (available in WHO recommendations), systematic review findings (chapter 3)
	In women with severe pre-eclampsia, a viable foetus and before 34 weeks of gestation, a policy of expectant management is recommended, provided that uncontrolled maternal hypertension, increasing maternal organ dysfunction or foetal distress are absent and can be monitored.		

	In women with severe pre-eclampsia, a viable foetus and between 34 and 36 (plus 6 days) weeks of gestation, a policy of expectant management may be recommended, provided that uncontrolled maternal hypertension, increasing maternal organ dysfunction or foetal distress are absent and can be monitored.		
	In women with severe pre-eclampsia at term, early delivery is recommended.		
	In women with mild pre-eclampsia or mild gestational hypertension at term, induction of labour is recommended.		
	Among diabetic women, induction of labour only for babies weighing over 4500 gm		
	Improve coverage of skilled birth attendant		
	Ensure 24/7 availability of basic and comprehensive emergency obstetric care		
Post partum	In women treated with antihypertensive drugs antenatally, continued antihypertensive treatment postpartum is recommended.	WHO recommendation on management of pre-eclampsia and eclampsia	Cochrane database systematic reviews (MgSO4)
	Treatment with antihypertensive drugs is recommended for severe postpartum hypertension.		
	After delivery, one fasting and one 2-hour after-meal glucose test should be done for women with GDM		
	Women with GDM to be tested for type 2 diabetes 6-12 weeks after delivery		

Appendix 4.2: Stakeholder consultation protocol

Date: 24/11/2020

To: Shafiqul Alam Sarker, MD, PhD
Chairperson
Research Review Committee

From: Tazeen Tahsina
Associate Scientist
Maternal and Child Health Division

Through: Shams El Arifeen
Senior Director and Senior Scientist
Maternal and Child Health Division

Subject: Request to review PhD protocol

I am pleased to submit PR20123 titled "Stakeholder consultation for developing an economic evaluation model for hypertensive disorder and diabetes during pregnancy" to the Research Review Committee.

The proposed research is a part of my PhD thesis on developing an economic evaluation model for scaling up effective intervention addressing hypertensive disorder and diabetes during pregnancy in Bangladesh. As part of the thesis, I would like to conduct a number of stakeholder consultations in Bangladesh in order to understand current practice and identify priority areas to be considered within the model. I am undertaking the PhD study at the Health Economic and Decision Science Programme, School of Health and Related Research, University of Sheffield. The PhD is funded by the Wellcome Trust Doctoral Training Programme and all research expenses will be paid by the programme.

All relevant documents are attached herewith:

1. RRC protocol
2. Consent forms and guidelines
3. Ethics certificates

icddr,b	RRC APPLICATION FORM

RESEARCH PROTOCOL **Number: PR-20123** **Version No. 1.00** **Version date: 23-11-2020**	**FOR OFFICE USE ONLY**			
	RRC Approval:	☐ Yes	☐ No	Date:
	ERC Approval:	☐ Yes	☐ No	Date:
	AEEC Approval:	☐ Yes	☐ No	Date:
	External IRB Approval	☐ Yes	☐ No	Date:
	Name of External IRB: _____			

Protocol Title:* (maximum 250 characters including space**)** Stakeholder consultation for developing an economic evaluation model for hypertensive disorder and diabetes during pregnancy

Short Title: (maximum **100** characters including space) Stakeholder consultation for an economic evaluation model

Key Words:* Stakeholder, hypertension, diabetes

Name of the Research Division Hosting the Protocol:*

☐ Health Systems and Population Studies Division (HSPSD)	☒ Maternal and Child Health Division (MCHD)
☐ Nutrition and Clinical Services Division (NCSD)	☐ Laboratory Sciences and Services Division (LSSD)
☐ Infectious Diseases Division (IDD)	☐ Other (specify) _____

Has the Protocol been Derived from an Activity:* ☒ No ☐ Yes (please provide following information):

Activity No. :

Activity Title:

PI:

Grant No.: Budget Code: Start Date: End Date:

icddr,b Strategic Priority/ Initiative (SP 2015-8):* (check all that apply**)**

☒ Reducing maternal and neonatal mortality ☐ Controlling enteric and respiratory infections ☐ Preventing and treating maternal and childhood malnutrition ☐ Detecting and controlling emerging and re-emerging infections	☐ Achieving universal health coverage ☐ Examining the health consequences of climate change ☐ Preventing and treating non-communicable diseases ☐ Others (specify) _____
Research Phase (4 Ds):* (check all that apply**)** ☐ Discovery ☐ Development	☐ Delivery ☒ Evaluation of Delivery
Anticipated Impact of Research:* (check all that apply and please provide details below**)** ☒ Knowledge Production ☒ Capacity Building	☒ Informing Policy ☒ Health and Health Sector Benefits ☒ Economic Benefits
Please provie details here:	

Which of the Sustainable Development Goal This Protocol Relates to?:* (check all that apply**)**

- ☐ 1. End poverty in all its forms everywhere
- ☐ 2. End hunger, achieve food security and improved nutrition and promote sustainable agriculture
- ☒ 3. Ensure healthy lives and promote well-being for all at all ages
- ☐ 4. Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all
- ☐ 5. Achieve gender equality and empower all women and girls
- ☐ 6. Ensure availability and sustainable management of water and sanitation for all
- ☐ 7. Ensure access to affordable, reliable, sustainable and modern energy for all
- ☐ 8. Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all
- ☐ 9. Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation
- ☐ 10. Reduce inequality within and among countries
- ☐ 11. Make cities and human settlements inclusive, safe, resilient and sustainable
- ☐ 12. Ensure sustainable consumption and production patterns
- ☐ 13. Take urgent action to combat climate change and its impacts
- ☐ 14. Conserve and sustainably use the oceans, seas and marine resources for sustainable development
- ☐ 15. Protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss
- ☐ 16. Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels
- ☐ 17. Strengthen the means of implementation and revitalize the global partnership for sustainable development

Does this Protocol Use the Gender Framework:* (Please visit: http://shetu.icddrb.org/index.php?option=com_content&view=article&id=265&Itemid=677 for Gender Alanysis Tool with instructions)	☐ Yes (please complete Gender Analysis Tool) ☒ No

If 'no' is the response, its reason(s) in brief: The protocol is focus on stakeholder consultations for a modelling exercise. Data for the model will be accessed through secondary sources. The population only involves pregnancy women and all children. No interventions will be given for the study.

Will this Research Specifically Benefit the Disadvantaged (economically, socially and/or otherwise**):**	☒ Yes ☐ No
Does this Protocol use Behaviour Change Communication:	☐ Yes ☒ No

Principal Investigator (Should be icddr,b staff):* Sex ☒ Female ☐ Male **Tazeen Tahsina** (Position, phone no, extension no, cell, and email address**):** Associate Scientist +8801747219821 tazeen@icddrb.org Do you have ethics certification? ☐ No ☒ Yes (please attach in your CV below) Do you have RBM training certification? ☒ No ☐ Yes (please attach the certificate with CV below)	Primary Scientific Division of the PI

Co-Principal Investigator(s) Internal: Sex ☐ Female ☐ Male (Position, phone no, extension no, cell, and email address **):** Signature or written consent of Co-PI: _____ (electronic signature or email or any sort of written consent) [if more than one, please copy and paste this row for additional Co-PIs] Do you have ethics certification? ☐ No ☐ Yes (please attach in your CV below) Do you have RBM training certification? ☐ No ☐ Yes (please attach the certificate with CV below)	Primary Scientific Division/ Programme of the Co-PI _____ _____ Approval of the Respective Senior Director/ Programme Head (Signature)
Co-Principal Investigator(s) - External: Sex ☐ Female ☐ Male Address (provide full official address, including land phone no(s), extension no. (if any), cell phone number, and email address). Signature or written consent of Co-PI: _____ (electronic signature or email or any sort of written consent) [if more than one, please copy and paste this row for additional Co-PIs]	

Co-Investigator(s) - Internal: Sex ☐ Female ☒ Male **Shams El Arifeen** Senior Scientist and Senior Director, MCHD shams@icddrb.org (Position, phone no, extension no, cell, and email address **):** Signature or written consent of Co-I: _____ (electronic signature or email or any sort of written consent) [if more than one, please copy and paste this row for additional Co-Is Do you have ethics certification? ☐ No ☐ Yes (please attach in your CV below) Do you have RBM training certification? ☐ No ☐ Yes (please attach the certificate with CV below)	Primary Scientific Division of the Co-I _____ Approval of the Respective Senior Director/ Programme Head (Signature)
Co-Investigator(s) – External: Sex ☒ Female ☐ Male **Address** (provide full official address, including land phone no(s), extension no. (if any), cell phone number, and email address): Chloe Thomas Research Fellow, Health Economics and Decision Modelling Section, School of Health and Related Research (S University of Sheffield , **Telephone:** +44 (0) 114 222 6125 **Fax:** +44 (0) 114 272 4095 **Email:** c.thomas@sheffield.ac.uk Signature or written consent of Co-I: _____ (electronic signature or email or any sort of written consent) [if more than one, please copy and paste this row for additional Co-Is]	

Co-Investigator(s) – External: Sex ☐ Female ☒ Male

Address (provide full official address, including land phone no(s), extension no. (if any), cell phone number, and email address):

Simon Dixon, Professor of Health Economics, Health Economics and Decision Modelling Section,

School of Health and Related Research (ScHARR), University of Sheffield , **Telephone:** +44 (0) 114 222 6125

Fax: +44 (0) 114 272 4095

Email: s.dixon@sheffield.ac.uk

Signature or written consent of Co-I: _____

(electronic signature or email or any sort of written consent)

[if more than one, please copy and paste this row for additional Co-Is]

Student Investigator(s) - Internal: Sex ☐ Female ☐ Male (Position, phone no, extension no, cell, and email address **):** Signature or written consent of Student Investitor: _____ (electronic signature or email or any sort of written consent) Have ethics certificate? ☐ No ☐ Yes (If Yes, please attach to your CV below)	Students Affiliation _____ Approval of the Respective Senior Director/ Programme Head (Signature)

Student Investigator(s) - External: Sex ☐ Female ☐ Male

Address (provide full official address, including land phone no(s), extension no. (if any), cell phone number, and email address):

Signature or written consent of Student Investitor: _____

(electronic signature or email or any sort of written consent)

Student Investigator(s) - External: Sex ☐ Female ☐ Male Address (provide full official address, including land phone no(s), extension no. (if any), cell phone number, and email address): Signature or written consent of Student Investitor: _____ (electronic signature or email or any sort of written consent)
Collaborating Institute(s): Please provide full official address

Country	
Contact person	
Department (including Division, Centre, Unit)	
Institution (with official address)	
Directorate (in case of GoB i.e. DGHS)	
Ministry (in case of GoB)	

Institution # 1
Institution # 2

Country	
Contact person	
Department (including Division, Centre, Unit)	
Institution (with official address)	
Directorate (in case of GoBi.e. DGHS)	
Ministry (in case of GoB)	

Institution # 3

Country	
Contact person	
Department (including Division, Centre, Unit)	
Institution (with official address)	
Directorate (in case of GoB i.e. DGHS)	
Ministry (in case of GoB)	

Note: If less than or more than three collaborating institutions, please delete or insert blocks as needed.

Contribution by the Members of the Scientific Team:

Members' Name	Contribution							
	Research idea/ concept	Study design	Protocol writing	Respond to external reviewers' comments	Defending at IRB	Developing data collection Tool(s)	Data Collection	Data analysi interpretatio of results
Tazeen Tahsina	☒	☒	☒	☒	☒	☒	☒	☒
Shams El Arifeen	☒	☒	☐	☐	☐	☐	☐	☒
	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐

Study Population: Sex, Age, Special Group and Ethnicity

Research Subject:

- ☒ Human
- ☐ Animal
- ☐ Microorganism
- ☐ Other (specify): _____

Sex:

- ☒ Male
- ☒ Female
- ☐ Transgender

Age:

- ☐ 0 – 4 years
- ☐ 5 – 10 years
- ☐ 11 – 17 years
- ☒ 18 – 64 years
- ☐ 65 +

Special Group:

- ☐ Pregnant Women
- ☐ Fetuses
- ☐ Prisoners
- ☐ Destitutes
- ☒ Service Providers
- ☐ Cognitively Impaired
- ☐ CSW
- ☐ Expatriates
- ☐ Immigrants
- ☐ Refugee
- ☐ Others (specify): _____

Ethnicity:

- ☐ No ethnic selection (Bangladeshi)
- ☐ Bangalee
- ☐ Tribal group
- ☐ Other (specify): _____

NOTE: It is icddr.b's policy to include men, women, children and transgender in its research projects involving participation of humans, unless there is strong justification(s) for their exclusion.

Consent Process: (Check all that apply**)**

- ☒ Written
- ☐ Oral
- ☐ Audio
- ☐ Video
- ☐ None

Language:

- ☐ Bangla
- ☐ English
- ☐ Other (specify: _____

Project/Study Site: (Check all that apply**) NA**

- ☐ Chakaria
- ☐ Bandarban
- ☐ Dhaka Hospital
- ☐ Kamalapur Field Site/HDSS
- ☐ Mirpur (Dhaka)
- ☐ Matlab DSS Area
- ☐ Matlab non-DSS Area
- ☐ Matlab Hospital
- ☐ Mirzapur
- ☐ Bianibazar (Sylhet)
- ☐ Kanaighat (Sylhet)
- ☐ Jakigonj (Sylhet)
- ☐ Other community in Dhaka

  Name: _____
- ☐ Other sites in Bangladesh

  Name: _____
- ☐ Multi-national Study

  Name of the country_____

Project/Study Type: (Check all that apply)

- ☐ Case Control Study
- ☐ Clinical Trial (Hospital/Clinic/Field)*
- ☐ Community-based Trial/Intervention
- ☐ Cross Sectional Survey
- ☐ Family Follow-up Study
- ☐ Longitudinal Study (cohort or follow-up)
- ☐ Meta-analysis
- ☒ Programme Evaluation
- ☐ Programme (Umbrella Project)
- ☐ Prophylactic Trial
- ☐ Record Review
- ☐ Secondary Data Analysis

  Protocol No. of Data Source: _____
- ☐ Surveillance/Monitoring
- ☐ Systematic Review
- ☐ Other (specify): _____

***Note**: International Committee of Medical Journal Editors (ICMJE) defines Clinical Trial as "*Any research project that prospectively assigns human participants to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome*".

PI of the RRC- and ERC-approved Clinical Trials should provide necessary information to IRB Secretariat (Research Administration) for registration and uploading into relevant websites (usually at the https://register.clinicaltrials.gov/). They should also provide relevant information to the IRB Secretariat in the event of amendment/modification after their approval by RRC and ERC.

In case of a multi-country study and if a study is registered elsewhere by the prime recipient or others; it does not need to be re-registered under icddr,b's account; provided evidence of NCT registration number is submitted to the IRB.

Biological Specimen:	
a) Will the biological specimen be stored for future use?	☐ Yes ☐ No ☒ Not applicable
b) If the response is 'yes', how long the specimens will be preserved?	_____ years
c) What types of tests will be carried out with the preserved specimens?	
d) Will the consent be obtained from the study participants for use of the preserved specimen for other initiative(s) unrelated to this study, without their re-consent?	☐ Yes ☐ No ☒ Not applicable
e) Will the specimens be shipped to other country/ countries? If yes, name of institution(s) and country/countries.	☐ Yes ☐ No ☒ Not applicable Name _____
f) If shipped to another country, will the surplus/unused specimen be returned to icddr,b? If the response is 'no', then the surplus/unused specimen must be destroyed.	☐ Yes ☐ No ☒ Not applicable
g) Who will be the custodian of the specimen at icddr,b?	
h) Who will be the custodian of the specimen when shipped outside Bangladesh?	
i) Who will be the owner(s) of the specimens?	
j) Has a MoU been signed with regards to collection, storage, use and ownership of specimen? If the response is 'yes', please attach a copy of the MoU.. If the response is 'no', appropriate justification should be provided for not signing a MoU.	☐ Yes ☐ No ☒ Not applicable

Proposed Sample Size:

Sub-group (Name of subgroup e.g. Men, Women) and Number

Name	Number	Name
(1) Stakeholders	15	(3)
(2)		(4)
		Total sample size

Determination of Risk: Does the Research Involve (Check all that apply**)**

- ☐ Human exposure to radioactive agents?
- ☐ Foetal tissue or abortus?
- ☐ Investigational new device?

  Specify: _____

- ☐ Existing data available from Co-investigator?
- ☐ Human exposure to infectious agents?
- ☐ Investigational new drug?
- ☐ Existing data available via public archives/sources?
- ☐ Pathological or diagnostic clinical specimen only?
- ☐ Observation of public behaviour?
- ☐ New treatment regime?

Will the information be recorded in such a manner that study participants can be identified from the information directly or through identifiers linked to the study participants? Y ☐

Does the research deal with sensitive aspects of the study participants' sexual behaviour, alcohol use or illegal conduct such as drug use? Y ☐

Could information on study participants, if available to people outside of the research team:

a) Place them at risk of criminal or civil liability? Y ☐

b) Damage their financial standing, reputation or employability, or social rejection, or lead to stigma, divorce etc.? Y ☐

Do you consider this research: (check one)

☐ Greater than minimal risk	☒ No more than minimal risk	☐ Only part of the diagnostic test

Note: Minimal Risk: The probability and the magnitude of the anticipated harm or discomfort to participants is not greater than those ordinarily encountered in daily life or during the performance of routine physical, psychological examinations or tests, e.g. the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than when the same is performed for routine management of patients.

Risk Group of Infectious Agent and Use of Recombinant DNA	
a) Will specimens containing infectious agent be collected?	☐ Yes ☐ No ☒ Not applicable

b) Will the study involve amplification by culture of infectious agents?	☐ Yes ☐ No ☒ Not applicable
c) If response to questions (a) and/or (b) is 'yes', to which Risk Group (RG) does the agent(s) belong? (Please visit http://shetu.icddrb.org/index.php?option=com_content&view=article&id=265&Itemid=677 to review list of microorganism by Risk Group)	☐ RG1 ☐ RG2 ☐ RG3 ☐ RG4
d) Does the study involve experiments with recombinant DNA?	☐ Yes ☐ No ☒ Not applicable

Does the study involve any biohazards materials/agents or microorganisms of risk group 2, 3, or 4 (GR2, GR-3 or GR4)?

☐ Yes ☒No

[If the response is 'yes'] I, (print name of the PI) affirm that we will use the standard icddr,b laboratory procedures for biosafety of the hazardous materials/agents or microorganisms in the conduction of the study.

_____

_____

Signature of the Principal Investigator
Date

Dissemination Plan: [please explicitly describe the plans for dissemination, including how the research findings would be shared with stakeholders, identifying them if known, and the mechanism to be used; anticipated type of publication (working papers, internal (institutional) publication, international publications, international conferences/seminars/workshops/ agencies. [Check all that are applicable]

Dissemination type	Response		Description (if the response is a yes)
Seminar for icddr,b scientists/ staff	☐ No	☐ Yes	
Internal publication	☐ No	☐ Yes	
Working paper	☐ No	☐ Yes	
Sharing with GoB (e.g. DGHS/ Ministry, others)	☐ No	☒ Yes	Findings will be shared with stakeholder through workshop communication
Sharing with national NGOs	☐ No	☐ Yes	
Presentation at national workshop/ seminar	☐ No	☐ Yes	
Presentation at international workshop/ conference	☐ No	☐ Yes	
Peer-reviewed publication	☐ No	☒ Yes	Relevant findings will be published in peer reviewed jo
Sharing with international agencies	☐ No	☐ Yes	
Sharing with donors	☐ No	☐ Yes	
Policy brief	☐ No	☐ Yes	
Other			
Other			

Funding:

Is the protocol fully funded?	☒ Yes	☐ No
If the answer is yes, please provide sponsor(s)'s name	1. University of Sheffield	
	2.	
Is the protocol partially funded?	☐ Yes	☐ No
If the answer is yes, please provide sponsor(s)'s name	1.	
	2.	

If fund has not been identified:

Is the proposal being submitted for funding?	☐ Yes	☐ No
If yes, name of the funding agency	1.	
	2.	

Conflict of interest:
Do any of the participating investigators and/or member(s) of their immediate families have an equity rela stockholder) with the sponsor of the project or manufacturer and/or owner of the test product or device to be stu as a consultant to any of the above?

☒ No ☐ Yes (please submit a written statement of disclosure to the Executive Director, icddr,b)

Proposed Budget: NA

Dates of Proposed Period of Support (Day, Month, Year - DD/MM/YY)

Beginning Date :

End Date :

Cost Required for the Budget Period ($)

Years	Direct Cost	Indirect Cost	Total Cost
Year-1			0
Year-2			0
Year-3			0
Year-4			0
Year-5			0
Total	0	0	0

Certification by the Principal Investigator:

I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept the responsibility for the scientific conduct of the project and to provide the required progress reports including updating protocol information in the NAVISION if a grant is awarded as a result of this application.

I also certify that I have read icddr,b Data Policies and understand the PIs' responsibilities related to archival and sharing of research data, and will remain fully compliant to the Policies. (Note: The Data Policies can be found here: http://shetu.icddrb.org/index.php?option=com_content&view=article&id=273&Itemid=685)

_____ 24/11/2020

Signature of PI **Date**

Approval of the Project by the Division Director of the Applicant:

The above-mentioned project has been discussed and reviewed at the Division level.

Shams El Arifeen	_____	24/11/2020
Name of the Division Director	Signature	Date of Approval

Table of Contents

☐ Check here if appendix is included

Project Summary

[The summary, within a word limit of 300, should be stand alone and be fully understandable.]

Principal Investigator: Tazeen Tahsina

Research Protocol Title: Stakeholder consultation for developing an economic evaluation model addressing hypertensive disorder and diabetes during pregnancy in Bangladesh

Proposed start date: January 1, 2021 Estimated end date: April 31, 2021

Background (brief):

a. Burden: Everyday there are 810 maternal deaths globally. Most often these deaths are related to complications during pregnancy or childbirth. While hypertensive disorders during pregnancy are the second leading cause of disability among women, diabetes also remains as a neglected emerging indirect causes of morbidity and mortality. The situation is no different in Bangladesh. Hypertensive disorders are the second leading cause of maternal death and indirect causes are increasingly taking up a larger share among the causes of death.

b. Knowledge gap: Hypertensive disorder and diabetes during pregnancy can lead to long term health consequences causing chronic diseases for a lifetime for both mothers and their babies. Most economic evaluations often limit themselves until childbirth and lifetime consequences are often ignored.

c. Relevance: The interaction between conditions like undernutrition, obesity, diabetes and hypertension remained unrecognized until recently. During the millennium development era maternal and child health programmes were designed primarily focusing on factors that directly affect maternal, neonatal and infant mortality. This resulted a large number of programme taking place especially in low and middle income countries around the areas of access to maternity services and ensuring survival of women and children. The NCD alliance called for including and integrating NCDs into sexual and reproductive health programme. The Global Strategy for Women's, Children's and Adolescent's health reaffirmed the life-course approach with its objectives centering around survive, thrive and transform.

Hypothesis (if any): NA

Objectives:

1. To identify and interview stakeholders on the draft conceptual framework for developing an economic evaluation model and finalise the model parameters.
2. To share the final model framework and share preliminary results with stakeholders and receive feedback

Methods: There will be in-depth interviews/ key informant interviews and workshops for consulting stakeholders on a one to one basis and in group.

Outcome measures/variables: The outcome of the proposed research will be a final conceptual framework and preliminary results of the economic evaluation model.

Description of the Research Project

Hypothesis to be tested:

In a hypothesis testing research proposal, briefly mention the hypothesis to be tested and provide the scientific basis of the hypothesis, critically examining the observations leading to the formulation of the hypothesis.

Does this research proposal involve testing of hypothesis: ☒ No ☐ Yes (describe below)

Specific Objectives:

Describe the specific objectives of the proposed study. State the specific parameters, gender aspects, biological functions, rates, and processes that will be assessed by specific methods.

The overarching objective of this exercise is to conduct stakeholder consultation for developing an economic evaluation model as part of a phd thesis

Specific objectives of the stakeholder consultation task are to:

1. Identify stakeholders to share the draft conceptual framework with
2. Interview stakeholders to identify and snowball for additional stakeholders
3. To conduct in depth interviews and explain the conceptual framework and receive feedback of stakeholders. This will cover:
    a. The problem and sequence of events
    b. Patient flow and care-seeking patterns (to describe hypothesised resource flow)
    c. Determining the model boundary through selection of perspective, interventions, outcomes and timeframe to be taken into account
    d. Costs data to be included (e g: if out of pocket payment is important)
4. To prioritise and identify interventions, outcomes and risk factors to be included in the model
5. To finalise the conceptual framework for the economic evaluation model
6. To develop a prototype of the model based on feedback from stakeholders and share with stakeholders for additional feedback
7. Present and share preliminary results through a workshop for feedback

Background of the Project including Preliminary Observations:

Provide scientific validity of the hypothesis based on background information of the proposed study and discuss previous works on the research topic, including information on sex, gender and diversity (ethnicity, SES) by citing specific references. Critically analyze available knowledge and discuss the questions and gaps in the knowledge that need to be filled to achieve the proposed aims. If there is no sufficient information on the subject, indicate the need to develop new knowledge.

Global situation of maternal health

Maternal health conditions are responsible for almost 12% of deaths among women of reproductive age worldwide (1). Maternal deaths are often called the tip of the iceberg. The base of these mortalities are the morbidities leading to the deaths and are often remain ignored due to lack of data and challenges in measurement (1). Pregnancy and childbirth related complications can lead to long term ill health for women and eventually impacting health of their child and all subsequent births.

Maternal morbidities can lead to serious consequence beyond the outcome for mother and newborn at birth. Estimates show that 15% of all pregnancies are attached to severe complication that requires skilled care (8). Studies suggest that maternal conditions were second largest cause of death among women globally. As far as disability-adjusted life-years (DALYs) is concerned, it was third for DALY lost among 15-44 years old women. Overall, there has been a decline in disabilities by 37.5% between 1990 and 2017. Obstructed labour and uterine rupture has been the primary reason for maternal disability followed by hypertensive disorder and other maternal disorders that includes diabetes (9).

Non-communicable diseases and maternal health

Non-communicable diseases (NCDs) contributed to over 73% of global deaths in 2017 worldwide (10). Around 65% of deaths among women occur due to NCDs and most of these are in low and middle income countries (10, 11). A high level United Nations meeting in 2011 recognised “maternal and child health is inextricably linked with non-communicable diseases and their risk factors”(12). Women with conditions like diabetes, anemia, cancer, obesity, hypertensive pregnancy disorders are at a higher risk of developing childbirth-related complications. These conditions often lead to adverse effects around childbirth such as preterm birth, maternal deaths, stillbirths and newborn deaths (12).

The Bangladesh context

According to the Bangladesh Maternal Mortality Survey 2001 and 2010 (19, 20), maternal mortality ratio (MMR) declined from 320 to 194 per 100,000 live births (21, 22). However, the 2016 survey revealed that the MMR has stalled since 2010 (21). The 4th health, population and nutrition sector programme has set a target of 105 per 100,000 live births in 2022 while the SDG target is set at 70 per 100,000 live births. The Government of Bangladesh has developed the Maternal Health Strategy 2015-2025 that is not only aligned with global commitments and initiatives but also emphasizes the need to strengthen important health system issues through multi-sectoral engagement and collaboration (10). However, all these interventions focus on the direct obstetric care while in Bangladesh around 24% is of death due to other indirect causes. 18% of maternal deaths were due or related to NCDs while other causes were risk factors for future development of chronic conditions (20). Investing in proven interventions to mitigate conditions such as pregnancy induced hypertension and diabetes may help reduce not only the burden of maternal mortality and morbidity but also help gain

better overall population health in future. This untapped area needs research and attention in order to make the right policy decisions to improve maternal and newborn health as well as reduce burden of NCDs.

The PhD thesis focuses on two important conditions; hypertensive disorder and diabetes during pregnancy that leads to adverse maternal and newborn health outcomes, and long term impact on health of women and their children. The primary aim is to assess and identify the most cost-effective approaches to preventing and treating pregnancy related hypertensive disorder and diabetes mellitus in the government funded health care facilities in Bangladesh. Since, the model will comprise of multiple disease conditions and there are multiple interventions and outcomes, it will be helpful to consult stakeholders to set some priorities and boundaries for the model.

Conceptual framework and stakekholder's role

Model development process when informed with choices and information from stakeholders helps the model to address real problems and inform decision making. "A conceptual modelling framework is a methodology that guides modellers through the development of a model structure."(Squires et al 2014) (23). Developing an economic evaluation model is an iterative process. It requires a number of decisions to be made by modellers. While developing a model, questions on what to choose arises at every stage of the way. These include decision regarding what interventions or comparators should be included, what are the possible health states and sequence of events, where data should come from and the methods to be followed. The conceptual framework is a representation of the understanding complexity of the problem and available choices for a specific problem developed by the modeller. (24) In the proposed research, the model explaining the problem and sequence of events, interventions and outcomes will be shared and agreement from stakeholders will be sought. (23, 24)

Stakeholder involvement helps the model to become as close as possible to real world. As the conceptual framework provides a complete picture of what are the possible model parameters to be included in the model, the initial draft framework can be a very complex one trying to cover as many risk factor, intervention, risk factor and outcomes as possible. It is essential to narrow down the focus of the model to be able to accrue benefits from specific interventions that are feasible to implement in the country and have sufficient evidence. The stakeholder consultation process should help narrow down the focus of the model answering questions like what should be included or excluded, if the current care pathway or sequence of events are logical and how the selected parameters should be included using existing evidence (24). Existing literature suggests inclusion of stakeholders in the framework development process to make the final models valid and credible. (23)

Defining stakeholders

Stakeholders are a group of people or organization who directly or indirectly have an interest in or involved in or made an investment in the topic area. There are no prescribed guidance on who should be included as stakeholder for economic evaluation model development. Some suggests stakeholders to be subject experts while others recommend inclusion of modellers, decision makers and health professionals. Patients/clients have been identified as stakeholders in several literature. For this research project it will include the relevant government bodies, practitioners at the central and local level (physicians, field level service providers), development partners, professional bodies and researchers who works on the specific or broader topic, programme implementer like Non-Government Organizations (NGOs) and partners in the research project. Patients are a key part of the stakeholder group who directly benefits from services. (23, 24, 25)

The purpose of developing conceptual framework can vary between ones that help define the problem and those that help to justify and explain the model. The proposed research will focus on a problem oriented conceptual framework which will eventually feed information into the model design. Such conceptual models will ensure understanding of the model among decision makers and practitioners and make it more relevant to the context of Bangladesh.

Research Design and Methods

Describe the research design and methods and procedures to be used in achieving the specific aims of the research project. If applicable, mention the type of personal protective equipment (PPE), use of aerosol confinement, and the need for the use BSL2 or BSL3 laboratory for different part of the intended research in the methods.. Define the study population with inclusion and exclusion criteria, the sampling design, list the important outcome and exposure variables, describe the data collection methods/tools, and include any follow-up plans if applicable. Justify the scientific validity of the methodological approach (biomedical, social, gender, or environmental). Also, discuss the limitations and difficulties of the proposed procedures and sufficiently justify the use of them.

Identifying and mapping stakeholders

The first step for identifying stakeholders for the study will be desk reviews. National strategies and five year plans, programme related operational plans contain lists of development partners and relevant bodies who are potential stakeholders for this research. Those documents can provide an exhaustive list of donors. A set of stakeholders can be identified through past working experiences and recommendations from the research team at the Maternal and Child Health Division of icddr,b.

While conducting interviews with the listed experts, I will ask for suggestions for additional expert. The sample will be completed through snowballing. A few patients who have the experience of receiving care at different tiers of the public health facilities will also be interviewed in order to understand the current care pathways.

Stakeholder consultation

For the purpose of this research, no single framework will be followed rather it will be a combination of all prescribed frameworks.

In depth interviews and a workshop will be held to interview the stakeholders. A draft conceptual framework will be shared with the stakeholders and the pathways will be explained. As identified by Squires (2014), there are several stages of a conceptual modelling framework; understanding the problem, choosing model options, determining scope of the model, deciding on level of details, setting the assumptions and finally decide on the type of model to be implemented. In order to touch base upon all the areas mentioned, a qualitative description of the quantitative model will be provided to develop a clear understanding of the problem statement, the disease pathways considered, current care, interventions, risk factors (population and socio-demographic characteristics) and the immediate and long term outcomes. Each stakeholder will be asked to provide feedback on the problem stated, disease pathways, current care pattern described, event sequence, interventions included in the model and outcomes considered. They will also be asked to prioritise a set of interventions and outcomes in order to narrow down the model's focus. The prioritisation will be done on the basis of feasibility of implementation. Once individual input has been received a workshop will be conducted with an updated model structure and for further feedback and consensus.

In Depth Interviews (IDIs):

During the IDIs, stakeholders will be shown the draft conceptual framework, given a qualitative description of the model and asked for their opinion on the model flow and the current care pattern.

Once feedback has been received they will be asked about the target population and risk factors to be considered within the model, interventions to be targeted and outcomes to be considered within the model. A semi structured guideline will be followed for the IDIs. There will be both closed and open ended questions. Open ended questions will cover areas like current treatment pattern and sequence of events. Closed ended questions will cover ranking of interventions and outcomes to be included in the model. A guideline has been added (annex 2).

In order to carry out the ranking exercises secure online polling package, such as Google Forms will be used and stakeholders will be asked to answer to specific questions during the interview and upload the answers in real time

Decision problem and objectives

The problem and objectives of the conceptual framework will be described to the stakeholders and asked if there are any missing piece of information to be added.

Patient flow/current care

The model will describe how patients get into the care pathway and end up with an immediate and a long term outcome. This will involve a description of the current care pathway. This will help get stakeholder views on capturing how the system works and what happens in reality. Stakeholders will be asked to consider whether both public and private facilities needs to be taken into account and possible implications to the model if only public sector is included. This section will be particularly relevant for patients who will be interviewed to know their experience of care.

Model scope/boundary

A set of questions will be directed on determining model perspective, scope in terms of timing and population and discuss the key assumptions to be made to develop the mode structure. Stakeholders will be asked the type of population characteristics may be most critical to take into account. For example, some may focus on age groups of women and target the interventions to specific age groups while others may be more concerned about equity and want to look at effects across different wealth quintiles. Additionally they will be asked about interventions, outcomes and resources to be incorporated within the model.

Interventions

The list of broad interventions identified in the reviews will be shown or read out and stakeholders will be asked which interventions are most relevant for consideration within the model. They will be asked if anything relevant needs to be added and to prioritise the interventions based on feasibility, relevance and importance in addressing the two conditions.

Outcomes

Stakeholders will be asked to list a set of outcomes that are most crucial for the problem and relevant for the interventions listed. They will also be asked to rank the outcomes for mothers and children and how important it is to capture both within the model.

Cost

Stakeholders will be shown the type of costs that can be included within model and asked for suggestions and prioritisation. For example, there has been national level costing exercises where salaries of existing government staff were not included as they come from revenue budget. Also they will be asked about inclusion of out of pocket payment and its relevance to the model's perspective.

Timeframe

The two disease conditions considered within the model has both short run and lifetime implications for health and resource needs for the public and private sector facilities.

Workshops:

Based on findings from in depth interviews, a draft modelling framework will be developed and run for preliminary results. The model and findings will be shared with the stakeholders in a workshop. The stakeholders will be those who participated in the interviews and have been exposed to the model framework previously.

A qualitative description of the preliminary model will be developed and shared in the workshop. The stakeholders will be asked to provide feedback on the model structure, the event sequence, interventions, outcomes, costs and timeframe of the model. Sources of data used will be described and stakeholders will be asked if they are aware of alternative sources of data relevant for the model.

Similar to the IDIs some ranking exercises will be conducted using google forms/ online polls will be used and stakeholders will be asked to answer to specific questions during the workshop and upload the answers in real time.

A second workshop will be held when model development is finished and when preliminary results are available. This workshop will take place towards the end of my phd.

Sample Size Calculation and Outcome (Primary and Secondary) Variable(s)

Clearly mention your assumptions. List the power and precision desired. Describe the optimal conditions to attain the sample size. Justify the sample size that is deemed sufficient to achieve the specific aims.

The sampling frame for the stakeholder consultation will be purposively designed. The objective is to cover a range of perspectives. Therefore, rather than reaching a saturation point like usual qualitative research studies, sample size for this will be driven by a list of essential stakeholders.

Inclusion criteria. This type of exercise is commonplace in modelling and good practice supports such approach to sampling and sample size (23,24).

Inclusion

- Participants are related/have interest in the topic area

Exclusion

- Not linked to the topic area

List of possible stakeholders to be included

Category of participant
Decision makers
Implementers
Practitioners at different tier of health facilities
Development partners
Researchers
Modellers
Patients
Total

Data Analysis

Describe plans for data analysis, including stratification by sex, gender and diversity. Indicate whether data will be analysed by the investigators themselves or by other professionals. Specify what statistical software packages will be used and if the study is blinded, when the code will be opened. For clinical trials, indicate if interim data analysis will be required to determine further course of the study.

All interviews will be summarised and used to generate a list of priority issues to be considered within the final model. A-priori themes according the interview guideline will be identified. All interview data will be extracted based on the themes. A summary report will be prepared based on

the thematic findings. Priority setting will be done in terms of suggestions received and ranking done by the stakeholders. In case too many alternatives are listed by the stakeholders, suggestions from policymakers will be given priority followed by practitioners, funders, researchers and patients. Google analytic may be used in order to analyse findings from google forms and polls.

Data Safety Monitoring Plan (DSMP)

All clinical investigations (research protocols testing biomedical and/or behavioural intervention(s)) should include the Data and Safety Monitoring Plan (DSMP). The purpose of DSMP is to provide a framework for appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data. It involves involvement of all investigators in periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome.

All participants will be anonymised. Only the PI will have access to the identity information if and when required. All recording will be stored in shared drive of the University of Sheffield. Only the investigators of the study will have access to the data.

Ethical Assurance for Protection of Human rights

Describe the justifications for conducting this research in human participants. If the study needs observations on sick individuals, provide sufficient reasons for using them. Indicate how participants' rights will be protected, and if there would be benefit or risk to each participants of the study. Discuss the ethical issues related to biomedical and social research for employing special procedures, such as invasive procedures in sick children, use of isotopes or any other hazardous materials, or social questionnaires relating to individual privacy. Discuss procedures safeguarding participants from injuries resulting from study procedures and/or interventions, whether physical, financial or social in nature. [Please see Guidelines]

Written informed consent forms have been developed for this study (Annex-1). The written consent forms will be used to confirm participant's agreement to take part in the interview and that they have read the Consent Form. It confirms the following

1. Participants understand their participation is voluntary
2. Session will be audio recorded upon consent
3. Data may be shared anonymously with key investigators working on the study

When participants are identified and approached, they will be given a consent form (Annex-1), which will be read to them if necessary. They will then be given as much time as needed.

Use of Animals

Describe if and the type and species of animals to be used in the study. Justify with reasons the use of particular animal species in the research and the compliance of the animal ethical guidelines for conducting the proposed procedures.

NA

Collaborative Arrangements

Describe if this study involves any scientific, administrative, fiscal, or programmatic arrangements with other national or international organizations or individuals. Indicate the nature and extent of collaboration and include a letter of agreement between the applicant or his/her organization and the collaborating organization.

The research activity will be conducted in collaboration between icddr,b and the University of Sheffield, United Kingdom.

Facilities Available

Describe the availability of physical facilities at site of conduction of the study. If applicable, describe the use of Biosafety Level 2 and/or 3 laboratory facilities. For clinical and laboratory-based studies, indicate the provision of hospital and other types of adequate patient care and laboratory support services. Identify the laboratory facilities and major equipment that will be required for the study. For field studies, describe the field area including its size, population, and means of communications plus field management plans specifying gender considerations for community and for research team members.

The PhD programme is fully funded through Wellcome Trust. All research expenses will be borne by the research grant through University of Sheffield.

Literature Cited

1. Koblinsky M, Chowdhury ME, Moran A, Ronsmans C. Maternal morbidity and disability and their consequences: neglected agenda in maternal health. Journal of health, population, and nutrition. 2012;30(2):124.
2. World Health Organization. Maternal Mortality 2019 [cited 2020 11 May]. Available from: https://www.who.int/news-room/fact-sheets/detail/maternal-mortality.
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Budget Justifications

Please provide one page statement justifying the budgeted amount for each major item, including the use of human resources, major equipment, and laboratory services.

NA

Other Support

Describe sources, amount, duration, and grant number of all other research funding currently granted to PI or under consideration.

NA

Biography of the Investigators

Provide biographical data in the following format for all key personnel including the Principal Investigator. Copy the same format for each of them.

Note: Biography of the External Investigators may, however, be submitted in the format as convenient to them..

1. **Name: Tazeen Tahsina**

2. **Present Position:** Associate Scientist

3. **Educational background**: (last degree and diploma & training relevant to the present research proposal)

	Institution	Year
PhD	University of Sheffield	Ongoing
MSc	Macquarie University Australia	2009
BSc	North South University	2006

4. **Ethics Certification:**

		If Yes		
		Issuing Authority	Registration No	Valid Until
No ☐	Yes ☒	NIH		

Note: If the response is "no", please get certification from CITI or NIH before study initiation and submit a copy to the Committee Coordination Secretariat

5. **List of ongoing research protocols/ activities**

Protocol/ Activity Number	Role in the protocol/ activity (PI, Co-PI, Co-I)	Starting date	End date	Percentage of time
ACT-01126	PI	01/09/2020	31/12/2020	20%
PR18007	PI	12/04/2018	30/09/2021	25%
PR17106	PI	28/01/2018	31/12/2022	20%

6. **Publications**

Types of publications	Numbers
a. Original scientific papers in peer-review journals	14
b. Peer reviewed articles and book chapters	1

c. Papers in conference proceedings	
d. Letters, editorials, annotations, and abstracts in peer-reviewed journals	
e. Working papers	
f. Monographs	1

7. Five recent publications including publications relevant to the present research protocol

7.1. Raihana S, Dibley MJ, Rahman MM, Tahsina T, Siddique MAB, Rahman QS, et al. Early initiation of breastfeeding and severe illness in the early newborn period: An observational study in rural Bangladesh. PLoS medicine. 2019;16(8):e1002904.

7.2. Tahsina T, Ali NB, Siddique MAB, Ahmed S, Rahman M, Islam S, et al. Determinants of hardship financing in coping with out of pocket payment for care seeking of under five children in selected rural areas of Bangladesh. PloS one. 2018;13(5):e0196237.

7.3. Tahsina T, Ali NB, Hoque DE, Huda TM, Salam SS, Hasan MM, et al. Out-of-pocket expenditure for seeking health care for sick children younger than 5 years of age in Bangladesh: findings from cross-sectional surveys, 2009 and 2012. Journal of Health, Population and Nutrition. 2017;36(1):33.

7.4. Tahsina T, Ali NB, Siddique MAB, Ahmed S, Rahman M, Islam S, et al. Determinants of hardship financing in coping with out of pocket payment for care seeking of under five children in selected rural areas of Bangladesh. PloS one. 2018;13(5):e0196237.

Co-investigator (Internal)

1. **Name: Shams El Arifeen**
2. **Present Position:** Senior Scientist and Director
   Maternal and Child Health Division, icddr,b

3. **Educational background**: (last degree and diploma& training relevant to the present research proposal)

	Institution	Year
M.B.B.S.	Dhaka Medical College, University of Dhaka, Dhaka Bangladesh	1978-83
M.P.H	Johns Hopkins University School of Hygiene and Public Health, Baltimore, USA	1990-91
DrPH	Johns Hopkins University School of Hygiene and Public Health, Baltimore, USA	1991-97

4. **Ethics Certification:**

		If Yes		
		Issuing Authority	Registration No	Valid Until
No ☐	Yes ☒	National Institutes of Health (NIH)		

Note: If the response is "no", please get certification from CITI or NIH before study initiation and submit a copy to the Committee Coordination Secretariat

5. **List of ongoing research protocols/ activities**

Protocol/ Activity Number	Role in the protocol/ activity (PI, Co-PI, Co-I)	Starting date	End date	Percentage of time
Activ. # 00-434	PI	January	December	15%
Pro #2033-024	PI	January	February	5%
PR-10012	PI	January	April	5%
Activ.# 00-454	PI	January	December	41%
Activ. # 00-314	PI	January	February	34%

Activ. #00-442	PI	March	September	5%

a. Publications

Types of publications	Numbers
a. Original scientific papers in peer-review journals	210
b. Peer reviewed articles and book chapters	
c. Papers in conference proceedings	
d. Letters, editorials, annotations, and abstracts in peer-reviewed journals	
e. Working papers	
f. Monographs	

6. Five recent publications including publications relevant to the present research protocol

6.1. Doi M, Sultana Rekha R, Ahmed S, Okada M, Kumar Roy A, El Arifeen S, Ekström EC, Raqib R, Wagatsuma Y. Association between calcium in cord blood and newborn size in Bangladesh. Br J Nutr. 2011:1-10

6.2. Choudhuri D, Huda T, Theodoratou E, Nair H, Zgaga L, Falconer R, Luksic I, Johnson HL, Zhang JS, El Arifeen S, Nelson CB, Borrow R, Campbell H, Rudan I. An evaluation of emerging vaccines for childhood meningococcal disease. BMC Public Health. 2011;11 Suppl 3:S29. Review

6.3. Catto AG, Zgaga L, Theodoratou E, Huda T, Nair H, El Arifeen S, Rudan I, Duke T, Campbell H. An evaluation of oxygen systems for treatment of childhood pneumonia. BMC Public Health. 2011;11 Suppl 3:S28. Review

6.4. Huda T, Nair H, Theodoratou E, Zgaga L, Fattom A, El Arifeen S, Rubens C, Campbell H, Rudan I. An evaluation of the emerging vaccines and immunotherapy against staphylococcal pneumonia in children. BMC Public Health. 2011;11 Suppl 3:S27. Review

6.5. Webster J, Theodoratou E, Nair H, Seong AC, Zgaga L, Huda T, Johnson HL, Madhi S, Rubens C, Zhang JS, El Arifeen S, Krause R, Jacobs TA, Brooks AW, Campbell H, Rudan I. An evaluation of emerging vaccines for childhood pneumococcal pneumonia. BMC Public Health. 2011;11 Suppl 3:S26. Review

Co-investigator (External)

1. **Name: Simon Dixon**

2. **Present Position:** Professor of Health Economics, University of Sheffield, United Kingdom

3. **Educational background**: (last degree and diploma & training relevant to the present research proposal)

	Institution	Year
Degree	University of Sheffield, UK	2008
Degree	University of York, UK	1992
Degree	University of Southampton, UK	1989
Training		
Training		

4. **Ethics Certification:**

		If Yes		
		Issuing Authority	Registration No	Valid Until
No ☒	Yes ☐			

Note: If the response is "no", please get certification from CITI or NIH before study initiation and submit a copy to the Committee Coordination Secretariat

5. **List of ongoing research protocols/ activities**

Protocol/ Activity Number	Role in the protocol/ activity (PI, Co-PI, Co-I)	Starting date	End date	Percentage of time
iROC	PI	4/2020	12/2020	5%
MND	PI	12/2020	6/2021	2%
SCAIT	Co-I	1/2019	6/2021	3%
UK-CHEP	PI	6/2019	1/2022	10%
TIME	Co-I	6/2018	6/2021	3%
FUTURE	Co-I	1/2017	9/2021	3%
Embedding	Co-I	1/2017	7/2021	3%
COMFORT	Co-I	3/2017	3/2021	2%
PRIME	Co-I	6/2018	6/2021	3%
MIS2	Co-I	3/2017	3/2021	2%

6. Publications

Types of publications	Numbers
g. Original scientific papers in peer-review journals	108
h. Peer reviewed articles and book chapters	1
i. Papers in conference proceedings	43
j. Letters, editorials, annotations, and abstracts in peer-reviewed journals	3
k. Working papers	3
l. Monographs	0

7. Five recent publications including publications relevant to the present research protocol

7.1. Thokala, P., Dodd, P., Baalbaki, H., Brennan, A., Dixon, S., & Lowrie, K. (2020). Developing Markov models from real-world data: A case study of heart failure modeling using administrative data. Value in Health, 23(6), 743-750.

7.2. Henderson C, Dixon S, Bauer A, Knapp M, Morrell CJ, Slade P, Walters SJ, Brugha T. Cost-effectiveness of PoNDER health visitor training for mothers at lower risk of depression: findings on prevention of postnatal depression from a cluster-randomised controlled trial. Psychological Medicine 49(08):1324-1334 Jun 2019

7.3. Alshreef A, MacQuilkan K, Dawkins B, Riddin J, Ward S, Meads D, Taylor M, Dixon S, Culyer AJ, Ruiz F et al. Cost-Effectiveness of Docetaxel and Paclitaxel for Adjuvant Treatment of Early Breast Cancer: Adaptation of a Model-Based Economic Evaluation From the United Kingdom to South Africa. Value in Health Regional Issues 19:65-74 01 Sep 2019

7.4. Jones GL, Brennan V, Jacques RM, Wood H, Dixon S, Radley S. Evaluating the impact of a 'virtual clinic' on patient experience, personal and provider costs of care in urinary incontinence: A randomised controlled trial. PLoS ONE 13(1) Article number e0189174 18 Jan 2018

7.5. Pollard DJ, Brennan A, Dixon S, et al. Cost-effectiveness of insulin pumps compared with multiple daily injections both provided with structured education for adults with type 1 diabetes: a health economic analysis of the Relative Effectiveness of Pumps over Structured Education (REPOSE) randomised controlled trial. BMJ Open 8(4) Article number e016766 07 Apr 2018

Co-investigator (External)

Name: Dr Chloe Thomas

Current position

Research Fellow, Health Economics and Decision Modelling Section, School of Health and Related Research (ScHARR), University of Sheffield (2014 onwards).

Qualifications/Date/Awarding Body

2017 MSc Health Economics and Decision Modelling (Distinction), University of Sheffield

2003 PhD, Genetics, University of Sheffield

1999 BSc hons (1st class), Genetics, University of Sheffield

Previous appointments

2008-2013 Research Associate, Department of Biomedical Science, University of Sheffield.

2005-2008 Postdoctoral Researcher, University of Nice – Sophia Antipolis, France.

Current and Recent Successful Research & Consultancy Projects

2020-2021 **Modelling the Impact of Covid-19 on Bowel Cancer Screening.** NIHR. Role: PI.

2020-2023 **Non-communicable Disease Modelling Partnership.** Public Health England. Role: Co-applicant and senior modeller.

2020-2021 **Modelling Strategies for Minimising Health Inequalities in Bowel Cancer Screening.** Cancer Research UK. Role: Co-applicant and lead modeller

2019-2022 **Evaluation of Cancer Screening and Awareness Programme in Leeds.** Yorkshire Cancer Research. Role: Co-applicant and modeller.

2018-2019 **Risk Stratification in the Bowel Cancer Screening Programme,** Bowel Cancer UK. Role: Lead modeller

2018-2019 **Optimising Bowel Cancer Screening Phase 2: Development of a new Microsimulation Model in Cancer of the Bowel (MiMiC-Bowel),** National Screening Committee. Role: Modeller.

2018-2022 **Scalable Behavioural Weight Management Programmes for the Prevention and Treatment of Type 2 Diabetes,** NIHR. Role: Co-applicant and modeller

2018 **Updated Modelling and Benefit Analysis Relating to the NHS Diabetes Prevention Programme Impact Analysis,** NHS England. Role: PI.

2017-2018 **Cardiovascular Disease Prevention Return on Investment Tool,** PHE. Role: PI.

2017 **Updating the NICE guidelines around Type 2 Diabetes Prevention,** NICE. Role: Co-applicant and lead modeller.

2017 **Optimising Bowel Cancer Screening Phase 1: Optimising the Cost-effectiveness of Repeated FIT Screening and Strategies Combining Bowel Scope and FIT,** National Screening Committee. Role: Modeller.

2016 **Health Economics Support to the NHS Diabetes Prevention Programme,** Public Health England. Role: Co-applicant and lead modeller.

2015 **Modelling Tool for Financial Planning of the National Diabetes Prevention Programme,** NHS England. Role: Co-applicant and lead modeller.

Recent Publications

Thomas, C., Brennan, A., Goka, E., Squires, H., Brenner, G., Bagguley, D., *et al.* (2020) What are the cost-savings and health benefits of improving detection and management for six high cardiovascular risk conditions in England? An economic evaluation. *BMJ Open.* http://dx.doi.org/10.1136/bmjopen-2020-037486

Thomas, C., Whyte, S., Kearns, B., & Chilcott, J.B. (2019) External validation of a colorectal cancer model against screening trial long-term follow-up data. *Value in Health*. DOI: 10.1016/j.jval.2019.06.005

Thomas, C., Sadler, S., Breeze, P., Squires, H., Gillet, M. & Brennan, A. (2017) Assessing the potential return on investment of the proposed NHS Diabetes Prevention Programme in different population subgroups: an economic evaluation. *BMJ Open*. DOI: 10.1136/bmjopen-2016-014953

Breeze, P., **Thomas, C**., Squires, H., Brennan, A., Greaves, C., Diggle, P.J., Brunner, E., Tabak, A., Preston, L. & Chilcott, J. (2017) Cost-effectiveness of population based, community, workplace, and individual policies for diabetes prevention in the UK. *Diabetic Medicine.* DOI: 10.1111/dme.13349

Breeze, P., **Thomas, C**., Squires, H., Brennan, A., Greaves, C., Diggle, P.J., Brunner, E., Tabak, A., Preston, L. & Chilcott, J. (2017) The impact of type 2 diabetes prevention programmes based on risk-identification and lifestyle intervention intensity strategies: a cost-effectiveness analysis. *Diabetic Medicine* DOI: 10.1111/dme.13314

Dunkley, A., Tyrer, F., Spong, R., Gray, L., Gillett, M.J., Doherty, Y., Martin-Stacey, L., Patel, N., Yates, T., Bhaumik, S., Chalk, T., Chudasama, Y., **Thomas, C.**, Sadler, S., Cooper, S., Gangadharan, S., Davies, M., Khunti, K. (2016) Screening for glucose intolerance and development of a lifestyle education programme for prevention of Type 2 diabetes in a population with intellectual disabilities. *NIHR Journals Library*

Angus, C., **Thomas, C**., Anderson, P., Meier, P. & Brennan, A. (2016) Estimating the cost-effectiveness of brief interventions for heavy drinking in primary health care across Europe. *European Journal of Public Health*. DOI: 10.1093/eurpub/ckw122

Thomas, C., Breeze, P., Strong, M., Brennan, A., Norman, P., Cameron, D. & Epton, T. (2016) The cost-effectiveness of an updated theory-based online health behaviour intervention for new university students: U@Uni2. *The Journal of Public Health and Epidemiology* 8(10):191-203 DOI: 10.5897/JPHE2016.0833

Kruger, J., Brennan, A., Strong, M., **Thomas, C**., Norman, P. & Epton, T. (2014) The cost-effectiveness of a theory-based online health behaviour intervention for new university students: an economic evaluation. *BMC Public Health* **14**:1011.

Annex 1a Consent form for KII/IDI (English)

Protocol No.	Version No. 1.00	Date: 23-11-2020

Protocol title: Global Health Exemplars in Maternal and Neonatal Mortality, Bangladesh

Consent form for key informants interview/in depth interview for Stakeholder consultation for developing and economic evaluation model for hypertensive disorder and diabetes in Bangladesh

Principal Investigator: Tazeen Tahsina

Research Organizations: This research is being conducted by Tazeen Tahsina for a PhD at the University of Sheffield in collaboration with icddr,b

Purpose of the research:

Asslamualaikum/Adab,

I have come from the International Centre for Diarrheal Disease Research, Bangladesh (icddr,b)/University of Sheffield. I am conducting a research titled "Developing a cost-effectiveness model for addressing hypertensive disorder and diabetes during pregnancy in Bangladesh". The information collected from this research will help in developing strategies and prioritising interventions targeting women with hypertensive disorder and diabetes and improve maternal and newborn health.

Why I have selected you?

As you are a health expert and working on this field for a long time, your opinion will help shape the model to make it more usable for decision regarding the two conditions mentioned above. I am inviting you to participate in this study to help me by providing valuable information and guiding the development of the model and finally find out the most cost-effective solutions.

Methods and Procedures:

If you agree to participate in this study, I will ask you some questions regarding policies and strategies, existing interventions to reduce mortality. If required, we may need to come to you again to complete this interview. During this interview, I will write down some question answers and note down some comments and record the interview. It will take around 40 minutes to conduct this interview.

Risks and Benefits:

There will be no or minimal risks related to your participation in this study. The information collected from you will be kept confidential and will only be used for research purpose. Participation in this study may not benefit you directly but the information you share will be very useful for further improvement of maternal and newborn health status of Bangladesh.

Privacy, anonymity and confidentiality:

I do hereby affirm privacy, anonymity and confidentiality of information identifying you will strictly be maintained. All information shared by you will be kept confidential and will be kept following the University's storage policies. None other than the investigators of this research and possible study monitor, and law enforcement agencies in special circumstances will have an access to the information. The information collected from this study will be stored outside country but the information identifying you will be strictly maintained and very few people will have access to this information. The questioning will be done in a place where your answers cannot be heard by other people. I would be happy to answer any questions about the study.

Future use of information:

Anonymous or abstracted information and data may be shared with other researchers within and outside the country. However, this will not conflict with or violate the maintenance of privacy, anonymity and confidentiality of information identifying participants in any way.

Right not to participate and withdraw:

You have the sole authority to decide about your own participation. You would also be able to withdraw from participation any time during the study, without showing any cause. Even if you refuse to participate in the study, we will get the same level of healthcare you used to get before. We may visit you again later, for a second visit, if needed and it will also be by random selection. If you agree to the first visit, you do not have to agree to the second.

Principle of compensation:

As mentioned earlier, your participation in this study is completely voluntary and you will not get any payment for participating in this study.

Contact person:

If you have questions about this study or if you feel that you have been treated unfairly or have been hurt by joining the study, you may communicate with the Principal Investigator of the study Tazeen Tahsina, Maternal and Child Health Division, icddr,b and PhD student, School of Health and Related Research, University of Sheffield by calling 8809666771100, ext. 3829, Mobile: 01747219821/+4407842562450. You can also contact icddr,b secretariat, Mr. M. A. Salam Khan (Phone: (+88 02) 9827084 or PABX (+88 02) 9827001-10, ext. 3206)

If you agree to our proposal of enrolling in our study, please indicate that by putting your signature at the specified space below. Thank you for your cooperation

Participant:I certify that all the above information was adequately explained to me and I understood the explanation

_____ _____

Signature of participant Date

_____ _____

Signature of the PI or his/her representative Date

(NOTE: In case of representative of the PI, she/he shall put her/his full name and designation)

Annex 2 Interview Guideline

I have explained to you the purpose of this research. Interviewer will detail out the problem stating the risk factors and outcomes for the two conditions. The participant will be asked about the problem and all risk factors and possible consequences arising from women suffering from hypertension and diabetes

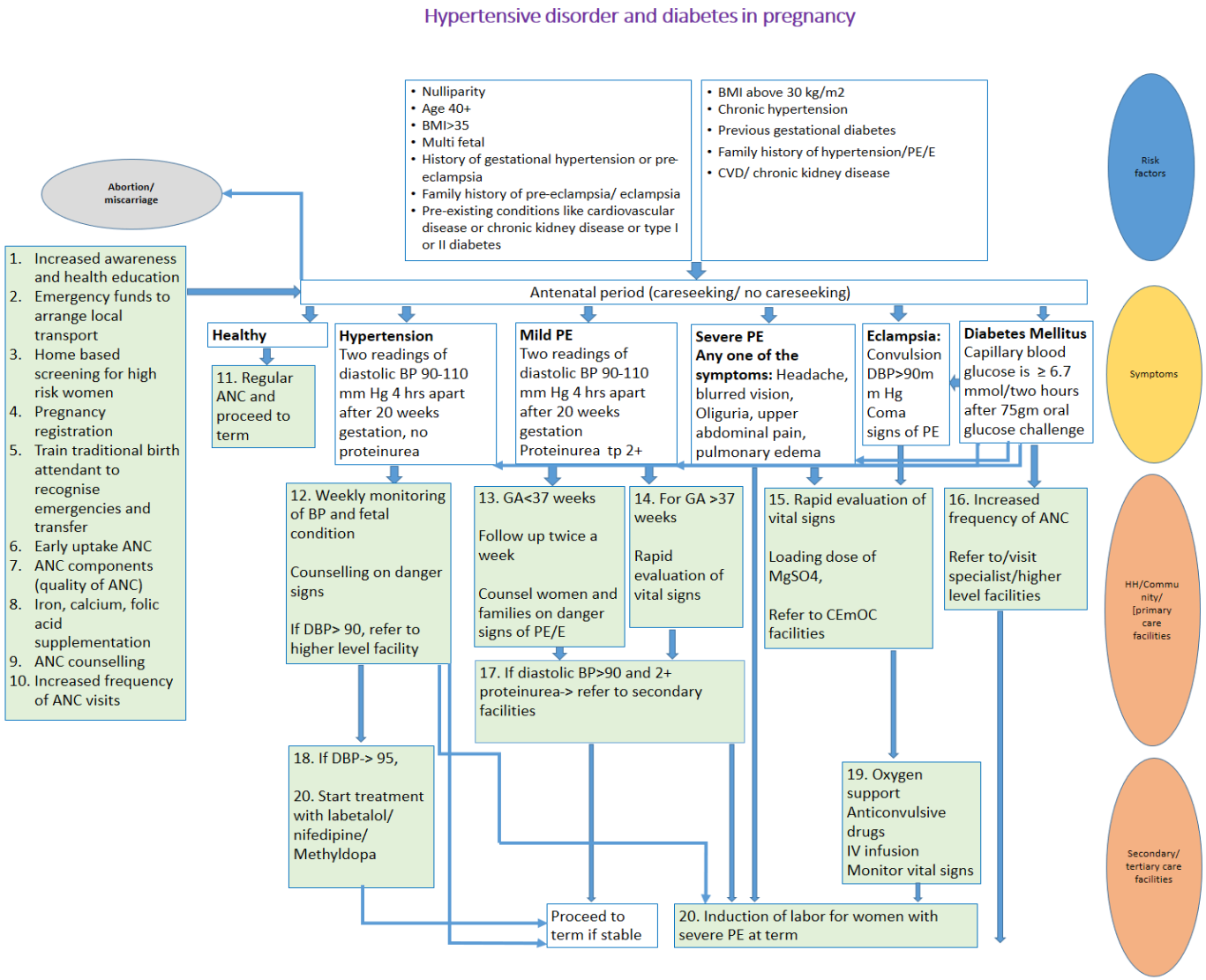
- How important do you think are the two conditions for women and children?
- Do you think all risk factors related to the two conditions have been captured here?
- If not, what would you like to add?
- Which risk factors are the most important in the context of Bangladesh/ which ones would you consider to be most important as an expert?
- Are there programmes/interventions in place to address the risk factors? Please elaborate
- Do you think the outcomes/ consequences listed here captures all short and long terms consequences for women and children?
- If not, what would you like to add?
- Are there programmes/interventions in place to address these problems? Please explain
- What type of interventions do you think are most important to address these outcomes/ reduce impact of hypertensive disorder/ diabetes during pregnancy?
- What do you think are the costs associated to interventions/treatment for the two conditions
- The model can be developed from the perspective of the policymakers/ the health system or the society? Which one would you think will be most relevant for our context?
- What should be length of impact considered within the model? In other words, what should be the timeframe for the model when it comes to consider women/when considering children
- Which of the listed outcomes do you think are the most important?
- Can you select five priority outcomes for the model?
- Can you rank them from most to least important?

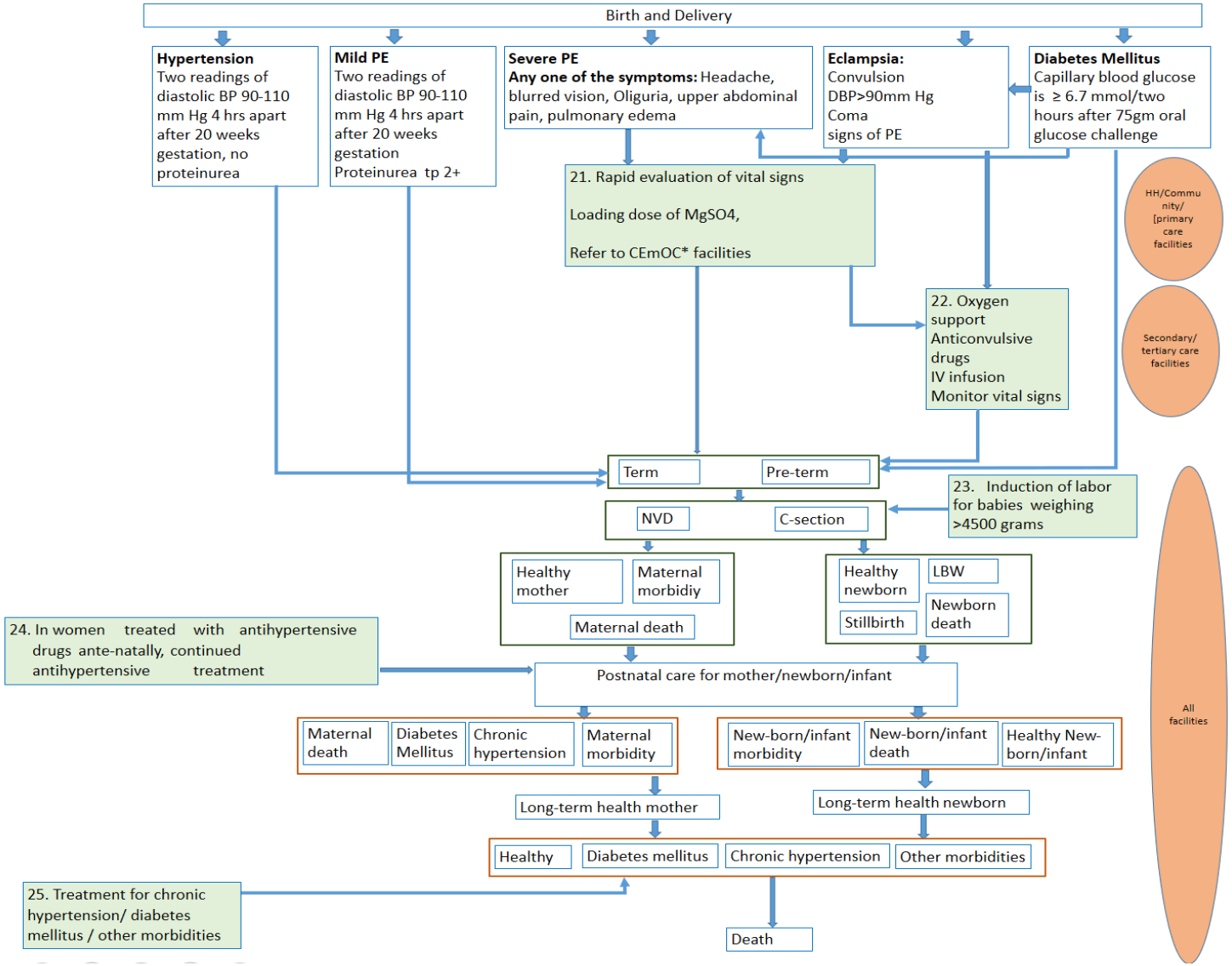
The interviewer will now describe the draft conceptual framework for diabetes and hypertensive disorder in pregnancy respectively. It will include describing the treatment pathway from antenatal, delivery, postpartum and long term effects and outcomes for each of the two conditions separately. The questions below will follow:

- Do you agree with the pathway of treatment described here or are there any missing events?

- If yes, please elaborate
- Do you agree to the list of interventions/treatment mentioned in the antenatal, delivery, postnatal and long term care?
- Which interventions do you think are the most important at each stage?
- If I ask you if select 5 interventions considering your recommended model perspective, outcomes and timeframe which ones will you choose?
- Now, we have five interventions, can you please rank them from most to least important?
- Can you please explain why you have chosen these interventions?

Appendix 4.3: Draft conceptual modelling framework




Birth and Delivery
Hypertension
Two readings of diastolic BP 90-110 mm Hg 4 hrs apart after 20 weeks gestation, no proteinurea
Mild PE
Two readings of diastolic BP 90-110 mm Hg 4 hrs apart after 20 weeks gestation
Proteinurea tp 2+
Severe PE
Any one of the symptoms: Headache, blurred vision, Oliguria, upper abdominal pain, pulmonary edema
Eclampsia:
Convulsion
DBP>90mm Hg
Coma
signs of PE
Diabetes Mellitus
Capillary blood glucose is ≥ 6.7 mmol/two hours after 75gm oral glucose challenge
21. Rapid evaluation of vital signs
Loading dose of MgSO4,
Refer to CEmOC* facilities
22. Oxygen support
Anticonvulsive drugs
IV infusion
Monitor vital signs
HH/Community/ [primary care facilities
Secondary/ tertiary care facilities
Term
Pre-term
NVD
C-section
23. Induction of labor for babies weighing >4500 grams
Healthy mother
Maternal morbidiy
Maternal death
Healthy newborn
LBW
Stillbirth
Newborn death
24. In women treated with antihypertensive drugs ante-natally, continued antihypertensive treatment
Postnatal care for mother/newborn/infant
Maternal death
Diabetes Mellitus
Chronic hypertension
Maternal morbidity
New-born/infant morbidity
New-born/infant death
Healthy New-born/infant
Long-term health mother
Long-term health newborn
Healthy
Diabetes mellitus
Chronic hypertension
Other morbidities
25. Treatment for chronic hypertension/ diabetes mellitus / other morbidities
Death
All facilities