ECONOMIC EVALUATION OF THE COMMUNITY-LEVEL INTERVENTIONS FOR PRE-ECLAMPSIA (CLIP) IN SINDH, PAKISTAN

by

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Abstract

Background

Hypertensive disorders of pregnancy, particularly pre-eclampsia and eclampsia (PE/E), can lead to life-threatening complications or even the death of a mother or a newborn. Because there are few clinical trials of community-based interventions for PE/E, there is little evidence about the cost-effectiveness of these interventions. The aim of this dissertation is to conduct an economic evaluation of the Community-Level Interventions for Pre-eclampsia (CLIP) combined with routine pregnancy care, compared to routine pregnancy care alone, in Sindh, Pakistan.

Methods

A mixed-methods (i.e., qualitative and quantitative) approach to economic evaluation was undertaken alongside the CLIP Trial. A literature review of published epidemiological and economic studies was carried out to document evidence on PE/E interventions and guide the design of the economic model. Data were collected through focus groups, a structured questionnaire embedded into CLIP Trial surveillance, a cross-sectional survey of health facilities, and program budgetary reviews. The cost-effectiveness analysis was performed using a societal perspective. Probabilistic analysis was applied to estimate incremental cost-effectiveness ratios (ICERs), and sensitivity analysis was done to characterize uncertainties.

Results

The literature review found economic studies mainly in developed countries and focused only on costs to the health system. Focus groups revealed a large burden of out-of-pocket spending and productivity losses to pregnant women and families. Health care providers and decision makers identified upfront technology costs as a key challenge for the health system. Maternal and newborn care costs varied significantly between and within public and private

sectors. In the probabilistic analysis of the base case, the incremental cost of the intervention as compared to control was $20,438, while the years of life lost was -37 (i.e., negative health gains), indicating a wide range of statistical uncertainty around ICERs. Overall, the probability that ICERs fell below the country-specific threshold was less than 30%.

Conclusion

This dissertation highlights knowledge gaps for costs and cost-effectiveness of PE/E interventions in low- and-middle-income countries (LMICs). The economic analysis indicates that CLIP is not a cost-effective strategy, compared to routine pregnancy care. More research is needed to conduct the process evaluation to inform policy decisions on resource allocation in Sindh, Pakistan.

Lay Summary

Pakistan has the highest rates of maternal and newborn mortality in South Asia. The Community-Level Interventions for Pre-eclampsia (CLIP) Trial introduced a mobile health (mHealth) intervention to provide home-based screening of hypertensive disorders of pregnancy, case management, and referrals by the Lady Health Workers in Sindh, Pakistan. In this study, we conducted an economic evaluation of CLIP interventions compared to routine pregnancy care alone. The economic literature on PE/E interventions mainly focused on costs to the health system. Focus groups with pregnant women revealed a large burden of out-of-pocket spending and productivity losses to families. Health care providers and decision makers identified challenges of initial investments in mHealth technologies. The cost-effectiveness analysis of CLIP interventions demonstrated higher costs relative to health benefits, indicating a wide range of statistical uncertainty in the results. Further research is needed to evaluate the cost-effectiveness of surveying households in community settings.

Preface

Asif contributed significantly to all elements of research presented in this dissertation. Asif conducted the literature review, contributed to the study design, prepared data collection instruments, and was involved in the process of data collection (focus groups and cross-sectional surveys) onsite. Asif developed the data analysis plans and performed both qualitative, as well as quantitative analyses. The design of an economic model for CLIP was guided by the literature review and qualitative analysis undertaken by Asif.

The work presented in the thesis has led to the following publications/manuscript submitted:

1. **Khowaja AR**, Mitton C, Bryan S, Magee LA, Bhutta ZA, von Dadelszen P. Economic evaluation of Community Level Interventions for Pre-eclampsia (CLIP) in South Asian and African countries: a study protocol. Implementation Science. 2015 May 26;10(1):76.

   This work is associated with Chapter 3 and outlines methodological undertakings for economic analysis of the CLIP Trials. Asif was responsible for literature review, developed study protocol, and served as the primary author on the publication.

2. **Khowaja AR**, Mitton C, Qureshi R, Bryan S, Magee LA, von Dadelszen P, Bhutta ZA. Societal perspective on cost drivers for health technology assessment in Sindh, Pakistan. International Journal of Technology Assessment in Health Care. 2017 July:1-7.

   This work is associated with Chapter 4 and describes qualitative research to explore cost drivers to guide the design of quantitative instruments for health resource utilization. Asif prepared the data collection tools, worked on ethics application,

trained data collectors, involved in the primary data collection onsite, performed qualitative data analysis and served as the primary author of the publication.

3. **Khowaja AR**, Mitton C, Qureshi R, Bryan S, Magee LA, von Dadelszen P, Bhutta ZA. A Comparison of Maternal and Newborn Health Services Costs in Sindh Pakistan. PLOS ONE. Submitted August 2017.

   This work is associated with Chapter 5 and outlines the cross-sectional survey of public and private health providers/facilities. Asif prepared the data collection tools, trained data collectors, involved in the primary data collection onsite, performed quantitative data analysis and served as the primary author of the publication.

Ethics

A written consent was obtained from every participant before conducting the study. All study participants were assigned a unique participant identification numbers to ensure their confidentiality. This study received ethical approval from the Ethics Review Committee (ERC) of the Aga Khan University, Karachi, Pakistan (ERC # 3230-OBS-ERC-14), and the Institutional Review Board of the University of British Columbia in Vancouver, Canada (ETHICS # H12-00132), as the central coordinating site.

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List of Abbreviations

ANC, antenatal care;

ANM, auxiliary nurse midwives;

APE, agente polivalente elementar,

ASHA, accredited social health activist;

CEA, cost-effectiveness analysis;

CEAC, cost-effectiveness acceptability curve;

CEmOC, comprehensive emergency obstetric care;

cHCPs, community health care providers;

CHEW, community health extension workers;

CI, confidence interval;

CISM, manhiça health research centre;

CLIP, community level interventions for pre-eclampsia;

cRCT, cluster randomized control trial;

DALY, disability-adjusted life years;

FG, focus group;

GDP, gross domestic product;

HDP, hypertensive disorders of pregnancy;

HLCF, higher-level care facility;

HRU, health resource utilization;

HTA, health technology assessment;

ICER, incremental cost-effectiveness ratio;

IRB, institutional review board;

ISPOR, international society of pharmacoeconomics and outcomes research;

LHWs, lady health workers;

LMIC, low-and-middle-income countries;

MDG, millennium development goals;

MDs, medical doctors;

mHealth, mobile health;

MMR, maternal mortality ratio;

MNH, maternal and newborn health;

OOP, out-of-pocket;

OR, odds ratio;

PE, pre-eclampsia;

PHC, primary health centre;

PIERs, pre-eclampsia integrated estimate of risk;

PKR, Pakistani rupees;

POM, piers on the move application;

PRE-EMPT, pre-eclampsia/eclampsia, monitoring, prevention and treatment;

QALY, quality-adjusted life years;

TBA, traditional birth attendants;

UBC, University of British Columbia;

UNICEF, United Nations Children's Emergency Fund;

WHO, World Health Organization;

WRA, women of reproductive age.

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helped in timely data collection and provided local insight on societal perspective reported in this thesis.

Most importantly, I would like to thank my parents, Yasmin Khowaja (spouse), and Aareer Khowaja and Aimen Khowaja (children) for their affection, prayers and constant support. Having them in my life is a true blessing, and I am forever grateful for their sacrifices and helping me cope-up with academic stressors or time pressures.

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Chapter 1: Introduction

1.1 Background

Reduction of adverse pregnancy outcomes has received much scholarly attention in the scientific reproductive, maternal, and perinatal health literature over the last two decades (1,2). Recent advancements in the diagnostic, preventive, and therapeutic interventions have contributed to a significant decline in maternal and perinatal mortality in developed countries; however, very little change is evident in low-and-middle-income countries (LMICs) (3,4). The hypertensive disorders of pregnancy (HDP), namely pre-eclampsia and eclampsia (PE/E), are a leading cause of high maternal and perinatal mortality in LMICs (5).

1.2 Definition of pre-eclampsia and eclampsia

PE is an acute onset of high blood pressure in pregnancy, when the systolic blood pressure is 140 mmHg or higher, or diastolic blood pressure is 90 mmHg or higher (6). Another definition describes PE as when a normotensive woman experiences a systolic blood pressure increase of 30 mmHg or more, or a diastolic blood pressure increase of 15 mmHg or more, at any point between week 20 of gestation and two weeks postpartum (7). Several clinical studies have suggested that PE is commonly reported towards the end of pregnancy, whereas a few studies reported that PE could be observed as early as week 20 of gestation (8). According to the classic definition, a woman identified with PE will present with the protein in the urine (proteinuria), swelling in the extremities (peripheral edema), headache, or a sudden increase in body weight, and may experience impaired vision (9).

Eclampsia is the more serious condition. It is characterized by uncontrolled seizures and may result in coma or death. In the absence of early identification and timely case management of PE, women are at higher risk of disseminated intravascular coagulation, pulmonary edema,

placental abruption, acute renal failure, circulatory collapse, and cerebral hemorrhage. Unmanaged PE may also result in severe fetal problems, including intrauterine growth retardation, birth asphyxia, premature birth, and low birth weight (10).

Review of the literature also revealed variations in international and research guidelines in terms of specific definitions for PE used in clinical or research contexts (11,12). Given such variations in the guidelines, trends of incidence for PE/E are not consistent in clinical settings versus population settings and may result in gross underestimation of the condition (13).

1.3 Situation analysis: global context of PE/E

Globally, PE is diagnosed in 10 million women, and results in 76,000 maternal deaths and 500,000 perinatal/neonatal deaths, every year (14). The situation analyses revealed that the risk of developing PE/E and maternal mortality varies greatly depending on the geographical setting where a woman experiences her pregnancy. In a hospital-based retrospective cohort study of 97,270 pregnant women, from 35 hospitals in central and northern Alberta, Canada, the incidence of PE was 1.7%, and there was a significant difference in the mean birth weight of babies (ranging from 547.5 grams to 239.5 grams) born to women identified with PE (15). In contrast, epidemiological studies conducted in LMICs report that women in these settings are seven times more likely to develop PE compared to women in developed settings (14). Over 99% of PE/E-associated maternal and perinatal deaths are clustered in South Asia and sub-Saharan Africa (16). Because the outcomes of PE/E are largely dependent on timely interventions, many affected women in rural and hard-to-reach settings suffer severe disability or lose their lives due to delays in early identification, triage, transport, and treatment (16). The odds of dying from PE/E are approximately 300 times higher for women living in the LMICs (17).

Given the biological plausibility for PE/E, the variation in the number of new cases reported per annum (incidence) has intrigued researchers. Some suggest that the variability of PE incidence is the consequence of different case definitions. Others attribute it to differences in diagnostic procedures or laboratory tests in various regions. It is likely that the burden of disease is changing in developed countries that have more sophisticated interventions for monitoring and treating PE/E.

1.4 Community-level interventions for pre-eclampsia (CLIP) trials

The CLIP Trials are three independently-powered cluster randomized control trials (cRCTs) that aimed to reduce pre-eclampsia-related and all-cause maternal and perinatal mortality and major morbidity by 20% or more in intervention clusters in Sindh Province (Pakistan), Maputo and Gaza provinces (Mozambique), and Karnataka State (India). The CLIP interventions introduced a mobile health (mHealth) platform to facilitate triage and treatment by community health workers, along with community engagement to improve care-seeking practices (18).

The CLIP package of care was supplemented with the routine pregnancy care, and consisted of:

- Provision of HDP-oriented antenatal care through home visits by community health care providers (cHCPs) who carried electronic tablets programmed with a mHealth application for identifying women at risk of PE [Pre-eclampsia Integrated Estimate of Risk (PIERS) (19), on the Move (POM) (20)].
- Community-based case management and referral recommendation(s) for women based on the CLIP "triggers." The recommendations consisted of one of the following, based on the risk profile of the woman:

- Treatment with oral methyldopa (antihypertensive therapy), intramuscular magnesium sulphate (i.m. MgSO4) (anticonvulsant therapy), and urgent transport (within 4 hours) to a health facility.
- Treatment with i.m. MgSO4 and urgent transport (within 4 hours) to a health facility.
- Urgent transport (within 4 hours) to a health facility.
- Non-urgent transport (within 24 hours) to a health facility.
- Continuation of routine care.

- Community engagement through one-on-one sessions with pregnant women, and group sessions with dyadic household decision makers (husbands, fathers-in-law) and community leaders about HDPs, signs/symptoms, potential consequences, pre-permissions for maternal transport, and fundraising activities for transport and treatment costs.

In the intervention group, the cHCPs were trained to inquire about the woman's symptoms, assess blood pressure using a digital device, and check for evidence of protein in urine using a dipstick on the first visit and on any subsequent visits where the systolic blood pressure was 140 mmHg or higher. This clinical assessment informed the diagnosis of and risk assessment for PE/E. More detailed description of the CLIP trial methods/protocol has been published elsewhere (18).

In the control group, pregnant women continued to receive routine pregnancy care at least every four weeks, either at a health facility or from cHCPs at home, as per the standard of care. The routine pregnancy care comprised of: 1) health education related to pregnancy care and birth preparedness, 2) psychological counselling on reproductive health and family planning, and 3)

advice/reminder on vaccinations. Those cHCPs conducting home visits were not trained to assess or counsel on HDP and did not have any components of the CLIP package of care to diagnose, triage, or treat PE/E in the control group. In addition, the household surveillance for collecting pregnancy outcomes and health system capacity enhancement through workshops/seminars for facility-level care providers were undertaken in both intervention and control groups.

1.5 The purpose

The aim of this study was an economic evaluation of the CLIP intervention to inform policy decisions about resource allocation for post-trial programme scale-up in Sindh, Pakistan, should the primary trial be found clinically effective.

1.6 Study hypothesis

The CLIP package combined with routine pregnancy care, compared to routine pregnancy care alone, will result in a low incremental cost-effectiveness ratio (ICER) in reducing maternal and perinatal mortality and major morbidities using a country-specific willingness to pay (WTP) threshold of USD$1,468 (i.e. GDP per capita as of 2016) in Pakistan.

1.7 Research questions

This dissertation is based on four key research questions aimed at understanding the appropriate design of the economic model and common reporting metrics necessary for an economic evaluation of the CLIP interventions in Sindh, Pakistan.

1. What is known about the costs and cost-effectiveness of PE/E interventions for risk reduction/complication prevention, screening/diagnosis, and appropriate case management in the developed countries and elsewhere in LMICs?

A comprehensive review of published epidemiological and economic studies that focus on PE/E interventions was done. Methodological approaches used in the cost-effectiveness studies guided the design of the economic model for the CLIP.

2. What are the costs to the health system and to pregnant women and their families related to mHealth interventions in LMICs?

   This question was explored through mixed-methods research to assess societal perspective (including costs to the health system and families) of cost drivers for health technology assessment in Sindh, Pakistan.

3. What is the cost of maternal and newborn health services at various levels of health facilities in the public and private health sectors?

   A cross-sectional survey of health providers/facilities was undertaken in the study catchment areas to determine the unit costs of various maternal and newborn health services in Sindh, Pakistan.

4. What are the costs relative to benefits for CLIP combined with routine pregnancy care, compared to routine pregnancy alone in Sindh, Pakistan?

   The incremental societal costs and years of life lost (YLL) were compared in the intervention and control groups. The model-based economic analysis was undertaken drawing input parameters from the CLIP Trial, and mixed-methods research in this study.

This thesis is organized into seven chapters: Chapter 1 describes the PE/E definitions, global context, study hypothesis, and research questions; Chapter 2 reports the review of epidemiological and economic literature on PE/E interventions; Chapter 3 presents the overview of study methodology and data collection plans for economic analysis in three CLIP countries.

The next four chapters focus on data, analyses, and findings related to economic evaluation of the CLIP Pakistan Trial: Chapter 4 explains the qualitative research on the societal perspective for cost drivers; Chapter 5 compares the maternal and newborn health services costs in the public and private health sectors; Chapter 6 illustrates the cost-effectiveness analysis of CLIP interventions, and Chapter 7 summarizes the main study findings and directions for future research.

Chapter 2: Evidence of costs and cost-effectiveness of pre-eclampsia / eclampsia interventions: a literature review

2.1 Background

The trajectory of PE/E could impact utilization of health services and may lead to life-threatening complications or even death of a mother or newborn in the absence of appropriate management (10). An economic study conducted in the United Kingdom reported that PE/E is one of the most common reasons for antenatal admission to hospitals (20%) and obstetric admissions to intensive care units (25%) (21). Studies in LMICs that evaluated the economic consequences of health care expenditures found that out-of-pocket (OOP) spending combined with the loss of household income due to ill health could plunge families into a vicious cycle of poverty (22). Understanding the cost and cost-effectiveness of alternative strategies for PE/E identification and appropriate case management is essential to inform decisions about resource allocation and guide the economic appraisal of recent initiatives such as CLIP in the context of LMICs.

2.2 Research question

What is known about the costs and cost-effectiveness of PE/E interventions for risk reduction/complication prevention, screening/diagnosis, and appropriate case management in the developed countries and elsewhere in LMICs?

2.3 Objectives

The primary objectives of this study were to describe the economic burden of PE/E, identify clinical interventions and strategies for PE/E, and document the cost-effectiveness of these interventions based on the recent literature. The secondary objective was to appraise

methodological approaches used in economic studies to guide the design of an economic model for the CLIP Trial.

2.4 Methods

2.4.1 Study design and search strategy

A literature review was conducted using research databases to identify epidemiological and economic studies related to PE/E interventions. Three electronic databases were searched: PubMed, EconLit, and Health Economics Evaluation Database (HEED), developed by the UK National Health Service.

The literature identified several clinical practice guidelines for HDP that describe PE/E differently, and no standard PE/E definition was recommended (12). This review used the definition of PE/E employed by the Society of Obstetrics and Gynecologists of Canada (SOGC) in reference to the CLIP Trial (23). The SOGC definition defines PE as an acute onset of hypertension, when the systolic blood pressure is 140 mmHg or higher, diastolic blood pressure is 90 mmHg or higher, and proteinuria is 1 or higher on dipstick or the PrCr ratio is 30 mg/mmol or higher on random urine. Eclampsia was defined as a serious condition characterized by uncontrolled seizures for women with signs and symptoms of PE after week 20 of gestation, which may result in a coma or death. The developing countries were defined as countries with gross national income per capita below US $11,905, according to the World Bank (24).

The key search expressions used in the databases were: (“cost of hypertensive disorders of pregnancy intervention in developing countries” OR “pre-eclampsia interventions in developing countries” OR “eclampsia interventions in low-and-middle income-countries” OR “cost-effectiveness of pre-eclampsia interventions in low-and-middle income countries” “cost minimization interventions for pre-eclampsia in developing countries” OR “economic evaluation

of pre-eclampsia interventions in low resource settings" OR "economic appraisal of pre-eclampsia and eclampsia measures in developing countries"). These search expressions returned a very limited number of epidemiological and economic studies in the developing countries, so terms related to "low-and-middle-income countries, developing countries, and/or low-resource settings" were omitted in subsequent searches.

2.4.2 Inclusion and exclusion criteria

Studies were considered eligible for review if they met the following inclusion criteria:

- Focus on health resource utilization or cost of illness related to PE/E
- Epidemiological investigations of PE/E interventions with focus on risk reduction/prevention, screening/diagnosis, and case management
- Economic evaluations that report on costs relative to health benefits of PE/E interventions
- Full-text articles available in English language
- Published between January 2002 and December 2017

Conference abstracts and non-research articles were excluded. Duplicate studies were identified and removed.

2.4.3 Screening and data extraction

Applying these search expressions to the electronic databases produced a list of articles for title screening. Abstracts of related studies were reviewed, and studies were excluded based on the criteria described above. During the review of full-text articles, we found references to two related studies conducted by The National Institute for Health and Care Excellence (NICE) in the UK. These two studies were included in the full-text review.

Data were extracted from full-text articles using a PICO (population, intervention, comparator, key outcomes) format to report on study characteristics (25). The summary table lists studies in chronological order according to the publication year. In the epidemiological publications, we reviewed point estimates in reference to the odds ratio (OR), relative risks (RR), and 95% confidence intervals (CI). Among the economic evaluation publications, we reviewed costs of interventions, health benefits as quality-adjusted life years (QALYs), net monetary benefit, cost savings, and ICER of comparators. Costs data included in this review represent United States dollars (US$), UK pounds (£), or Euro (€). This review also reports on methodological approaches in the economic studies, such as sources of cost and outcome data, modeling technique, outcome parameters, perspective adopted, discounting, time horizon, and methods for dealing with uncertainty.

2.5 Results

Of the 473 articles retrieved from PubMed, Econ.Lit, and HEED searches, 447 were excluded because they were duplicates (n=6), did not focus on PE/E interventions/cost-effectiveness (n=420) or were not original research studies (n=21). The remaining 28 studies (26 articles retrieved plus 2 NICE articles) were reviewed. Of these 28, 15 publications (54%) represent a wide range of economic studies such as cost analysis, cost-benefit analysis, cost-effectiveness analysis, and budget/financial impact analysis. The epidemiological studies (n=13) include cross-sectional surveys, case-control, prospective cohort, and clinical trials. Only summary findings from the meta-analyses were reviewed, as some primary studies reported in the meta-analyses neither met the inclusion criteria nor showed-up in the literature search (Figure 1, pg 26).

2.5.1 Economic burden of PE/E

Three studies on the topic of cost of illness were included in this review. These studies examined PE/E-related costs and the financial impact on the health system mainly in a public-payer context. Studies from the US reported that hospitalization costs for PE management and associated complications averaged $11,208 per patient (26). This translated into an aggregated cost to the US health care system of $1.03 billion in maternal health care costs and $1.15 billion in costs for infants born to mothers with PE (27). Another follow-up study reported excessive maternity services resulting in higher costs of PE (average €5,243 per case), compared to €2,452 per case for an uncomplicated pregnancy (28). This study also estimated the annual national costs ranging from €6.5 to 9.1 million, as the prevalence of PE increased from 5% to 7%. Economic studies related to the financial burden of PE/E to society, and particularly OOP spending to pregnant women and their families, were not available in the literature (Table 1, pg 21).

2.5.2 Interventions for risk reduction/complication prevention of PE/E

Six epidemiological studies and one economic study on the topic of risk reduction and prevention of PE/E were included in this review. A recent meta-analysis on the prophylactic use of aspirin reported significant risk reduction (OR = 0.84, 95% CI: 0.11 to 0.35) of PE in the East Asian population (29). A cost-benefit analysis on the prophylactic use of low-dose aspirin (81 mg) compared with no prophylaxis demonstrated cost savings of $377 million in direct medical care in the US annually. In this study, low-dose aspirin was found to have over 90% probability of cost-effectiveness at the WTP threshold of $100,000 per neonatal QALYs gained (30). Another meta-analysis on calcium supplementation during pregnancy found 45% risk

reduction of PE in the LMICs (31). We did not find any publications that support the cost-effectiveness of calcium supplementation during pregnancy.

Furthermore, several observational studies have suggested lifestyle or dietary modifications for preventing PE/E, but no evidence on the cost-effectiveness was found in the published literature. A longitudinal study from rural Congo found dietary intake of less than three servings of vegetables per day increased PE risk by 33%, whereas moderate physical activity reduced the risk by 37% (32). There is an abundance of literature on the role of vitamins supplementation in PE risk reduction. In Uganda, a randomized placebo-control trial evaluated the use of vitamin C (1,000 milligrams as ascorbic acid) compared to placebo. In this study, investigators did not find a significant difference in the incidence of PE between the intervention and control groups (33). Another study from Bangladesh reported higher odds of developing PE/E (OR= 5.14, 95% CI: 1.98 to 13.37) in women with vitamin D deficiency (34). Administration of folic acid together with multivitamins was found to reduce the risk of developing PE by 63% (95% CI: 0.18 to 0.75) (35) (Table 1, pg 21).

2.5.3 Interventions for screening/diagnosis of PE/E

Three epidemiological studies and six economic studies about screening and diagnostic tests were included in this review. Most studies focused on PE diagnosis in the antepartum period, and very few addressed prognostic investigations in the postpartum period. A recent study reported an early prediction of PE through spot urinary albumin-to-creatinine ratio of 9.8mg or more per gram of creatinine. The sensitivity of this test was as low as 67%, and specificity was as high as 76% (36). The economic analysis evaluated three alternative diagnostic practices: (i) Protein-creatinine ratio (PCR) alone; (ii) Automated urine analysis followed by PCR; and (iii) Automated urine analysis followed by 24-hour urine collection. In a cohort of

60,000 pregnant women with mild to moderate hypertension, PCR alone was less expensive (i.e., £226,800) and generated higher QALYs compared to other two alternatives (37). Another economic study of women with gestational hypertension compared visual dipstick urine analysis versus automated urine analysis using a reagent-strip reading device. This study found an incremental cost of £51,540 for the automated procedure and incremental QALYs of 415 in a cohort of 60,000 women with moderate gestational hypertension (38). The economic study evaluated Doppler tests for identification of PE and concluded no evidence of cost-effectiveness for high-risk versus low-risk pregnancies (39).

Literature also revealed an emerging scope of the mHealth technologies and novel serum tests of placental biomarkers for PE identification and risk stratification of adverse pregnancy outcomes. A recent study reported the high accuracy of a handheld semi-automated blood pressure device (Microlife 3AS1-2) used for PE screening, which costs less than $20 in LMICs (40). Others have reported the role of potential placental biomarkers, namely alpha-fetoprotein, placental growth factor, soluble tumor necrosis factor receptor-1, and retinol binding protein-4 in the prediction of early onset of PE (41). A study from Israel evaluated the economic benefit of first-trimester screening of multiple placental biomarkers compared with no screening. This study found a cost per QALY of less than $10,000 for screening, given the prevalence of pre-eclampsia at 3% (42). Another recent study, from the Italian national health service, evaluated the budget impact of placental biomarker screening compared to standard practice for prediction of PE. This study reported health care costs as low as €1,714 in women who received biomarker screening, compared to €2,384 in the group that underwent standard diagnosis. This demonstrated substantial cost savings for placental biomarkers through improvement in diagnostic accuracy and reduction in unnecessary maternal hospitalization (43). Similarly,

placental biomarkers (SFlt-1 and PlGF), compared to standard diagnosis, were attributed to cost savings of £945 per pregnancy in the UK (44) (Table 1, pg 21).

2.5.4 Interventions for appropriate case management of PE/E

Four epidemiological studies and five economic studies on the topic of case management of PE/E were included in this review. A number of clinical trials have evaluated the choice of surgical and therapeutic interventions for case management or prevention of complications associated with PE/E. An open-randomized controlled trial evaluated immediate delivery versus expectant monitoring for HDP between 34 and 37 weeks of gestation (HYPITAT-II). Investigators found that immediate delivery reduces the risk of adverse maternal outcomes (RR=0.36, 95% CI: 0.21 to 1.11) in women with non-severe hypertensive disorders at 34 to 37 weeks of gestation (45). The trial-based economic evaluation compared costs of labor induction and expectant monitoring in women identified with PE at term. A study from the Netherlands found that inducing labor for immediate birth resulted in cost savings of €831 (95%CI: €144 to €1,561) per woman identified with mild or moderate levels of hypertension at 34 to 37 weeks of gestation (46). Another multicenter trial on the Control of Hypertension in Pregnancy Study (CHIPS) evaluated less-tight (i.e., target diastolic blood pressure 100 mmHg) versus tight control (target diastolic blood pressure 85 mmHg) with most commonly used antihypertensive drugs (either methyldopa or labetalol). In this study, women in the less-tight control group were found to have significantly higher maternal hypertension (incremental prevalence 13.1%, p-value <0.001) (47,48). In British Columbia, Canada, the cost analysis of the CHIPS Trial indicated higher health system costs of woman-and-infant hospitalization in the less-tight control strategy ($30,593) compared to tight control ($24,776) (49).

Furthermore, the use of magnesium sulphate (MgSO4) compared to a placebo was evaluated in a Magpie Trial. This study found that prophylactic use of MgSO4 prevented deaths or serious morbidity (RR= 0.84, 95% CI: 0.60 to 1.18) (50). Similarly, prophylactic use of MgSO4 was evaluated in a randomized control trial (PIPES) in Dhaka, Bangladesh, which found that a low-dose regime reduced the incidence of eclampsia by 1.48% (51). The economic analysis of the Magpie Trial reported ICERs for preventing each case of eclampsia with MgSO4 intervention as low as $456 in low-income countries, compared to $21,202 in high-income countries (52). In Pakistan, investigators reported lower costs of $0.56 for a single loading dose of MgSO4, compared to a cost of $2.40 for the standard prophylaxis regimen (53). Another study reported that a carefully designed outpatient management program, including patient education, blood pressure monitoring, and urine protein measurement for women with PE saved an average of $2.50 per woman compared to standard pregnancy care (54) (Table 1, pg 21).

2.5.5 Methodological approaches on economic studies

Six economic studies included in this review evaluated the cost-effectiveness of PE/E interventions using the decision analytic tree model. Only two studies used trial-based economic evaluation, and a few reported on cost-benefit or budget impact analysis. The model parameters for health outcomes were mainly drawn from previously published literature, Cochrane review, and interviews/consultation with clinical experts or health care payers. The cost inputs were derived from multiple sources including national health services/administrative databases, health insurance providers, and health facility records. Almost all studies reported from the health system perspective (i.e., public payer); one study reported on societal perspective in the Netherlands. Only four studies reported on discounting; a 3% discount rate was applied. The majority of economic studies (n=7) modeled a time horizon of one year or less, and sensitivity

analysis was undertaken in many studies to address parameter uncertainties. The health outcome parameters varied in many studies, such as incremental cost per PE case identified, the incremental cost per E case averted, the incremental cost per PE case managed, and cost savings per pregnancy (Table 2, pg 25).

2.6 Discussion

This chapter reports on the epidemiological and economic literature that focuses on costs and cost-effectiveness of PE/E interventions. Our review identified a number of PE/E interventions that appear to be effective (e.g. diet, and physical activity, prophylactic administration of aspirin and treatment with magnesium sulphate). The epidemiological evidence on PE risk reduction or complication prevention strategies is largely fragmented, as few randomized controlled trials exist. More emphasis is given to the early identification and case management of PE/E to avert disease-related complications and mortality. The economic literature on the cost-effectiveness of PE/E interventions only represents work done in developed (western) countries, and knowledge gaps exist for cost-effectiveness of PE/E interventions in the context of LMICs. All studies identified in this review investigated either clinical or laboratory related intervention and lacked information on comprehensive community-based interventions for PE/E. The CLIP package of care focused more on the community-based HDP screening, case management and community engagement aspects for the design of the intervention.

The rising cost of care and alarmingly high OOP expenses in health care are important challenges to health systems in LMICs (22). The economic studies in this review focused on health system costs and included only the public payer's perspective. Ironically, the literature on societal costs related to PE/E is almost nonexistent in parts of the world where most PE/E-related deaths occur. Incorporating a societal perspective (i.e., including costs to pregnant women and

their families and to the health system) provides a complete reflection of the financial burden and health outcomes. Recent guidelines on the economic evaluation strongly recommended societal perspective for cost-effectiveness analyses (55). Further research is needed to understand and explore the societal perspective of cost drivers related to PE/E care in low-resource settings. Such in-depth information is critical to inform the economic analysis of the CLIP Trial.

The findings from this review highlight a potential issue of contextual variation for costs and health outcomes, as reported in the economic studies. The cost input parameters were derived from multiple sources including published literature, active clinical trials, national health services databases, and consultation with clinical experts or health care payers. Such an inclusive approach to data collection, although beneficial to capture a wide range of information, may introduce the uncertainty of costs parameters available from multiple sources. Investigators did not explain how they dealt with possible cost uncertainties, particularly in four economic studies in which sensitivity analysis was not performed. This finding suggests that it is important to include sensitivity analysis in the economic evaluation of the CLIP Trial. Moreover, the health outcome parameters in the selected economic studies were inconsistent and reflected on surrogate outcomes rather than the tangible outcomes (e.g., number of lives saved, or life years saved) commonly used in the economic literature in LMICs (56). Thus, policy decisions related to program allocative efficiency—that is, choosing an alternative strategy with lower cost and more health gains—are severely compromised when health outcomes are inconsistently reported for alternative strategies (57). This finding further informed the inclusion and modeling of life years saved as the standard health outcome metric in the economic evaluation of the CLIP Trial.

In LMICs, the health care system includes the private and public health sectors—a major divide that is seldom included in economic analyses. The costs of diagnostic tests, drugs, their

administration, and health facility-level admissions vary substantially between the public and private health sectors (58). It is imperative to assess, particularly in the societal perspective, because individuals may pay differently for similar health services. Further research on ascertaining unit costs of maternal and newborn health services at public and private health facilities (i.e., a real-world scenario) will be useful to inform the economic analysis of the CLIP Trial. Furthermore, the contextual variations can be anticipated in the price of mobile health technology, Internet infrastructure, and health care costs between countries in the same region, which suggest country-specific economic analysis in the selected CLIP countries.

2.6.1 Strengths and limitations

This literature review reports on the epidemiological and economic evidence on costs and cost-effectiveness of PE/E interventions evaluated in the last 15 years. The knowledge gaps highlighted in this review generated important areas for future research on PE/E interventions, particularly relevant in the context of LMICs. The methodological approaches in the cost-effectiveness studies included in this review provided important directions in the design of economic appraisals of future PE/E interventions, such as the CLIP Trials. This review includes four limitations that warrant discussion: (i) the literature review focused on epidemiological and economic studies published in 2002 or later, and there is a possibility of missing information published before 2002; (ii) the literature review examined only English-language publications, so there is a possibility of missing information published in other languages; (iii) many studies were conducted in the developed countries, so findings may not apply generally to LMICs; and (iv) there is the possibility that this review is affected by publication bias, i.e., authors selectively publishing epidemiological studies with direction and strength of findings that favor clinically effective interventions (59).

2.7 Conclusions

Reduction and prevention of PE/E risks and complications has received little attention in the current epidemiological and economic literature. The evidence on cost and cost-effectiveness of P/E interventions concentrated on the health system perspective and lacked information on societal costs. Most of these studies were conducted in developed countries, and knowledge of cost-effective PE/E interventions is very limited in the context of LMICs, where the majority of the disease burden and associated mortality occur. Ascertaining costs of health services from a mix of public and private health facilities and consistent use of health outcome parameters will be beneficial in the future.

Table 1. List of articles included in the literature review

Scope	Publication, year	Study methodology	Study population (P)	Intervention (I)	Comparator (C)	Study outcomes (O)
Risk-reduction or complication prevention	Jie Gan et al. 2016	A systematic review and meta-analysis	Women at risk of pre-eclampsia (cohort of East Asian and non-East Asian pregnancies)	Low-dose Aspirin	Placebo or no-treatment	Low-dose Aspirin reduced pre-eclampsia risk (OR = 0.20, 95% CI: 0.11–0.35) in East-Asian; and non-East Asians (OR = 0.84, 95% CI: 0.77–0.92).
	Werner et al. 2015	Cost-benefit analysis	Pregnant women in the United States of America	Universal prophylaxis of low-dose Aspirin	No prophylaxis	Universal prophylaxis offers net monetary benefit of $365 million assuming four million births each year in US.
	Agrawal et al. 2015	Cross-sectional survey	Indian women of reproductive age (15-49 years) who have had live birth in the last five years	NA	NA	Iron and folic acid supplementation reduced frequency of pre-eclampsia or eclampsia symptoms.
	Kiondo et al. 2014	A randomized placebo controlled clinical trial	Uganda pregnant women aged 15-42 years living 15KM or less from the hospital	1000mg of vitamin C (as ascorbic acid)	Placebo	No difference in vitamin and placebo groups on the incidence of pre-eclampsia (3.1% versus 4.1%; RR 0.77; 95% CI: 0.37-1.56), and severe pre-eclampsia (1.2% versus 1.0%; RR 1.25; 95% CI: 0.34-4.65).
	Ullah et al. 2013	Case control study	Women identified with pre-eclampsia, eclampsia, and normotensive pregnancies in Bangladesh	NA	NA	Vitamin D insufficiency (i.e. 25 (OH) D levels < 30ng/ml) was the risk factor for pre-eclampsia and eclampsia (OR 3.9 (95% CI=1.18-12.87).
	Imdad et al. 2011	Meta-analysis	All pregnancies in developing countries	Calcium supplementation	Placebo	Calcium supplementation in pregnancy led to risk reduction of pre-eclampsia (RR 0.41; 95 % CI 0.24-0.69), neonatal mortality (RR 0.70; 95 % CI 0.56-0.88), and pre-term births (RR 0.88, 95 % CI 0.78-0.99).
	Longo-Mbenza et al. 2008	Hospital-based longitudinal assessments	African rural black pregnant women hospitalized	NA	NA	Diet rich in vegetables and physical activity prevents pregnancy-induced hypertension.

Scope	Publication, year	Study methodology	Study population (P)	Intervention (I)	Comparator (C)	Study outcomes (O)
Screening/ diagnosis	Frusca et al. 2017	Budget impact analysis	Women with suspected pre-eclampsia in Itlay	Placental biomarker (i.e. sFlt-1/PlGF ratio)	Standard pre-eclampsia screening	Lower healthcare costs €1714 in women screened with placental biomarker, compared to €2384 in standard screening.
	Nupur Gupta et al. 2017	A retrospective study of urine samples	Early pregnancies i.e., before 20 weeks of gestation.	NA	NA	Spot urinary albumin-to-creatinine ratio (i.e., > 9.6 mg/g of creatinine) was strong predictor of pre-eclampsia, indicating 67% sensitivity and 76% specificity.
	Nevalainen et al. 2017	A retrospective study of maternal serum obtained/analyzed at the hospital setting	Pregnant women in the first trimester in Finland	NA	NA	Biomarkers such as Alpha fetoprotein (AFP), placental growth factor (PIGF), soluble tumor necrosis factor receptor-1 (sTNFR1) and retinol binding protein-4 (RBP4) were found strong predictor of early onset of pre-eclampsia.
	Hannah L et al. 2015	Prospective observational study	Pregnant women in low-and-middle income countries.	NA	NA	Microlife 3AS1-2 BP device was recommended for use in pregnancy, and preeclampsia screening.
	Shmueli et al. 2012	Cost-effectiveness analysis	Pregnant women in Israel	Routine screening using placental biomarkers	Uterine Doppler as the standard care	The ICER for intervention was USD$24,723 per pre-eclampsia case averted at 5% prevalence. The cost per quality of life-adjusted life year with screening was <USD$10,000 at prevalence of 3%.
	Hadker et al. 2010	Financial impact analysis	Pregnant women receiving obstetric care in UK	Novel biomarkers test (sFlt-1 and PlGF)	Combination of Doppler, BP monitoring, and serum uric acid	The average cost of care was £1,781 per patient with new test, versus £2,726 with standard diagnostic tests. Cost saving of £945 per pregnancy.
	NICE 2010	Cost-effectiveness analysis	Women with gestational hypertension in United Kingdom	Automated urine analysis	Visual urine analysis	Automated urine analysis was cost-effective strategy resulting in an ICER <£20,000/QALY.
	NICE 2010	Cost-effectiveness analysis	Women with gestational hypertension in United Kingdom.	Protein creatinine ratio alone (PCR)	Auto + PCR strategy; and Auto + 24 hour urine collection	Protein creatinine ration (PCR) alone was cost-effective strategy resulting in an ICER <£20,000/QALY.

Scope	Publication, year	Study methodology	Study population (P)	Intervention (I)	Comparator (C)	Study outcomes (O)
Screening/ diagnosis (continued)	Meads et al. 2008	Systematic review and economic modeling	Pregnancies identified with pre-eclampsia in UK	Test-treatment combination with 27 diagnostic alternatives	No test-treat all	The average cost of diagnostic tests ranged from £5 (for blood tests) to £20 (for Doppler tests). None of the scenarios were found cost-effective; favoured no-test & treat all strategy.
Case management	Keepanasseril et al. 2017	A randomized controlled trial (PIPES)	Women with severe pre-eclampsia in Bangladesh	Prophylactic low-dose of magnesium sulphate	Loading dose of magnesium sulphate	Incidence of eclampsia was 1.48% in low-dose regime compared to 2.98% in loading dose; this finding was statistically non-significant with p-value=0.321.
	Rashid A et al. 2016	Cost analysis of the CHIPS trial	Pregnant women identified with gestational hypertension at 14 weeks to 33 weeks (6 days) of gestation	Less tight control of blood pressure (target diastolic 100 mm Hg)	Tight control of blood pressure (target diastolic 85 mm Hg)	Tight control reduces the risk to neonates and saves costs, albeit statistically insignificant, to healthcare system. In British Columbia, (less tight control cost $30 593.69 versus tight control $24 776.51; Difference $5817; 95% confidence interval, −$385 to $12 349; *P*=0.073).
	Broekhuijsen et al. 2015	An open-label randomized controlled trial (HYPITAT)	Pregnant women between 34 – 37 weeks of gestation in Netherland	Immediate delivery	Expectant monitoring	Immediate delivery reduces the adverse maternal outcomes (RR: 0·36, 95% CI 0·12-1·11; p=0·069) in women with non-severe hypertension at 34-37 weeks of gestation.
	Magee et al. 2015	An open, international, multicentre trial (CHIPS)	Pregnant women identified with gestational hypertension at 14 weeks to 33 weeks (6 days) gestation	Less tight control of blood pressure (target diastolic 100 mm Hg)	Tight control of blood pressure (target diastolic 85 mm Hg)	The trial did not find significant difference in the risk of pregnancy loss, high –level neonatal care, or overall maternal complication between two groups. The less-tight control was associated with significantly higher occurrence of severe maternal hypertension.
	Vijgen et al. 2010	Trial-based economic evaluation of HYPITAT	Pregnant women between 34 – 37 weeks of gestation in Netherland	Immediate delivery	Expectant monitoring	Induction of labour is less costly at €1259; than expectant monitoring at €2700.

Scope	Publication, year	Study methodology	Study population (P)	Intervention (I)	Comparator (C)	Study outcomes (O)
Case management (continued)	Shoaib et al. 2009	Cost analysis	Pregnant women identified with pre-eclampsia in the hospital setting of Pakistan	Loading dose of magnesium sulphate	Standard regime for prophylaxis	Single loading dose was found less costly ($0.56) , compared to cost of $2.40 for the standard prophylaxis regime.
	The Magpie Trial follow-up study group 2006	A randomized trial (Magpie trial)	Pregnant women identified with pre-eclampsia in United Kingdom.	Magnesium sulphate	Placebo	Magnesium sulphate was found to have reduced incidence of eclampsia, and less maternal deaths in the intervention group (RR= 0.84, 95% CI: 0.60 to 1.18).
	Barton JR et al. 2006	Cost-benefit analysis	Women identified with hypertensive condition	Outpatient care (inclusive of patient education, BP and proteinuria monitoring)	Standard pregnancy care	Outpatient management program saved an average of $2.50 per woman compared to standard pregnancy care.
	Simon et al. 2006	Cost-effectiveness (Magpie trial)	Pregnant women identified with pre-eclampsia in United Kingdom	Magnesium sulphate	Placebo	Magnesium sulphate was found less costly and prevented more eclampsia cases in low-income countries (ICER $456), than in high-income countries (ICERs $21,202).
Cost of illness related to PE/E	Fox A et al. 2017	Cross-sectional cost analysis	Women identified with pre-eclampsia in United States	NA	NA	The annual cost for PE care ranges from €6.5 to 9.1 million in the national healthcare system in United States.
	Rui Li et al. 2017	Administrative cost analysis	Women with pre-eclampsia hospitalized in the United States	NA	NA	The aggregated cost of PE related maternal hospitalization is estimated as $1.03 billion and infants care cost $1.15 billion in United States.
	Agency for healthcare 2005	Cost analysis	Women identified with pre-eclampsia in United States	NA	NA	The average cost for PE management is $11,208 per woman.
	Longo-Mbenza et al. 2008	Hospital-based longitudinal assessments.	African rural black pregnant women hospitalized.	NA	NA	Diet rich in vegetables and physical activity prevents pregnancy-induced hypertension.

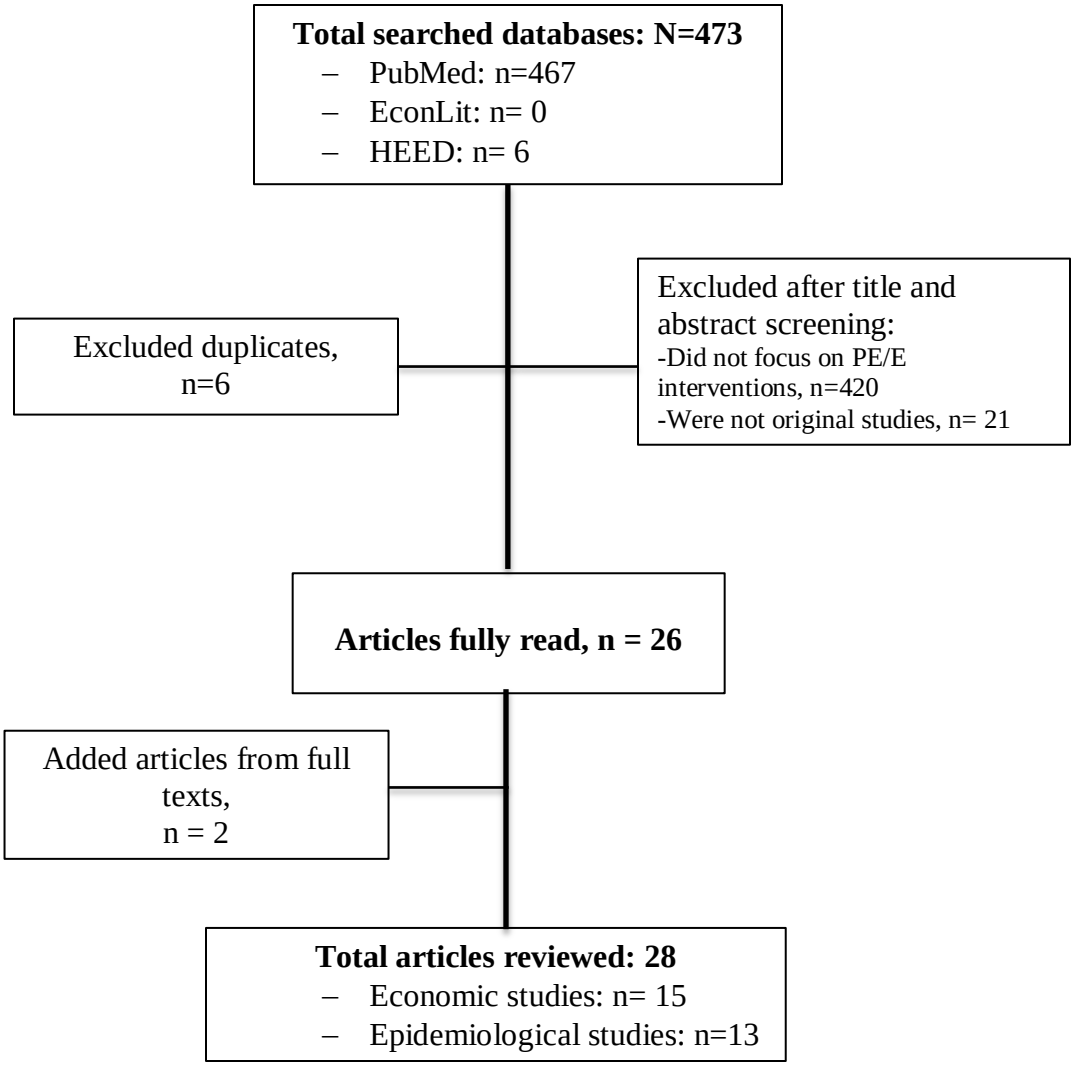
NA= Not applicable.

Table 2. Methodological approaches on selected economic studies

Publication, year	Source data	Modeling technique	Perspective	Discounting	Time horizon	Method of dealing uncertainty	Economic outcome
Frusca et al. 2017	Previous epidemiological study (i.e. PROGNOSIS), literature review, clinical opinion	Decision tree analysis	Public payer	Yes, 3%	5 years	Sensitivity analysis	Incremental cost per PE case predicted
Rashid A et al. 2016	Multi-center CHIPS trial, and provincial health insurance database	Descriptive cost analysis	Public payer	No	1 year, single pregnancy	No	Incremental cost per PE case treated
Werner et al. 2015	National Health Services-NHS UK	Decision tree analysis	Public payer	Yes, 3%	1 year, single pregnancy	Sensitivity analysis	Net monetary benefit
Shmueli et al. 2012	Literature review and Israel health services database	Decision tree analysis	Public payer	Yes, 3%	30 years	Sensitivity analysis	Incremental cost per PE case averted
Hadker et al. 2010	Literature review, interviews with clinicians/ payers, and review of NHS database in UK	Decision tree analysis	Public payer	No	No	Sensitivity analysis	Cost saved per pregnancy
NICE 2010	Literature review and NHS UK	Decision tree analysis	Public payer	Yes, 3%	1 year, single pregnancy	No	Incremental cost per PE case predicted
Vijgen et al. 2010	HYPITAT trial and health services administrative data	Trial-based CEA	Societal	No	1 year, single pregnancy	Sensitivity analysis	Incremental cost per PE case treated
Shoaib et al. 2009	Tertiary level health facility in Pakistan	Descriptive cost analysis	Treatment provider (hospital)	No	1 year, single pregnancy	No	Incremental cost per case PE treated
Meads et al. 2008	Literature review and Cochrane for Pregnancy and childbirth group	Decision tree analysis	Public payer	No	No	Probabilistic sensitivity analysis	Incremental cost per PE case predicted
Barton JR et al. 2006	Literature review and health facility admissions	Cost benefit analysis	Treatment provider (hospital)	No	1 year, single pregnancy	No	Cost saved per pregnancy
Simon et al. 2006	Magpie Trial and national health system	Trial-based CEA	Treatment provider (hospital)	No	< 1 year	Sensitivity analysis	Incremental cost per case PE averted

CEA = Cost-effectiveness analysis; UK = United Kingdom

Figure 1. CONSORT diagram



Chapter 3: Economic evaluation of Community Level Interventions for Pre-eclampsia (CLIP) in South Asian and African countries: a study protocol

3.1 Background

Economic evaluation of health interventions can play a pivotal role in the priority setting and can inform health care decision makers with evidence relevant to resource allocation (60). The World Health Organization (WHO) strongly recommends cost-effective interventions as a key aspect of achieving Sustainable Development Goals (SDGs)- 3 (i.e., reduction of global maternal mortality ratio to less than 70 per 100,000 live births); and SDGs 3.1 (i.e., reduction of under 5 child mortality ratio to less than 25 per 1000 live births) by 2030 (61). The CLIP Trial provided a unique and timely opportunity for economic evaluation of a well-designed community-based trial that directly aligns with SDGs.

3.1.1 Rationale for conducting economic evaluation of the CLIP interventions

Adam et al. conducted a cost-effectiveness analysis of WHO-recommended strategies for maternal and neonatal health, and demonstrated the benefits of comprehensive community-based antenatal, intrapartum, and postnatal interventions for reducing maternal and neonatal mortality in sub-Saharan Africa and South East Asia (62). They highlighted that packages of maternal and newborn interventions can be more cost-effective than singular interventions. In our context, the CLIP Trial combined a package of otherwise singular evidence-based interventions (blood pressure monitoring (63), urine dipstick testing (38), $MgSO_4$ (52), methyldopa (64), mHealth technology (20), antenatal visits by cHCPs (65), community engagement (66), timely referral, and triage at a health facility (67). This combined package of care must be evaluated to determine if it is a cost-effective intervention in reducing maternal and perinatal mortality. It is well recognized that economic studies embedded within clinical trials have high internal validity

and timeliness (68). In this context, the International Society for Pharmacoeconomics and Outcome Research (ISPOR) recommended collecting trial outcome data, health resources used, and health state utilities directly from the study participants recruited in the trial (69).

The CLIP Trial was conducted across three countries, and so assessment of the economic impact (costs and benefits) alongside the trial (i.e., concurrent with it) were integral to building a robust cost-effectiveness model to supplement the trial outcomes. This is critical because the CLIP Trial introduced new costs in health service delivery (e.g., mHealth and task shifting to cHCPs), which have budgetary implications for health systems in the selected CLIP countries. Post-trial program scale-up of CLIP interventions must be informed through both the impact of the package of intervention and the cost of achieving any incremental benefits in the context of selected South Asian and African countries. The CLIP Trial's collaborating partners MoH in the respective countries expressed a clear desire to ascertain the long-term implications of the CLIP package of care. These stakeholders unanimously endorsed conducting an economic appraisal of CLIP to further inform policy decisions around resource allocation and program scale-up, thereby serving as models for other LMICs.

3.2 Objectives

The primary objectives were to:

- Qualitatively identify the cost drivers (resources needed) during trial implementation to inform design of the model;
- Assess the cost of maternal and newborn health services at various levels of health facilities in the study catchments;
- Determine the costs and health benefits of the CLIP plus routine pregnancy care, compared with routine pregnancy care alone;

- Estimate the ICER of the CLIP plus routine pregnancy care, compared with routine pregnancy care alone.

The secondary objective was to:

- Perform the temporal analysis of program-related cost and rate of pregnancy outcomes over the study period in the CLIP plus routine pregnancy care, compared to routine pregnancy care alone.

3.3 Methods

3.3.1 Research design

A mixed-methods (i.e., qualitative, and quantitative) approach to economic evaluation was undertaken alongside the trial. Mixed-methods were critical in the context of three CLIP countries, where we had different health delivery systems, health financing, resource allocation interests, diversity of community beliefs about pre-eclampsia/eclampsia, care-seeking behaviours and treatment preferences.

3.3.2 Research plan

The research was conducted in three inter-linked phases over a four-year period (Figure 2, pg 38).

- Phase 1 refers to model design and data collection instruments guided by the literature review. Findings from the qualitative assessments triangulated contextual aspects of the costs from societal perspective to support interpretation of the economic analysis.
- In Phase 2, based on the learning in Phase 1, we embedded health resource utilization instruments into the trial surveillance for prospective data collection alongside the trial. The parallel surveys provided unit cost estimates for MNH services at health facilities.
- Phase 3 refers to analytical procedures, after the trial outcomes were available to run the

cost-effectiveness analysis.

3.3.3 Study settings and duration

The sites for the CLIP Trial in Pakistan include the districts of Matiari and Hyderabad in the southern province of Sindh; the Provinces of Gaza and Maputo in Mozambique; and the Belgaum and Bagalkot districts in the State of Karnataka, India.

In Pakistan, the pilot trial recruitments began on February 7th, 2014 and were completed as of January 18th, 2015 in four clusters (i.e., 2 intervention; and 2 control clusters). The recruitment for definitive trial was undertaken from January 19th, 2015 to December 31st, 2016 in twenty clusters (i.e. 10 intervention; and 10 control clusters) in Pakistan. In India, the pilot trial recruitments began on February 1st, 2014 and were completed as of October 31st, 2014 in four clusters (i.e., 2 intervention; and 2 control clusters). The recruitment for definitive trial was undertaken from November 1st, 2014 to October 31st, 2016 in twelve clusters (i.e. 6 intervention; and 6 control clusters) in India. In Mozambique, the recruitment for definitive trial was undertaken from February 24th, 2015 to February 24th, 2017 in twelve clusters (i.e. 6 intervention; and 6 control clusters).

3.3.4 Target population

Pregnant women aged 15- 49 years (except Mozambique where the eligibility age is 12-49 years) recruited in the CLIP Trial in both intervention and control clusters were eligible to take part in the economic data collection.

3.3.5 Study perspective

The CEA was based on a societal perspective, accounting for both costs to healthcare system and cost to families of the pregnant women.

3.3.6 Qualitative exploration of cost drivers

Focus groups (FGs) are a commonly used method of data collection in qualitative research to gather group opinions (70). Specifically, the FGs in this study were aimed to better understand the contextual variations of intervention delivery, and resources used for costing work. Besides health care providers and care receivers in a community, studies have reported that women in LMICs are situated in cultural contexts, where men in their lives are traditionally the decision makers surrounding women's health issues (71). As inclusively as possible, the community perspectives were obtained from groups of:

- Pregnant women identified as at risk due to a HDP;
- Male decision makers (husbands / fathers-in-law) of pregnant women identified as at risk of a HDP;
- Community healthcare providers (cHCPs);
- Medical doctors at referral health facilities;
- District-level health decision/policy makers.

3.3.7 Description of cost variables

The total costs were calculated through a standardized ingredients approach (72), which involved gathering sufficient information about the quantities and unit cost of physical inputs needed in the intervention and control groups. This included cost to the healthcare system and cost to the family (Figure 3, pg 39).

3.3.8 Cost to the healthcare system

The costs included resources used in the implementation of the CLIP interventions. The capital costs were comprised of clinical devices, and mHealth technology used in the home-based screening of HDPs. The recurrent operating costs included the community-based patient

management, referral and follow-up (i.e., drugs, supplies, patient transport), and community engagement (i.e., personnel, venue, refreshment and transport allowance for participants).

Additional program costs included:

- Cash incentives to cHCPs for follow-up household visits, such as Lady Health Workers (LHW) in Pakistan, Agente Polivalente Elementar (community health agents) in Mozambique, and Accredited Social Health Activists (ASHA) in India;
- Cost of cHCPs' trainings, and transport costs when accompanying any identified HDP woman to a referral health facility;

3.3.9 Cost to the family

All relevant out-of-pocket (OOP) spending for routine ANC, diagnostic tests and/or procedures during pregnancy, ambulatory care for pregnancy related illnesses at the PHC, as well as higher-level care facilities (HLCF), often characterized by secondary and tertiary level hospitals. In addition, costs associated with in-patient overnight hospitalization, childbirth related admissions, and transportation to-and-from health facilities. The productivity/time losses were asked for all visits to PHC, and HLCF, inclusive of childbirth.

3.3.10 Cost to society

The total societal costs (i.e., combining of costs to the healthcare system and cost to the family) were calculated by summing across all cost categories.

3.3.11 Methods and instruments for data collection

The information about resources utilized and unit costs were collected from primary and secondary data sources in the intervention and control groups. A consistent approach was followed to collect these data in the intervention and control clusters, except for POM utilization, which only occurred in the intervention clusters (Table 3, pg 37).

3.3.12 Health resource utilization

Structured health resource utilization (HRU) questionnaires were embedded into the CLIP Trial surveillance forms and administered to all pregnant women recruited in intervention and control clusters. These questionnaires were translated into study site languages (Sindhi/Urdu in Pakistan, Portuguese in Mozambique, and Kannada in India), and are as follows:

- *Form 1: Pregnancy registration:* Project research assistants (RAs) completed this form only once for every pregnancy identified during the trial period in the intervention and control groups. This form served to establish the baseline information for all women recruited in the trial. The key variables included socio-demographic profile, medical history, care-seeking characteristics, and health facility utilization in the previous pregnancy.
- *Form 2: Regular community surveillance*: Project RAs administered this form once every three months until delivery and once post-delivery capturing data for the 42 days after childbirth, for each pregnant woman recruited in the intervention and control groups. The key variables included HRU, such as frequency of hospital visits, type of health facility (public or private), level of health facility (primary, secondary, or tertiary), level of care (in-patient or out-patient), length of stay, diagnostic tests, and clinical interventions for pregnant women and newborn. Also, information was collected on return transport trips, and days of missed wages. The regular surveillance visits at equal- and shorter time intervals were to address the possibility of recall bias, and review of medical records at health facilities was to triangulate the information on resource utilization.
- *Form 3: Health facility utilization*: This is based on patient hospital admission chart review for women recruited in the CLIP Trial, and was completed by project medical

officers (MDs) during their monthly visits at all referral health facilities in the catchments of intervention and control groups. The key variables included diagnostic and clinical services utilized by pregnant women and/or newborns at health facilities.

- *The PIERS on the Move (POM) data*: The information about home-based screening of HDP and frequency of home visits were captured from the POM data set. POM data was maintained electronically for all the women recruited in the intervention clusters.

3.3.13 Maternal and newborn health services costs

In order to obtain the unit cost of hospitalizations (e.g., bed charges, nursing services), drugs, and diagnostics, a cross sectional survey of health care providers/facilities was conducted.

3.3.14 Program implementation costs

The unit cost estimates for the CLIP Trial intervention package included the cost of a blood pressure device, urine dipstick, oxygen saturation prop, cost of community engagement, and cost of training sessions were determined from the trial budget/financial reports/invoices for each site in the CLIP Trial. These cost estimates were verified from the central trial office (PRE-EMPT, UBC). In addition, the information about incentive and transport expenses of LHWs was obtained from the review of CLIP trial financial reports.

3.3.15 Outcome variables (effectiveness)

The CLIP Trial primary outcome was the reduction in combined maternal and/or perinatal adverse outcomes between the intervention and control groups. The project RAs assessed the trial outcomes every three months during community surveillance visits at the households for all women recruited in the intervention and controls groups. The trial-based health outcomes were translated into years of life lost (YLL) and years lost due to disability (YLD) components of the disability-adjusted-life-years (DALYs) with 3% discounting and no-

age weighting (73).

3.3.16 Data analysis

Qualitative data were analysed using QSR NVivo v10 software, and responses were coded to form similar categories. These were refined through thematic analysis. Data were interpreted through close communication between local researchers and international team to ensure accuracy. Quantitative data were analyzed to compare frequencies/proportions of health resource utilization in the intervention and control groups. Inferential analysis was performed to estimate regression-adjusted mean cost, $\pm$ standard errors (SE), 95% confidence intervals and p-values.

Because outcomes of pregnancy can be assessed over a short span (i.e. 40– 42 weeks of time horizon), the decision analytic tree model can be used for comparative analysis of costs and effectiveness between two alternatives. Previously conducted cost-effectiveness studies for PE/E have mainly used a decision analytic tree model. Our primary analysis for this study was model based, using parameter estimates for costs and effectiveness coming from the CLIP Trial. (Figure 4, pg 40). We calculated ICERs using Monte Carlo simulation (for 10,000 iterations) in Microsoft Excel. The ICERs were calculated first from a healthcare system perspective and then from a societal perspective. ICERs for the system perspective as the reference case are of interest to country-specific health policy makers for resource allocation decisions, when switching from routine pregnancy care to CLIP plus routine pregnancy care, should CLIP be found effective. Critically, however, the ICER from a societal perspective is to facilitate discourse on the full opportunity cost in the context of the selected CLIP country. The uncertainties were characterized through one-way sensitivity analyses. The ICERs were interpreted using country-specific thresholds.

3.4 Possible study limitations

There is a possibility of recall bias for the health resource utilization variables obtained on the surveillance; however, we limited the recall length to the most recent hospitalization. In addition, some non-financial factors, such as patient and provider preferences could possibly have influenced families' health care utilization. The methodological consistency in collecting costs and outcomes in both intervention and control groups, supplemented by the qualitative data for designing the cost-effectiveness model for each site, increased the internal study validity.

Table 3. Methods for collecting resource utilization and cost information

Type of data	Intervention Group	Control Group
Health resource utilization	Health resource utilization questionnaire integrated with CLIP Trial surveillance tools for intervention and control groups: Form 1: Pregnancy Registration Form 2: Regular community surveillance Form 3: Health facility utilization	
	PIERS on the Move (POM) data	N/A
Unit costs	Cross-sectional survey of public and private health providers/facilities for maternal and newborn health services costs	
	Review of site-specific CLIP Trial budget (costing for intervention package)	N/A
N/A = Not applicable		

Figure 2. Research plan for economic evaluation of the CLIP interventions

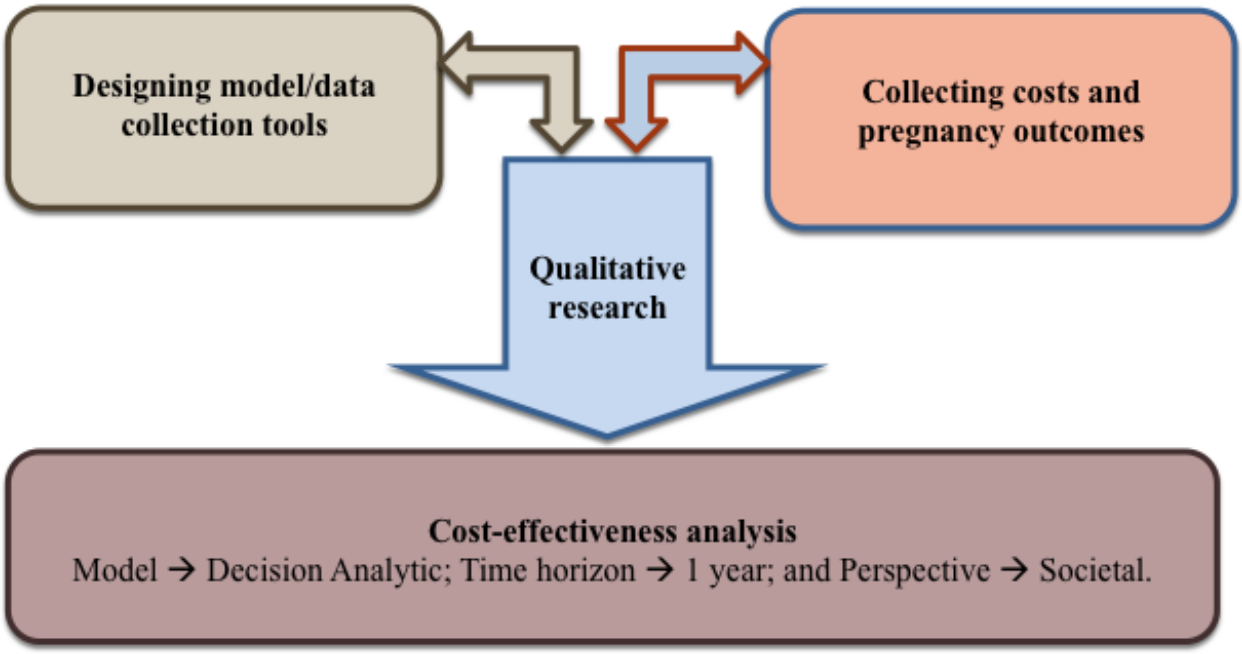
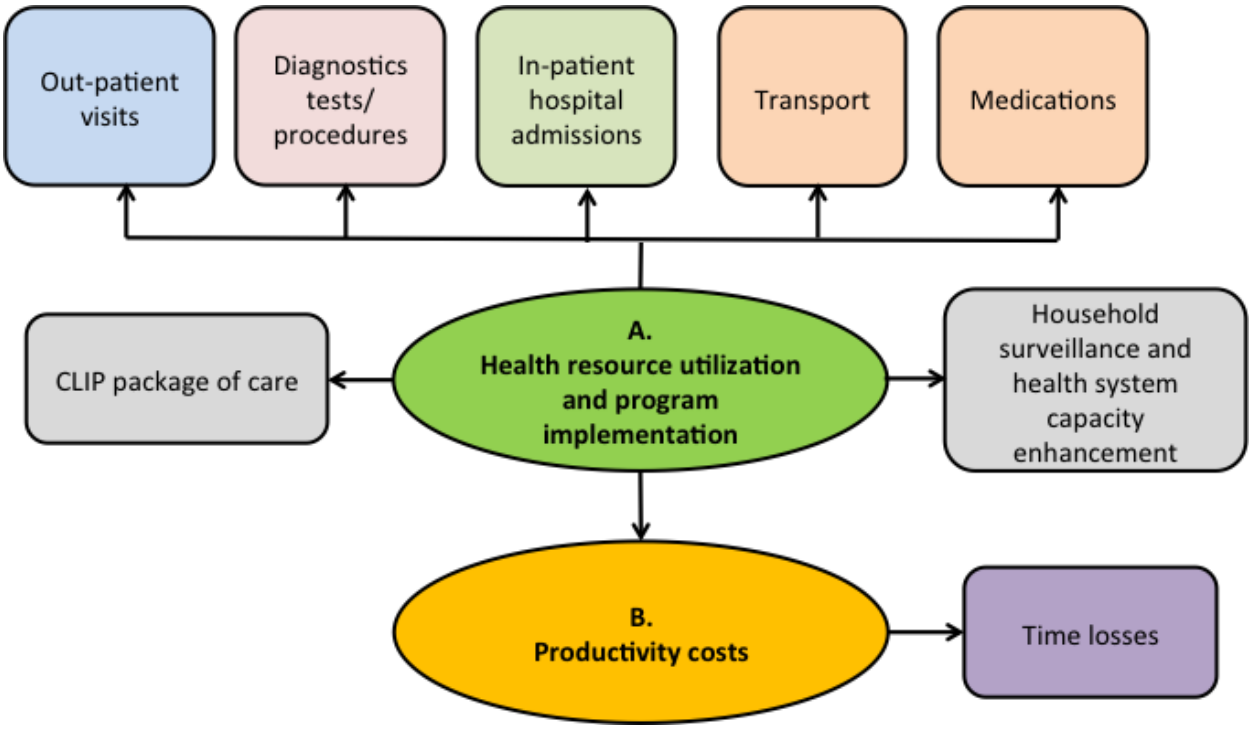


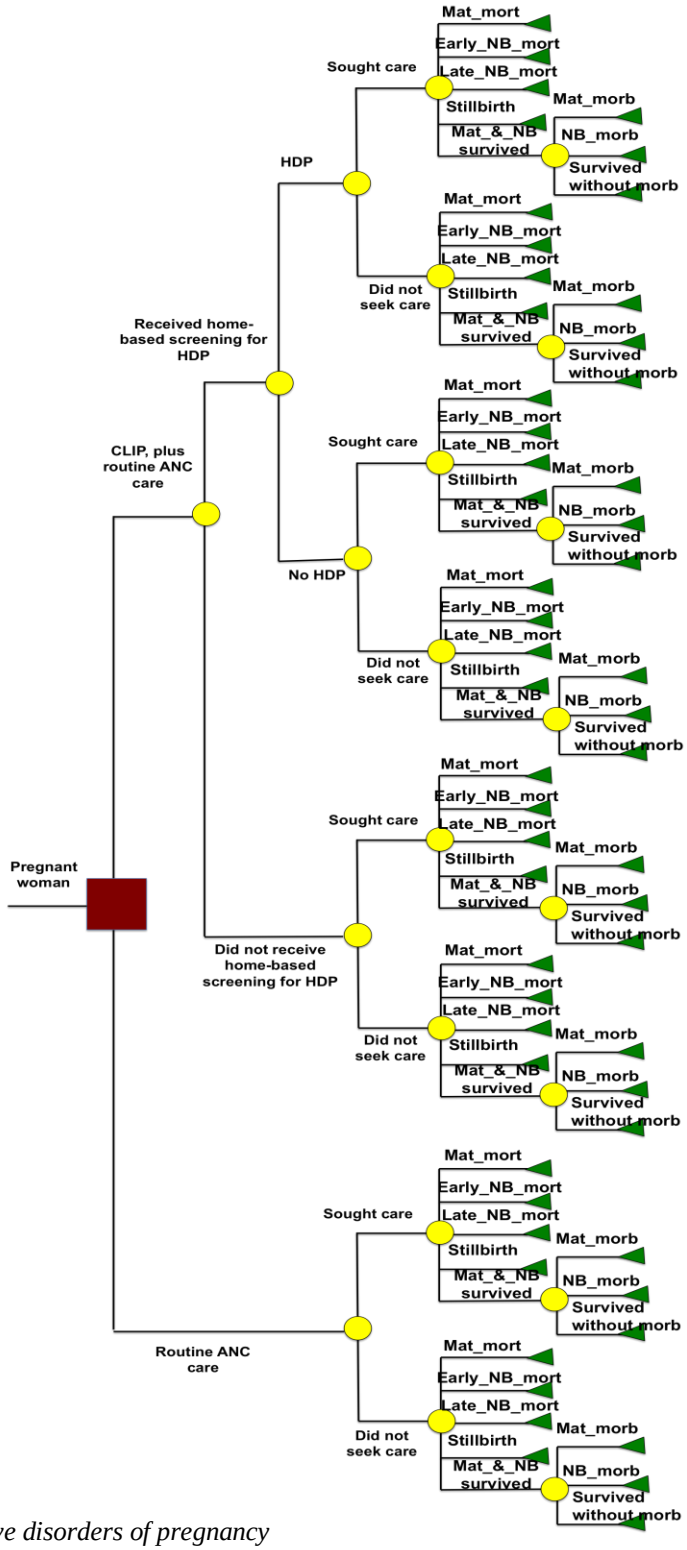
Figure 3. Societal costs: model inputs



A. Health resource utilization represents medical and non-medical costs of maternal and newborn care.

B. Productivity loss represents work hours/missed wages due to illness and disease.

Figure 4. Decision analytic tree model



Mat=Maternal;
NB=Newborn;
Morb=Morbidity;
Mort=Mortality;
HDP=Hypertensive disorders of pregnancy

Chapter 4: Societal perspective on cost drivers for health technology assessment in Sindh, Pakistan

4.1 Background

Globally, maternal and newborn mortality trends have declined, albeit slowly, over the last 10 years in LMICs (74). Rapidly increasing costs of care, shortages of trained personnel, cultural barriers that delay care-seeking, and geographical remoteness continue to impose considerable challenges for health systems in LMICs that are struggling to achieve new sustainable development goals for mortality reduction by 2030 (75). In response, policy-makers are considering technological innovations such as mobile health (mHealth) interfaces to bridge gaps in MNCH service coverage in LMICs. Currently, health technologies are used for early detection of disease, vaccination reminders, behaviour change for child survival interventions, and training/retention of health care providers (76).

Economic evaluation, conducted as part of HTA, provides a systematic approach to collect evidence about costs and effectiveness from the diverse perspectives of care providers, care receivers and community stakeholders (77). Such an inclusive approach is imperative to guide the use of health technologies and inform policy decisions on resource allocation for program scale-up. The literature on economic evaluation embedded in HTA is sparse; of the 1,412 studies currently registered with clinical trials, only 124 (~9%) are in LMICs (78). A knowledge gap in this area undermines future investment for technological innovations in health care in LMICs.

Pakistan is the world's sixth largest country in terms of population; and belongs to a group of LMICs according to the World Bank classification (i.e. gross national income per capita in international dollar $1,046 to $4,125) (79). Pakistan's health care delivery system is bifurcated

into private and public sectors. The private health sector includes informal care providers (i.e., traditional birth attendants, spiritual healers, and quack doctors) and formal medical clinics and/or hospitals. The public health sector is comprised of primary, secondary and tertiary levels of health facilities (80). An extension of primary level care includes community-based LHWs recruited by the National Program for Family Planning and Primary Healthcare. LHWs are aged 18 to 45 years and are local residents who have attended a minimum 8 years of schooling. Having received 15 months of on-the job training in the area of MNCH, a LHW covers a catchment of 1000 people and provides door-to-door basic services inclusive of routine ANC, vaccination, health education, and psychological counseling on reproductive health and family planning (81). Overall, health care-seeking practices portray a dismal picture suggesting that only 65% of pregnant women seek routine ANC; nearly 48% of deliveries occur without the assistance of a skilled care provider and fewer than 50% of women seek either postpartum and/or newborn care (82). It is estimated that the maternal mortality ratio (MMR) is as high as 276 per 100,000 live births; and infant mortality rate (IMR) is as high as 74 per 1000 live births (82).

The literature review in Chapter 2 reported on knowledge gaps for cost-effectiveness of PE/E interventions in LMICs. Previous economic studies on PE diagnosis and case-management restricted focus to health provider costs, such as the cost of drugs, devices and human resource. The societal perspective, inclusive of OOP costs to patients/families and opportunity costs, albeit a very important driver for public policy, were excluded from these cost-effectiveness analyses.

4.2 Objectives

This study aimed to assess community experiences of health resource utilization and perceived cost drivers, using a societal perspective.

4.3 Methods

4.3.1 Study design and conceptual framework

Qualitative research was undertaken alongside the CLIP trial during November to December 2014. The conceptual framework was guided by a phenomenological approach that attempts to understand people's experience in regard to specific phenomenon of common interest. It is based on participants' view of the situation and how they interpret those experiences (83). The phenomenological research design was relevant to our study, as we explored lived experiences about costs of patient screening, referral, treatment and transport to health facilities in a diverse group of participants (Figure 5, pg 56).

4.3.2 Study setting

This study was conducted in two districts (i.e., Matiari, and Hyderabad) of the southern Sindh province in Pakistan. Matiari is a rural district located 25 kilometers north of Hyderabad with a population of approximately 0.6 million (84). Hyderabad is a semi-urban setting with population of over 1 million making it the second largest district of Sindh province (85). A vast majority of residents are Muslims, agriculturalist by occupation; and Sindhi/ Urdu languages are widely spoken in these districts. Overall, literacy rates are 40% in Matiari and 50% in Hyderabad.

4.3.3 Participant inclusions/exclusions

Beyond the published CLIP trial protocol (10), pregnant women were eligible for this qualitative study if they were: (i) within an intervention cluster; (ii) identified as being hypertensive (i.e. systolic blood pressure $\geq$ 140mmHg) during a CLIP pilot cRCT visit; and (iii) available for a discussion lasting at least 60 minutes. The literature suggested that household decision makers traditionally make decisions about women's health issues in LMICs(71). As

inclusively as possible, household decision makers (e.g. husbands, mothers-in-law, fathers-in-law) of hypertensive pregnant women were eligible if they also expressed availability for at least 60 minutes of discussion. LHWs, and medical doctors (MDs) were eligible, if they participated in the implementation of the CLIP pilot cRCT. The health decision-/policy-makers were eligible if they were involved in decisions related to the execution of the CLIP pilot cRCT. Participants' characteristics varied in terms of age, schooling years, and occupation (Table 4, pg 53).

4.3.4 Sampling procedures

A purposive sampling strategy was imperative to this study design as we needed individuals or groups with lived experiences (i.e. information-rich cases) who could provide insight based on their own experiences related to HDP care sought/provided during the CLIP pilot cRCT. The sampling framework included 4 intervention clusters (~400 pregnancies per cluster in one year), in which we estimated 80 pregnant women would experience HDP (i.e. 5% of all pregnancies). Pregnant women and household decision-makers were identified through the trial recruitment logs, while health care providers and decision-/policy-makers were identified through health facility networks. The project-trained RAs approached eligible participants in their respective settings (i.e. either at their home or workplace) and invited them to take part in the study. We had anticipated 5 FGs (at least one FG per each group); however, we increased the number of FGs (two FGs per group; except health decision-/policy-makers) to achieve data saturation. In total, nine FGs were conducted: two with pregnant women/mothers-in-law (n=19 in total), two with husbands/fathers-in-law (n=17), two with LHWs (n=19), two with medical doctors at health facilities (n=20), and one with district-level health decision-/policy-makers (n=10). Participants were reimbursed for study-related transportation costs.

4.3.5 Data collection

The FG guides were developed from the literature review. Key constructs included out-of-pocket (OOP) costs related to care seeking during pregnancy (86), and health service utilization in the context of LMICs (87). Participants of the study were asked to reflect on lived experiences and interpret situations related to financial costs as a result of their participation in a one-year pilot phase of the CLIP cRCT. FG guides were developed in English as the main language of literature review. FG guides were translated into Sindhi; and back translated into English. They were pilot-tested for comprehension and cultural sensitivity. Native Sindhi-speaking and project-trained RAs moderated the FGs. The RAs were local residents, with undergraduate degrees, who had experience as data collectors in previous maternal health research. Given cultural tradition related to the veil system, women are not allowed to participate in public meetings in the presence of men. To respect the cultural values and participants' preferences, FGs were held separately with women and men. Likewise, separate FGs were organized for LHWs, MDs and health decision-/policy-makers given the logistics and ease of care providers. Data saturation was determined through a review of FG transcripts for new emerging codes/ideas, and the saturation point was deemed to have been reached when transcripts returned no new codes.

4.3.6 Data analysis and quality control

FGs were taped using a digital voice-recorder and transcribed verbatim in Sindhi. The transcripts were imported to NVivo version 11 software [QSR, Doncaster Vic, Australia] for data analysis. The analysis of FG data was conducted in the same language [Sindhi], using the new version of NViVo that allows for coding in languages other than English. This increased rigor in the data analysis and prevented meaning loss from translation. The participants' attributes were

analyzed, and their responses were coded on a hierarchy of tree nodes (i.e. branches of relevant constructs). A combined approach to data analysis inclusive of inductive and deductive reasoning was used to interpret emerging themes/sub-themes (88). The descriptive coding list provided a comprehensive understanding of thematic areas for subsequent interpretations (Table 5, pg 54).

Data quality was ensured through random observations of FGs by field coordinators and a public health scientist, 10% (audit-trail) verifications of the content of manual transcripts by audio-recording reviews, and weekly debriefing sessions with moderators/transcribers. The FG moderator recorded a self-reflection after each session to describe personal thoughts and impressions to better contextualize the data, as well as to protect against self-bias.

4.4 Results

Participants' discussions were categorized into emerging themes and sub-themes as HDP-related health resource utilization, and/or as perceived costs to family, health system and program implementation.

4.4.1 Health care resource utilization for HDP

The theme on resource utilization suggested patterns and types of care sought from health facilities in the catchments. Almost all pregnant women reported having sought health care after they were identified as hypertensive and referred to a health facility by LHWs. The majority visited public secondary and tertiary health facilities that were usually located outside study clusters, requiring families to arrange transport. In most cases, women were delivered by Cesarean delivery (C-section). One woman described her experience of visiting a distantly located public health facility in the following quote:

"We traveled to Shadadpur government hospital for the treatment. Doctors told … [me] … that my blood pressure was extremely high and I had to deliver the baby. They said that normal delivery is unlikely because of high blood pressure, therefore, they did C-section to deliver my baby". Participant 6, FG 1, pregnant women and mothers-in-law

A few pregnant women stated that they visited private general practitioners because of easy access, family preferences, and past unfavorable experiences with public sector health facilities.

4.4.2 Perceived cost drivers

The theme on perceived cost drivers contextualized a broad range of costs to care receivers, health care providers and decision-/policy-makers.

- *OOP costs*

Pregnant women (i.e. care-receivers) emphasized OOP expenditure as the main barrier to seeking timely care. The OOP costs were described as in- and out-patient care, diagnostic procedures, informal care received from traditional healers, self-medication at home, childbirth, and transport to health facilities. The reported lump sum OOP costs ranged from 50 Pakistani rupees (PKR) (US$0.5) for diagnostic procedures to 10,000 PKR ($100) for in-patient hospitalization for childbirth (Table 6, pg 55).

The OOP costs were usually perceived as a large financial burden for the family of a pregnant woman, and they had a substantial impact on their economic conditions and wellbeing. One husband described this in the following quote:

"We don't have savings for emergencies related pregnancy and childbirth. [We had to sell] family assets and borrowed money from friends/neighbors… It took us several months to pay back the borrowings." Participant 7, FG 1, husbands and fathers-in-law

Alternatively, costs deterred families from seeking care:

"Because I did not have money, we didn't go to hospital when my wife was identified as hypertensive during the current pregnancy….we cannot afford health care expenses!". Participant 7, FG 2, husbands and fathers-in-law

Participants stated that husbands (in most cases) and/or mothers-in-law were responsible for accompanying pregnant women when they were transported to a health facility. Additionally, blood relatives, and/or family friends were often reported to have stayed with, and remained involved in patient care, when a pregnant woman was hospitalized for HDP management and for childbirth. A vast majority of family members were paid a lump sum wage of 150 to 500 PKR ($1.5 to 5) per day, or a fixed salary of 8000 to 13000 PKR ($80 to 130) per month. Consequently, missed wages for family members were considered to be a double economic burden for the family and others involved.

- *Health system costs*

LHWs and MDs (i.e. care providers) revealed health system costs associated with human resources, transport, and communication. LHWs described making once-monthly home visits to provide basic antenatal care to pregnant women in their catchment areas. Home visits were described to include screening pregnant woman for HDP, initial case management (if the pregnant woman was identified at risk for adverse birth outcomes), and referrals to health facilities. The duration of a completely routine visit, where the pregnant woman was found to be in good health, was 20 to 30 minutes. A more typical visit would take 30-60 minutes to complete if the pregnant woman required medications and/or the family needed counseling about referral to a health facility. One LHW described her typical home visit experience in the following quote:

"A pregnant woman would often speak about her problems. Most women have a problem of anemia and complain of pain. They share domestic worries related to their husband's lack of support and misunderstandings with mothers-in-law. Therefore, it sometimes takes one hour to complete a visit." Participant 6, FG 1, LHWs

Moreover, a few LHWs mentioned families' expectations that they (LHWs) accompany pregnant women to health care facilities and exchange their cell phone numbers to maintain communication for emergencies.

MDs practicing at primary and secondary health facilities considered performing basic diagnostic tests such as blood pressure monitoring, blood sugar testing, proteinuria measurement, and ultrasound imaging. Prescribing patterns revealed frequent use of oral tablet methyldopa (aldomet) to treat high blood pressure, injection [of] diazepam to control seizures, and referral to higher-level health facility for severe complications during pregnancy. MDs practicing at tertiary-level health facilities considered advanced maternal and fetal tests, such as 24-hour urine collection, blood tests (i.e., serum uric acid, prothrombin time, activated partial thromboplastin time, electrolyte profile, complete blood count, lipid profile, liver function tests), and fetal imaging. All recommended close monitoring as an in-patient and interventions that included intravenous administration of magnesium sulfate, blood transfusion, and Cesarean delivery.

- *Program implementation costs*

Health decision-/policy-makers recognized program implementation costs (such as mobile health infrastructure, staff training, and monitoring/supervision) as major investments for the health system. All health decision-/policy-makers believed that mHealth technologies have potential to improve maternal and perinatal health in LMICs. They discussed the prerequisites for effective program implementation: (i) a major initial investment in establishing the mHealth

platform (e.g., purchase of electronic tablet devices for app-guided clinical care, computers for downloading and data-sharing, and high speed internet to facilitate data synchronization); and (ii) patient screening equipment (e.g., digital blood pressure devices, pulse oximeters, and urine dipsticks). Many health decision-/policy-makers reported the need to train all existing staff through refresher programs and to provide ongoing monitoring and supervision.

4.5 Discussion

This paper reports a societal perspective of cost drivers relevant to stakeholders considering the CLIP interventions, and has demonstrated that care-seeking practices vary between public and private health sectors in Sindh, Pakistan. Our findings further highlighted contextual aspects of resource utilization that guided the design of a comprehensive questionnaire for quantitative ascertainment of individual level health resource utilization during the trial period.

Given ever-increasing reliance on technology use in health care, there are implications for incremental costs to society (89). We found that referral of pregnant women requiring treatment at health facility resulted in the OOP costs; and productivity loss/missed wages further added financial burden on families and/or primary caregivers. Our findings are corroborated with other studies from developing countries that indicate over 50% of total health spending as OOP (90). Ironically, OOP costs are often omitted from cost analyses because such costs are assumed to be irrelevant for program implementation. A recent cost analysis of peer health workers and mHealth support interventions for improving AIDS care in Uganda lacked OOP costs in their analysis (91). We also interpreted from FGs that the sicker a patient was, in terms of severity and complication, and/or if the decisions to seek care were delayed, the higher the OOP costs

incurred. Thus, our findings point to the need to consider OOP costs when conducting economic evaluation of health technologies in LMICs.

The program implementation as indicated in this study suggests incremental costs to the provincial public health department, as health technology procurement and trainings require substantial investments. Program costs are often feared to increase the burden on existing health budgets in LMICs. It is likely that community-based screening and/or interventions using mHealth platform will influence care-seeking behaviours. Our argument is supported by a randomized control trial that demonstrated that short message services (SMS) and cell phone reminders (i.e. the intervention group), compared with no reminders (i.e. the control group), were associated with significantly higher attendance rates at health promotion centres (92). Another cost-effectiveness study from Pakistan reported higher costs related to personnel time, equipment and supplies in community-based response stimulation and nutrition interventions on early child development (93).

The economic appraisal of emerging health technologies plays a pivotal role in policy advocacy and resource allocation for post-trial program scale-up (94). We found that health decision-/policy-makers supported mHealth initiative, and expressed their interest in finding cost-effectiveness of the CLIP interventions in Sindh, Pakistan. These findings are similar to those observed in a qualitative study in the UK, where health authorities strongly recommended economic evaluation to advise policy decisions in health care (95).

4.5.1 Strengths and limitations

The International Society of Pharmacoeconomics and Outcome Research (ISPOR) recommend in-depth assessment of jurisdiction-specific costs and outcome parameters for decision-analytical models of multi-national trials. In this study, we used a pragmatic approach

to assess cost drivers necessary for the economic analysis alongside the CLIP trial in Sindh, Pakistan. FGs with a wide range of stakeholders in relation to the CLIP trial further add methodological rigor to the overall study. We recognize that combine FGs for pregnant women- and mothers-in-law; husbands- and fathers-in-law may have resulted in social desirability bias and it is the main limitation of current study.

The transferability of our study findings is limited to care-receivers, care-providers, and program implementers in relation to the CLIP trial in Sindh, Pakistan. The methodological approaches as reported in this study may guide future health economics studies evaluating MNCH interventions in Pakistan and other LMICs.

4.6 Conclusions

A thorough understanding of care-seeking practices revealed financial implications for families of pregnant women, and program costs for the health system during implementation of CLIP trial. The societal perspective provided contextual information, and revealed a more comprehensive description of cost drivers that can be used to design an economic model to fulfill the needs of health decision-/policy-makers considering CLIP interventions in Sindh, Pakistan.

Table 4. Focus group participants' characteristics

Groups	# of focus groups	Number of participants	Age in years Mean (+SD)	Schooling years Mean (+SD)	Occupation (n, frequency of participants)
Pregnant women with pregnancy hypertension	02	12	24.5 (3.8)	3.1 (4.7)	8 Housewife 4 unskilled labour work
Mothers-in-law		07	44.2 (4.2)	0 (-)	6 Housewife 1 unskilled labour work
Husband of pregnant women with pregnancy hypertension	02	13	26.3 (5.2)	3.7 (4.1)	9 unskilled labour work 3 Farmers 1 Employed in grouped services
Fathers-in-law		04	43.8 (2.1)	0.75 (1.5)	2 Farmers 1 unskilled labour work 1 Business
Community care providers	02	19	31.2 (4.8)	11.1 (2.0)	19 Employed as LHW
Medical doctors at referral health facilities	02	20	33.7 (5.6)	17.8 (1.1)	11 OBGYN specialist 9 General physician
District health decision/policy makers	01	10	53.4 (3.3)	17.1 (1.2)	8 General physician 1 Specialists 1 Administration
Total	**09**	**85**			

LHW, Lady health worker
OBGYN, Obstetrics and gynecologist

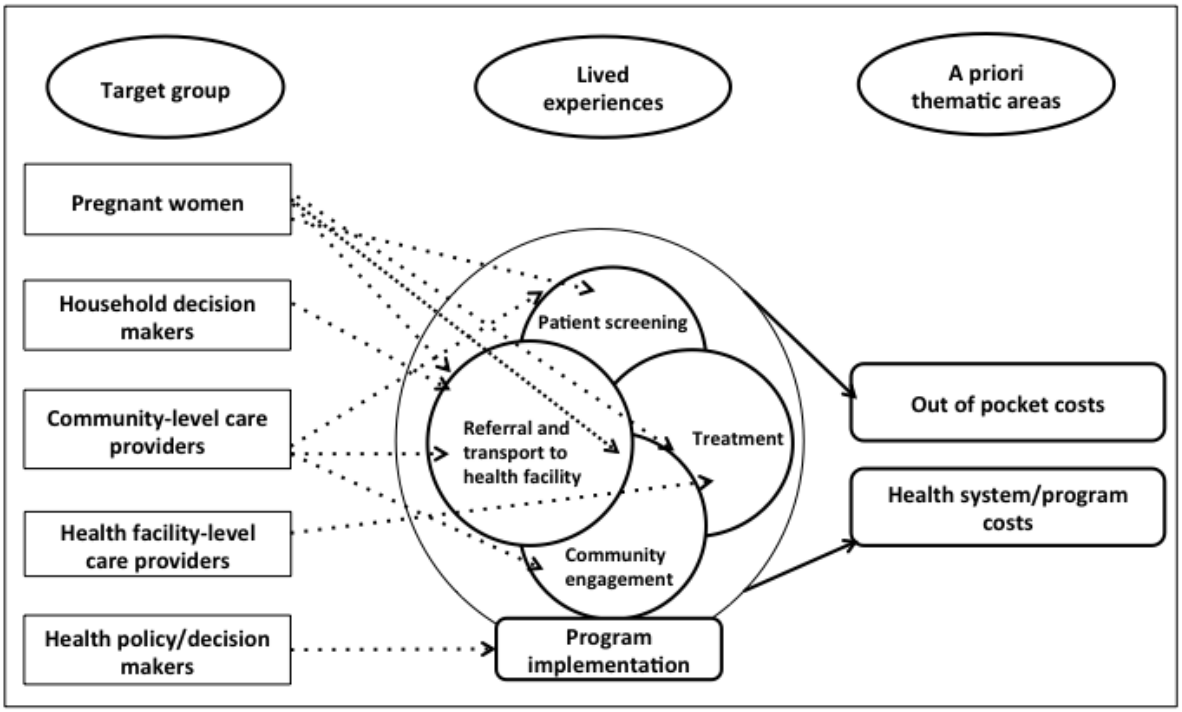
Table 5. Descriptive coding list for thematic analysis

Program implementation	**Thematic areas related to cost drivers using societal perspective**		
	Out-of-pocket costs	Health system costs	Program implementation costs
Patient screening, and out-patient visits	Diagnostic procedures	Human resource [personnel time]	Procurement of technologies for patient screening
	Out-patient doctor's visit	Laboratory tests	Trainings for technology-use
			mHealth platform to support technology implementation
Referral and transport to health facility	Transport to-and-from health facility	Transport for home-based visits	Cellular communication
	Missed wages by family and/or care-givers	Accompanying women to hospital	Access to computer and internet
Treatment	In-patient hospitalization, other than childbirth	Initial case-management for sick women	Monitoring and feedback
	In-patient hospitalization for childbirth	Clinical procedures	
	Medications	Medications	
	Care received from traditional care-providers	Specialist consultations	
Community engagement	Opportunity costs to attend sessions	Personnel time	Materials, and logistic support

Table 6. Lump sum out-of-pocket costs related to healthcare sought for HDP

Health resource utilization	Cost in PKR (US$)	
	Minimum	Maximum
Diagnostic procedures	50 (0.5)	3500 (35.0)
Out-patient doctor's visit	150 (1.5)	1500 (15.0)
In-patient hospitalization, other than childbirth	2500 (25.0)	7000 (70.0)
In-patient hospitalization for childbirth	3000 (30.0)	10000 (100.0)
Transport to-and-from health facility	500 (5.0)	3500 (35.0)
Childbirth at home [Conducted by traditional birth attendant]	1000 (10.0)	1500 (15.0)
Self-medication	800 (8.0)	2000 (20.0)
Missed wages (inclusive of woman and caregiver)	900 (9.0)	5000 (50.0)
US$ currency exchange rate of 2015		

Figure 5. Conceptual framework and approach for societal perspective



Chapter 5: A comparison of maternal and newborn health services costs in Sindh, Pakistan

5.1 Background

The cost of care influences decisions related to care seeking, and utilization of MNH services (96). Data related to health expenditures in Pakistan revealed a declining trend of GDP spending on health over the past decade; currently as low as 2.4%. It is further estimated that over 80% of healthcare spending is out-of-pocket, and predominately in the private sector (97). This shift towards the beneficial use of HT integration has implications for incremental costs to patients, health systems and society at large (98). However, a lack of compressive knowledge of the cost of MNH services at different levels of care confounds policy decisions about introducing existing interventions, and impedes economic appraisal of emerging HT in Pakistan.

The assessment of cost-effectiveness of the CLIP trials requires a thorough understanding of maternal and newborn costs at health facilities in the CLIP countries. In designing an economic model for the CLIP trial in Pakistan, similar challenges were faced, as health facility costs were unknown for care received during pregnancy, delivery and early newborn stages in both private and public sectors.

5.2 Objectives

The primary objective of this study was to estimate the cost of MNH services. The secondary objective was to compare cost of MNH services within and/or between public and private health sectors in Pakistan.

5.3 Methods

5.3.1 Study design

A cross-sectional survey of health provider/facilities was conducted during January to March 2016, as part of a large economic evaluation of the CLIP Trial in Sindh, Pakistan. The provision of basic, as well as comprehensive, emergency obstetric and newborn care (EmONC) services, were available in the private health sector (i.e. 100% out-of-pocket costs to patients), and the public health sector (i.e. nearly 100% health system costs, and very little OOP costs for patients [transport, food and diagnostics]).

Health facilities were clustered into three broad categories: primary, secondary and tertiary levels. Categorization was based on the population served, hospital size (usually, number of beds), and the provision of clinical subspecialty services and intensive care. The primary level health facilities provide health services to less than 50,000 people, with inpatient capacity of 0 to 10 beds, and focus on basic obstetric and newborn care. The secondary level hospitals provide health services to over 1 million people, with inpatient capacity of 40 to 60 beds, and focus on basic and EmONC services. The tertiary level hospitals serve as the referral point, provide multispecialty clinical services, and offer intensive care facilities to a wider population (80).

5.3.2 Inclusion and exclusion criteria

The healthcare providers and facilities were considered eligible if they met these criteria: (i) geographical location within study catchments; (ii) secondary and tertiary level hospitals in the public health sector, to which pregnant women are referred by LHWs under the National Program; and (iii) private healthcare providers and facilities, where pregnant women self-refer for pregnancy care and childbirth. Primary level facilities in the public health sector; and healthcare providers and facilities that declined to participate were excluded (Figure 6, pg 68).

5.3.3 Sampling procedures

Healthcare providers and facilities were selected from a sampling frame, inclusive of public and private health sector in the study catchments, as previously described (99). Public health facilities were identified through the National LHWs Program and private healthcare providers and facilities were identified through the trial network. The project field coordinator approached the administrative staff at health facilities and invited them to participate in the study.

5.3.4 Methods of data collection

A structured questionnaire was used to collect costing data of MNH services. The key variables included: routine antenatal care (ANC), ambulatory visits (AV) for maternal and newborn care, diagnostic tests and imaging, overnight inpatient admission, childbirth and blood transfusion. Project RAs; registered midwives who were bachelor degree holders with MNH research experience) were trained by a Senior Scientist, who is a native speaker of the local Sindhi language, and had experience in MNH research in Sindh.

RAs visited healthcare providers and facilities and ascertained unit costs from billing departments as they were charged to patients in the form of fee-for-service at the private facilities. However, a simultaneous allocation method was used to estimate the unit costs in the public facilities because resources were shared between service departments (94). The allocation of costs was based on an estimate of resource-use for shared costs (i.e. staffing, utility, laundry, housekeeping, repair-and-maintenance, and patient food), and independent costs (medication, supplies, equipment, and furniture/fixture). The department-level costs were later divided by the average number of patients attending clinics and the number of beds to calculate the unit costs

for ambulatory visits and inpatient admissions, respectively. The costs were estimated in the local currency, Pakistani Rupee (PKR), and later converted into US$ [1 US$ = 104.7 PKR].

5.3.5 Data analysis

Descriptive analyses were performed to calculate mean and standard deviations for cost estimates from public and private hospitals, except tertiary level hospitals where point-estimates were reported. The analyses of variance (ANOVA) tests compared overall mean costs within and between public and private health sectors, and statistically significant differences were interpreted with p-value (two-tailed) <0.05. Analyses were performed using SPSS version 24.

5.4 Results

A total of 43 eligible healthcare providers and facilities (n=36 private; n=7 public) were approached within the study catchments. The refusal rate varied from 14% (n=1/7) to 27.8% (n=10/36) in the public and private health sectors, respectively. The final cost analysis included 25 facilities in the private health sector (19 primary-, five secondary- and one tertiary-level facilities), and six facilities in the public health sector (five secondary- and one tertiary-level facilities). The public facilities were geographically scattered, whereas private healthcare providers and facilities were in close proximity.

5.4.1 Cost of maternal health services

An AV for routine ANC from a medical doctor costs $3.6 ($\pm$SD 2.1) at secondary level; and $0.9 at tertiary level public facilities. In the private health sector, the mean cost of AV for routine ANC were $2.2 ($\pm$1.9) in medical clinics, $2.8 ($\pm$2.6) in secondary level, and ($6) in tertiary level facilities. The AV was less costly for routine ANC provided by midwives ($0.6 $\pm$ 0.3) and traditional birth attendants ($0.5 $\pm$ 0). The costs of many diagnostic tests or imaging

were similar within all levels of public facilities. In the private health sector, costs of diagnostic tests were much higher at the tertiary level.

The cost of inpatient general ward admission was higher in the tertiary level, compared with secondary-level public facilities ($57.5 versus, 3.4 ± 1.7). The costs of delivery were low at secondary level facilities for spontaneous childbirth ($45.4 ±SD 30.7 versus, 79), and assisted childbirth, compared with the tertiary level public facility ($50.2 ±SD 33.8 versus, 86), respectively. The cost of Caesarean delivery was less in the public tertiary facility, compared with the private tertiary facility ($223.8 versus, 400). Significant differences were found in the overall mean costs for maternal health services within/between public and private facilities at p-values < 0.05 (Table 7, pg 66).

5.4.2 Cost of newborn health services

The mean cost of newborn AV in the secondary-level hospitals was $2.7 ± 1.8 compared with $0.4 at the public sector tertiary-level hospital. Newborn AV costs were lowest ($0.5 ± 0) when provided by midwife and traditional birth attendants in the private health sector. The cost of fetal ultrasound, newborn x-ray, and blood grouping differed substantially at all levels of health facilities in public and private sectors. Phototherapy was only available at tertiary-level facilities, and cost ranged from $1 to 2 in the public and private sectors, respectively. The cost of newborn admission into a nursery was low in the public compared with private tertiary-level facilities ($10.3 versus, 13.8 ± 3.7). However, the cost of newborn intensive care admission was higher in the public compared with private tertiary-level facilities ($22.3 versus, $19 ± 7.8). Significant differences were found in the overall mean costs for newborn health services within/between public and private facilities (Table 8, pg 67).

5.5 Discussion

This paper reports the costs of a wide range of MNH services relevant to families (i.e. out-of-pocket) and health systems, and has demonstrated that these costs vary significantly at different levels of health facilities within and between public and private sectors in Sindh, Pakistan. Our findings provide a robust measure of unit-costs by service type and levels of health facility for future economic studies aiming to estimate cost-of-illness in the area of maternal and newborn care in Sindh, Pakistan.

PE/E are serious conditions during pregnancy requiring frequent AVs for routine antenatal care, diagnostic tests and health facility admissions in the event of disease complications. The costs of health services at private health facilities as reported in this study suggest a large financial burden related to out-of-pocket payments on families (tables 7 and 8, pg 66-67). We found a progressive trend in the costs for AV dependent on the level of private health care (i.e. costs lower at medical clinics and higher at the tertiary level). Similarly, the costs of diagnostic tests and imaging were higher in private facilities. A previous study evaluated role of public spending on healthcare across 11 Asian countries. Authors in that study found that distribution of public health infrastructure is mainly biased towards the provision of services for the wealthy (pro-rich) in many LMICs, and that transition towards pro-poor healthcare requires limiting the user fees, protecting the poor from catastrophic expenditure on health, and creating a wide network of public health facilities (100).

The private sector is expanding within the health industry in LMICs, and employs social marketing techniques to attract patient volume (58). In a previous qualitative study, authors found that many women sought pregnancy-related care from private health facilities (101). Despite higher costs, decisions to seek care are often dominated by the perception of quality of

care at such facilities (102). In another study, authors assessed patients' perception about service quality in Pakistan, and reported that private health facilities deliver better quality of care to patients compared with public facilities (103). Guided by our local field observations, we determined that the private health sector tends to offer cutting-edge diagnostic technologies (i.e. latest and/or expensive imported machines from abroad) to meet the growing demand for precision medicine in Pakistan. We assume that the private health sector could offer lower inpatient prices possibly through cost containment (i.e. controlling overhead expenditures, rational distribution of lower- and higher- cadre of medical staff based on patient volume), and operating with low profit margins to attract greater patient volumes. More efforts are needed to regulate the private sector and promote strategic purchasing to be able to lower health services costs. This study does not estimate profit margins on the cost of MNH services in private sector.

Our findings further highlight the policy implications for health systems, as AV for maternal and newborn care are more costly at the secondary-, compared with tertiary-, level public facilities in Pakistan. These findings are similar to those observed in the Northern Province of Pakistan, where AV costs were higher (i.e. $4.1) at basic health units, and probably reflect ambulatory costs being mainly dependent upon the number of patients attending outpatient clinics (i.e., fewer patients, more cost per AV) (104). Upon reviewing records of patient registry at secondary-level facilities, we found that fewer pregnant women were attending outpatient clinics (range: 25 to 50 per day), compared with 250 to 500 per day) at the tertiary level public facility. Previous studies indicated several factors such as inadequate staffing, poor facilities for in-patient admissions, and a poorly-coordinated referral system are responsible for low patient-volumes at lower-level health facilities (105,106). Furthermore, we found that costs of inpatient admissions, other than for delivery, were much higher in the public facilities. The

cost allocation exercise indicated higher operating costs (i.e., staff salaries, equipment, medication, and overheads) at inpatient departments. Others also reported increased cost burden in public health facilities, assuming that patients are presenting with severe illnesses and/or disease complications (requiring longer inpatient stays) as a result of delaying care (107).

The economic appraisal of emerging HT requires robust data on costs and health outcomes using a societal perspective, inclusive of care receivers, care providers and health system (108). Our findings are critical to calculate real-world cost-inputs representing public and private health sectors, as we embark upon analysing MNH resource utilization (end-user data) reported from the intervention and control groups in the CLIP Trial in Pakistan. In addition, the methodological approaches and our findings may guide future health economics studies evaluating MNH interventions in Pakistan and other LMICs.

5.5.1 Strengths and limitations

To our knowledge, this is the first study to estimate the cost of MNH services at different levels of health facilities in the public and private sectors in Pakistan. We benefitted from high participation (86%) of public secondary- and tertiary-level facilities. The primary-level health facilities were omitted from our analysis because they did not serve as a referral point for EmONC services in the community. Also, primary health facilities were large in numbers, which would have required additional project expenses to capture all possible facilities. We recognize that costing information from primary-level facilities may have been important for comparative analysis across three tiers of public health system in Pakistan and it is the main limitation of current study.

Collecting evidence-based information on costs and health outcomes is often challenging in the absence of electronic medical records and poor data keeping in LMICS (109). We faced

similar challenges in public and private health sectors. It was a resource-intensive exercise, requiring frequent long-distance travel to public hospitals and several in-person meetings with people in the clinical, budget and finance departments. In the private health sector, people were reluctant to share costing information on MNH services and hospital budgets (i.e. revenue and expenses) due to fear of litigation. Also, some private health facilities were only open in the evening, which created operational difficulties for the project RAs and data collection. We encountered a high refusal rate in the private health sector because of operational difficulties and reluctance to share costing information with persons other than patients. We increased the sample size particularly in the private sector by three-fold, compared to the public health sector, to address the possibility of non-response bias in data collection.

5.6 Conclusions

This economic appraisal of MNH services revealed cost disparities within public health sector suggesting higher costs for AV at the secondary-level, and inpatient admissions at tertiary-level health facilities in Sindh, Pakistan. The private sector stands-out as an expensive choice of care provider for diagnostics and delivery. An understanding of MNH costs is critical to guide resource allocation within the public sector and for risk mitigation against excessive out-of-pocket costs through third party payer for services in the private sector.

Table 7. Cost of maternal health services in public and private health sectors

Variables	*Public Health Sector Costs (USD)*			*Private Health Sector Out-of-pocket Costs (USD)*				**Mean Difference**	***p-value***
	Secondary hospitals (n= 5) Mean (±SD)	Tertiary hospital* (n=1)	Overall public (n=6) Mean (±SD)	Clinics/care provider (n= 19) Mean (SD)	Secondary hospitals (n=5) Mean (±SD)	Tertiary hospital* (n=1)	Overall private (n=25) Mean (±SD)	(Overall Private minus Public)	
Ambulatory visits for routine antenatal care (cost per visit)									<0.0001
Medical doctor	3.6 (2.1)	0.9	2.3 (2.1)	2.2 (1.9)	2.8 (2.6)	6	3.7 (2.2)	1.4	
Nurse	NA	NA	-	1.7 (2.1)	NA	NA	1.7 (2.1)	1.7	
Midwife	NA	NA	-	0.6 (0.3)	NA	NA	0.6 (0.3)	0.6	
Traditional birth attendant	NA	NA	-	0.5 (0)	NA	NA	0.5 (0)	0.5	
Diagnostic tests (cost per test)									
Pregnancy ultrasound	0.5 (0)	0.5	0.5 (0)	2.8 (1.1)	3.9 (3.2)	6	4.2 (2.4)	3.7	
Complete blood count	0.9 (0.9)	0.4	0.7 (0.6)	2 (1.4)	3.8 (2.2)	5.2	3.7 (2.2)	3	
Culture	1.3 (1.1)	0.6	0.9 (0.8)	NA	6.9 (6.6)	4.2	5.6 (4.9)	4.7	
Creatinine	0.4 (0.2)	0.4	0.4 (0.1)	NA	3.4 (2.8)	4.3	3.9 (2.2)	3.5	
Serum albumin	0.4 (0.2)	0.2	0.3 (0.1)	NA	3.2 (0.8)	3.2	3.2 (0.8)	2.9	<0.0001
Aspartate Aminotransferase	NA	NA	-	NA	6	NA	6	6	
Alanine aminotransferase	NA	0.8	0.8	NA	3.8 (2.7)	1.9	2.9 (1.3)	2.1	
Urine dipstick	0.3 (0)	NA	0.3 (0)	0.8 (0.5)	1.3 (1.2)	NA	1.1 (0.9)	0.8	
Urine microscopy	0.3 (0)	0.2	0.3 (0.1)	NA	1.8 (1.5)	2.6	2.2 (1.4)	1.9	
Chest x-ray	0.9 (0.6)	0.5	0.7 (0.3)	NA	2.5 (1.4)	6	4.3 (2.1)	3.6	
CT scan	NA	15	15	NA	NA	20	20	5	
In-patient admissions (cost per overnight stay)									0.0136
General ward	3.4 (1.7)	57.5	30.5 (38.3)	4.2 (1.4)	8.5 (11.1)	15.2	9.3 (8.7)	-21.2	
Intensive care	NA	151.2	151.2	NA	NA	36.5	36.5	-114.7	
Delivery and blood transfusion (cost per procedure)									<0.0001
Spontaneous vaginal delivery	45.4 (30.7)	79.1	62.3 (30.7)	33.3 (14.8)	86 (92.4)	150	89.8 (93.1)	27.5	
Assisted vaginal delivery	50.2 (33.8)	86.6	68.4 (33.8)	35.8 (23.7)	106 (108.8)	200	113.9 (104.6)	45.5	
C-section	NA	223.8	223.8	NA	304 (167.2)	400	352 (154.3)	128.2	
Blood transfusion	NA	20.1	20.1	NA	17.8 (22.3)	25.8	21.8 (19.6)	1.7	

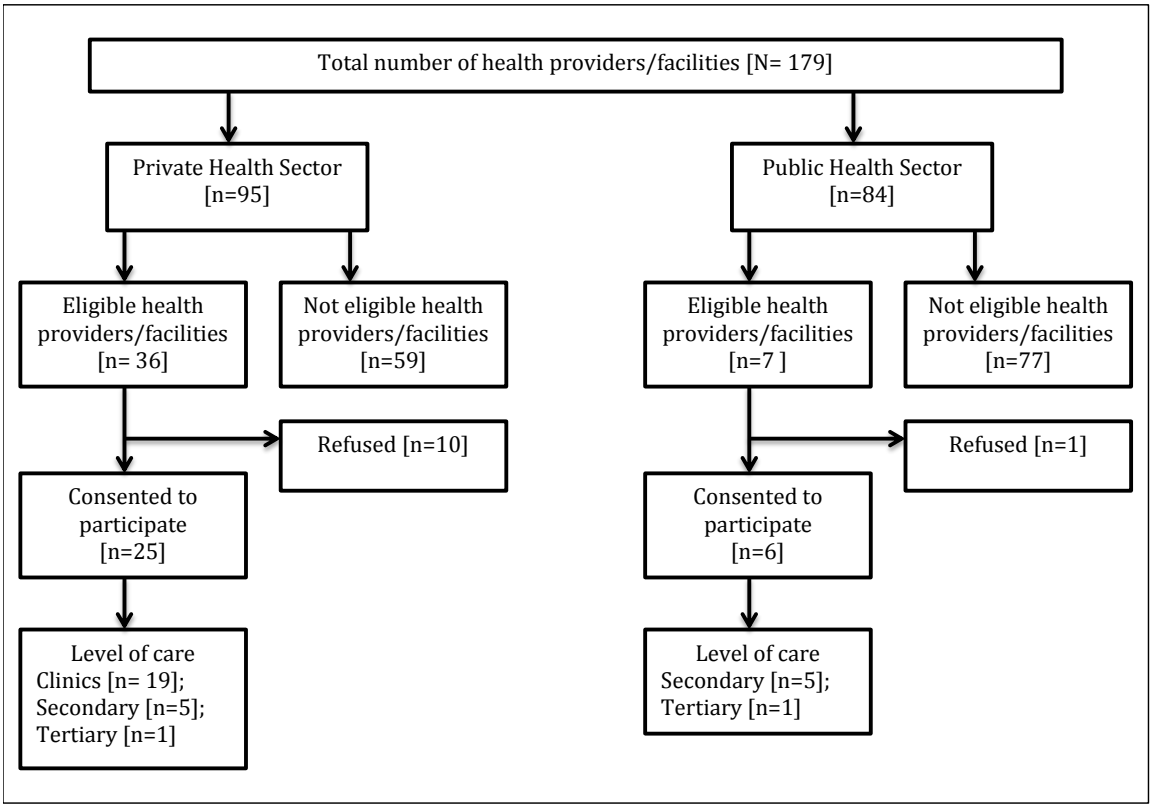
** Mean and standard deviation not calculated for one facility; NA= not available at designated health facility*

Table 8. Cost of newborn health services in public and private health sectors

Variables	*Public Health Sector Costs (USD)*			*Private Health Sector Out-of-pocket Costs (USD)*				**Mean Difference**	***p-value***
	Secondary hospitals (n= 5) Mean (±SD)	Tertiary hospital* (n=1)	Overall public (n=6) Mean (±SD)	Clinics/care provider (n= 19) Mean (SD)	Secondary hospitals (n=5) Mean (±SD)	Tertiary hospital* (n=1)	Overall private (n=25) Mean (±SD)	(Overall Private minus Public)	
Ambulatory visits for newborn care (cost per visit)									0.0001
Medical doctor	2.7 (1.8)	0.4	1.6 (1.7)	1(0)	2.6 (1.1)	2	1.9 (1.1)	0.3	
Nurse	NA	NA	-	2.3 (2.5)	NA	NA	2.3 (2.5)	2.3	
Midwife	NA	NA	-	0.5 (0)	NA	NA	0.5 (0)	0.5	
Traditional birth attendant	NA	NA	-	0.5 (0)	NA	NA	0.5 (0)	0.5	
Diagnostic tests (cost per test)									<0.0001
Fetal ultrasound	0.5 (0)	0.5	0.5 (0)	4 (0)	6.3 (6.4)	6	5.4 (4.7)	4.9	
Fetal x-ray	1 (0)	0.5	0.5 (0.3)	1.5 (0)	3.8 (2.3)	6	3.8 (2.4)	3.3	
Blood grouping	0.3 (0)	0.2	0.3 (0.1)	NA	2.2 (2.8)	3.4	2.8 (2.3)	2.5	
Arterial blood gases	NA	NA	-	NA	12.9 (0)	8.5	10.7 (3.1)	10.7	
Phototherapy	NA	1	1	NA	NA	2	2	1	
In-patient admissions (cost per overnight stay)									0.0011
Nursery	NA	10.3	10.3	NA	11.2 (0)	16.4	13.8 (3.7)	3.5	
General ward	4.5 (0)	8.2	6.4 (2.6)	NA	5.9 (1.28)	12.1	9 (3.6)	2.6	
Intensive care	NA	22.3	22.3	NA	17.8 (10.6)	20.2	19 (7.8)	-3.3	

** Mean and standard deviation not calculated for one facility; NA= not available at designated health facility*

Figure 6. Healthcare providers and facilities in the public and private health sector



Chapter 6: Cost-effectiveness of the Community Level Interventions for Pre-eclampsia (CLIP) in Sindh, Pakistan

6.1 Background

Several epidemiological studies have demonstrated the positive impact of community-based interventions, specifically those involving LHWs in various parts of Pakistan. Bhutta et al. evaluated a package of community-based interventions (i.e., use of clean delivery kits, promotion of routine ANC and maternal health education, facility births, and newborn care) delivered by LHWs in Sindh, Pakistan. In that study, investigators found reductions of 21% for stillbirth and 15% for neonatal mortality (110). In another cluster randomized equivalence trial, LHWs provided mothers with oral amoxicillin for children aged 2 to 59 months with severe pneumonia in the intervention group, compared to oral cotrimoxazole and referral to a health facility (standard of care). This study reported a significant reduction in the treatment failure (i.e., risk difference of -8.9%; 95% CI: -12.4% to -5.4%) in the intervention group in the Punjab province of Pakistan (111). Given the ever-expanding role of LHWs in pregnancy and newborn care, the ministry of health is considering additional investments to promote LHWs as frontline care providers for preventive and community-based management or referral services in Pakistan (81).

As discussed in Chapter 3, the CLIP introduces the mHealth innovation for HDP screening, risk stratification, and case management initiated by LHWs in community settings. As with the introduction of new technologies, there may be financial implications to the health system with post-trial scale-up. Economic evaluation of the CLIP interventions was imperative to inform the decisions on resource allocation for programme scale-up, should the trial find evidence on clinical-effectiveness. Therefore, the economic analysis was conducted to estimate costs relative to benefits associated with the CLIP package of care.

6.2 Objectives

The primary objective was to estimate the incremental costs and health benefits of CLIP plus routine pregnancy care, compared with routine pregnancy care alone. The secondary objective was to perform the temporal analysis of program-related costs and rate of pregnancy outcomes over the study period in the intervention and control group.

6.3 Methods

6.3.1 Study design

Economic evaluation was conducted alongside the trial to assess the costs relative to benefits for the CLIP package of care combined with routine pregnancy care, in comparison to routine pregnancy care alone. The decision analytic model was used, drawing input parameters from the CLIP Trial and mixed-methods research used in this study. Gamma distribution was applied to cost inputs, and lognormal distribution was applied to pregnancy outcome inputs (Table 9, pg 85).

6.3.2 Data analysis

The costs to the health system included resources used to implement the CLIP Trial. The capital costs comprised of clinical devices and mHealth technology used in home-based screening for HDPs. Recurrent operating costs included community-based patient management, referral and follow-up (i.e., drugs, supplies, patient transport), and community engagement (i.e., personnel, venue, refreshment, transport allowance for participants). LHW costs included costs of training, the incentive for pregnancy registration, and transport for home visits. Because health system capacity enhancement and surveillance for the ascertainment of pregnancy outcomes occurred simultaneously in both groups, these costs were equally distributed in the intervention and control groups. Costs to women and families included maternal and newborn

HRU such as ambulatory visits, overnight hospitalization, diagnostic tests and procedures, childbirth, transport to and from a health facility, and productivity losses. Descriptive analysis was done to calculate the frequency and proportion of maternal and newborn HRU in the intervention and control groups. A generalized linear mixed-model regression was performed to compare mean cost, standard errors, 95% CI and p-values between two groups. The gamma distribution was used in the regression analysis to address the skewed nature of cost data (112). Tests for correlations and multicollinearity were applied on the total costs and explanatory variables to fit the model. The fixed variables included age, years of schooling, comorbidities, and health care-seeking behaviors. The random variables included baseline neonatal mortality ratio and population index. Two variables (permission for routine ANC and permission for obstetric emergencies) were highly correlated, with suggested Pearson Correlation value = 0.93 and Variance Inflation Factor-IVF= 28.2. After discarding one variable (permission for obstetric emergencies), IVF score reduced to 1 for all explanatory variables. The societal cost was calculated as the sum of the costs: maternal and newborn HRU, the CLIP package of care, LHWs incentive/transport, surveillance for ascertaining pregnancy outcomes, and health system capacity enhancement. The annual equivalent costs in Pakistani rupees (PKR) was converted to US dollars using average currency exchange rates of 2014-2016 (104.7 PKR = 1 US$).

DALY is a common outcome metric widely used in the economic literature, and this represents the sum of YLL and YLD. A recent publication from the Global Burden of Disease (GBD) provides instructions and tools for calculating YLL and YLD in LMICs (113). The average age of maternal and newborn deaths was used to calculate YLL with respect to the country-specific life expectancy tables for Pakistan (114). Similarly, we calculated YLL for stillbirths using the value on a standard life table for life expectancy at birth. The YLD were

derived taking into account the epidemiological rates for maternal and newborn morbidities observed in the trial period, and were multiplied with disability weights (DWs) as reported on the recent publication from Global Burden of Diseases (56,113). However, we faced some challenges in determining YLD for maternal and newborn morbidities, as DWs are not established for several severe conditions. Thus, we restricted our analysis only to include YLL in the economic model, as the principal component of DALYs.

Both costs and health outcomes were discounted at a rate of 3%, and estimated incremental cost per life-year saved. In the base-case analysis, the ICERs were calculated first from a health care system perspective, and then from a societal perspective. A probabilistic analysis (a Bayesian approach that allows the effects of joint uncertainty across all input parameters) of the base case was performed using Monte Carlo simulations to select values at random from 10,000 iterations in Microsoft Excel. Results of the probabilistic analysis were plotted on a cost-effectiveness plane to represent the distribution of the ICER. The results were interpreted through the use of a cost-effectiveness acceptability curve (CEAC) showing the probability that ICERs fell below the acceptable WTP threshold. In this study, WTP threshold represents the GDP per capita in 2016 in Pakistan (i.e., $1,468) (115).

We applied one-way sensitivity analyses by varying the parameter estimates using a plausible range to test their influence on the ICER. The parameter estimates included the percentage of effect size as 1%, 20%; percentage of discount rate as 0%, 6%; currency exchange rate 2014, 2016; and cost of CLIP implementation $\pm$10%. The outputs from sensitivity analysis were plotted on a tornado diagram.

For the secondary objective, an exploratory analysis was done to compare quarterly trends for costs and trial-based composite adverse pregnancy outcome (combined maternal and

perinatal mortality and severe morbidity) over the study period. The capital costs of electronic tablets and phones were annualized over the expected useful life of 5 years; and digital clinical devices (blood pressure monitor and pulse-oximeter) were annualized over the expected useful life of 10 years. The recurrent operating costs such as clinical supplies, drugs, and transport were based on the number of women who delivered in each quarter. The rate of composite adverse pregnancy outcomes was translated into health benefits as "rate of adverse outcomes avoided" (1 minus the rate of adverse pregnancy outcomes). The average cost per pregnancy and rate of health benefits were compared in the intervention and control groups over the study period.

6.4 Results

6.4.1 Trial recruitments and participants' characteristics

In all, 20,264 pregnancies were included in the 10 clusters randomly assigned to receive CLIP interventions, and 19,180 pregnancies were included in the 10 control clusters. Only seven women withdrew from the study; three in the intervention group, and four in the control group. A very small proportion of pregnant women was lost to follow-up; 752 in the intervention group (3.7%) and 864 in the control group (4.5%). At the trial closeout period, roughly 5% of pregnancies in both the intervention (n=1,063) and control (n=967) groups were undelivered or still on follow-up.

The mean ($\pm$SD) maternal age in the intervention group was 28 years ($\pm$4.7), compared to 27.6 years ($\pm$4.4) in the control group. Other characteristics such as mean gestational age, maternal primary education ($\geq$ 5 years of schooling), husbands with primary education, and parity did not significantly differ between two groups. A large majority of pregnant women were unemployed or engaged in unpaid domestic services: 16,180 (80%) in the intervention group, compared to 14,159 (74%) in the control group. In the intervention group, about one-third of

women (n=6,846) reported their husband's occupation as skilled manual laborer, and another 19% (n=3,859) reported work in agriculture. Fewer women (n=5,784, 30%) reported skilled manual labor as the occupation of their husband in the control group. Other medical conditions did not differ between two groups, except that anemia was higher in the control group (n=4,508, 24%) than in the intervention group (n=3,890, 19%). Care-seeking preferences revealed that a higher proportion of women in the control group were allowed by their husbands to seek care for both routine ANC (n=16,128, 84%) and pregnancy-related emergencies (n=15,674, 82%). A slightly higher proportion of women in the intervention group (n=5,517, 27%) reported having funds saved for pregnancy-related emergencies, compared to women in the control group (n=4,487, 23%) (Table 10, pg 86).

6.4.2 Trial-based maternal and newborn health resource utilization

The maternal and newborn HRU estimates are reported on for followed-up pregnancies to compare costs and health benefits in cases where we have complete information over the full term of pregnancy. There were 18,449 followed-up pregnancies of 20,264 (91%) in the intervention group, and 17,349 of 19,180 (90.5%) in the control groups. Of these, 16,013 women (87%) reported routine ANC visits in the intervention group, as compared to 14,266 women (82%) in the control group. Approximately 90% women sought routine ANC from medical doctor in both groups. The mean ($\pm$SD) routine ANC visits in the intervention group was 4.4 visits ($\pm$4.1), compared to 3.3 visits ($\pm$3.2) in the control group. The ambulatory visits at HLCF for pregnancy-related illnesses were slightly higher in the control group compared to the intervention group, with a mean difference of 0.5 visits. All diagnostic tests were reported at higher rates in the control group except urine dipstick, which was lower in the control group (n=6,843, 39%) than in the intervention group (n=8,010, 43%). There were some differences in

the maternal hospital admissions between the two groups, indicating higher intensive care admissions in the intervention group. The mean (±SD) length of stay in the intensive care unit was 2.4 (±1.0) in the intervention group, compared to 2.1 (±1.1) in the control group.

Approximately 24% of women in both groups reported having a home birth. A higher proportion of women in the intervention group (n=7,756, 43.5%) reported childbirth at a private health facility compared to the control group (n=6,566, 39%). Of births taking place at a health facility, a higher proportion of women in the control group reported spontaneous vaginal birth (9,094 of 12,726, 71%) compared to the intervention group (9,107 of 13,558, 67%). The proportions for Caesarean section were almost similar in the intervention group (n=3,227, 24%) and control group (n=2,715, 22%). Transport trips to health facility were slightly higher in the intervention group, with a mean difference of 0.7 trips. The hired wageworker to assist pregnant woman in the household chores, however, was as high as 9.4% (n=1,738) in the intervention group, compared to only 3.3% (n= 580) in the control group (Table 11, pg 87).

Fewer women reported ambulatory visits for newborn illnesses in the intervention group (1,430 of 18,449, 8%) compared to the control (1,901 of 17,349, 11%). Over 90% women sought newborn care from medical doctor in both groups. The mean (±SD) ambulatory visits for newborn care in the intervention group was 1.9 visits (±1.5), compared to 1.8 visits (±1.4) in the control group. The newborn diagnostic tests were almost similar in both groups. There were some differences in the newborn hospital admissions between the two groups, indicating higher intensive care admissions in the intervention group. Overall, the mean (±SD) length of newborn hospital stay in the intervention group was 1.9 (±1.4), compared to 1.7 (±1.2) in the control group. The mean transport trips to health facility and missed daily wages due to newborn illness were higher in the intervention group (Table 12, pg 89).

6.4.3 Costs to health system

The LHWs in CLIP clusters were supplied with a handbag containing clinical supplies, a Microlife VSA blood pressure device ($22), a PX-43-B Kenek pulse oximeter ($20), and either a Mobile Q-Noir A7 phone ($126) or a Q-300 8GB tablet ($143) to carry out the home visits (Table 13, pg 90).

The total financial cost of the intervention (including CLIP package of care, LHWs, surveillance, and health system capacity enhancement) was $530,755, compared to $313,602 for usual practice in the control group. The cost of the CLIP package of care (excluding surveillance, LHWs, and health system capacity costs) was $137,756. Of this total, community engagement accounted for 52% ($71,942), home-based HDP screening for 44% ($60,949), and community-based HDP case management for only 4% ($4,864) (Table 14, pg 91). The community engagement session targeted male members of the community (number of sessions = 820), and cost approximately $88 per session (cost $4 per person). Home-based HDP screening was performed on 11,461 women (cost $5.30 per woman), and the women received a total of 58,409 screening visits (cost $1.10 per visit). The cost of providing CLIP trainings, incentive and transport to make follow-up home visits by LHWs was $79,398 (cost $4 per woman). The compliance with CLIP-POM recommendations were as follows:

1) Of 406 visits requiring non-urgent referrals, 311 (76.6%) were accepted;

2) Of 220 visits requiring urgent referrals, 169 (76.8%) were accepted;

3) Of 168 visits requiring MgSO4 treatment, 98 (58.3%) were accepted;

4) Of 155 visits requiring Methyldopa treatment, 150 (96.8%) were accepted.

6.4.4 Costs to pregnant women and their families

The total financial cost of maternal HRU was $2,153,346 in the intervention group, and $1,879,995 in control group. Regression analysis revealed statistically significant differences in the mean costs for most of the explanatory variables (such as the maternal age, maternal primary education, husbands with primary education, parity, savings for pregnancy-related emergencies, and medical conditions including high blood pressure, seizures, and diabetes) with p-values <0.05 (Table 15, pg 92).

The regression-adjusted mean cost of maternal care was $163.40 (95% CI: $51 to 529) in the intervention group compared to $156.70 (95% CI: $49 to 506) in the control group, with p-value: 0.958. The total financial cost of newborn health resource utilization was $14,260 in the intervention group, compared to $17,961 in the control group. The regression-adjusted mean cost of newborn care was $4.00 (95% CI: $0.70 to 23.41) in the intervention group compared to $4.2 (95% CI $0.60 to 24.60) in the control group, with p-value: 0.964. The regression-adjusted mean cost of combined maternal and newborn care was $164 (95% CI: $51 to 528) in the intervention group and $158 (95% CI: $49 to 507) in the control group, with p-value: 0.962, suggesting no significant difference overall between two groups (Table 16, pg 93).

6.4.5 Effectiveness (YLL and YLD)

Maternal mortality rates were estimated at 2.71 (per 1,000 identified pregnancies) in the intervention group and 2.66 in the control group. Maternal deaths were translated into 76 and 64 YLL in the intervention and control groups, respectively. The early neonatal mortality rate was estimated at 40.5 (per 1,000 identified pregnancies) in the intervention group, compared to 42.7 in the control group. The YLL resulting from early neonatal death was calculated at 1,214 and 1,237 in the intervention and control groups, respectively. Stillbirth rate was estimated at 46.2

(per 1,000 identified pregnancies) in the intervention group, compared to 49.6 in the control group. Stillbirths resulted in a low of 1,373 YLL in the intervention group and 1,439 YLL in the control group. The combined YLL were slightly higher in the intervention group (YLL=2,968) than in the control group (YLL=2,957) (Table 17, pg 94). Similarly, the combined maternal YLD were higher in the intervention group (YLD=1,264) than in the control group (YLD=1,244). The results are summarized in Table 18, pg 95.

6.4.6 Incremental cost-effectiveness estimates

In the probabilistic analysis of the base case, the incremental cost of the intervention group compared to the control group was $14,592, while the YLL was -37 (i.e., negative health gains in the intervention group compared to the control group) using a program perspective. Similarly, the societal perspective revealed the incremental cost of the intervention group compared to the control group was $20,438, while the YLL was -37 (Table 19, pg 97). The cost-effectiveness plane demonstrated statistical uncertainty around ICER, indicating a wider distribution extending from the northeast quadrant to the northwest quadrant. The mean ICER fell into the northwest quadrant, suggesting higher costs and negative health gains (health loss) (Figure 7, pg 99). The CEAC quantifies the uncertainty by demonstrating the probability of ICERs at a given WTP. The probability of ICERs falling under the standard WTP threshold of $1,468 was 26%. In a conservative scenario with WTP threshold of $489 (i.e., one-third of GDP per capita), the probability of ICERs falling under this threshold further decreased to 16% (Figure 8, pg 100).

Upon characterizing uncertainty of individual variables, the sensitivity analysis revealed an inverse relationship between trial-based effect size and estimated ICER, suggesting a high degree of uncertainty associated with this variable. When the effect size was assumed to be as

low as 1%, the ICER increased to $420 per life-year saved. The ICER substantially declined to $21 per life-year saved when the effect size was hypothetically increased to 20%. Several other scenarios, including varying the discount rate (0% versus 6%), varying the currency exchange rate (2014 versus 2016) and varying the implementation costs (from -10% to +10%), did not dramatically change the results (Figure 9, pg 101).

6.4.7 Time trends for costs relative to outcomes

The annualized program-related costs were estimated at $178,199 in the intervention group and $106,706 in control group. The average cost in the intervention group was as high as $71 per pregnancy in the first quarter of 2015 and as low as $29 per pregnancy in the first quarter of 2017 (Figure 10-A, pg 102). The average costs were $52 in the first quarter of 2015 and $18 in the first quarter of 2017 in the control group. The rate of adverse pregnancy outcomes avoided steadily improved over the study period in both groups. The gain was relatively higher in the control group, compared to the intervention group (Figure 10-B, pg 102).

6.5 Discussion

This chapter reports the incremental cost relative to health benefit for CLIP combined with routine pregnancy care compared to routine pregnancy care alone. The mean ICER in this study suggests that the intervention requires additional cost but may result in lower or even zero health benefit. In the economic literature, this scenario is referred to as the intervention being dominated by the control. The probabilistic analysis demonstrated a wide range of statistical uncertainty around ICERs and highlights low probability for the intervention to be acceptable at a standard WTP threshold in Pakistan.

There is a plethora of scientific evidence in support of community-based interventions in LMICs. Previously, several economic studies have reported favorable (i.e., lower) ICERs for

similar community-based interventions in South Asia and Africa. A recent study on newborn home visits by trained volunteers, compared to routine home visits by untrained volunteers, in rural Ghana, reported an ICER of $379 (95%CI: $227 -873) per life-year saved (116). Similarly, other studies evaluated women's group interventions compared to the current practice of individual-level pregnancy care and found ICERs of $375 and $138 in Bangladesh and Nepal, respectively (117,118). A few studies also reported much lower ICERs, such as newborn home visits by community care provider (ICER= $8) in India (119), training traditional birth attendants (ICER= $23) in Zambia (120), and women's group interventions (ICER= $112) in Malawi (121). More importantly, the intervention effect size ranged from 40% to 73% in these studies, which likely is an important driver for finding more favorable ICERs. In the CLIP Trial, the economic findings were driven by a statistically insignificant effect size and wide confidence intervals for maternal and perinatal outcomes (Table 20, pag 98). The ICERs falling in the Northwest quadrant on the cost-effectiveness plane suggested higher cost and negative health consequence. It is debatable that a screening-cum-educational intervention (such as the CLIP package) may have resulted in the unintended health consequences or potential harm to some study participants. In particular, higher rates of adverse pregnancy outcomes related to severe maternal and newborn morbidities were important drivers of negative health consequences. Further investigation is needed to perform the disaggregated analysis of mortality and morbidity outcomes taking into account the socio-demographic characteristics, contextual factors (e.g. access to the health system, and ability to pay for services), intervention coverage, and dose-response comparing intervention and control groups. However, smaller sample size for mortality outcomes, lower statistical precision, and wider uncertainty levels will be major limitations for sub-group analysis.

The time trend analysis suggests lower costs to rates of adverse outcomes avoided in the control group compared to the intervention group. Although the rates of adverse outcomes avoided improved in both groups, they improved more in the control group indicating a possibility of a 'Hawthorne effect'. During the trial period, the control group may have benefited from household surveillance and activities related to health system capacity enhancement. Clearly, our study findings raise an important research question: are simple health interventions both less costly and more effective than complex health interventions? The Medical Research Council in the UK describes that complex interventions contain several interacting components, which makes impact evaluation more difficult because there are multiple process-related outcomes (122). Howe et al. reported that cluster trials involving complex health interventions often yield non-significant results, and are costly to implement (123). CLIP meets the classic definition of a complex health intervention (124), so it is plausible that higher costs relative to benefits in the intervention group actually reflect inherent methodological limitation(s) associated with the cluster design or the complex nature of the intervention. We did not find any supporting literature to differentiate the cost-effectiveness of simple versus complex health interventions, and future research in this area is highly recommended. It is worth noting that the temporal trends also indicated a learning curve with a possibility of finding incremental health gains in the intervention group, should the time-to-effect be lengthened. More research is needed to assess the long-term benefits of the CLIP interventions, compared to household surveillance embedded into the routine pregnancy care.

This study finding highlights the substantial burden of OOP costs to pregnant women and their families. The mean cost of maternal health resource utilization was higher in the intervention group. The increased number of intensive care admissions and relatively more

deliveries taking place in the private health sector could explain incremental maternal costs in the intervention group. Although the protocol-driven health resource utilization remained less than 2%, it may also have contributed towards higher costs in the intervention group. The majority (~71%) of these costs were out-of-pocket. Only 27% (n=5,517) of women reported fund savings at the time of pregnancy registration; higher cost of care associated with obstetric emergencies implied greater financial burden for families. This was further triangulated with our initial FGs, where participants revealed poverty and unaffordability of health services as the main reasons for delaying care. In the absence of a safety net, catastrophic expenditures resulting from pregnancy complications are likely to plunge families into a vicious cycle of poverty. Community-based strategies such as creating village committees for pooling of resources in Rwanda (125), voucher schemes for patient transport in Bangladesh (126), and active community participation on a photo-voice project in Contra Costa (127) have improved care-seeking practices, increased demand for skilled births, and reduced maternal and newborn mortalities elsewhere.

6.5.1 Strengths and limitations

The prospective data collection on a large pregnancy cohort alongside the CLIP Trial was a major strength, and a pragmatic approach to real-world costs from the private and public health sectors added methodological rigor to our subsequent cost-effectiveness analysis. Our cost-effectiveness estimates are robust, as we have accounted in our analysis for possible uncertainties related to costs and health outcomes.

We faced several challenges in calculating YLD component of the DALYs, as the disability weights (DWs) for many severe maternal and newborn conditions evaluated in the CLIP Trial are not established. Severe conditions include maternal coma, disseminated intravascular coagulation, newborn seizures (excluding epilepsy), newborn coma, and bleeding,

which may enormously contribute to disability burden in this vulnerable population. A few other acute conditions, such as feeding/breathing difficulty in a newborn, neonatal jaundice, and newborn infections could possibly result in long-term motor or cognitive impairments, are not considered in DW calculations by GBD. We also noticed some inconsistencies in DWs for a few conditions. For instance, DW of maternal hemorrhage (loss of more than 1 litre of blood) is reported as 0.324, which is more than the DW of 0.316 for stroke, a much more severe lifelong disability. Other limitations, such as premature home births and congenital malformations, where we often lack clinical newborn assessments by a certified health professional, may grossly underestimate the disability burden at a population level. Clearly, more research is needed for a comprehensive understanding of DWs, to capture the most prevalent and likely severe conditions during the pregnancy and postpartum periods.

The economic analysis was undertaken on the completed follow-up cases captured in the trial closeout surveillance data as of August/September 2017, and additional data cleaning may result in random invalidation of few cases in both groups. Some limitations related to health resource utilization data include women lost to follow-up and unavailability of medical charts at the health facility. In the CLIP Trial, only a small fraction of women were lost to follow-up and still on follow-up. Schafer, in his paper on statistical methods in medical research, highlights that list-wise deletion, when the data is missing completely at random, provides estimates that are unbiased (128). Bouhlila et al. recommend using multiple imputations using a chained equation approach when the sample size is fairly small and missing data exceed 20% (129). The health facility admission charts were available only for 1% of pregnancies recruited in the trial (416 of 39,444), a consequence of poor medical record-keeping practices at the health facilities. This might have underestimated the intensity of HRU for women who were hospitalized or sought

emergency care after they were referred from the community. Lack of medical chart verification is an important limitation to health resource utilization, particularly for women who were very sick and may have received intensive care at the health facility.

6.6 Conclusions

The economic analysis suggests that the CLIP package combined with routine pregnancy care is not a cost-effective strategy when compared to routine pregnancy care alone. More research is needed to explore the contextual aspects (i.e. enabling and impeding factors) during trial-implementation period through subsequent process-evaluation design. Interventions involving mHealth technologies also have financial implications of start-up costs for health care system, so budget impact analysis is imperative to inform policy decisions about resource allocation. This also relates to finding an extra funding envelope, or possible areas for disinvestment (i.e. opportunity cost) to support future similar initiatives in Pakistan, and elsewhere in LMICs.

Table 9. Model input parameters and type of distributions

Model inputs parameters	Value	95% confidence intervals	Source	Distribution
Probabilities				
Maternal mortality, T1	0.0027	0.002, 0.004	CLIP Trial	Log-normal
Maternal morbidity, T1	0.1088	0.104, 0.113		
Early neonatal mortality, T1	0.0404	0.037, 0.043		
Late, neonatal mortality, T1	0.0096	0.008, 0.011		
Early/late neonatal morbidity, T1	0.0992	0.009, 0.010		
Stillbirths, T1	0.0462	0.043, 0.049		
Composite adverse outcomes, T1	0.2655	0.258, 0.272		
Screened for HDP, T1	0.5655	0.553, 0.576		
HDP prevalence, T1	0.0501	0.045, 0.055		
Sought care, T1	0.8902	0.877, 0.903		
Maternal mortality, T0	0.0026	0.002, 0.003		
Maternal morbidity, T0	0.0895	0.085, 0.094		
Early neonatal mortality, T0	0.0426	0.039, 0.045		
Late, neonatal mortality, T0	0.0078	0.006, 0.009		
Early/late neonatal morbidity, T0	0.0651	0.061, 0.068		
Stillbirths, T0	0.0496	0.046, 0.052		
Composite adverse outcomes, T0	0.2187	0.210, 0.234		
Sought care, T0	0.8827	0.864, 0.896		
Average cost (in USD$)				
CLIP-home based screening for HDP, T1	$5.3	4.7, 5.8	Financial reports, budgets, and mixed-methods research alongside CLIP trial	Gamma
CLIP-community engagement, T1	$4	3.6, 4.4		
CLIP-LHWs training and support, T1	$4	3.6, 4.4		
Surveillance and health capacity enhancement, T1	$16	14.4, 17.6		
Surveillance & health capacity enhancement, T0	$17	15.3, 18.7		
Maternal HRU, T1	$163	51.0, 529.0		
Newborn HRU, T1	$4	0.7, 23.4		
Maternal HRU, T0	$157	49.0, 506.0		
Newborn HRU, T0	$4.2	0.6, 24.6		
Years of life lost				
Maternal mortality	44	38, 50	CLIP Trial and GBD	Log-normal
Perinatal, early/late neonatal mortality, and stillbirths	68	-		

T1 = Intervention; T0= control; HRU = Health resource utilization; HDP = Hypertensive disorders of pregnancy; GBD = Global Burden of Disease

Table 10. Baseline characteristics at enrollment

Variables	Intervention [N=20,264]	Control [N=19,180]
Socio-demographic profile		
Maternal age in years, mean (±SD)	28 (4.7)	27.6 (4.4)
Gestational age in weeks at enrollment, mean (±SD)	21 (8.3)	21.3 (8.2)
Maternal primary education, number (%)	3972 (19.6)	3276 (17.1)
Husbands with primary education, number (%)	9532 (47.2)	8246 (43.2)
Parity, mean (±SD)	2.5 (2.4)	2.7 (2.5)
Maternal occupation, number (%)		
• *Unemployed / unpaid domestic services*	*16180 (80)*	*14159 (74)*
• *Unskilled manual labour*	*601 (3)*	*1599 (8.3)*
• *Skilled manual labour*	*585 (2.8)*	*721 (3.8)*
• *Agricultural work*	*458 (2.3)*	*444 (2.3)*
• *Others (Professional, sales, student)*	*151 (0.8)*	*71 (0.4)*
• *Don't know / Missing*	*2289 (11.1)*	*2186 (11.2)*
Husband's occupation, number (%)		
• *Unemployed*	*393 (2)*	*241 (1.3)*
• *Domestic services*	*287 (1.4)*	*114 (0.6)*
• *Unskilled manual labour*	*3595 (17.7)*	*6485 (34)*
• *Skilled manual labour*	*6846 (34)*	*5784 (30)*
• *Agricultural work*	*3859 (19)*	*2449 (12.3)*
• *Sales and services*	*1253 (6.3)*	*823 (4.3)*
• *Professionals / managerial*	*1310 (6.5)*	*769 (4)*
• *Others (clerical, student)*	*398 (2)*	*514 (2.5)*
• *Don't know / Missing*	*2248 (11)*	*2129 (11)*
Medical conditions/illnesses, number (%)		
High blood pressure	1184 (6)	1005 (5)
Seizures	214 (1)	110 (1)
Diabetes	99 (0.5)	102 (1)
Tuberculosis	115 (0.6)	72 (0.4)
Anemia	3890 (19)	4508 (24)
Worms	49 (0.2)	56 (0.3)
Care-seeking preferences, number (%):		
Allowed to seek routine antenatal care	15728 (78)	16128 (84)
Allowed to seek care in the event of health emergency	15388 (76)	15674 (82)
Require care from family/friend, who would otherwise work for wages	2806 (14)	2232 (12)
Funds saved for pregnancy related emergencies	5517 (27)	4487 (23)
Cluster-level variables		
Baseline neonatal mortality rate (per 1,000 live births) in last 12 months	29.74	27.96
Population density	4.10	5.28

Table 11. Maternal health resource utilization

Variables	Intervention [N=18,449]		Control [N=17,349]		Mean difference (Int. – Cont.)
	n (%)	Mean (±SD)	n (%)	Mean (±SD)	
Received routine antenatal care (ANC), from*:	[n=16013, 87%]		[n=14266, 82%]		
• *Medical doctor*	*14449 (90)*	4.4 (4.1)	*13192 (91)*	3.3 (3.2)	1.1
• *Nurse*	*269 (2)*		*206 (2)*		
• *Midwife*	*546 (3)*		*98 (1)*		
• *Lady Health Worker*	*2864 (18)*		*69 (0.5)*		
• *Any provider-pilot*	*936 (6)*		*835 (6)*		
Ambulatory care for pregnancy related ailments, other than routine ANC					
Primary Health Centre (PHC) visit	2992 (16)	2.5 (1.6)	3152 (18)	2.5 (1.7)	-
Higher Level Care Facility (HLCF) visit	2631 (14)	2.8 (1.9)	2509 (15)	2.3 (1.6)	0.5
Diagnostic tests/procedures*					
Imaging / scanning:	[n=18041, 98%]		[n=16931, 97%]		
• *Ultrasound*	*17829 (99)*	2.5 (1.7)	*16688 (99)*	3 (2.1)	-0.5
• *Chest x-ray*	*2866 (16)*		*3392 (20)*		
• *CT scan*	*2817 (16)*		*3364 (20)*		
Blood tests:	[n=10120, 55%]		[n=10732, 62%]		
• *Complete blood count (CBC)*	*9635 (95)*	0.7 (0.9)	*10630 (99)*	0.8 (0.9)	-0.1
• *Other blood tests: (Culture, Creatinine, AST/ALT)*	*3676 (34)*		*3630 (35)*		
Urine tests:	[n=8010, 43%]	0.5 (0.7)	[n=6843, 39%]	0.3 (0.6)	0.2
• *Dipstick*	*7734 (97)*		*6552 (96)*		
• *Lab/microscopy*	*3960 (49)*		*3678 (54)*		
In-patient admissions at higher level health facility-HLCF					
In-patient admissions HLCF setting:	[n=365, 2%]		[n=542, 3%]		
• *General ward (GW)*	*123 (34)*	1.9 (1.1)	*386 (71)*	2.2 (1.2)	-0.3
• *Intensive care unit (ICU)*	*120 (33)*	2.4 (1.0)	*49 (9.6)*	2.1 (1.1)	0.3
• *Both, GW and ICU*	*4 (1)*	-	*2 (0.4)*	-	-
• *GW or ICU-pilot*	*118 (32)*	3.4 (4.5)	*105 (19)*	3.1 (2.6)	0.3

Variables	Intervention [N=18,449]		Control [N=17,349]		Mean difference (Int. – Cont.)
	n (%)	Mean (±SD)	n (%)	Mean (±SD)	
Delivery related information					
Deliveries, excluding miscarriage	[n=17,891, 97%]		[n=16,849, 97%]		
Place of delivery					
• *Home*	*4277 (24)*	-	*4072 (24)*	-	-
• *Public health facility*	*5802 (32.2)*		*6160 (36.7)*		
• *Private health facility*	*7756 (43.5)*		*6566 (39)*		
• *En-route*	*56 (0.3)*		*51 (0.3)*		
Type of delivery [of those delivered at health facility]	[n=13,558, 76%]		[n=12,726, 76%]		
• *Spontaneous vaginal delivery*	*9107 (67)*	-	*9094 (71)*	-	-
• *Assisted vaginal delivery*	*1224 (9)*		*917 (7)*		
• *Caesarean-section*	*3227 (24)*		*2715 (22)*		
Others: Transport, productivity losses due to illness and wage-worker					
Transport to health facility	16046 (87)	4.6 (3.2)	14860 (86)	3.9 (2.6)	0.7
Productivity/time losses (# of days missed wages due to ill health/hospitalization)	5719 (31)	2.3 (5.1)	5638 (33)	2.3 (5.4)	-
Hired wage-worker for household chores	1738 (9.4)	0.3 (2.2)	580 (3.3)	0.2 (1.3)	0.1
Protocol driven resource utilization					
Non-urgent (24 hours) referrals to health facility	287 (1.6)	-	-	-	-
Urgent (4 hours) referrals to health facility	155 (0.8)	-	-	-	-

** Represents multiple response question*

Table 12. Newborn health resource utilization

Variables	Intervention [N=18,449]		Control [N=17,349]		Mean difference (Int. – Cont.)
	n (%)	Mean (±SD)	n (%)	Mean (±SD)	
Ambulatory care*					
Newborn illness and/or complications	[n=1430, 8%]		[n=1901, 11%]		
• *Medical doctor*	*1332 (93)*		*1858 (97)*		
• *Nurse*	*15 (1)*	1.9 (1.5)	*16 (1)*	1.8 (1.4)	0.1
• *Midwife*	*9 (0.6)*		*12 (0.6)*		
• *Lady Health Worker*	*8 (0.5)*		*13 (0.7)*		
• *Traditional healer*	*55 (4)*		*33 (2)*		
Diagnostic tests/procedures*					
Diagnostic tests:	[n=164, 1%]		[n=205, 1.2%]		
• *Phototherapy*	*23 (14)*	0.5 (1.1)	*11 (5)*	0.6 (1)	-0.1
• *Fetal imaging*	*75 (46)*		*101 (49)*		
• *Blood tests*	*145 (88)*		*172 (84)*		
In-patient admissions at higher level health facility-HLCF					
In-patient admissions	[n=241, 1.3%]		[n=324, 2%]		
HLCF setting:					
• *General ward (GW)*	*147 (61)*	1.9 (1.4)	*227 (70)*	1.7 (1.2)	0.2
• *Intensive care unit (ICU)*	*80 (33)*		*75 (23)*		
• *Both, GW and ICU*	*14 (6)*		*22 (7)*		
Others: Transport, productivity losses due to illness and wage-worker					
Transport to health facility	976 (5.3)	2.1 (1.4)	1037 (6)	1.9 (1.2)	0.2
Productivity/time losses (# of days missed wages due to ill health/hospitalization)	683 (3.7)	4.2(8.4)	752 (4.3)	3.2 (7.6)	1

** Represents multiple response question*

Table 13. CLIP handbag items in Sindh, Pakistan

Items	Quantity procured	Unit costs (US$)
Microlife VSA blood pressure monitoring device	390 devices	22.2
Large size cuff for blood pressure device	197 cuffs	11.2
PX-13-B Kenek pulse oximeter device	377 devices	20.1
Mobile device (Model Q-Noir A7 phone)	92 phones	125.6
Mobile device (Model Q-300 tablet 7.0")	566 tablets	143
Urine specimen cups	30 packs (250 cups/pack)	25.3
Urine dipsticks	105 packs (100 sticks/pack)	16.7
Dipstick colour-code sheet	70 packs (100 sheets/pack)	18.7
Adhesive bandages	12 packs (100 bandages/pack)	0.7
Alcohol swabs	15 packs (100 swabs/pack)	1.7
Syringes (10ml)	14 packs (100 syringes/pack)	7.5
Needles (23 gram)	9 packs (100 needles/pack)	1.6
Hand-gloves	8 packs (100 gloves/pack)	2.9
Needle cutters	11 packs (3 cutters/pack)	7.2
Disposal/sharp boxes	42 boxes	0.6
CLIP-card with polythene bag	16 packs (1000 cards/pack)	26.7
Magnesium sulphate (10ml) injection	242 packs (5 vials/pack)	0.6
Methyldopa (250mg) tablet	19 packs (100 tablets/pack)	3.5

1 US$ = 104.7 PKR (average exchange rate of 2014-2016 http://www.sbp.org.pk/); figures are rounded off to the nearest tenth.

Table 14. Societal costs comparing intervention and control

Costs in, US$*	Intervention	Control
(A) Costs to health system (program-related)		
CLIP package of care: home-based screening for HDP, community-based HDP management/referral, and community engagement)	$137,756	-
Incentive, trainings and transport for Lady Health Workers	$79,398	-
Health system capacity enhancement (workshop, and seminar)	$3,573	$3,573
Surveillance for ascertainment of trial outcomes (personnel, mobile technology and transport)	$309,848	$309,848
Sub-total (A)	***$530,755***	***$313,602***
(B) Costs to pregnant women and their families		
Maternal health resource utilization and productivity losses	$2,153,346	$1,879,995
Newborn health resource utilization and productivity losses	$14,260	$17,961
Sub-total (B)	***$2,167,606***	***$1,897,956***
Total societal costs (A + B)	**$2,698,361**	**$2,211,558**

HDP = Hypertensive disorders of pregnancy;
Exchange rate: 1 US$ = 104.7 PKR (average exchange rate of 2014-2016 http://www.sbp.org.pk/).
** Discounted at 3% rate*

Table 15. Regression-adjusted coefficients for study variables

Model Term	Coefficient ▼	Std.Error	t	Sig.	95% Confidence Interval	
					Lower	Upper
Intercept	6.314	0.607	10.399	.000	5.124	7.504
pr_di_age	-0.008	0.001	-8.498	.000	-0.010	-0.007
PW_edu_cat=0	-0.326	0.013	-25.612	.000	-0.351	-0.301
PW_edu_cat=1	0[a]					
parity_cat=0	-0.516	0.011	-47.116	.000	-0.538	-0.495
parity_cat=1	0[a]					
husb_edu_cat=0	-0.194	0.010	-19.590	.000	-0.213	-0.174
husb_edu_cat=1	0[a]					
Arm=1	0.040	0.837	0.048	.962	-1.600	1.680
Arm=2	0[a]					
funds_saved_OE=0	-0.111	0.011	-10.303	.000	-0.132	-0.090
funds_saved_OE=1	0[a]					
HBP_told=0	-0.161	0.021	-7.739	.000	-0.202	-0.120
HBP_told=1	0[a]					
seizures_told=0	-0.160	0.052	-3.072	.002	-0.262	-0.058
seizures_told=1	0[a]					
diabetes_told=0	-0.139	0.065	-2.129	.033	-0.266	-0.011
diabetes_told=1	0[a]					
TB_told=0	0.044	0.068	0.651	.515	-0.089	0.178
TB_told=1	0[a]					

Probability distribution:Gamma
Link function:Log

[a]This coefficient is set to zero because it is redundant.

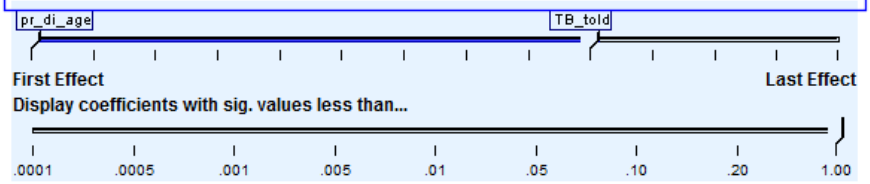


Table 16. Regression-adjusted cost estimates for resource utilization (in US$)

Variables	Mean	Std. Error	95% Confidence Interval	
			Lower	Upper
Maternal health resource utilization, (p-value = 0.958)				
Intervention	$163.4	98	$51	$529
Control	$156.7	94	$49	$506
Newborn health resource utilization, (p-value = 0.964)				
Intervention	$4	3.6	$0.7	$23.4
Control	$4.2	3.8	$0.6	$24.6
Combined maternal and newborn health resource utilization, (p-value = 0.962)				
Intervention	$164	98	$51	$528
Control	$158	94	$49	$507

Intracluster correlation coefficient (ICC)= 0.02
Adjusted for maternal age, maternal primary education, husbands with primary education, parity, savings for pregnancy-related emergencies, and medical conditions including high blood pressure, seizures, and diabetes.

Table 17. Years of life lost (YLL) in the intervention and control groups

Outcomes	Intervention			Control		
	n	Rate*	YLL	n	Rate*	YLL
Maternal deaths	55	2.71	76	51	2.66	64
Early neonatal deaths	820	40.5	1,214	818	42.7	1,237
Late neonatal deaths	196	9.7	305	151	7.9	217
Stillbirths	937	46.2	1,373	952	49.6	1439
Combined YLL for maternal, perinatal and neonatal deaths			**2,968**			**2,957**

** Rate per 1000 identified pregnancies; CI= Confidence intervals*

Table 18. Years lost due to disability (YLD) in the intervention and control groups

Outcomes	Intervention			Control		
	n	Rate* (95% CI)	YLD	n	Rate* (95% CI)	YLD
Maternal morbidities (excluding maternal deaths)						
Eclampsia	29	1.43 (0.90, 2.12)	0.0	16	0.79 (0.49, 1.3)	0.0
Stroke	63	3.11 (2.41, 3.92)	489	85	4.19 (3.5, 5.9)	660
Antepartum haemorrhage	639	31.53 (2.90, 3.43)	72	483	23.84 (22.7, 27.6)	54
Obstetric sepsis	1,472	72.64 (69.1, 76.4)	193	1,189	58.68 (56.5, 65.3)	156
Vesicovaginal or rectovaginal fistula	56	2.76 (2.11, 3.61)	470	39	1.92 (1.4, 2.9)	328
Dialysis	1	0.05 (0.02, 0.24)	14	2	0.10 (0.07, 0.34)	28
Blood transfusion	235	11.60 (10.1, 13.2)	26	161	7.95 (5.2, 9.7)	18
Coma	26	1.28 (0.85, 1.84)	NR	22	1.09 (0.73, 1.8)	NR
Disseminated intravascular coagulation (DIC)	4	0.20 (0.62, 0.47)	NR	6	0.30 (0.21, 0.43)	NR
CPR	4	0.20 (0.62, 0.47)	NR	5	0.25 (0.18, 0.33)	NR
Mechanical ventilation	10	0.49 (0.25, 0.88)	NR	8	0.39 (0.27, 0.52)	NR
Intervention for major post-partum haemorrhage	1	0.05 (0.02, 0.24)	NR	4	0.20 (0.11, 0.31)	NR
(A) Sub-total YLD for maternal morbidities			***1,264***			***1,244***
Newborn morbidities (excluding newborn deaths)						
Feeding difficulty	722	37.64 (33.1, 39.3)	0.0	188	9.80 (8.4, 11.3)	0.0
Breathing difficulty	230	11.99 (9.9, 13.2)	0.0	174	9.07 (7.7, 10.5)	0.0
Lethargy	464	24.19 (20.8, 26.7)	0.0	455	23.72 (21.6, 25.7)	0.0
Hypothermia	271	14.13 (11.8, 16.2)	0.0	170	8.86 (7.6, 10.3)	0.0
Jaundice	324	16.89 (14.3, 18.8)	0.0	327	17.05 (15.2, 18.9)	0.0
Seizures	161	8.39 (6.78, 10.2)	NR	134	6.99 (5.8, 8.2)	NR
Coma	11	0.57 (0.28, 0.94)	NR	13	0.68 (0.37, 1.13)	NR

Outcomes	Intervention			Control		
	n	Rate* (95% CI)	YLD	n	Rate* (95% CI)	YLD
Newborn morbidities (excluding newborn deaths) continued						
Umbilical cord infection	273	14.23 (11.9, 16.2)	NR	232	12.10 (10.6, 13.7)	NR
Skin infection	2	0.10 (0.90, 0.33)	NR	0	0.00 -	NR
Bleeding	55	2.87 (2.1, 3.6)	NR	26	1.36 (0.90, 1.95)	NR
(B) Sub-total YLD for newborn morbidities			**-**			**-**
Total (A+B)			**1,264**			**1,244**

** Rate per 1000 identified pregnancies; NR = not reported by Global burden of Diseases; Zero YLD represents acute conditions*

Table 19. Probabilistic cost-effectiveness estimates (10,000 iterations)

Outcomes*	Intervention	Control	Increment[#]	ICER (95% CI)
Program perspective: Combined YLL for maternal, perinatal, and early/late neonatal outcomes				
Mean cost (in US$)	$31,695	$17,103	$14,592	Intervention is dominated
Mean YLL	2,962	2,925	-37	
Societal perspective: Combined YLL for maternal, perinatal, and early/late neonatal outcomes				
Mean cost (in US$)	$179,670	$159,232	$20,438	Intervention is dominated
Mean YLL	2,962	2,925	-37	

** per 1000 identified pregnancies*

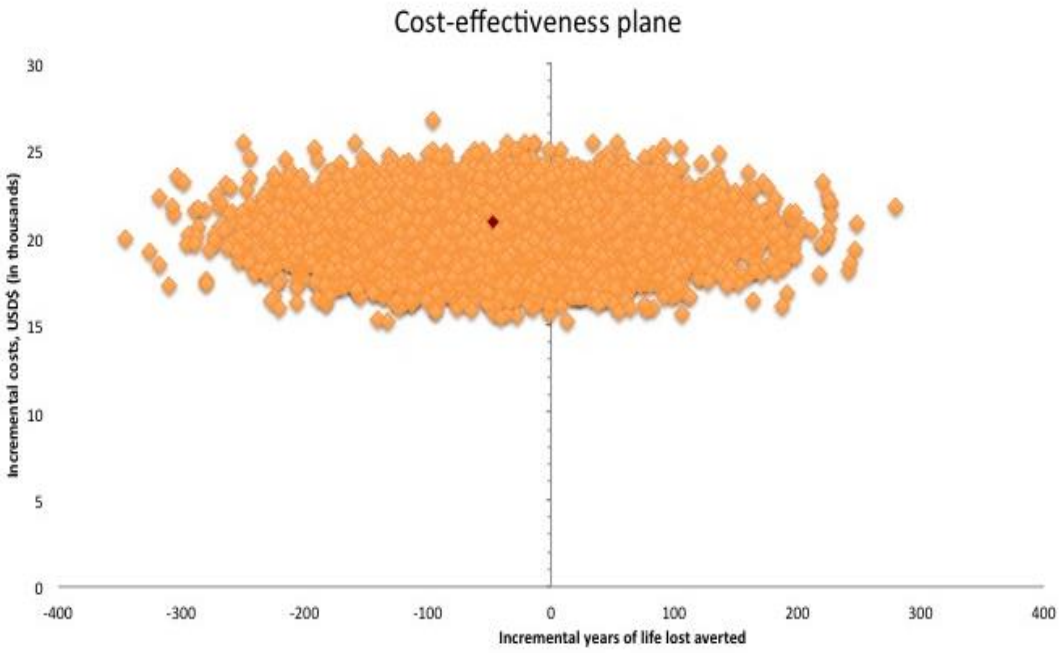
[#] Incremental costs = Intervention, minus control; Incremental YLL= Control, minus intervention

Table 20. Regression adjusted effect size for maternal and perinatal outcomes

Clinical outcome parameters	***Adjusted odds ratio (95% confidence intervals)***	***% Protective effectiveness (1 – adjusted odds ratio)***
Maternal mortality	1.08 (0.69 – 1.72)	-8%
Maternal morbidity	1.10 (0.57 – 2.14)	-10%
Perinatal and late neonatal mortality	0.94 (0.86 – 1.03)	6%
Neonatal morbidity	1.22 (0.77 – 1.95)	-22%
Composite adverse pregnancy outcomes	1.20 (0.84 – 1.72)	-20%

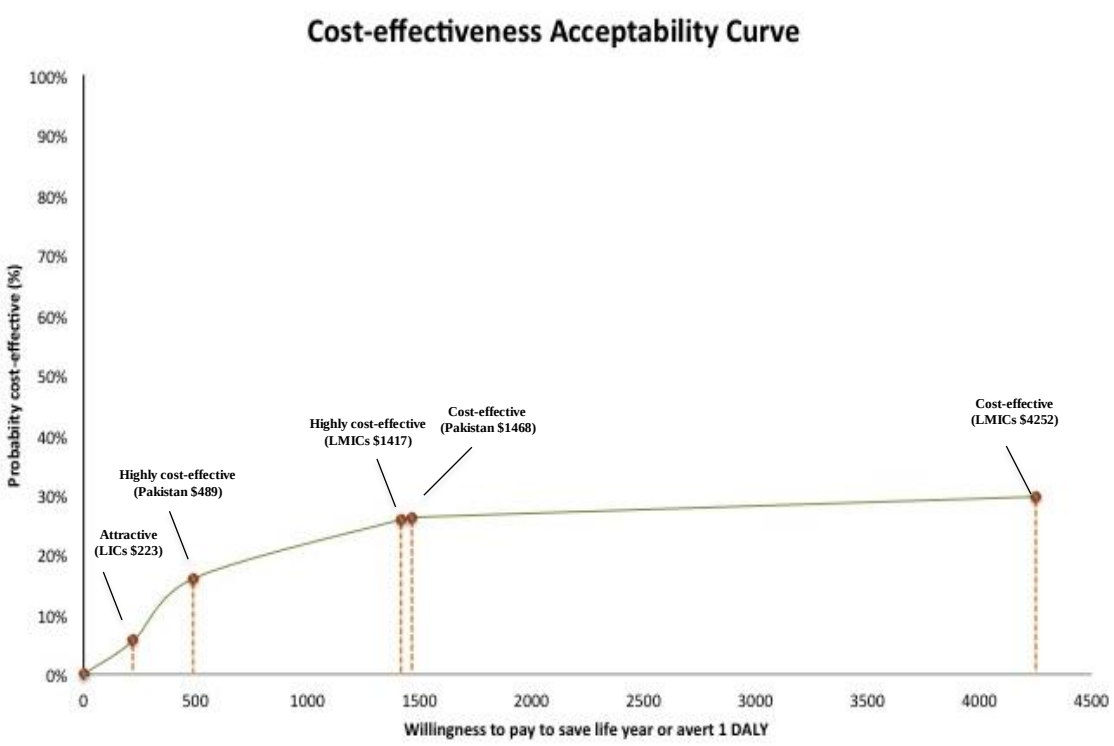
Adjusted for maternal age, maternal primary education, husbands' with primary education, parity, and baseline neonatal mortality.

Figure 7. Cost-effectiveness plane showing statistical uncertainty



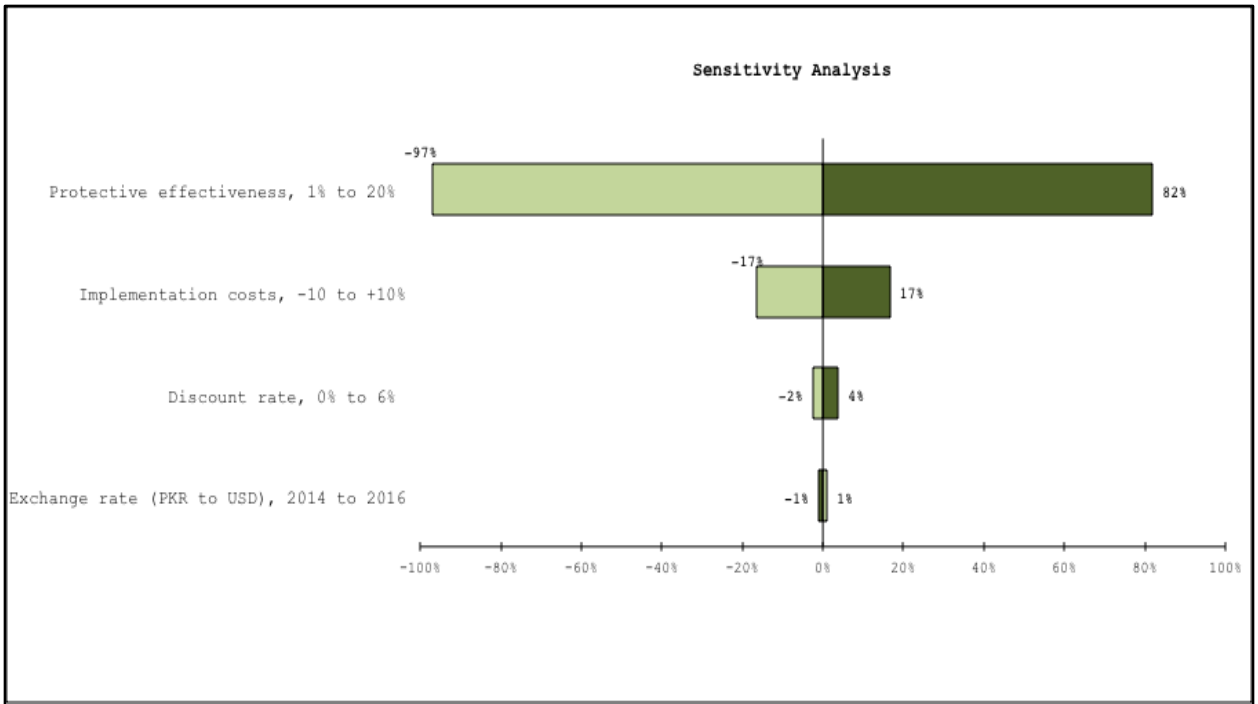
This graph represents probabilistic analysis using Monte Carlo simulation for 10,000 iterations. On X-axis, we have incremental years of life lost averted, and Y-axis we have incremental cost in thousands. Each do represents a single ICER from the probabilistic model. The highlighted dot represents the mean ICER. Data points falling northwest of the origin indicate the possibility that (positive) costs will incur relative to no or even negative health benefit.

Figure 8. Cost-effectiveness acceptability curve for the CLIP Trial



This graph represents probability of ICERs at given willingness to pay threshold. On X-axis, we have willingness to pay to life years saved; and Y-axis we have probability around ICERs. LIC = Low-income countries; LMIC = Low-and-Middle income countries.

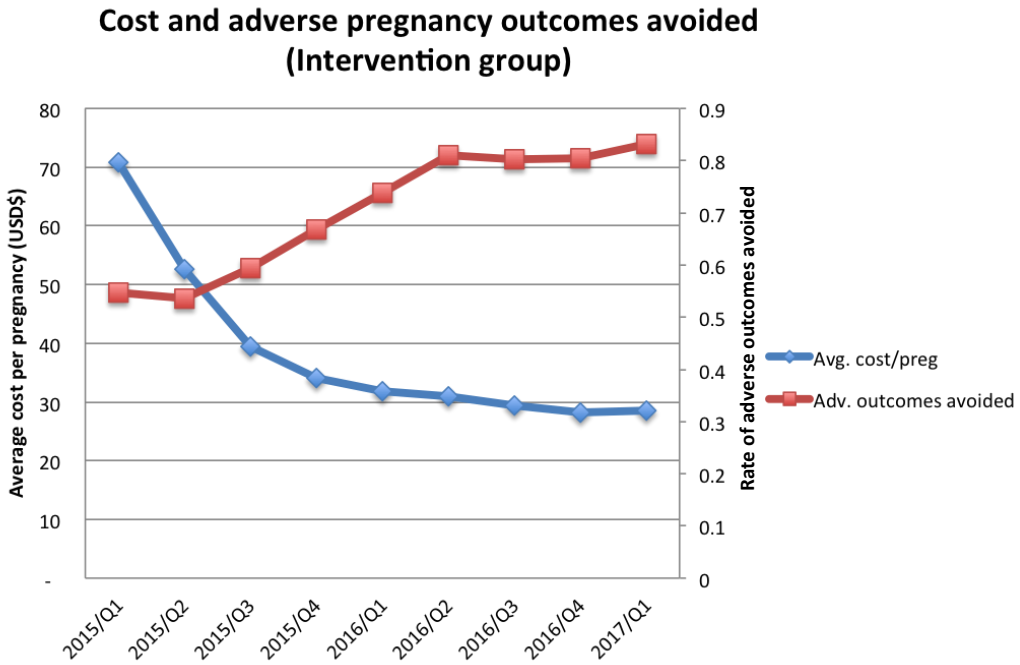
Figure 9. One-way sensitivity analysis



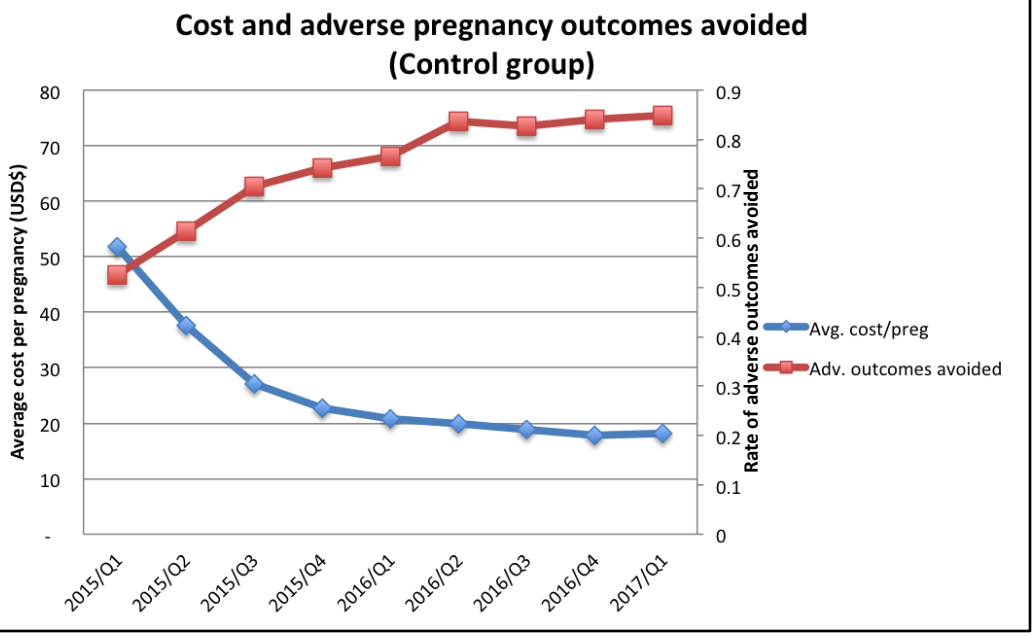
Dark green bars indicate the direction and magnitude of change of the ICER when the given input variable is at its minimum plausible value, whereas light green bars indicate the direction and magnitude of change of the ICER when the same input variable is at its maximum plausible value. Variables listed towards the top of this diagram contribute more to the overall uncertainty in the cost-effectiveness ratio than do those towards the bottom, which contribute relatively little to the uncertainty in the cost-effectiveness ratio.

Figure 10. Time trends for costs and rate of adverse pregnancy outcomes avoided

10A.



10B.



Chapter 7: Conclusions

7.1 Summary of findings

The objective of this dissertation was an economic appraisal of the CLIP package of care combined with routine pregnancy care, compared to routine pregnancy care alone, in Sindh, Pakistan. We investigated the evidence about costs and cost-effectiveness of CLIP interventions to inform policy decisions about resource allocation for post-trial scale-up, should the intervention findings provide evidence of clinical effectiveness.

The literature review in Chapter 2 identified knowledge gaps for societal costs, and contextual limitation of scientific evidence about cost-effective PE/E interventions only to developed (western) countries, as not many economic studies exist in the area of PE/E identification and appropriate case management in LMICs. The cost-effective measures as reported in previous economic studies, such as automated urine analysis, parental administration of MgSO4, and immediate delivery are mainly available at the health facility level. Thus, evidence about costs and cost-effectiveness of comprehensive community-based PE/E interventions is grossly lacking.

Chapter 3 provided an overview of a mixed-methods approach to economic evaluation, illustrated contextual relevance to collect costs and health outcomes data alongside the trial, and reflected on the important considerations for economic model design (i.e., use of decision tree analysis, societal perspective, appropriate discount rates, methods of dealing with uncertainties, and relevant health outcome measures), as indicated in the literature review.

The FGs with pregnant women and dyadic decision makers in the community indicated a large burden of OOP costs and productivity losses due to ill health of the mother or newborn, as presented in Chapter 4. The sociocultural circumstances in which a woman requires her

husband's permission for care-seeking, lacks financial savings for pregnancy-related emergencies, anticipates higher transportation costs for visit to the health facility, or requires a family member or friend to accompany her during hospitalization together make women and their families vulnerable to catastrophic expenditure on health. Much attention is needed in the areas of community-based provision of basic health services, micro-financing schemes for obstetric emergencies, local transport arrangements, health education, community engagement and interaction, risk stratification, and timely referral of sick woman to a health facility, to avert long-term financial consequences and improve maternal and newborn health in LMICs.

The survey of health care providers and facilities highlighted cost disparities within and between public and private health sectors, as presented in Chapter 5. Despite lower costs for inpatient care and delivery-related hospitalizations in the public health sector, many women sought care from private facilities. Close geographic distance, long operating hours, and shorter wait times (as identified in FGs) could have contributed to the higher rates of private health facility utilization. The private sector can also provide cutting-edge diagnostic and therapeutic technologies that may not be available in the public sector, albeit at relatively higher cost. Considering that the role of the private sector is rapidly expanding to almost all rural and urban settings, the economic principle of supply-induced demand could explain this preference for private care providers. This was relevant, as the rate of Caesarean section was higher in the private sector. Unless pregnant women have community-based safety nets or some financial savings, they and their families will continue to face the higher burden of OOP spending as a result of health resource utilization in the private sector.

Economic evaluation of the CLIP implementation revealed financial implications of incremental costs to the health care system, as shown in Chapter 6. The cost of mHealth

infrastructure, particularly upfront costs to purchase digital clinical devices and smartphones or tablets, requires a huge initial financial investment from the health care system. Health benefits of such interventions yield a long-term return on investments, so strong scientific evidence, constant policy advocacy, ever-increasing political will, and winning public support are essential elements to promote mHealth initiatives in LMICs. This supports our argument in the literature review to have more research done on epidemiological and economic aspects of such initiatives so that decisions about resource allocations are informed by robust evidence.

The cost-effectiveness of the CLIP interventions, as indicated in Chapter 6, suggests incremental costs and no evidence of health benefits. The probabilistic analysis demonstrated greater uncertainty around ICERs, which is largely explained by statistically insignificant effect size and wide confidence intervals. The economic evaluation is based on a utilitarian philosophy implying "good for larger society," in which decisions are mainly weighted in reference to societal WTP for a given intervention. For example, those interventions that produce a DALY for $1,468 or less (i.e., GDP per capita in Pakistan) are a bargain, whereas those that require more than $1,468 are considered unaffordable. In this study, the probability of ICERs falling below the acceptable WTP threshold was less than 30%. Such a low probability implies "bigger buck for lower bang," a common phrase used in the economic literature to explain interventions yielding in low value for money. This relates to an emerging debate in the economic literature on the fallacy of the threshold in the cost-effectiveness analysis. GDP per capita can be quite volatile given the unpredictability of economic situations in low-income countries. An arbitrary, high WTP threshold can be extremely welcoming to many new interventions. But these interventions may be less cost-effective than expected and may become a drain on the health budget rather than being a good use of it. More research is needed to determine an appropriate

threshold, and to investigate the effect of changing threshold levels (i.e., high or low) on existing and future maternal and newborn health interventions in LMICs.

Advantages of using a mixed-methods approach in economic analysis alongside the trial include real-time data collection, qualitative exploration of community preferences for care utilization and cost drivers that are not typically measured in the quantitative design, capturing real-world costs including health system and patient perspectives, consistency and rigor in data collection and analysis, triangulation of findings, and timely results for decision making.

7.2 Implications

This dissertation highlights several implications relevant to the national program of LHWs, health care providers, communities, and future research. The economic analysis findings are useful to inform policy decisions on future investments and/or disinvestments when planning maternal and child health services in Pakistan. The routine pregnancy care demonstrated a strong case for program-related efficiency gains in the delivery of MNH services in Pakistan. Shortage of publicly funded community-based health services further affects the way individuals seek care, assuming that many patients and families will have no choice but to seek care from the private health sector resulting in higher OOP costs. Therefore, the role of public-private partnership, financial protection programs through micro-insurance or community-based financial safety nets, and health services regulations can be instrumental in bridging the service delivery gaps for routine pregnancy care. On other hand, integration of mHealth component into routine pregnancy care requires a careful consideration of incremental costs to health system. For instance, it is estimated that countrywide, CLIP implementation would require additional funding of about $28.5 million per year, given an incremental cost of $284 per each of 100,000 LHWs in the national program. Such an incremental cost may have a detrimental effect on other

public health programs (such as the expanded program on immunization, MNCH, blindness prevention, and hepatitis control) funded by the federal government in Pakistan. According to the official budget release for the year 2016-17, $231million was earmarked for the national health services, of which less than 5% was allocated for public health programs. This mismatch of funding should be seen as a significant barrier to health innovation that could lead to a public health crisis in Pakistan. A long-term fiscal solution could be possible with price negotiation with technology partners and the active involvement of civil society representatives. Such an inclusive approach will foster more avenues for technology development and applications in the area of global maternal and newborn health.

This study also draws the attention of policymakers to individual components of the CLIP package of care, as some of these could be feasibly and affordably integrated into the existing LHWs service delivery platform. Guided by our local field observations, we determined that: (i) community engagement had the potential to maximize the program reach/coverage through active participation of women and household decision makers; (ii) equipping community health workers with blood pressure devices improved HDP diagnosis and initiated timely patient referral; and (iii) training care providers led to compliance with a standard management regime as more women received antihypertensive and MgSO4 treatments.

The successful implementation of these interventions has greater implications for task shift to LHWs in Sindh, Pakistan. The World Health Organization has strongly suggested shifting specific tasks (e.g., clinical screening and management) normally performed by high-level care providers to lower-level care providers, to address inefficiencies in the health system and to improve population health outcomes.

The use of a mixed-methods approach alongside the trial is a resource intensive exercise but offers several advantages for collecting data, interpretation of findings, perform data triangulation, and strategizing ways of communicating and interpreting findings to all stakeholders in the study. The involvement of community stakeholders and health policy decision makers at the initial stage also reflected patient-oriented research, where study participants are engaged throughout the process of research. Holding FGs with all stakeholders was an important step in understanding cost drivers relevant and important to health care providers and pregnant women and their families.

Although subsequent interactions and participation in the annual meetings were limited to health decision makers in the LHWs program, we plan on organizing a knowledge translation seminar to keep the wider communities informed about the study results. Economic evidence of cost-effectiveness is only one necessary factor under consideration in the decision-making process. Other factors such as system innovation, the burden of disease, unmet need, political willingness, and feasibility aspects also come into play. In this connection, a higher-level policy dialogue with the ministry of health, stakeholders from other preventive programs, and donor agency representatives will provide an opportunity to discuss and reflect on key study findings and indicate areas of future research in Pakistan. I hope to facilitate this policy discussion, and share evidence-based findings, and my field experience in maternal and newborn health in Sindh, Pakistan.

This dissertation indicates several areas that would benefit from future research: (i) process evaluation to explore contextual aspects (i.e. enabling and impeding factors) during trial implementation, and sub-group analysis to assess health benefits comparing intervention and control groups; (ii) real-time economic evidence of the costs and cost-effectiveness of novel

strategies to identify and manage PE/E using mHealth applications, clinical digital devices, and placental biomarkers in LMICs; (iii) landscape analysis on the determinants for the use of private health facilities despite higher OOP costs; (iv) comparative analysis of maternal and newborn outcomes between private and public health facilities; (v) exploration of DWs for severe newborn conditions; (vi) determining appropriate WTP threshold and effects of changing threshold levels on existing MNCH interventions; (vii) cost-effectiveness of household surveillance and health system capacity enhancement; and (viii) potential cost savings associated with task shift to LHWs using a societal perspective.

7.3 Conclusions

This dissertation identified critical knowledge gaps related to cost and cost-effectiveness of PE/E interventions in LMICs. The societal perspective on cost drivers in particular highlighted a large burden of OOP spending and productivity losses for pregnant women and their families. The health care providers and district-level decision and policy makers critically appraised the merits of health technology use and identified financial challenges related to large initial investments into mHealth devices and Internet technology. Economic analysis revealed that CLIP is not a cost-effective strategy compared to routine pregnancy care alone. Further research is needed to understand the contextual aspects of trial implementation through process evaluation. Also, future economic studies evaluating simple versus complex health interventions will add value to the existing body of literature and guide policy decisions on resource allocation in the area of MNH in Pakistan and elsewhere.

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Appendices

Table 21. Sensitivity analysis for health resource utilization

(A) Summary of routine antenatal care costs

Group		Excluding ANC visits in pilot phase	Assuming 50% of ANC visits to MD in pilot phase	Assuming 80% of ANC visits to MD in pilot phase
Intervention	Min.	0.0	0.0	0.0
	Mean	9.3	10.3	10.7
	Max.	99	99	99
Control	Min.	0.0	0.0	0.0
	Mean	8.2	9.0	9.4
	Max.	87	87	87
	Mean diff.	1.1	1.3	1.3

MD = Medical doctor

(B) Summary of in-patient hospitalization costs

Group		Excluding hospitalization in pilot phase	Assuming 50% of hospitalization to GW in pilot phase	Assuming 80% of hospitalization to GW in pilot phase
Intervention	Min.	0.0	0.0	0.0
	Mean	118	180	156
	Max.	385	641	641
Control	Min.	0.0	0.0	0.0
	Mean	54	87	74
	Max.	339	539	539
	Mean diff.	64	93	82

GW = General ward

Table 22. Multi-collinearity diagnostic outputs

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
		B	Std. Error	Beta	t	Sig.	Tolerance	VIF
1	(Constant)	64.411	13.948		4.618	.000		
	maternal_mortality	112.245	44.792	.042	2.506	.012	.985	1.015
	matmorbid	20.898	4.222	.085	4.949	.000	.943	1.061
	pr_di_age	-.665	.402	-.028	-1.656	.098	.952	1.051
	PW_edu_cat	46.094	4.787	.170	9.628	.000	.882	1.133
	parity_cat	53.055	4.201	.215	12.628	.000	.955	1.047
	husb_edu_cat	19.232	3.737	.091	5.146	.000	.890	1.124
	Arm	6.460	3.676	.030	1.757	.079	.975	1.025
	per_obtained_RANC	33.590	20.991	.143	1.600	.110	.034	28.986
	per_obtained_emerg_PC	-19.209	20.840	-.082	-.922	.357	.035	28.886
	funds_saved_OE	9.321	4.009	.040	2.325	.020	.940	1.063
	Hasshebeentoldthatshehasseizures	.115	.234	.009	.490	.624	.772	1.296
	Hasshebeentoldthatshehasdiabetes	-.041	.163	-.005	-.251	.802	.790	1.266
	HassheeverbeentoldshehasTB	-.222	.241	-.016	-.919	.358	.873	1.146
	Doessheneedcarefromfamilyorfriendswhowouldotherwiseworkforwagesa	3.269	4.876	.012	.671	.503	.898	1.113

a. Dependent Variable: G_total_Mat_NB_costs

Table 23. Correlation co-efficient matrix

Correlations

		maternal_mortality	matmorbid	pr_di_age	PW_edu_cat	parity_cat	husb_edu_cat	Arm	G_total_Mat_NB_costs	per_obtained_RANC	per_obtained_emerg_PC	funds_saved_OE	Hasshebeentoldthatshehasseizures	Hasshebeentoldthatshehasdiabetes	HassheeverbeentoldshehasTB	anaemia	Doesshehaveahistoryofworms	Doesshenedcarefromfamilyorfriendswhowouldotherwiseworkforwagesa	rs_po_outcome	neomorbidity	stillbirth	rs_po_alive
maternal_mortality	Pearson Correlation	1	.025**	.014**	-.009	-.003	-.010	.000	.007	.003	.003	-.002	.008	-.002	-.005	.004	-.003	-.006	-.010	.[b]	.053**	-.011
	Sig. (2-tailed)		.000	.006	.096	.633	.069	.943	.219	.544	.550	.773	.147	.765	.378	.469	.574	.254	.052	.	.000	.055
	N	35728	35674	35728	35728	35728	35728	35728	35697	35728	35728	35728	35728	35728	35728	35728	35657	35728	35661	4056	32324	32697
matmorbid	Pearson Correlation	.025**	1	.004	-.001	.001	-.005	-.012*	.032**	-.068**	-.072**	.024**	.003	.005	.000	.041**	.003	.002	-.015**	.[b]	.043**	-.007
	Sig. (2-tailed)	.000		.497	.882	.810	.369	.024	.000	.000	.000	.000	.588	.352	.938	.000	.596	.648	.004	.	.000	.185
	N	35674	35675	35675	35675	35675	35675	35675	35653	35675	35675	35675	35675	35675	35675	35604	35675	35626	4051	32296	32668
pr_di_age	Pearson Correlation	.014**	.004	1	-.114**	-.164**	-.058**	-.026**	-.099**	.010	-.006	-.016**	-.094**	-.077**	-.101**	.034**	.003	-.004	.006	.[b]	.007	-.007
	Sig. (2-tailed)	.006	.497		.000	.000	.000	.000	.000	.057	.268	.003	.000	.000	.000	.000	.521	.407	.224	.	.185	.190
	N	35728	35675	35729	35729	35729	35729	35729	35698	35729	35729	35729	35729	35729	35729	35729	35658	35729	35662	4056	32325	32698
PW_edu_cat	Pearson Correlation	-.009	-.001	-.114**	1	.130**	.314**	-.032**	.243**	.004	.005	.129**	-.004	-.007	-.017**	.000	-.003	-.011*	-.006	.[b]	-.023**	-.001
	Sig. (2-tailed)	.096	.882	.000		.000	.000	.000	.000	.477	.365	.000	.399	.164	.002	.991	.565	.034	.283	.	.000	.892
	N	35728	35675	35729	35729	35729	35729	35729	35698	35729	35729	35729	35729	35729	35729	35729	35658	35729	35662	4056	32325	32698
parity_cat	Pearson Correlation	-.003	.001	-.164**	.130**	1	.128**	-.028**	.249**	.044**	.033**	.072**	.011*	.010	.011*	.003	-.013*	.017**	-.020**	.[b]	.003	-.004
	Sig. (2-tailed)	.633	.810	.000	.000		.000	.000	.000	.000	.000	.000	.033	.057	.034	.549	.017	.001	.000	.	.568	.433
	N	35728	35675	35729	35729	35729	35729	35729	35698	35729	35729	35729	35729	35729	35729	35729	35658	35729	35662	4056	32325	32698
husb_edu_cat	Pearson Correlation	-.010	-.005	-.058**	.314**	.128**	1	-.038**	.194**	.013*	.019**	.109**	-.017**	-.013*	-.029**	.016**	.002	-.004	-.013*	.[b]	-.011	.007
	Sig. (2-tailed)	.069	.369	.000	.000	.000		.000	.000	.013	.000	.000	.001	.016	.000	.002	.753	.442	.015	.	.055	.178
	N	35728	35675	35729	35729	35729	35729	35729	35698	35729	35729	35729	35729	35729	35729	35729	35658	35729	35662	4056	32325	32698
Arm	Pearson Correlation	.000	-.012*	-.026**	-.032**	-.028**	-.038**	1	-.040**	.095**	.084**	-.042**	-.011*	-.023**	-.009	.052**	-.004	-.029**	.000	.[b]	.010	.002
	Sig. (2-tailed)	.943	.024	.000	.000	.000	.000		.000	.000	.000	.000	.044	.000	.097	.000	.502	.000	.957	.	.074	.664
	N	35728	35675	35729	35729	35729	35729	35729	35698	35729	35729	35729	35729	35729	35729	35729	35658	35729	35662	4056	32325	32698
G_total_Mat_NB_costs	Pearson Correlation	.007	.032**	-.099**	.243**	.249**	.194**	-.040**	1	.003	.013*	.108**	.009	-.004	-.006	.031**	-.005	.011*	.064**	.[b]	-.028**	-.002
	Sig. (2-tailed)	.219	.000	.000	.000	.000	.000	.000		.617	.013	.000	.082	.439	.291	.000	.317	.040	.000	.	.000	.689
	N	35697	35653	35698	35698	35698	35698	35698	35698	35698	35698	35698	35698	35698	35698	35698	35627	35698	35639	4055	32310	32681
per_obtained_RANC	Pearson Correlation	.003	-.068**	.010	.004	.044**	.013*	.095**	.003	1	.928**	-.048**	-.042**	-.031**	-.043**	-.029**	-.010	.136**	.007	.[b]	-.011	.004
	Sig. (2-tailed)	.544	.000	.057	.477	.000	.013	.000	.617		.000	.000	.000	.000	.000	.000	.064	.000	.215	.	.053	.511
	N	35728	35675	35729	35729	35729	35729	35729	35698	35729	35729	35729	35729	35729	35729	35729	35658	35729	35662	4056	32325	32698
per_obtained_emerg_PC	Pearson Correlation	.003	-.072**	-.006	.005	.033**	.019**	.084**	.013*	.928**	1	-.047**	-.039**	-.030**	-.042**	-.016**	-.013*	.142**	.006	.[b]	-.013*	.004
	Sig. (2-tailed)	.550	.000	.268	.365	.000	.000	.000	.013	.000		.000	.000	.000	.000	.003	.012	.000	.224	.	.020	.495
	N	35728	35675	35729	35729	35729	35729	35729	35698	35729	35729	35729	35729	35729	35729	35729	35658	35729	35662	4056	32325	32698
funds_saved_OE	Pearson Correlation	-.002	.024**	-.016**	.129**	.072**	.109**	-.042**	.108**	-.048**	-.047**	1	-.010	-.007	-.018**	.064**	-.001	.047**	.003	.[b]	-.012*	.002
	Sig. (2-tailed)	.773	.000	.003	.000	.000	.000	.000	.000	.000	.000		.053	.200	.001	.000	.879	.000	.600	.	.030	.779
	N	35728	35675	35729	35729	35729	35729	35729	35698	35729	35729	35729	35729	35729	35729	35729	35658	35729	35662	4056	32325	32698
Hasshebeentoldthatshehasseizures	Pearson Correlation	.008	.003	-.094**	-.004	.011*	-.017**	-.011*	.009	-.042**	-.039**	-.010	1	.363**	.359**	-.008	.190**	.014**	-.004	.[b]	.026**	-.003
	Sig. (2-tailed)	.147	.588	.000	.399	.033	.001	.044	.082	.000	.000	.053		.000	.000	.112	.000	.010	.498	.	.000	.567
	N	35728	35675	35729	35729	35729	35729	35729	35698	35729	35729	35729	35729	35729	35729	35729	35658	35729	35662	4056	32325	32698
Hasshebeentoldthatshehasdiabetes	Pearson Correlation	-.002	.005	-.077**	-.007	.010	-.013*	-.023**	-.004	-.031**	-.030**	-.007	.363**	1	.368**	.002	.156**	.031**	.000	.[b]	.005	-.004
	Sig. (2-tailed)	.765	.352	.000	.164	.057	.016	.000	.439	.000	.000	.200	.000		.000	.654	.000	.000	.991	.	.330	.515
	N	35728	35675	35729	35729	35729	35729	35729	35698	35729	35729	35729	35729	35729	35729	35729	35658	35729	35662	4056	32325	32698
HassheeverbeentoldshehasTB	Pearson Correlation	-.005	.000	-.101**	-.017**	.011*	-.029**	-.009	-.006	-.043**	-.042**	-.018**	.359**	.368**	1	-.005	.218**	.021**	.036**	.[b]	.015**	-.003
	Sig. (2-tailed)	.378	.938	.000	.002	.034	.000	.097	.291	.000	.000	.001	.000	.000		.362	.000	.000	.000	.	.006	.587
	N	35728	35675	35729	35729	35729	35729	35729	35698	35729	35729	35729	35729	35729	35729	35729	35658	35729	35662	4056	32325	32698
anaemia	Pearson Correlation	.004	.041**	.034**	.000	.003	.016**	.052**	.031**	-.029**	-.016**	.064**	-.008	.002	-.005	1	-.004	.080**	.002	.[b]	-.004	-.006
	Sig. (2-tailed)	.469	.000	.000	.991	.549	.002	.000	.000	.000	.003	.000	.112	.654	.362		.425	.000	.754	.	.491	.315
	N	35728	35675	35729	35729	35729	35729	35729	35698	35729	35729	35729	35729	35729	35729	35729	35658	35729	35662	4056	32325	32698
Doesshehaveahistoryofworms	Pearson Correlation	-.003	.003	.003	-.003	-.013*	.002	-.004	-.005	-.010	-.013*	-.001	.190**	.156**	.218**	-.004	1	.026**	.000	.[b]	-.001	.000
	Sig. (2-tailed)	.574	.596	.521	.565	.017	.753	.502	.317	.064	.012	.879	.000	.000	.000	.425		.000	.995	.	.830	.959
	N	35657	35604	35658	35658	35658	35658	35658	35627	35658	35658	35658	35658	35658	35658	35658	35658	35658	35591	4046	32264	32642
Doesshenedcarefromfamilyorfriendswhowouldotherwiseworkforwagesa	Pearson Correlation	-.006	.002	-.004	-.011*	.017**	-.004	-.029**	.011*	.136**	.142**	.047**	.014**	.031**	.021**	.080**	.026**	1	.011*	.[b]	-.009	.004
	Sig. (2-tailed)	.254	.648	.407	.034	.001	.442	.000	.040	.000	.000	.000	.010	.000	.000	.000	.000		.047	.	.109	.473
	N	35728	35675	35729	35729	35729	35729	35729	35698	35729	35729	35729	35729	35729	35729	35729	35658	35729	35662	4056	32325	32698
rs_po_outcome	Pearson Correlation	-.010	-.015**	.006	-.006	-.020**	-.013*	.000	.064**	.007	.006	.003	-.004	.000	.036**	.002	.000	.011*	1	.[b]	-.403**	.000
	Sig. (2-tailed)	.052	.004	.224	.283	.000	.015	.957	.000	.215	.224	.600	.498	.991	.000	.754	.995	.047		.	.000	.961
	N	35661	35626	35662	35662	35662	35662	35662	35639	35662	35662	35662	35662	35662	35662	35662	35591	35662	35662	4056	32325	32698
neomorbidity	Pearson Correlation	.[b]	.[b]	.[b]	.[b]	.[b]	.[b]	.[b]	.[b]	.[b]	.[b]	.[b]	.[b]	.[b]	.[b]	.[b]	.[b]	.[b]	.[b]	.[b]	.[b]	.[b]
	Sig. (2-tailed)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	N	4056	4051	4056	4056	4056	4056	4056	4055	4056	4056	4056	4056	4056	4056	4056	4046	4056	4056	4056	3203	4044
stillbirth	Pearson Correlation	.053**	.043**	.007	-.023**	.003	-.011	.010	-.028**	-.011	-.013*	-.012*	.026**	.005	.015**	-.004	-.001	-.009	-.403**	.[b]	1	.[b]
	Sig. (2-tailed)	.000	.000	.185	.000	.568	.055	.074	.000	.053	.020	.030	.000	.330	.006	.491	.830	.109	.000	.	.	.000
	N	32324	32296	32325	32325	32325	32325	32325	32310	32325	32325	32325	32325	32325	32325	32325	32264	32325	32325	3203	32325	30441
rs_po_alive	Pearson Correlation	-.011	-.007	-.007	-.001	-.004	.007	.002	-.002	.004	.004	.002	-.003	-.004	-.003	-.006	.000	.004	.000	.[b]	.[b]	1
	Sig. (2-tailed)	.055	.185	.190	.892	.433	.178	.664	.689	.511	.495	.779	.567	.515	.587	.315	.959	.473	.961	.	.000	
	N	32697	32668	32698	32698	32698	32698	32698	32681	32698	32698	32698	32698	32698	32698	32698	32642	32698	32698	4044	30441	32698

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

b. Cannot be computed because at least one of the variables is constant.

Table 24. Multi-collinearity diagnostic outputs

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
		B	Std. Error	Beta	t	Sig.	Tolerance	VIF
1	(Constant)	64.386	13.948		4.616	.000		
	maternal_mortality	112.234	44.791	.042	2.506	.012	.985	1.015
	matmorbid	20.962	4.222	.085	4.965	.000	.943	1.061
	pr_di_age	-.664	.402	-.028	-1.654	.098	.952	1.051
	PW_edu_cat	46.150	4.787	.170	9.641	.000	.882	1.133
	parity_cat	53.137	4.200	.215	12.651	.000	.956	1.046
	husb_edu_cat	19.214	3.737	.091	5.142	.000	.890	1.124
	Arm	6.376	3.675	.029	1.735	.083	.976	1.025
	per_obtained_RANC	14.624	4.150	.062	3.524	.000	.883	1.133
	funds_saved_OE	9.365	4.008	.040	2.336	.020	.941	1.063
	Hasshebeentoldthatshehasseizures	.113	.234	.009	.481	.630	.772	1.296
	Hasshebeentoldthatshehasdiabetes	-.037	.162	-.004	-.225	.822	.791	1.265
	Doesshehaveahistoryofworms	-.654	.331	-.037	-1.979	.048	.770	1.298
	Doessheneedcarefromfamilyorfriendswhowouldotherwiseworkforwagesa	3.213	4.875	.012	.659	.510	.899	1.113

a. Dependent Variable: G_total_Mat_NB_costs

Table 25. Focus group guide: Pregnant women identified with HDP

Topic I. Costs drivers and health resource utilization as result of the CLIP package of care
1. What were you preferences for health facility and why, after you received referral advice (***non-urgent***) from Community Health Worker?
2. What were you preferences for health facility and why, after you received referral advice (***urgent***) from Community Health Worker?
3. What cost(s) you were to pay, after you received referral advice (***urgent or non-urgent***) from Community Health Worker?
4. What cost(s) you were to pay, after you received medication (***MgSO4 or Methyldopa***) from Community Health Worker?
5. Explain with examples of any additional out-of-pocket expense(s) i.e., costs that you did not anticipate as result of accepting referral or medication advice from Community Health Worker?

Topic II: Perceived cost benefits of the CLIP package of care and task-sharing to community health care workers
1. What is your opinion about the benefits of equipping community health workers with the CLIP Package of care (blood pressure monitoring device, urine dipstick, cell phone PIERS on the move application, and pulse-oximeter)?
a. Her knowledge or capacity development
b. Strengthening her rapport with the community
c. Bridging program or service delivery gap at the community
2. How do you think, the PIERS on the move recommended (referral or medication) advice from community health worker would have benefited other pregnant women or family in the intervention areas?
a. Improving health condition of woman
b. Decreasing financial load on the family as result of pregnancy complications
3. Reflecting on your experiences, how do you think your decision would have affected you or family?
a. Impact of your decision of accepting or refusing referral advice?
b. Impact of your decision of accepting or refusing medication advice?
4. Explain your general feelings or thoughts (having participated) for the CLIP package of care in your area.

Table 26. Focus group guide: Husband of pregnant women identified with HDP

Topic I: Costs drivers and health resource utilization as result of the CLIP package of care
1. What were you preferences for health facility and why, after your wife received referral advice (***non-urgent***) from Community Health Worker?
2. What were you preferences for health facility and why, after your wife received referral advice (***urgent***) from Community Health Worker?
3. What cost(s) you were to pay, after your wife received referral advice (***urgent or non-urgent***) from Community Health Worker?
4. What cost(s) you were to pay, after your wife received medication (***MgSO4 or Methyldopa***) from Community Health Worker?
5. Explain with examples of any additional out-of-pocket expense(s) i.e., costs that you did not anticipate as result of your wife accepting referral or medication advice from Community Health Worker?

Topic II: Perceived cost benefits of the CLIP package of care and task-shifting to community health care workers
1. What is your opinion about the benefits of equipping community health workers with the CLIP Package of care (blood pressure monitoring device, urine dipstick, cell phone PIERS on the move application, and pulse-oximeter)?
a. Her knowledge or capacity development
b. Strengthening her rapport with the community
c. Bridging program or service delivery gap at the community
2. How do you think, the PIERS on the move guided recommendation (referral or medication) from community health worker would have benefited other pregnant women or family in the intervention areas?
a. Improving health condition of woman
b. Decreasing financial load on the family as result of pregnancy complications
3. Reflecting on your experiences, how do you think your decision would have affected your wife / daughter in-law or family?
a. Impact of your decision of accepting or refusing referral advice?
b. Impact of your decision of accepting or refusing medication advice?
4. Explain your general feelings or thoughts (having your wife /daughter-in-law participated) for the CLIP Trial in your area.

Table 27. Focus group guide: LHWs/LHS in the intervention clusters

Topic I: Costs drivers and health resource utilization as result of the CLIP package of care
1. How would you describe your experience of home-visit for CLIP package of care assessments?
a. Patient assessment (blood pressure monitoring, urine dipstick testing, oxygen saturation measurement, and putting data on cell phone application)
b. Explaining the recommendations (transport or medications)
c. Administering the medication (methyldopa or MgSO4)
2. How much additional time, you think it may have taken to complete CLIP package of care assessments for each pregnant woman, other than routine visit activities?
3. What were the expectations of pregnant woman or her family from you for emergency or on-request visits for any of the CLIP package of care assessments, other than routine visits?
4. What were the numbers of extra home-visit did you make for CLIP package of care assessments, other than routine visits?
5. Explain with examples of any additional out-of-pocket expense(s) for you i.e., costs that you did not anticipate as result of your visit for CLIP package of care assessments, referral, and medication advice to pregnant women?

Topic II: Perceived cost benefits of the CLIP package of care and task-shifting to community health care workers
1. What is your opinion about the benefits of equipping community health workers with the CLIP Package of care (blood pressure monitoring device, urine dipstick, cell phone PIERS on the move application, and pulse-oximeter)?
a. Knowledge or capacity development
b. Strengthening rapport with the community
c. Bridging program or service delivery gap at the community
2. How do you think, the PIERS on the move recommended (referral or medication) advice from you would have benefited pregnant women or family in the intervention areas?
a. Improving health condition of woman
b. Decreasing financial load on the family as result of pregnancy complications
3. Explain your general feelings or thoughts (having participated) for the CLIP package of care in your area.

Table 28. Focus group guide: District level health decision/policy makers

Topic I: Costs drivers as result of the CLIP package of care
1. What are the program and/or health system costs that you would ascribe to LHW's home-visit for CLIP package of care?
d. Patient assessment (blood pressure monitoring, urine dipstick testing, oxygen saturation measurement, and putting data on cell phone application)
e. Explaining the recommendations (transport or medications)
f. Administering the medication (methyldopa or MgSO4)
2. What additional resources (that may have implications on program costs), you think it may have taken for LHW s to complete CLIP package of care visits for each pregnant woman, other than routine visit activities?
3. Explain with examples of any additional program expense(s) i.e., costs that you did not anticipate as result of your visit for CLIP package of care assessments, referral, and medication advice to pregnant women?

Topic II: Perceived cost benefits of the CLIP package of care and task-shifting to community health care workers
1. What is your opinion about the benefits of equipping community health workers with the CLIP Package of care (blood pressure monitoring device, urine dipstick, cell phone PIERS on the move application, and pulse-oximeter)?
a. Her knowledge or capacity development
b. Strengthening her rapport with the community
c. Bridging program or service delivery gap at the community
2. How do you think, the PIERS on the move guided recommendation (referral or medication) from community health worker would have benefited pregnant women or family in the intervention areas?
a. Improving health condition of woman
b. Decreasing financial load on the family as result of pregnancy complications
3. Explain your feelings or thoughts for the CLIP package of care, in general.

Table 29. Unit costing proforma

National LHWs Program

S#	Section 1: Manpower support per cluster during definitive phase of the CLIP Trial												
Cluster number →		1	2	3	4	5	6	7	8	9	10	11	12
1	# of health workers (LHWs) serving in the cluster												
2	# of supervisor(s) to health workers (LHWs) serving in the cluster												
3	Average # of households in each health worker's catchments												
4	Average # of pregnant women in health worker's catchments (at any given time)												
5	Total # of women enrolled for the CLIP Trial												
6	Total # of women enrolled in POM												
7	Total # of community engagement sessions conducted in intervention cluster												
8	Total # of community engagement sessions attended by health workers (LHWs) in intervention cluster												
9	Average time to travel to conduct POM visit												
10	Average time to conduct one POM visit per woman: first visit												
11	Average time to conduct one POM visit per woman: subsequent visits												
12	Total # of CLIP training sessions conducted for health workers (LHWs)												
13	Total # of CLIP training sessions conducted for health workers' (LHWs) supervisors												

Section 2: Program costing			
Category	***Specification***	***Cost in INR.*** ***[If not applicable, put NA]***	***Working notes***
	i. Incentive of a health worker (LHWs) per month		
Health workers (LHWs)	ii. Stipend/incentive of a health worker (LHWs) for CLIP work (per PW)		
	iii. Average transport cost for a POM visit (per PW) (avg. of inside and outside cluster)		
	iv. Average transport cost accompanying pregnant woman for routine ANC care to PHC (one-side trip per person) (avg. of pub and private vehicle)		
	v. Average transport cost accompanying pregnant woman for routine ANC care to higher health facility (one side trip per person) (avg. of pub and private vehicle)		
	vi. Average transport cost accompanying pregnant woman for emergency referral within 24 hours by CLIP triggers (one side trip per person) (avg. of pub and private vehicle)		
	vii. Average transport cost accompanying pregnant woman for emergency referral within 4 hours by CLIP triggers (one side trip per person) (avg. of pub and private vehicle)		
Supervision & mentoring	i. Salary of a government appointed supervisor to health workers (LHWs) (per month)		
	ii. Stipend/incentive of a Supervisor to health workers (LHWs) for CLIP work (per PW)		
	iii. Average monthly cost of a supervisory visit by CLIP staff for monitoring purposes per health worker (LHWs)		
Training & support for CLIP	i. Cost of training manual per health worker (LHWs)		
	ii. Cost of training manual per health worker (LHWs)		
	iii. Cost of stationary / supplies per health worker (LHWs)		
	iv. Average cost of POM supplies per health worker (LHWs) in any given time *Mobile devices* *MgSO4* *Methyldopa Tablets*		

Section 2: Program costing				
Training & support for CLIP (continued)		*Urine dipstick* *Handbag* *Gloves plastic (for health worker while doing urine dipstick)* *Gloves surgical (for health worker while giving injection)* *Syringe10ml* *Ampoule cutter,* *Urine cups* *Disposal box* *Batteries* *Per CLIP kit (inclusive of two 10ml MgSO4 ampules, two 10ml syringes, two swabs, and a box with instructions, labels, and two surgical gloves)* *Per CLIP kit Methyldopa (inclusive of three Methyldopa tablets each 250mg strength, a label and a A8 size envelope, a moisture-free inner envelope)* *Other items (specify)*		
	v.	Total cost of POM kit maintenance (inclusive of Table and CLIP injection kit) per health worker (LHWs)		
	vi.	Average cost of community engagement visual-aids or posters per health worker (LHWs) to be displayed in community in the overall trial period		
	vii.	Average cost of facility posters per health worker (LHWs) to be displayed in referral facility in the overall trial period		
	viii.	Average cost of central team visit for training of health workers (LHWs)		
	ix.	Average cost of incentive for attending one training session per health worker (LHWs)		
	x.	Average cost of incentive for attending one training session per health worker (LHWs)		
	xi.	Average cost of refreshment during training session (per session)		

Table 30. Unit costing proforma health facilities

HEALTH FACILITY UTILIZATION

Section 1: Health Facility Identification	
Name of health facility	
Type of health facility [Mark X]	Private clinic | Private secondary hospital | Private tertiary hospital
Country/District / Site	
Date of visit	
Form completed by:	
Form checked by:	

Section 2: Maternal out-patient services		
Category	***Specification***	***Cost*** ***[If not applicable, put NA; Round off to nearest integer]***
Routine antenatal care (per visit)	viii. First visit	
	ix. Subsequent visit	
Investigations	iv. Pregnancy ultrasound	
	v. Blood test: complete blood count (CBC)	
	vi. Blood test: Culture	
	vii. Blood test: LFT	
	viii. Blood test: Blood urea	
	ix. Blood test: Serum creatinine	
	x. Blood test: Coagulation profile	
	xi. Urine dipstick test for urine albumin and sugar	
	xii. Urine routine test *(inclusive of urine albumin, sugar and microscopy)*	
	xiii. X-ray: chest	
	xiv. Biophysical profile	
	xv. Non-stress test (NST)	

Section 3: Maternal in-patient services, other than delivery		
Category	***Specification***	***Cost.*** ***[If not applicable, put NA; Round off to nearest integer]***
Overnight admission in this facility	i. General ward (per night)	
	ii. Intensive care unit (per night)	
Blood transfusion (per unit)	i. pRBC	
	ii. Platelets: RDP	
	iii. Platelets: SDP	
	iv. Fresh Frozen Plasma	
	v. Whole blood	
	i. Mechanical ventilation (per day)	

Section 3: Maternal in-patient services, other than delivery		
Maternal interventions	ii. Dialysis (per day)	
	iii. Brace Sutures (per procedure)	
	iv. Internal iliac artery ligation (per procedure)	
	v. Hysterectomy (per procedure)	

Section 4: Delivery related admissions		
Category	***Specification***	***Cost*** ***[If not applicable, put NA; Round off to nearest integer]***
Cost of delivery in this facility	i. Spontaneous delivery	
	ii. Assisted vaginal delivery	
	iii. Caesarean delivery	

Section 5: Newborn out-patient services		
Category	***Specification***	***Cost*** ***[If not applicable, put NA; Round off to nearest integer]***
Newborn visits at this facility (per visit)	i. First visit	
	ii. Subsequent visit	
Investigations	i. Fetal imaging: ultrasound	
	ii. Fetal imaging: x-ray chest	
	iii. Echocardiography	
	iv. Blood test: Serum bilirubin	
	v. Blood test: Blood group	
	vi. Blood test: Arterial blood gases	

Section 6: Newborn in-patient services, other than delivery		
Category	***Specification***	***Cost*** ***[If not applicable, put NA; Round off to nearest integer]***
Overnight admission in this facility (per night stay)	i. Neonatal special / intensive care unit	
Newborn interventions	i. Mechanical ventilation (per day)	
	ii. CPAP (per day)	
	iii. Phototherapy: single surface (per day)	
	iv. Phototherapy: double surface (per day)	

Table 31. Disability weights: maternal morbidities in the CLIP Trial

CLIP Trial outcome	Description of condition	Disability weight (Range)	Assumption (citation)
Eclampsia	Occurrence of generalised convulsions during pregnancy, labour or within 42 days of delivery in the absence of epilepsy or another condition predisposing to convulsions	0.00	This outcome is acute, and women either die or survive without significant sequelae. (Global Burden of Disease (GBD)-2016/17; Table 5, page# 809)
Stroke	Hemiparesis and/or blindness developed during pregnancy or in the 42 days postpartum lasting greater than 48 hours	0.316 (0.206 – 0.437)	Acute ischemic stroke. (GBD-2016/17; Table 5, page# 820)
Coma	Prolonged unconsciousness ≥12 hours	Not reported	GBD does not list this condition.
Antepartum haemorrhage	Vaginal bleeding ≥ 15 mL with or without pain before the onset of labour	0.114 (0.078 – 0.159)	Maternal haemorrhage (< 1 L blood lost). (GBD-2016/17; Table 5, page# 809)
Disseminated intravascular coagulation (DIC)	Abnormal bleeding from mucosa (mouth and/or ears)	Not reported	GBD does not list this condition.
Obstetric sepsis	Fever and one of: abdominal/uterine tenderness, foul smelling vaginal discharge/lochia, productive cough and shortness of breath, dysuria or flank pain, headache and neck stiffness.	0.133 (0.088 – 0.19)	Puerperal sepsis (GBD-2016/17; Table 5, page# 809)
Vesicovaginal or rectovaginal fistula	Continuous loss of urine and/or faeces after delivery	0.342 (0.227 – 0.478)	Vesicovaginal fistula (GBD-2016/17; Table 5, page# 810)
CPR	A set of emergency procedures including chest compressions and lung ventilation applied in cardiac arrest victims.	0.00	GBD does not list this condition. We assume that woman undergoing this life saving intervention will either die or survive with no disability.

CLIP Trial outcome	Description of condition	Disability weight (Range)	Assumption (citation)
Dialysis	Haemodialysis and/or peritoneal dialysis	0.571 (0.398 – 0.725)	End stage renal disease on dialysis due to hypertension. (GBD-2016/17; Table 5, page# 829)
Mechanical ventilation	Intubation and ventilation not related to anaesthesia	0.00	GBD does not list this condition. GBD does not list this condition. We assume that woman undergoing this life saving intervention will either die or survive with no disability.
Blood transfusion	Require ≥1 unit	0.114 (0.078 – 0.159)	We are using a conservative estimate for maternal haemorrhage (< 1 L blood lost). (GBD-2016/17; Table 5, page# 809)
Interventions for post-partum haemorrhage	Brace sutures, external and internal uterine compression, anti-shock garment use, internal iliac artery ligation and/or hysterectomy with or without transfusion.	0.00	GBD does not list this condition. GBD does not list this condition. We assume that woman undergoing this life saving intervention will either die or survive with no disability.

Table 32. Disability weights: newborn morbidities in the CLIP Trial

CLIP Trial outcome	Disability weight (range)	Assumption (Source)
Feeding difficulty	0.00	This outcome is acute- and primary based on subjective recall. Newborns may survive without any significant sequelae.
Breathing difficulty	0.00	
Seizures	Not reported	GBD does not list this condition.
Lethargy	0.00	This outcome is acute- and primary based on subjective recall. Newborns may survive without any significant sequelae.
Coma	Not reported	GBD does not list this condition.
Fever	0.00	This outcome is acute- and primary based on subjective recall. Newborns may survive without any significant sequelae.
Hypothermia	0.00	
Umbilical cord infection	0.00	This outcome is acute- and primary based on subjective recall. Newborns may survive without any significant sequelae.
Skin infection	0.00	
Bleeding	Not reported	GBD does not list this condition.
Jaundice	0.00	This outcome is acute- and primary based on subjective recall. Newborns may survive without any significant sequelae.
Vomiting / diarrhea	0.00	