

**Mobilizing Misoprostol:
Exploring Policies and Practices in Refugee, Conflict, Crisis, and Emergency Settings**

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Abstract

Misoprostol is medication used globally for the prevention and treatment of post-partum hemorrhage, incomplete abortion management, and early induced abortion. The drug is widely recognized as a life-saving commodity in low-resource settings due to its thermostable properties, manageable routes of administration, and cost-effectiveness. Currently, there is limited research regarding misoprostol use in refugee, conflict, crisis, and emergency settings. The purpose of this study is to document policies regarding misoprostol use in crisis settings, clarify the position and alignment of these policies, and understand how policies affect misoprostol use on the ground. Using policy analysis and key informant interviews, this study concludes that misalignment among misoprostol policies and implementation gaps exist. Study recommendations are to integrate misoprostol in updated reproductive health kits, include the drug on the EML for currently excluded indications, map its use in crisis settings, and support relationship building between development and humanitarian sectors for improved programming.

Le misoprostol est un médicament utilisé pour la prévention et le traitement d'hémorragie du post-partum, le traitement d'avortement incomplet, et l'avortement précoce. Il existe peu de recherche concernant l'utilisation du misoprostol dans les contextes de réfugié, conflit, crise, et les situations d'urgence. Le but de cette étude est de documenter les politiques relatives à l'utilisation du misoprostol dans les situations de crise, de clarifier la position de ces politiques, et de comprendre comment les politiques influencent l'utilisation du misoprostol en pratique. En utilisant l'analyse des politiques et des entretiens avec des informateurs, cette étude conclut que le désalignement entre les politiques et les lacunes d'exécution existent. Les enquêtes futures comporteront sur l'intégration du misoprostol dans les kits de santé reproductive, inclusion sur le EML, analyse de son utilisation dans les situations de crise, et de soutenir le renforcement de les relations pour améliorer la programmation.

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List of Acronyms and Abbreviations

AMTSL	Active management of the third stage of labor
BMJ	British Medical Journal
CPIA	Country Policy and Institutional Assessment
D&C	Dilation and curettage
EML	Essential Medicines List
EmOC	Emergency obstetric care
FIGO	International Federation of Gynecology and Obstetrics
FDA	Food and Drug Administration
GBV	Gender based violence
GRADE	Grading of recommendations assessment, development, and evaluation
HRBA	Human rights based approach
LMP	Last menstrual period
IAFM	Inter-Agency Field Manual for Reproductive Health in Humanitarian Settings
IASC	Inter-Agency Standing Committee
IAWG	Inter-Agency Working Group for Reproductive Health in Crises
ICPD	International Conference on Population and Development
ICRC	International Committee of the Red Cross
IDP	Internally displaced person
IRC	International Rescue Committee
IUD	Intrauterine device
MDG	Millennium Development Goals
MISP	Minimum Initial Service Package
MOH	Ministry of Health
MOM	Mobile Obstetrics Maternal Health Worker Project
MSF	Médecins Sans Frontières
MVA	Manual vacuum aspiration
NGO	Non-governmental organization
NSAID	Non-steroidal anti-inflammatory drug
PAC	Post abortion care
PPH	Post-partum hemorrhage
RH Kit	Reproductive health kit
RCT	Randomized controlled trial
STI	Sexually transmitted infection
TBA	Traditional birth attendant
TOP	Termination of pregnancy
UN	United Nations
UNICEF	United Nations Children's Fund
UNFPA	United Nations Population Fund
UNHCR	United Nations High Commissioner for Refugees
WHO	World Health Organization
WRC	Women's Refugee Commission

Chapter 1: Introduction

Over the last twenty years collaborative global efforts demonstrate a steady shift in the humanitarian field to recognize reproductive health services for refugees and persons displaced by conflict, crisis, and emergency as a priority alongside the need for sanitation, shelter, and food (1-3). The 1994 International Conference on Population and Development (ICPD) in Cairo, Egypt championed a landmark global consensus to situate reproductive health within basic human rights structures; a stance that was validated the following year at the 1995 Fourth World Conference on Women in Beijing, China (4, 5). Both reports make specific mention of displaced populations and have guided reproductive health improvements in these settings. However, despite proactive progress and policy change, attention to the reproductive health needs of women living in refugee, conflict, crisis, and emergency settings remains challenging, and at times unmet.

The World Health Organization (WHO) estimates that 529,000 women die each year from pregnancy-related causes; 99% of maternal mortality takes place in developing countries and is linked to avoidable causes (6); one third of these global deaths occur in fragile states (7). Of the 34 countries identified as fragile states by the World Bank, most are those documented having a very high maternal mortality including, Sierra Leone, South Sudan, and Afghanistan (8). Global estimates by United Nations (UN) agencies indicate that maternal mortality in developing regions is 240/100,000 live birth compared with 16/100,000 in developed regions (9). In conflict affected settings, median adjusted maternal mortality has been recorded as high as 1,000/100,000 live births (10). In these contexts, female morbidity and mortality is dramatically impacted by limited access to emergency obstetric care (EmOC), lack of skilled providers, and an unmet need for family planning. While women are disproportionately vulnerable in humanitarian settings, it has only been within the

last two decades that gender perspectives have entered into contextual policy discussions (11). More than ever before, normative bodies, such as the WHO, are generating technical guidance and policy. The overall impact of a scaled up policy environment should be considered, and whether the development of policy translates into augmented resources and successful implementation should be explored.

Misoprostol is a drug increasingly used in low-resource settings due to its thermostability and versatile characteristics. The drug is well-documented to be an effective agent to prevent and treat post-partum hemorrhage (PPH), manage incomplete abortion, and safely induce an early abortion alone and in conjunction with mifepristone (12). As of 2005, misoprostol was listed on the WHO's Essential Medicines List (EML) for first trimester medication abortion in conjunction with mifepristone; since then its inclusion on the EML has extended to PPH prevention and incomplete abortion management. Misoprostol is also a UN Lifesaving Commodity for Women and Children for post-partum hemorrhage care (13, 14). Despite clear evidence in support of misoprostol in low-resource contexts, it is not well known how the drug is being used in refugee, conflict, crisis, and emergency settings. Therefore, given the global movement to improve access to comprehensive reproductive health services and reduce maternal mortality in low-resource settings, an understanding of how misoprostol is addressed at the policy level could provide insight into the policy-making process and its implementation in the field. This study also serves as an important exercise to understand better the mechanisms that foster relationships between health focused normative bodies and implementing organizations, and where misoprostol is situated on their agendas.

1.1 Research Purpose, Questions, and Objectives

The purposes of this study is to explore misoprostol-related policy set by international normative bodies and develop a deeper understanding of how these policies translate into practice within the humanitarian landscape. This project is timely as it coincides with additions made to the WHO EML in 2011 and the recent establishment of a misoprostol committee within the Inter-Agency Working Group for Reproductive Health in Crises (IAWG). Currently, there is limited research exploring the implications of normative body policy in refugee, conflict, crisis, and emergency settings, and none examining policy related to misoprostol. Developing a greater understanding of policy and practice mechanisms may be useful for future policy recommendations and reform. As well, the findings of this study may support efforts to open up dialogue between actors in humanitarian contexts working to improve women's reproductive health and reduce maternal mortality in fragile states. Therefore, using a qualitative multi-methods approach I aim to address three distinct research questions:

1. What are the established policies set by normative bodies surrounding misoprostol use for PPH prevention and treatment, incomplete abortion management, and early induced abortion in refugee, conflict, crisis and emergency settings?
2. To what degree do misoprostol policies for PPH care, incomplete abortion management, and early induced abortion align between normative bodies?
3. To what degree do the practices of organizations implementing misoprostol in refugee, conflict, crisis, and emergency settings align with normative body policy?

The scope of this research is also guided by objectives that correspond with the research questions. This project specifically aims to:

1. Document policies related to misoprostol use in crisis settings set by normative bodies including, WHO, IAWG, United Nations Population Fund (UNFPA), and United Nations High Commissioner for Refugees (UNHCR);
2. Clarify the positioning and alignment of global normative body policies; and
3. Increase knowledge of how global policies affect misoprostol practice and programming among implementing organizations.

The expected outcomes of the study are that the concentration of policy guidance for misoprostol use exists in development fields and that there is limited application of policy and programming in refugee, conflict, crisis, and emergency settings. Moreover, specific misoprostol guidelines for fragile settings may be ambiguous and inconsistent, leading to confusion among stakeholders. I anticipate that the study findings will indicate a need for policy clarification and/or revision to implementation practices.

1.2 Definitions of Terms

The following concepts are defined to demonstrate the meaning of key terms used in this thesis. Using Babbie's (2011) specification of concepts for scientific inquiry, a nominal definition is provided for each term. As such, there is no claim that the definition represents a "real entity" or "essential nature" of a term (15, p132).

Normative body: An organization or agency established as a global authority responsible for settings norms and standards. The body is obliged to provide leadership and technical support, shape international policy agendas, and monitor and evaluate global trends.

Health policy: Courses of action (and inaction) that affect the set of institutions, organizations, services, and funding arrangements of the health system. Health policy includes policy made in the public sector (by government), private sector, and intended actions of organizations external to the health system, which have an impact on health (16).

Refugee, conflict, crisis, and emergency setting: An event or series of events, which represents a critical threat to the health, safety, security or well-being of a community, or other large group of people, usually over a significant geographic area. Armed conflicts, epidemics, famine, natural disasters, and other major emergencies may all involve or lead to these contexts and extends beyond the mandate or capacity of any single agency (17).

Fragile state: Country with the presence of a UN and/or regional peace-keeping, peace-building, or political mission during the past three years, or a harmonized average Country Policy and Institutional Assessment (CPIA) rating of 3.2 or less on the World Bank's Harmonized list of Fragile Situations. The CPIA measurement tool clusters countries based on four criteria: economic management, structural policies, policies for social inclusion and equity, and public sector management and institutions (18).

Maternal mortality: Death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of pregnancy, from any cause related to or aggravated by the pregnancy, or its management but not from accidental or incidental causes (9). For the purpose of this study, the maternal mortality ratio (number of maternal deaths during a given time period per 100,000 live births during the same time period) and maternal

mortality rate (number of maternal deaths in a given period per 100,000 women of reproductive age during the same time period) are used to measure this construct.

Post-partum hemorrhage: Blood loss of 500 mL or more within 24 hours after birth, while severe PPH is defined as a blood loss of 1000 mL or more within the same timeframe (19).

Incomplete abortion: Retained products of conception within the uterus following either a spontaneous, or induced abortion in which the cervix is open, or partially open (20).

Early induced abortion: Termination during the first 9 weeks (63 days) of pregnancy. Gestational age is measured by the number of weeks or days since the first day of the woman's last menstrual period (LMP) (21).

Unsafe abortion: A procedure for terminating an unwanted pregnancy either by a person lacking the necessary skills or in an environment lacking minimal medical standards or both (21).

1.3 Strategy of Inquiry, Theoretical Framework, and Assumptions

This research was conducted using an interpretive constructivist paradigm in order to better understand multiple and complex realities (22). Indeed, the purpose of this research is to identify meaning from professional experiences and perceptions on certain issues. This social constructivist framework is applied using the ontological, epistemological, and axiological assumptions detailed by Creswell (2013), which state that there exist multiple

realities that are shaped through individual experiences and social interactions. The framework also assumes that the researcher and participant co-construct a reality that is based on their individual experiences, and that research is value-laden with potential biases. Using this approach aligns with the understanding that the researcher's values and positioning impacts the overall nature of the study. Therefore, I acknowledge that my own values as a feminist and proponent of reproductive health as a human right may have influenced components of this study.

1.4 Thesis Structure

This thesis takes on the following structure to answer and discuss the research questions. To begin, I introduce the humanitarian landscape and identify relevant structures and actors that operate within these complex settings. Then I provide a critical appraisal of the global evidence regarding misoprostol for four indications of use: PPH prevention, PPH treatment, incomplete abortion management, and early induced abortion as a single agent. Subsequently, I describe the multi-methods qualitative methodology used for this study. Next, I present the results from the in-depth policy analysis and key informant interviews. Using these results I explore in detail the implications for policy and practice gaps, and consider the barriers for addressing the issues raised as a result of the study. Finally, I conclude by summarizing the study and present recommendations for future research and advocacy.

Chapter 2: Background

In order to understand the global practices of misoprostol in refugee, conflict, crisis, and emergency settings, it is important to consider the characteristics of these populations and their overarching social contexts, health systems, and policy frameworks. This chapter aims to provide sufficient background while highlighting key global structures and actors pertaining to misoprostol integration in humanitarian settings.

2.1 Global context of refugee, conflict, crisis, and emergency settings

Refugee, conflict, crisis, and emergency contexts are commonly explored under the umbrella term humanitarian settings. Humanitarian settings broadly refer to regions affected by political instability, armed conflict, natural or technological disasters, forced migration, or massive population displacement, food shortages, and collapse of public health and social infrastructure. Today, these settings include, but are not limited to, the 2010 earthquake in Haiti, the conflict affected Karen State of Eastern Burma, and the displacement of Darfuri refugees from the Sudan into Eastern Chad. In these settings, extensive damage to fundamental infrastructure, basic health care, and social services is prevalent. As such, humanitarian settings often elicit a global response from non-affected nations or governments, multilateral institutions, and non-governmental organizations (23, 24). International incidents, or the remnants of the aftermath, can be detrimental to the physical, mental, and social well-being of an affected individual or population (25-27).

2.1.1 Displaced populations in humanitarian settings

The overwhelming loss of social structures including family support, community networks, and a sense of personal identity is debilitating and can contribute to overall vulnerability of living in an emergency, or conflict setting. Displaced populations have an increased susceptibility to poor health outcomes compared to other groups in humanitarian contexts, as they are often unable to meet basic needs. Internally displaced persons (IDPs), stateless people, and refugees are sub-groups of this demographic (23, 24). UNHCR reports that by the end of 2012, 45.2 million people were forcibly displaced worldwide; 15.4 million declared refugees and 28.8 million IDPs, accounting for the highest levels of displacement since 1994 (28). In protracted conflict and emergency settings, estimating displacement can be challenging and underestimated since unofficial refugee camps and undocumented migrants make up a significant part of the landscape (29, 30).

IDPs, stateless persons, and refugees should be distinguished given their diverse displacement experiences. In 1951 the United Nations Convention Relating to the Status of Refugees termed refugees as “individuals who flee their country owing to a well-founded fear of persecution due to race, religion, nationality, membership of a particular social group or political opinion” (31, p14). Despite assumptions that the term refugee suggests short-term temporality, IAWG reports that on average, refugees are displaced from their native homes for 17 years (32). These findings suggest that opportunities for reintegration are limited, and persons are being born into refugee status and remaining as such into adolescence.

Stateless populations are often grouped with refugees despite the distinction that unlike refugees, they are without nationality, or have an official relationship with a sovereign state (33). This status significantly limits their active participation in society and ability to exercise their fundamental human rights. IDPs are individuals forced from their home due to

reasons similar to previously discussed groups including, natural disasters, political persecution, and war. However, IDPs remain within the official borders of their country and fall under the legal protection of their native government. Brennan and Nandy (2001) suggest that due to distinct access barriers, ambiguous international mandates, and the reality that the laws of protection for refugees under the Refugee Convention do not extend to IDPs, they are a more challenging population for implementing agencies and humanitarian groups to reach (24).

2.2 Trends in refugee, conflict, crisis, and emergency settings

Patterns in humanitarian settings indicate that the number of international armed conflicts has decreased in recent decades. However, contemporary conflicts are increasingly protracted, focused within state borders, and driven by ethnic contention and economic motivators (30). Consequently, acute emergencies and protracted crises requiring humanitarian intervention has doubled over 30 years (23). Interpretation of this growing trend suggests global shifts towards urbanization, population growth in vulnerable areas, and climate change, or environmental deterioration as correlating factors (23). The Center for Research on the Epidemiology of Disasters predicts that these factors will increasingly prompt recurrent crises that will dramatically affect those currently living in post-crisis, or disaster affected settings (34). As populations living in post-crisis settings continue to grow, so too does the challenge to re-develop infrastructure and services in the aftermath. With limited access to health services and minimal functional resources, these populations will increasingly face extraordinary health risks impacting disease, malnourishment, and mortality (35).

2.2.1 Urbanization of refugee populations

In the last decade, the phenomenon of urbanized displacement has challenged traditional mechanisms behind humanitarian intervention (36). Displaced persons seeking refuge in large cities is rapidly increasing and fewer are residing inside the camp system (30, 37). UNHCR estimates that 50% of all refugees are located in urban centers; this figure is projected to reach 60% by 2030 (38). In urbanized settings, it has been suggested that “the humanitarian community is outside of its comfort zone,” as refugees are less visible, and therefore it is more challenging to identify and address their needs (39, pS25). Host-countries already experiencing intermittent health service provision, lack of security, and fragmented infrastructure, create an environment posing significant challenges for addressing the health needs of urban refugees (30). Some research has gone as far as to say urbanization among displaced populations is a threat to public health advancements and risks creating modernized humanitarian disasters (40).

2.2.2 Gender-based violence

The lasting impact of conflict, crisis, and emergency settings is rarely gender neutral (35). Forms of gender-based violence (GBV) including, rape, sexual assault, and domestic abuse are becoming increasingly tied to humanitarian contexts, especially ones precipitated by extremely violent conflict (41, 42). Numerous past and current histories of conflict and crisis deliberately use rape as a systematic tool to propagate conflict. Although rape in conflict is pervasive, due to widely anticipated underreporting, it is difficult to accurately ascertain how prevalent GBV is among refugee or displaced populations. Normative bodies, including the World Bank, are developing methodologies and evaluation tools to assess the

extent to which violence against women is perpetrated in conflict zones and emergency settings. However, this work is preliminary and has only been tested in a handful of countries (35). Understanding GBV and how sexual violence is exercised in humanitarian settings demonstrates the importance of addressing women's reproductive health in these environments. The availability of emergency contraception, family planning services and counseling, and safe abortion options can dramatically impact the well-being on women living in these circumstances (43). A myriad of training tools have been developed to ensure health care provider's clinical practice includes delivering emergency contraception, post-exposure prophylaxis, and sexually transmitted infection (STI) treatment among survivors of sexual assault in humanitarian settings (43, 44). However, clinic access and lack of funds remain barriers for survivors of sexual assault, and some refugee camp-based clinics have policies limiting access to emergency contraception (29).

2.3 Women's reproductive health in conflict, crisis, refugee, and emergency settings

Over the last two decades, a committed combination of research and advocacy has advanced the status of reproductive health on global health agendas (1, 3). However, it remains that the experiences of conflict and displacement seriously impact maternal health and mortality outcomes. Women remain one of the most marginalized groups in humanitarian settings, and with children are estimated to make up 80% of all refugees and IDPs (42). Displaced women encounter greater overall health risks given the services and commodities they previously accessed may become unavailable. It can be exceptionally challenging to identify and make use of reproductive health services in a foreign setting, as they may be delivered in a different language, or by unknown practitioners potentially using

unfamiliar cultural practices (45). Moreover, displaced women often face indirect challenges related to their reproductive health due to the overall structures of loss following displacement including, malnutrition, unavailability of safe services, and lack of family support (2).

2.3.1 Maternal health in refugee, conflict, crisis and, emergency settings

WHO reports that between 1990 and 2010 global maternal mortality was reduced by 47% (9). The 5th UN Millennium Development Goal (MDG) aims to improve maternal health and reduce the maternal mortality ratio by 75%. While there have been significant global achievements made to improving maternal health, countries that constitute refugee, or humanitarian settings do not follow this trend (9, 46).

Developing countries account for 99% of global maternal mortality, with most of the global burden residing in sub-Saharan Africa and Southern Asia. One third of these maternal deaths occur in fragile states (7). WHO estimates that 15% of all pregnant women develop potentially life-threatening complications requiring skilled intervention (47). In emergency settings this can be attributed to a lack of EmOC, the absence of trained providers, or unsafe practices (45). Worldwide, displaced women experience higher rates of unwanted and unintended pregnancy than during pre-displacement and such rates are higher than nationals from their host country. In refugee settings, basic family planning services often go unmet and women struggle with unwanted, unplanned, or poorly spaced pregnancies (45). Socio-economic and cultural factors greatly impact availability of commodities; for example, the host country may not have dedicated family planning products or the government may not endorse family planning practices. Humanitarian organizations are encouraged to counsel on

and supply family planning commodities, and consider where differences between pre- and post-displacement needs exist (45).

2.3.2 Overarching health systems in refugee, conflict, crisis, and emergency settings

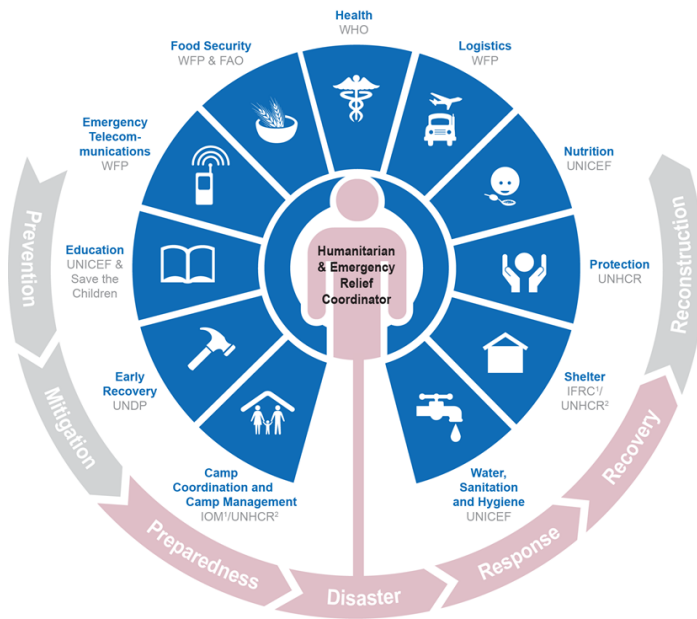
Influx of displaced populations can have immense impacts on a host-region's health infrastructure. UNHCR reports that low-income countries host over 80% of global refugees (28). In lower income countries, local health clinics and hospitals are often already ill-equipped to provide a high standard of care for its own nationals and thus the unique needs of an incoming population places exceptional demand on the health system. Existing health systems may already be under stress if they have been affected by loss of staff, corruption, or damage due to an existing conflict, or complex emergency (45). These structures make it exceptionally challenging to meet international standards and policies requiring comprehensive reproductive health services. Establishing capacity to rebuild health systems and provide health services is complex and involves commitment from country, community, international agency, and donor stakeholders (48). Research on health system frameworks and case studies in post-conflict regions has demonstrated successful models for rebuilding and strengthening health systems, but the barriers remain significant (49-52).

2.4 Humanitarian Architecture and Reproductive Health

The humanitarian arena is made up of a multi-sectorial blend of international organizations and agencies including but not limited to, the UNFPA, the UNHCR, Médecins Sans Frontières (MSF), the International Rescue Committee (IRC), and the International

Committee of the Red Cross (ICRC). Some perspectives suggest the landscape of humanitarian work is becoming narrower due to security threats and less confidence in principles of impartiality and neutrality (30). However, within the current scope of international work, reproductive health is widely acknowledged as being on the humanitarian agenda (53). In 2011 the Sphere Handbook, the primary resource for all humanitarian agencies and actors, expanded to include a new chapter on sexual and reproductive health, defining this as an essential health service (54). The UN along with international non-UN agencies developed the Global Cluster Approach to improve coordination among partners, reduce implementation gaps, and limit agency overlap during all phases of emergency preparedness, response, and recovery (See Figure 2.1). Leaders for the Cluster specifically addressing health issues, WHO and the Inter-Agency Standing Committee (IASC), included reproductive health in 2009 revisions within their global guidelines. Their recommendations include provision of EmOC, family planning, and improving mechanisms to protect against and report on GBV (55).

Figure 2.1: Health Cluster Approach
 Source: Inter-Agency Standing Committee (IASC), 2012 (56)



In 1995, following ICPD, IAWG, a collaborative working group for reproductive health in crises, was established. This multi-sectorial group brings together a membership of over 30 diverse bodies including UN agencies, academic research bodies, governmental representatives, and non-governmental organizations, committed to providing comprehensive reproductive health care to those most affected by refugee and humanitarian settings (57). In 1999, IAWG released the first field manual addressing reproductive health needs and guidelines for crisis settings; it was revised in 2010 and renamed the Inter-Agency Field Manual on Reproductive Health in Humanitarian Settings (IAFM) (32).

The context of refugee, conflict, crisis, and emergency settings greatly impacts the reproductive health of affected and displaced populations. As global refugee and IDP demographics continue to grow and concentrate in urbanized centers of low-income countries,

distinct priorities and approaches are required. The humanitarian actors and agencies discussed in this chapter continue to influence health policy agendas by developing technical guidelines and systematized resources. This includes integrating the reproductive health kits (RH Kits) distributed by UNFPA during the early stages of crisis. Moving forward, it is important to explore the policy structures and actors that influence policy-making processes for humanitarian response.

Chapter 3: Conceptual Policy Frameworks

This chapter examines policy theory and frameworks in order to provide background for exploring and analyzing misoprostol-related policies. I begin by explaining the principles of health policy analysis and discuss the nature of global health policy environments. Finally, I explore health policy models and frameworks, and specifically detail Walt and Gilson's (1994) health policy triangle framework and explore its four substantive elements further.

3.1 Principles of Policy Analysis and Global Health Policy Environments

Policy analysis is an area of multi-disciplinary inquiry that draws from a diverse set of both qualitative and quantitative methodologies. Although quantitative economic assessments and cost-benefit analyses have become popular tools in health policy analysis, qualitative approaches are beneficial for exploring values and human action as contributors to policy and the policy-making process (58). The primary objective of policy analysis is to gather knowledge about the policy process, identify past successes or failures, and ultimately improve future reform and health outcomes (16). This thesis provides a retrospective analysis of normative body policies in an effort to understand current dynamics. This approach allows the researcher to analyze how policy issues make it onto global health agendas, the various content of such policies, and whether the policies are perceived as successful during implementation (16). Indeed, prospective policy analysis is also used throughout analysis in order to provide prescriptive recommendations for advancing misoprostol practices. Understanding implementation, defined as moving from policy to practice, and potential gaps are other important concepts to be studied. Traditionally, top-down and bottom-up approaches are common theoretical models to explain policy implementation. Top-down

implementation theory considers formulating policy and its implementation to be exclusively separate entities in which “subordinate levels of a policy system put into practice the intentions of higher levels based on the setting of objectives” (16, p121). Supporting theorists have suggested the model adds empirical value to discerning failed and successful implementation, and several have established necessary conditions, or pre-conditions, for successful outcomes (59, 60). Conversely, bottom up implementation theorists suggest lower-level agencies and actors play an active role in implementation and are capable of revising intended policy in order to produce modified outcomes. Numerous studies demonstrate how health service providers and their contextual environments shape policy implementation using Lipsky’s concept of street-level bureaucrats (61-64).

Over the past 10 years scholars have acknowledged a shift in the nature of policy and policy-making, which points to the involvement of a much larger array of actors in the policy process. As such, policy environments are increasingly impacted by inter-organizational collaborations, global civil society, and funding mandates. More than ever, domestic strategies are being influenced by global policy agendas and strategies, especially in low-resource settings where policy decisions are often shaped by external donors and international initiatives (16, 65). Although a large body of work focuses on national contexts of policy-making, this thesis addresses global dimensions at normative body levels, for example UN agencies. Although technical norms and standards set by normative bodies are typically developed using a systematic evidence-based process, the agency has no authority to impose policies on independent countries (16). However, in cases of complex emergency or natural disaster, the response is often lead by UN actors and agencies, which is why exploring systems and commodities intended for these settings is important.

3.2 The Health Policy Triangle

In the process of bringing attention to a limited evidence-base for policy analysis application in ‘developing countries,’ Walt and Gilson (1994) established a conceptual framework designed to go beyond examining the content of policy (65). The health policy triangle model, shown in Figure 3.1, proposes that an interactive and influential relationship exists between policy content, context, process, and actors. Although it appears to be a simplified framework, the interrelationship between the four factors creates a highly complex process, for which the model is used by both beginner and experienced researchers. Given Walt and Gilson (1994) originally intended for the framework to advance understandings of the policy process in low-resource settings, this thesis uses it to analyze misoprostol-related policy development and implementation in refugee, conflict, crisis, and emergency settings. In this section I explain the four elements that make up the health policy triangle in detail to demonstrate relevance to the study design and research questions.

Figure 3.1: Health policy analysis triangle
Source: Walt and Gilson, (1994) (65, p354).



3.2.1 Policy Content

Inquiry surrounding the subject matter of policy and analyzing its intended goals and outcomes is a common approach in research. Walt and Gilson's (1994) model suggests a more complex interrelationship in the policy-making process and intends to shift policy analysis discussions to consider multi-factorial influencers. The model stems from the understanding that isolating policy content from the actors who make decisions, their contextual environments, and systems that impact policy outcomes and reform is reductionist and does not represent accurate policy environments (65). Policies are commonly disseminated as written documents with standard formatting as per the issuing organization. Policies should be clear about the strategy, intended measures, and limitations. They should also address the course of action to be taken if unexpected problems arise in order to strengthen the content issues, and advance or expand their scope (66). However, despite the method of promotion and dissemination, policies *should be* well known despite written content. Misoprostol-related content in normative body policy will fall within categories of reproductive health and maternal newborn health initiatives. To align with study criteria, subject matter related to PPH prevention and treatment, incomplete abortion management, and early induced abortion will be explored.

3.2.2 Policy Context

Policy development is significantly impacted by systemic factors unique to local, national, or global environments. Structural factors including openness of political systems, strength of economies, security of national infrastructure, or level of technological advancement can all contribute to whether or not policy is successfully adopted. Although

context is commonly perceived as unchanged, instability generated from the onset of an emergency or crisis can rapidly change policy implementation, and may require new strategies. Cultural factors among displaced persons may also impact health policy in fragile settings, given language barriers, limited access to health services, and the stigma associated with being displaced. Further, the persecution of ethnic minorities in conflict and crisis affected settings may be another important factor impacting whether or not policy addresses the needs of specific demographics. Values within international funding culture may also play a role in shaping contextual environments. Often advancing various components of reproductive health policy and practice can be challenging, given the strong presence of religiously affiliated humanitarian organizations, or agencies that operate with funding restrictions. Within refugee, conflict, crisis, and emergency settings, the presence of international humanitarian groups and long-term development actors may also shape the contextual environment and potentially influence what is raised on Ministry of Health (MOH) and normative body policy agendas.

3.2.3 Policy Process

The mechanisms through which policy is established, formulated, implemented, advocated, and evaluated have been conceptualized in many ways, including streams, systems, and institutional models. Most well known in field of public and health policy is the stages heuristic model, which demonstrates the policy process as taking place into four independent stages: agenda setting, formulation, implementation, and evaluation (67, 68). In this model, agenda setting refers to identifying how an issue gets raised as being of policy relevance and concern over another. Policy formulation reflects the way in which actors

decide on and communicate policy decisions leading to implementation. Often challenges arise during application, yet inability to put policy into practice does not directly indicate lack of commitment. In fragmented health settings failure to implement can be explained by limited available resources and human capacity, which is impacted by context and involved actors. The final stage monitors and explores the policy consequences after implementation and aims to measure whether objectives have been met and what long-term outcomes are (16, 66). Although it is a useful exercise to consider policy as taking place in phases, the model is widely acknowledged as inherently theoretical, and not an accurate reflection of overlapping complexities. This is especially relevant in unstable contexts given the ability for crises to escalate and evolve over time, thus leading to health policy being reformed or reverted during immediate or protracted onset. Rapidly opening up policy discussions in these settings to provide commodities to meet the needs of a population has been successful at advancing access to emergency contraception in conflict-affected countries where a dedicated product had previously not been available.

3.2.4 Policy Actors

At the core of the health policy triangle framework are actors who influence the policy-making process at all levels. Actors can include individuals, agencies, and governments who despite being separate organizational entities may take part in collaborative networking and working group efforts to address issues. Policy actors are often perceived as either official actors, those who have the power to create and enforce policies through institutional or legislative positions, or unofficial actors who participate informally based on their expertise, advocacy, interests, or alignment with organizational activities (69).

Theorists commonly raise concepts of power in relation to policy actors to understand and explain better the distribution of power in policy-making. Acknowledging that certain actors wield power that is used to advance organizational or individual agendas is inherent of policy being political in nature.

Actors involved in crisis-affected settings often shift and are re-defined over time, given that their roles and competencies continue to evolve (66). UN agencies, including the United Nations Children's Fund (UNICEF), UNHCR, and WHO, provide numerous technical capacities during international emergencies. However, when WHO is involved in programming following a conflict or emergency situation, this role may limit the influence the agency can have as a central policy-making player (70). The complexity of the relationships between UN agencies can be influenced by distribution of power and responsibility between regional offices and main headquarters, and over-extension in numerous project areas (66). Intervention among humanitarian donor agencies, ICRC, and international NGOs also lends to the complex nature of actors involved in the policy process. Despite independent goals and mandates, commonly these groups merge to share expertise and develop standards and policies; one notable example is the creation of the Sphere Handbook. The establishment and on-going work of the IAWG is another example of collective reproductive health actors merging their expertise, resources, and influence to achieve common goals.

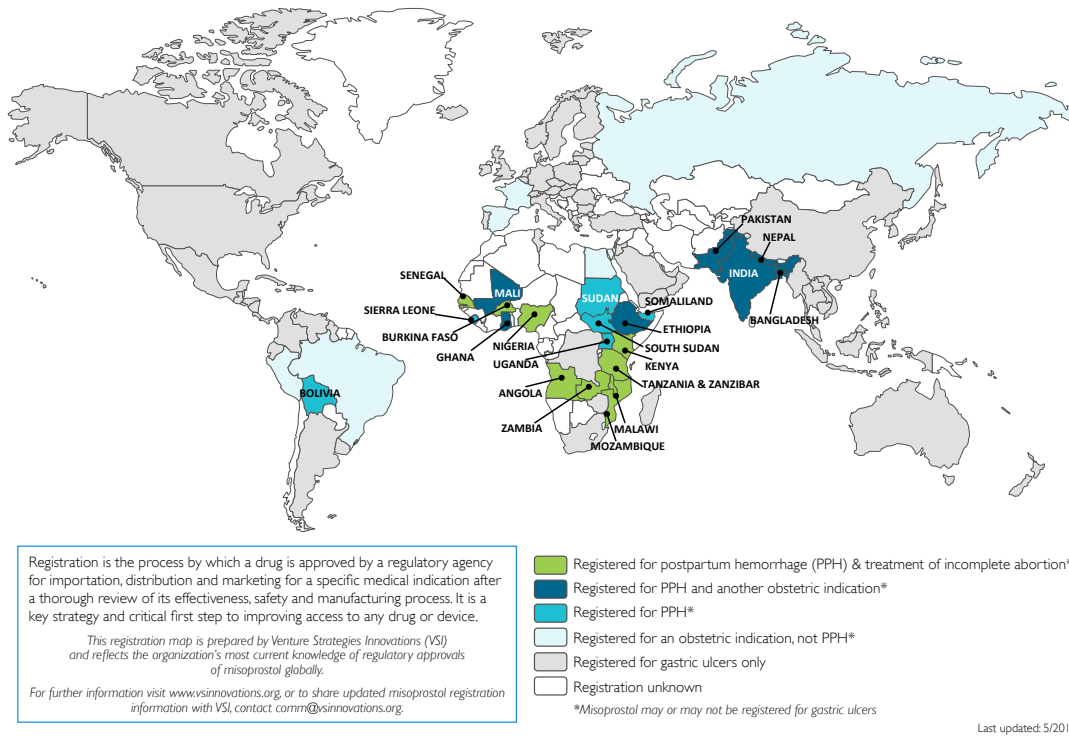
Chapter 4: Global Evidence for Misoprostol

The following chapter provides background on current global evidence pertaining to misoprostol and its known uses. In this section, I begin by exploring the history of misoprostol and its emergence in reproductive health practice. Next, I examine the safety and efficacy of misoprostol regimens and introduce the global research on misoprostol for the four indications explored in this thesis: PPH prevention, PPH treatment, incomplete abortion management, and early induced abortion as a solo agent.

4.1 Misoprostol

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE₁) is a synthetic prostaglandin E₁ analogue. The medication became widely available in the mid-1980s for the prevention of non-steroidal anti-inflammatory drug (NSAID) induced gastric ulcers. Typically registered under the brand name Cytotec®, misoprostol was approved by the US Food and Drug Administration (FDA) for its anti-ulcer indication in 1988. However, misoprostol's uterine contracting and cervical ripening properties deem it an important drug for obstetric and gynecological practice (12). Currently, misoprostol is widely used off-label for numerous reproductive health indications, including the induction of labor, treatment of intrauterine fetal demise, and cervical preparation prior to surgery or instrumentation. Misoprostol is now registered in more than 85 countries for prevention of gastric ulcers, PPH prevention, treatment of incomplete abortion, and other obstetric indications (See Figure 4.1).

Figure 4.1: Global Misoprostol Registration by Indication
 Source: Venture Strategies Innovations, 2013 (71).



Although misoprostol is not approved by the US FDA, and only registered for reproductive health indications in a handful of countries, its off-label use for these indications is widespread. Off-label use of a drug typically refers to use for a purpose other than what is included on the approved label, or package insert. Off-label use is common and is clinically appropriate when justified by a high quality evidence-base (72, 73). In more recent years, misoprostol has also been used for PPH prevention and treatment, incomplete abortion management, and early induced medication abortion, either alone or in conjunction with mifepristone. Misoprostol is advantageous for use in a number of contexts given it is inexpensive, widely available, thermostable, light stable, and has manageable side effects

(74). These properties make it an important alternative for reproductive health indications in refugee, conflict, crisis, and emergency settings.

4.2 Global research on PPH prevention with misoprostol

The evidence-based misoprostol regimen for PPH prevention is a single 600mcg oral dose immediately after a vaginal delivery (19). This regimen is part of active management of the third stage of labor (AMTSL), which is the established standard of care to reduce the risk of PPH. AMTSL includes three key phases; prophylactic administration of a uterotonic agent within one minute after the birth, clamping and cutting the umbilical cord following the delivery, and controlled cord traction after placental separation (19, 75, 76). However, studies conducted in 9 countries in hospital settings showed misoprostol alone to be more effective at preventing PPH versus when no uterotonic was administered (77).

The preferred uterotonic agent for use during AMTSL is oxytocin (10 IU, IV/IM), (19). A systematic review compared 2.5-10 IU oxytocin with 600mcg oral misoprostol regimens and confirmed that misoprostol is not as effective as injectable oxytocin (77). Of the six trials (21,977 women) included in analysis, it was reported that blood loss >1000 mL increased with the use of misoprostol compared with the 10 IU oxytocin IM regimen (77). However, two meta-analyses that examined the effectiveness of misoprostol compared with oxytocin, suggested that the overall increased risk of PPH following the use of misoprostol was only 4-5.8% greater than when oxytocin was used (78, 79). Other injectable uterotonics including, ergometrine and Syntometrine, are considered alternatives to oxytocin. However, ergometrine is contraindicated with women who have a history of hypertension, health disease, retained placenta, pre-eclampsia, and eclampsia; it may increase the risk of retained

placenta, given it induces tonic contractions (80). Syntometrine is a combination drug of 5 IU oxytocin, and 0.5 mcg ergometrine, and shares the same contraindications as ergometrine.

Although the toxic dose of misoprostol remains unknown, the drug is widely accepted as safe, well-tolerated, and subject to minor side effects (74). Side effects include shivering and fever (81); nausea and vomiting may also occur, but none have been shown to endanger the life of the mother, or newborn post-partum (82). There is evidence to suggest that lower doses of the drug may decrease the occurrence of side effects for various indications (83). However, there is not a solid evidence-base for this recommendation and researchers are calling for more studies in order to establish whether reduced dosing can maintain effective interventions (81, 84).

PPH is the leading cause of death in low-income countries and accounts for 25% of global maternal mortality (19). As discussed, oxytocin is the gold standard for preventing PPH, yet since it is an injectable and requires refrigeration, oxytocin is unavailable in some settings. Many contextual factors impact PPH-related mortality and given the varying needs of patients and providers in resource poor settings, alternative interventions have been identified as key (85). Misoprostol is considered an effective intervention to prevent and treat PPH in settings where injectables are not otherwise available or feasible, thus relevant for health service delivery in community settings.

In 2005 the first placebo controlled trial to assess misoprostol use for PPH prevention during home births was successfully conducted (86). Although WHO and global normative bodies have promoted facility-based births, 50% of all births in developing countries are estimated to take place in the home and are attended by an unskilled provider (87). Given this overwhelming situation, most at risk women cannot access skilled providers and require alternative measures (85, 87). Over the last decade, research assessing misoprostol's impact

on reducing PPH at all levels of provision has been undertaken (88-90). Most recent efforts include a series of pilot studies assessing scale-up potential of misoprostol for community-based distribution (84, 91-93). However, these studies assessed the efficacy of misoprostol as a uterotonic agent as part of the AMTSL regimen, and not as a single intervention. A 2013 study that assessed advanced distribution of misoprostol found high rates of correct dosing and use, and determined it feasible to achieve high coverage of misoprostol distribution when community health systems are engaged (89). Moreover, a study exploring mortality forecasting projected 38% of maternal mortality could be reduced with misoprostol use for PPH prevention alone (94). Other theoretical modeling studies found comparable results indicating prophylactic use of misoprostol in community settings may reduce PPH-related mortality at home births (95). However, other systematic review research suggests misoprostol has no impact on increasing or decreasing maternal morbidity and mortality related to PPH (83). There also remains a small body of research that questions the methodology of clinical trials that assessed misoprostol effectiveness in low-income countries' community settings (96).

4.3 Global research on PPH treatment with misoprostol

The recommended regimen for the treatment of PPH using misoprostol is 800mcg sublingual misoprostol (19, 97). Oxytocin (40 IU) is well established as the gold standard for the treatment of PPH. However, in 2010, a double-blind, randomized, non-inferiority trial established that misoprostol might be a suitable first-line alternative to treat PPH if oxytocin is not available. Further, the trial concluded that misoprostol had an efficacy of 90% at stopping bleeding within 20 minutes; oxytocin was recorded as being 95% effective at

stopping bleeding (98). A second trial of the same design concluded that misoprostol is clinically equivalent to oxytocin when used to stop excessive PPH due to uterine atony in women who received prophylactic oxytocin during the third stage of labor (99). Thus far, all randomized controlled trials (RCTs) exploring misoprostol treatment have reported on rectal or sublingual routes (100). Given its faster absorption, quicker onset, greater bioavailability, and less invasive nature, sublingual delivery remains the preferred method. Rectal routes of misoprostol administration (1000mcg) are used in cases where the woman is unresponsive to first-line oxytocin (101, 102).

Side effects and contraindications experienced during treatment of PPH using misoprostol are rarely prolonged or serious and include, shivering, fever, nausea, vomiting, diarrhea (74, 99). A 2012 review of misoprostol for PPH indications suggested more data to support the safety profile may improve uptake within international and national level health policy, but acknowledged that conducting rigorous RCTs comparing a 200mcg difference in dosage for treatment would require exhaustive resources and be better used for other efforts to reduce PPH-related morbidity and mortality (100). Literature exploring misoprostol for treatment outside of a hospital or facility-based setting is limited. Misoprostol for PPH treatment has not garnered the same level of commitment and acceptance as its use for prevention; this may be due to challenges arising with diagnosing atonic PPH, which is considered beyond the capacity of community level health workers (103).

Documented misoprostol intervention for PPH prevention and treatment in humanitarian settings is limited; more evidence is found in the grey literature from implementing agency reports or summaries (104). However, a multi-year (2005-2008) community based effort along the Thailand-Burma border known as the *Mobile Obstetric Maternal Health Worker* (MOM) project successfully systematized and integrated

misoprostol for PPH indications among community health workers. The MOM project trained traditional birth attendants (TBAs) and health workers in the field on topics including EmOC, antenatal care, postnatal care, and family planning counselling and services. Health workers were trained to administer misoprostol within the EmOC module at central health sites or in a woman's home (105). Project evaluations in 2009 established that expanded access to misoprostol and distribution of the drug among TBAs is feasible and builds capacity in protracted conflict settings to reduce morbidity and mortality (106, 107). The MOM project also offers a unique context in which the voices of community-based stakeholders and health workers in protracted conflict areas appears in the peer-reviewed literature and establishes a potential model for prospective misoprostol projects in similar protracted, or displacement contexts (106).

4.4 Global research on incomplete abortion management with misoprostol

The evidence-based regimen for managing incomplete abortion using medication is a single dose of 400mcg sublingual, or 600mcg oral misoprostol. Many studies have compared the safety, efficacy, and acceptability of misoprostol compared with manual vacuum aspiration (MVA), which is another recommended modality for managing incomplete abortion (108-110). The efficacy of MVA for this indication is 100%, and typically patients experience fewer side effects, but greater pain when compared with misoprostol (108, 109). Systematic analyses suggest misoprostol achieves similar effectiveness for treating incomplete abortion. Among studies that administered 600mcg oral or 400mcg sublingual misoprostol to more than 100 patients within 7 days before follow up, there was an average of 95% efficacy (111).

Contraindications of misoprostol for incomplete abortion include, pelvic infection or sepsis, established bleeding disorders, concurrent anticoagulant therapy, hemodynamic instability or shock, and confirmed or suspected ectopic pregnancy (112, 113). Pain, cramping, and moderate to heavy bleeding are common side effects of this regimen for incomplete abortion management (111). Endometrial and pelvic infection is a rare side effect of misoprostol for incomplete abortion management, but can be treated with oral antibiotics if infection is suspected. Moreover, women may experience chills or fever, nausea, vomiting, or diarrhea, which are all possible side effects associated with the medication (111).

Misoprostol for incomplete abortion and post abortion care (PAC) has been identified as an important non-invasive technology for low-resource settings where supplies and providers are limited and MVA may not be available (111, 114). The literature demonstrates that treating incomplete abortion using the evidence based misoprostol (94.4% efficacy), or aspiration (100.0% efficacy) regimen are both highly successful interventions (115). As a non-surgical option, misoprostol is a safe alternative for women who do not want to experience instrumentation, anaesthesia, or inpatient care. High levels of satisfaction have been documented among women who were treated for incomplete abortion using misoprostol (116-119). A study examining misoprostol for PAC in low-level facilities without previous experience providing the service, reported 98% of participants stated they would select misoprostol to manage incomplete abortion in the future, and 97.9% indicated they would recommend the regimen to other women (116). Currently, misoprostol is recommended to manage incomplete abortion by both WHO and the International Federation of Gynecology and Obstetrics (FIGO) (120). Thus, there exists a favourable policy environment for integrating misoprostol for this indication. There is also commitment among governments to address incomplete abortion, and scale-up efforts are being pursued (121).

The importance of addressing complications related to incomplete and spontaneous abortion has been well documented. Spontaneous and induced abortion reflect similar symptoms, thus health care workers are known to report induced abortion as spontaneous given national contexts and legal restrictions (122). Public health strategies including, misoprostol for PAC and consortia with dedicated task forces to promote such models have been established (114, 123). Scaling up PAC initiatives may reduce maternal morbidity and mortality, decrease abortion-related stigma, and act as a preliminary effort for liberalizing restrictive national abortion laws and policies (123, 124). As such, PAC is widely accepted as a priority measure in restrictive settings where unsafe and self-induced abortion is common (115).

4.5 Global research on early induced abortion with misoprostol alone

The evidence-based regimen for early induced abortion using misoprostol alone is 800mcg vaginal, or sublingual misoprostol repeated at intervals no less than 3 hours, but no more than 12 hours for up to 3 doses (21). The gold standard medication abortion regimen established by WHO recommends a combination of 200mcg oral mifepristone and 800mcg vaginal, buccal, or sublingual misoprostol for a medication abortion up to 9 weeks LMP (21). Additional studies have shown the combined regimen is more effective than misoprostol alone, and results in a success rate of 95% to 98% (125-127). Compared with the gold standard, the efficacy of misoprostol alone is 75-90% effective in completing abortion (21). However, in settings where mifepristone is unavailable, regimens including misoprostol alone are considered important alternatives (128-131).

For all medication abortion regimens, contraindications include coagulopathies and severe anemia. Patients may also experience cramping and prolonged menstrual bleeding (21). Misoprostol alone has very few contraindications. However, use may be of concern in patients with prostaglandin allergies, or with severe gastro-intestinal conditions (131). Among the most commonly reported side effects of misoprostol use are vomiting, nausea, diarrhea, chills, fever, and dizziness (132). In high doses and early exposure, misoprostol is associated with teratogenicity (133). However, studies of population registries demonstrate incidence of abnormalities following misoprostol use is not high, given its common use (74, 113). Risk of uterine rupture also remains a concern, as risk may increase with gestational age and whether the woman has previous uterine scarring (74).

Unintended and unwanted pregnancy is of great concern among displaced populations. In crisis settings it has been shown that there exists unmet need for family planning services since access can be discontinuous, limited, or non-existent (134-136). Although emergency contraception is being integrated more readily into crisis response, women have little awareness about the medication and provider knowledge is limited (137, 138). Moreover, displaced women are at high-risk for unintended pregnancy as they are at heightened risk of domestic violence and rape. Women are also more likely to be forced to engage in remunerative sex work to support themselves, their families, and ensure protection (3, 139). One in five women of reproductive age will be pregnant at any given time during an international emergency; 40% of such pregnancies are unintended and up to 50% result in induced abortion (140). Unsafe abortion is the third leading cause of global maternal mortality and is of even greater consequence in fragile states. Unsafe abortion accounts for approximately 13% of all global maternal deaths, yet UNFPA estimates unsafe abortion accounts for 25-50% of maternal mortality in refugee settings (141). Highest incidence rates

of unsafe practices have been documented in Eastern and Middle Africa (36 per 1,000 women of reproductive age), South America (32 per 1,000 women of reproductive age), and South-Eastern Asia (17 per 1,000 women of reproductive age) (142).

Despite reduced efficacy, medication abortion using a misoprostol-alone regimen has been discussed as an important alternative to reduce unsafe abortion practices (143-145). This is especially relevant given the widespread lack of access to mifepristone and its perceived high cost in low-resource settings. Creinin et al. (2005), dispute that mifepristone regimens are likely to be less expensive than misoprostol alone, given its higher efficacy and less need for patient follow-up (146). Introducing and improving access to mifepristone in-country remains the focus of global advocates, health providers, policy makers, and researchers. However, registering mifepristone is difficult in countries where abortion is severely legally restricted, given it is generally only used for induced abortion. Misoprostol is an important alternative since the drug is commonly already available in-country; thus the regulatory hurdle does not need to be overcome. Therefore, expanding knowledge about and access to misoprostol has been widely perceived as an effective harm reduction strategy (144, 147).

Harm reduction reflects interventions that reduce the harms of an activity without prohibition or abstinence (148). Integrating misoprostol using this frame offers a safer alternative for women who would otherwise revert to unsafe practices and enables policy makers to perceive unsafe abortion as a public health issue. Evidence demonstrates that misoprostol is positively associated with reducing morbidity and mortality related to unsafe abortion, and suggests exploring its use in other legally restrictive settings is warranted (144, 149-153).

After the 2010 earthquake in Haiti reports emerged of misoprostol being widely available in the community (154). Although misoprostol is not on the national drug list and had been banned in Haiti until 2009, its presence in pharmacies and among street-level vendors indicated a widening channel being used. Humanitarian teams providing reproductive health services in Haiti following the earthquake claim to have seen wide variation in misoprostol dosing. Reports of women taking too little misoprostol and not expelling the fetus, or taking too many tablets and experiencing cramping, pyrexia, and severe bleeding were documented; this can be directly attributed to drug use without medically accurate information or provider consultation (154). Peer-reviewed research corroborates that pharmacy vendors commonly provide incomplete or inaccurate information about misoprostol for induced abortion to presenting patients (145, 155). This can include providing inaccurate dosing and regimens, limited discussion on contraindications, and telling women not to reveal where they accessed misoprostol. Garcia et al. (2011) concluded that pharmacy access to misoprostol was associated with the socioeconomic status, location, and type of pharmacy (155). This is significant when considering how women access misoprostol to terminate a pregnancy during a crisis or emergency.

Chapter 5: Methods

This chapter describes the two-tiered methodology used to conduct this qualitative study, which includes document review, applied policy analysis, and key informant interviews. I begin by explaining the document review process, which includes the review and analysis of misoprostol-related normative body policy, technical reports, and guidelines. Next, I discuss the methods used for sampling, coordinating, and conducting in-depth interviews, as well as the content and thematic analysis techniques employed.

5.1 Policy document review and analysis

The documents used for this study include policy documents providing guidance on one or more of the four indications for misoprostol use: PPH prevention, PPH treatment, incomplete abortion management, and early induced abortion with misoprostol alone. Given the aim of this thesis is to generate new knowledge on the overarching policies and practices that promote or inhibit misoprostol programming, program evaluation reports and humanitarian field manuals from various international organizations were also considered. The preliminary policy documents being reviewed derive from WHO, UNHCR, UNFPA, and IAWG. I reviewed the most current policy statements, as well as previous versions published over the last ten years, in order to indicate occurrences of policy reform.

The aim of the policy analysis is to understand better the origins of misoprostol-related policies, how they were developed, and the global settings where they have been implemented. As explored in detail in Chapter 3, I use Walt and Gilson's (1994) policy triangle framework to analyze normative body policies. This framework stems from political economy perspectives and considers how the policy-making process is shaped by four

interacting elements: context, content, process, and actors (65). In the analysis I review five reproductive health policy documents: WHO's Essential Medicines List (2013), IAFM for Reproductive Health in Humanitarian Settings, (2010), MISP, WHO Recommendations for post-partum hemorrhage (2012), and WHO Safe abortion: technical and policy guidance for health systems (2012). They were examined to identify what content relates to misoprostol use, the processes through which the policy was formed, what broader contextual factors impact misoprostol policies in refugee, conflict, crisis, and emergency settings, and which actors were involved in generating evidence, dossier applications, and publication. By exploring these elements in depth, a summary of the policy process was conceptualized and global recommendations for misoprostol inclusion on normative lists compiled.

5.2 Qualitative key informant interviews

5.2.1 Sampling

Potential key informants were purposively sampled using online search tools, academic institution websites, and conference reports and agendas. I emailed an invitation to participate in an interview to 33 prospective key informants from 24 various international agencies, international or national NGOs, research and advocacy groups, and academic institutions between October 2013 and January 2014. The email included a brief background of the researcher and university affiliation, subject matter of the project, and proposed structure of the interview. Key informants who responded and expressed interest were emailed an informed consent document and scheduled an interview. A second reminder invitation was sent to prospective key informants if no contact was made after two weeks. Key informants were eligible to participate if he/she: works in the field of reproductive

health; holds a senior level director/research, coordinator, or policy maker position at a relevant organization; has a specialized knowledge in misoprostol-related policy and/or programming; and has sufficient fluency in English to complete the interview. Ultimately, research participants were included based on their responsiveness and expressed interest to participate in an interview. During data collection, snowball sampling was utilized to identify other key informants with related policy or implementation experience. Snowball sampling was done at the end of the interview by asking the interviewee if he/she knew of any colleagues who may be interested in participating in the study. I ultimately contacted 33 prospective key informants and completed 21 interviews.

5.2.2 Data Collection

I conducted in-depth open-ended interviews between October 2013 and February 2014. All interviews took place in English over the telephone (n=9) or via Skype (n=12) and averaged 45 minutes. My supervisor observed and participated in the first two scheduled interviews as part of the interview training. Following the first two interviews, the interview guide was slightly modified to improve flow. Verbal informed consent was obtained from all participants prior to beginning the interview. Using the same semi-structured interview guide, key informants were asked to begin by introducing their professional background and involvement with their respective organization(s) or institute(s). The interview progressed to discuss their professional experiences working on reproductive health and misoprostol-related projects in refugee, conflict, crisis, and emergency settings. Next, I explored key informants opinions and knowledge of policies that guide misoprostol-related work, the degree to which these policies are adhered to, and existing barriers. Finally, key informants

were asked to comment on possible future directions to advance and improve misoprostol programming in fragile contexts. All participants gave permission for their interview to be audio-recorded. Data from the digital audio recording device was downloaded to a password-protected desktop and transcribed verbatim. Transcription took place within one week of the interview to ensure oral to written text was as precise as possible. Intonations and marginal words were included in all transcripts to indicate the tone and flow of the speaker. All transcript data was organized using ATLAS.ti 6.2 software, which was the primary platform used for analysis.

5.2.3 Data Analysis

Both content and thematic analysis approaches were used iteratively to analyze the data. There are many similarities between the two approaches, but to systematize and align with peer-reviewed methods I used Elo and Kyngäs' (2008) guidelines for content analysis, and Braun and Clarke's (2006) work on thematic analysis (156, 157). Content analysis is a systematic process through which a researcher establishes codes and categories to determine structure, patterns, frequencies, and trends (156, 158). This approach was used for two primary applications: to measure frequency of concepts discussed by key informants and develop conceptual network models using nodes and links in ATLAS.ti 6.2.

Thematic analysis is widely acknowledged as a flexible approach to analyze data, given its application in multiple fields and theoretical approaches (157, 159, 160). I applied this method in order to align with theoretical assumptions and supplement the in-depth policy analysis. As such, I determined the approach to be an effective methodology for this study. Braun and Clarke (2006) identify a six phase approach to analyzing qualitative data:

familiarizing yourself with the data, generating initial codes, searching for themes, reviewing themes, defining and naming themes, and producing the report, which has been used to strategically guide this analysis (157).

I began this analysis by *familiarizing* myself with the data by reading through all transcripts to gain a general overview of the content. I summarized all interviews into a one-paged text in order to give a brief overview and highlight key information. I also wrote memos to aid in interpreting what had occurred during each interview, document emerging topics, and express my opinions on information provided by key informants. Next, I *generated initial codes* for all interview data by creating a list of thirty-three identified codes from the data set and ascribing one or more codes to each sentence or complete idea. Both inductive and deductive coding was used during analysis. *A priori* codes were pre-determined before analysis based on the nature of the interview guide and my current knowledge base; inductive codes emerged from the data from participant responses during analysis. Some researchers use the term “emerge” to indicate a passive process in which themes “reside” in data (161). In conducting this analysis, I’ve acknowledged the active role of the researcher in searching for and identifying themes, and ultimately reporting on them, which is linked to my own theoretical positioning and values (157).

After *identifying potential primary and sub-themes*, I *reviewed themes* by rereading transcripts and verifying codes twice to ensure enough data could substantiate each theme, and that a coherent pattern existed in collated and extracted quotes. In the fifth phase of analysis I *defined themes* by refining definitions and generating distinct names for each one. The following themes were identified: availability and accessibility of misoprostol, normative body policy influence, role of global actors, implementation barriers, and UNFPA RH Kits. During analysis I approached my supervisor with questions about identified codes

and themes. My supervisor was available to review main findings and provided early feedback. A final write-up using narratives and extracted quotes to explain and substantiate the prevalence of the themes was *produced in a final report*, which is reflected in the subsequent results chapter.

5.3 Ethics

This study received ethics approval from the Office of Research Ethics and Integrity at the University of Ottawa, Canada (File H02-13-01) on 22 February 2013. The approval letter is included as Appendix A.

6. Results

This chapter presents the findings from both the policy analysis and qualitative interviews. The results from reviewing various policy editions are discussed and structured into chart form to address the research question: what are the established normative body policies surrounding misoprostol use? The second section discusses the perspectives expressed by key informants during the in-depth interviews and are arranged in the following subsections: perceived situation of misoprostol in humanitarian settings, policies perceived to influence misoprostol use in humanitarian settings, perceived adherence to misoprostol related policy in humanitarian settings, and perceived barriers to addressing misoprostol policy and practices in humanitarian settings.

6.1 Policy Findings

Five global health policies from two normative bodies were deemed the most significant in providing guidance for misoprostol-related indications: WHO's EML, Inter-Agency Field Manual for Reproductive Health in Crisis (IAFM), MISIP, WHO Recommendations for post-partum hemorrhage, and WHO Safe abortion: technical and policy guidance for health systems 2nd Edition. Policies were selected by reviewing the current peer-reviewed and grey literature, and supplemented by commentary from key informants who discussed policies impacting their work. The findings suggest policy content dispersed among the five documents address all four indications explored in this thesis, but noticeably a regimen for PPH treatment is excluded from the EML and IAFM. Recommendations for misoprostol alone regimens for early induced abortion are also

excluded from the EML. Contextually, only the IAFM explicitly addresses structures and needs that are unique to refugee, conflict, crisis and emergency settings.

Table 6.1. Misoprostol regimen recommendations by normative body policy

Policy	Misoprostol for PPH prevention ^a	Misoprostol for PPH treatment ^a	Misoprostol for incomplete abortion	Misoprostol alone for early induced abortion ^{a b}
Essential Medicines List 18 th Edition, WHO (2013)	600 µg p.o. *	No recommendation	600 µg p.o. 400 µg SL	No recommendation for misoprostol alone
Inter-Agency Field Manual for Reproductive Health in Crisis, (2010) ^c	600 µg p.o. *	No recommendation	600 µg p.o.	<i>Up to 9 weeks LMP: 800 µg (PV or SL) 3-12 hours up to 3 doses</i>
Recommendations for post-partum hemorrhage WHO (2012)	600 µg p.o. *	800 µg SL * ⁺	No recommendation	No recommendation
Safe abortion: technical and policy guidance for health systems 2 nd Edition, WHO (2012)	No recommendation	No recommendation	600 µg p.o. 400 µg SL	<i>Up to 9 weeks LMP: 800 µg (PV or SL) 3-12 hours up to 3 doses^a</i>

^a Regimen is not included in Inter-Agency RH Kits.

^b Where permitted under national law and where culturally acceptable.

^c Guidance directly from WHO recommendations.

* When oxytocin is unavailable or cannot be safely used.

⁺ If bleeding does not respond to oxytocin.

p.o. Oral administration.

PV Vaginal administration.

SL Sublingual administration.

6.2 Normative body policy and positioning on misoprostol

Research over the last decade clearly situates reproductive health on global policy agendas at all intervention levels (3, 162, 163). Although government policy decisions are often central in health policy-making discussions, in humanitarian settings, normative

international bodies and subsidiary non-governmental organizations may be more significant players than the state (3). While there exists interconnectedness between the two, the subset of misoprostol-related policies set by normative bodies primarily guides implementation. Commonly, states will adopt proposed guidelines or incorporate sections of recommendations into their national action plans or strategies. However, the core of misoprostol recommendations and policy guidance stems from normative bodies including, WHO, UNFPA, working groups such as IAWG, and research organizations including Gynuity Health Projects and Ipas. Global normative body positioning on misoprostol is explored further by critically examining WHO's EML, IAWG's IAFM, MISP, WHO Recommendations for post-partum hemorrhage, and WHO Safe abortion: technical and policy guidance for health systems 2nd Edition.

6.2.1 WHO's Essential Medicines List

The WHO exercises its positioning around misoprostol using a variety of policies, recommendations, and toolkits. Most notably misoprostol mobilization in refugee, conflict, crisis, and emergency settings has been supported by its inclusion on the EML. WHO's EML is an internationally recognized directory of medicines that are deemed of high-priority to meet global health needs. Using an evidence-based review process that examines safety, efficacy, cost-effectiveness, and other criteria, an EML Expert Committee updates the list every two years to determine new inclusions, changes, and removals of medicines. The most recent edition (18th) was released in April 2013. The EML serves as an important benchmark to help national MOHs and policy makers identify where to center their resources and efforts, and has been described as one of the most valuable WHO projects in the last three decades

(164). The EML application process and Expert Committee review has shaped misoprostol-related global health policy, and is an influential policy-making process. The findings demonstrate that actors involved in clinical research, technical assistance, and advocacy are central to the application process and implementation.

The first misoprostol EML application was submitted for a range of reproductive health indications in 2003 by Makerere University (Uganda) and was not accepted. The first submission was followed by three applications in 2005 for first trimester medication abortion in conjunction with mifepristone, which was submitted by the Geneva Foundation for Medical Education and Research (Switzerland). The second application was for the induction of labor on behalf of British Medical Journal (BMJ) Knowledge through the WHO Department of Reproductive Health and Research; both applications were successful in listing misoprostol. The WHO Department of Reproductive Health and Research submitted the third application in 2005 for the treatment of PPH and was rejected. In 2009 Venture Strategies Innovations and Gynuity Health Projects (both US-based organizations) submitted an application to include misoprostol for prevention of PPH, but was ultimately not accepted. However, the EML Committee did include misoprostol for the second application supported by Gynuity Health Projects that year for incomplete abortion management. A range of organizations including, Engender Health, Path, and FIGO supported both applications. In 2011 the EML Committee accepted the joint application submitted by Venture Strategies Innovations and Gynuity Health Projects to include misoprostol for the prevention of PPH. Additionally, during this 18th Expert Committee session, the drug was moved from the complementary to the core list of essential medicines.

Before its inclusion on the 18th edition for PPH prevention, WHO was perceived to be positioned ambiguously around misoprostol for PPH indications, and contributing to

country-level reluctance to register the drug on national lists (165, 166). Currently, the WHO has not endorsed misoprostol for PPH treatment citing mixed-evidence as the main reason for its exclusion. However, the current literature reflects a growing body of research that supports the potential efficacy of misoprostol for this indication (99, 167). Misoprostol as a solo abortion agent has also not been included on WHO's EML, although WHO does include a misoprostol- alone regimen in their safe abortion technical guidelines. Advanced distribution of misoprostol in the community is also not endorsed by WHO. However, the normative body has stated it recognizes the critical role of lay health workers, and promotes task shifting in settings where skilled birth attendants are not present (19, 168).

The current findings do not consider the impact of the EML on country-level policy-making. However, key informant interview data suggests that the EML does drive policy change at the national level through encouraging registration and inclusion on national essential drugs lists. Distinct mention was given to countries in sub-Saharan Africa who key informants described as being most open to EML informed national policy change.

6.2.2 Inter-Agency Field Manual on Reproductive Health in Crises (IAFM)

The IAWG collaborative generated the initial version of its manual, Reproductive Health in Refugee Settings: An Inter-agency Field Manual in 1996. The updated and field-tested version was released in 1999 and included nine chapters on a range of reproductive health issues (169). After its launch, IAWG worked to extend content beyond refugee contexts including, GBV, sexually transmitted infections (STI), and comprehensive abortion care. A decade later, its 2010 version was renamed the Inter-Agency Field Manual for Reproductive Health in Humanitarian Settings, and provided technical guidance for

reproductive health in crisis settings beyond the refugee context; the new manual included recommendations relevant for persons affected by conflict or complex emergency settings. The objective of the IAFM is to provide evidence-based knowledge for reproductive health service provision in humanitarian settings that respects the cultural norms and values of the population, while providing a space to monitor and evaluate reproductive health interventions. The IAFM targets a multidisciplinary audience of program directors, policy makers, and health practitioners including midwives, nurses, and TBAs and contains chapters on family planning, maternal and newborn health, GBV, and STIs. The latest edition includes a new chapter dedicated to technical guidance for comprehensive abortion care.

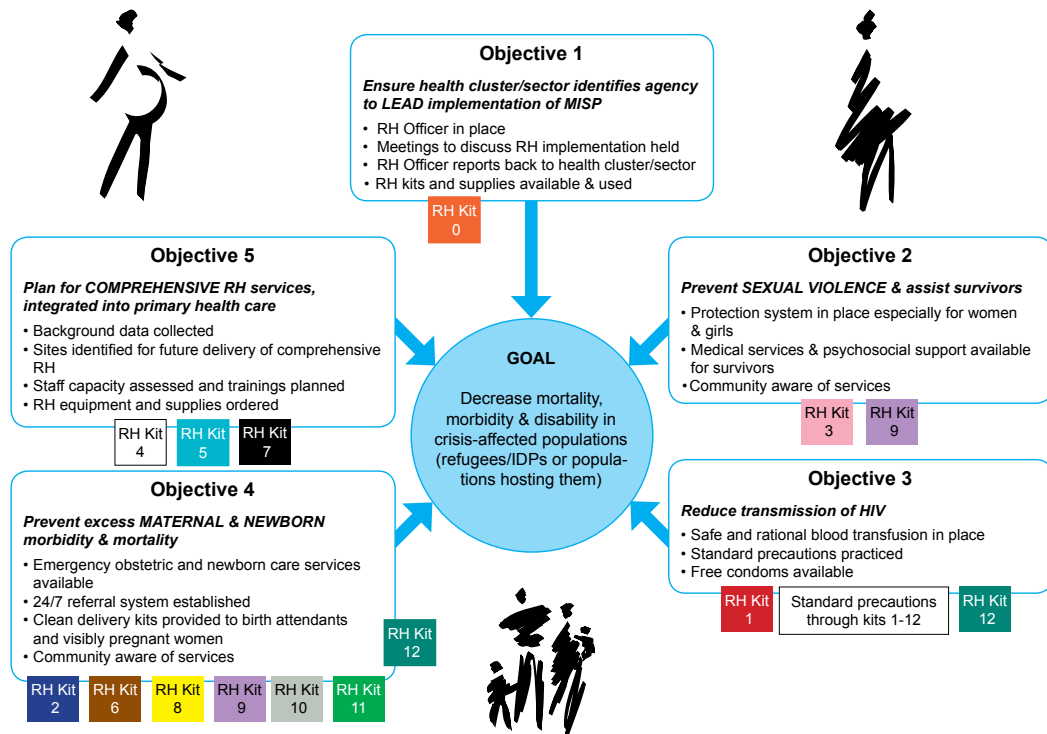
The 2010 revised IAFM recommends misoprostol regimens for PPH prevention, incomplete abortion management, and early induced abortion, in three of the seven chapters. The IAFM clearly states that the technical guidance included in the field manual is based on established WHO recommendations. IAWG recommends a uterotonic drug to prevent PPH as part of the directives for AMTSL. The Field Manual indicates that crisis settings may lack skilled staff, or resources that may not support safe injection or proper storage. In these cases, misoprostol is the recommended alternative to oxytocin for PPH prevention. The IAFM emphasizes the importance of including misoprostol within crises interventions, especially for improving PAC to manage incomplete abortion. The IAWG positioning assumes that without availability of MVA, sterilized instruments, or trained providers in these settings, misoprostol offers an alternative for saving lives. Unlike WHO's EML, IAFM establishes guidance for using misoprostol alone for early induced abortion, but indicates that the regimen is less effective than when used in conjunction with mifepristone.

6.2.3 Minimum Initial Service Package (MISP)

The MISP outlines the priority areas of reproductive health that agencies should address in the immediate wake (72 hours) of a crisis. The model, as seen in Figure 2.2, provides dual technical guidance for programming and outlines the contents of reproductive health packages. The MISP supports on the ground coordination and service delivery in the preliminary phases of crisis when crude mortality rate surpasses 1 per 10,000 deaths per day (170). Both the Sphere Minimum Standards in the Disaster Response Handbook and IAFM contain sections on the MISP. Its inclusion aims to ensure all actors engaging in emergency, or crisis response are adequately educated on reproductive health issues (171).

The MISP was first integrated into policy in the initial field-test version of *Reproductive Health in Refugee Situations: An Inter-agency Field Manual* in 1996. Following revision it was updated for inclusion in the 2010 version of the IAFM. In 2003, 2004, 2005, 2007, and 2010 the Women's Refugee Commission (WRC) undertook evaluations of the MISP and discovered a number of implementation gaps relating to sustaining systems and coordination (170). Subsequent assessments have shown improved awareness and knowledge of the MISP among humanitarian actors.

Figure 6.1: The Minimum Initial Service Package (MISP) for Reproductive Health
 Source: Women’s Refugee Commission (WRC), 2011 (170, p99)



The MISP outlines twelve prepackaged Inter-Agency RH Kits, and helps facilitate coordinated procurement. The RH Kits align with the objectives of the IAFM and are distributed by UNFPA (170). Various essential drugs, commodities, and equipment make up the Kits, which are used to address logistical problems and provide priority reproductive health services during the early phases of a crisis (172). UNFPA organizes the Kits into three block levels, which are all designed to provide services for three months’ time for varying population sizes. Block 1 (Kit 0-5) is intended for use among health service providers at the primary health care and community level. This first Kit level includes clean delivery kits, post-rape treatment, and oral or injectable contraception. Kits 6-10 constitute Block 2 and are intended to be used by skilled health care providers with training in midwifery, or advanced obstetric and neonatal skills. Therefore, these Kits are used in a clinic or hospital setting, and

service 30,000 persons. Manual vacuum extraction devices are available through Kits 10A/B, and although contraception is available through the first block, Kit 7 includes medicines and technologies to insert an intrauterine device (IUD) (172). Misoprostol is currently only included in Kit 8: management of miscarriage and complications of abortion, which treats sepsis, incomplete evacuation, and bleeding (170). Block 3 (Kit 11-12) is the final Kit level and is used at surgical obstetric levels following referral. Materials and medicines in these Kits enable skilled health care providers to perform caesarean sections, resuscitate the mother or infant, and treat sepsis or eclampsia (172).

There is little evidence about the success, barriers, and outcomes of the RH Kit system, specifically regarding ordering and disseminating Kit 8. A 2012 thesis evaluating UNFPA networks and supply chains recorded that 287 management of complications of abortion Kits were procured in 2011 for emergency aid (173). Kit 8 has a relatively narrower shelf life than other kits (24 months) since it requires cold storage and has high inventory costs, given its weight exceeds 20kg and/or a volume greater than 0.1m³. Moreover, low product variety within the Kit was assumed given there is no heterogeneity between commodities supplied by different distribution hubs (173).

6.2.4 WHO recommendations for prevention and treatment of post-partum hemorrhage

In 2012, WHO developed and launched updated guidelines for the prevention and treatment of PPH. This document followed previous normative recommendations created for prevention of PPH (2007), and the management of PPH and retained placenta (2009) (174, 175). Actors involved in creating the guidelines included, WHO Department of Reproductive Health and Research, WHO Department of Maternal, Newborn, Child, and Adolescent

Health, two external experts, and a group of international stakeholders with expertise in maternal and newborn health, or research synthesis (19). The guide was developed using a five-stage approach for research and knowledge dissemination; all scientific evidence was assessed using Grading of Recommendations Assessment, Development, and Evaluation (GRADE). GRADE was developed by a collaborative working group of health experts, and offers a systematic and transparent approach to evaluate the quality and strength of clinical recommendations. The method is currently used by a number of international health organizations, and is the basis for WHO recommendations, and Cochrane Collaboration reviews. Cochrane systematic reviews of randomized control trials were the primary source of evidence used to establish these 2012 recommendations.

The updated guideline included 32 recommendations with a corresponding grade of very low, low, moderate, or high, which demonstrates the quality of the supporting evidence determined by the guideline development group. Within the prevention guidelines, misoprostol and other injectable uterotonics were included and strongly recommended (with moderate-quality evidence) in settings where oxytocin is unavailable. Guideline 4 also recommends 600mcg oral misoprostol for administration by community health care workers where skilled birth attendants and oxytocin are unavailable. However, the guideline development group concluded that due to insufficient evidence it could not recommend antenatal (before birth) distribution of misoprostol, which primarily impacts community-based integration. Recommendations for PPH treatment within the updated guidelines include 800mcg sublingual misoprostol when intravenous oxytocin is unavailable, or if the bleeding does not respond to oxytocin (strong recommendation, low-quality evidence).

6.2.5 WHO Safe abortion: technical and policy guidance for health systems 2nd edition

The first version of WHO's *Safe abortion: technical and policy guidance for health systems*, was published in 2003 (176). Motivation for WHO to develop safe abortion guidelines may have been influenced by the 1999 UN General Assembly meeting where recommendations made at the ICPD were reviewed and accepted (177). The UN General Assembly consensus statement states that "in circumstances where abortion is not against the law, health systems should train and equip health-service providers and should take other measures to ensure that such abortion is safe and accessible"(178, p15). Since 2003 significant amounts of research and evaluations were conducted regarding safe abortion care; thus the second edition was developed to reflect new available evidence. The revision included substantial updates made for safe abortion clinical care. New sections were also created that provided guidance to governments, and policymakers about how to apply human rights based approaches (HRBA) and national abortion legislation (179).

Similar to the WHO PPH guidelines, a guideline development group for the second edition was formed and comprised of staff from WHO Department of Reproductive Health and Research, and global experts in health service provision, women's health and human rights, and methodologists (21). The panel considered evidence related to clinical, technical, and programmatic topics, but Cochrane systematic reviews of clinical trials were the primary source of evidence. Again, evidence was assessed and rated using the GRADE approach, and resulted in evidence profiles and GRADE tables for each recommendation (21). The WHO Secretariat expects that the safe abortion guidelines will be reviewed in 2016 to assess whether further updates are required.

The first edition of the guidelines discussed misoprostol alone for early induced abortion as a possible intervention. However, at the time no comparative studies had been

conducted, and WHO did not give specific recommendations for misoprostol as a single agent. In the updated guidelines a recommendation is given for repeated doses of 800mcg vaginal, or sublingual misoprostol alone up to 9 weeks LMP when mifepristone, or MVA is unavailable.

6.3 Key Informant sample characteristics

Between October 2013 and February 2014, I conducted in-depth open-ended interviews with 21 key informants from 16 different international agencies, NGOs, and/or academic institutions with relevant misoprostol policy or programming experience. International normative bodies employed three participants, eight informants were from NGOs and humanitarian organizations, seven represented research and advocacy based organizations, and three were members of academic research institutions. In four cases there was overlap between participants involvement with international organizations and academic institutions. In these scenarios the actor was categorized by the primary focus of their current professional work involving misoprostol related subject matter. Together key informant experience ranged between two and twenty five years working on reproductive health related issues.

Seventeen participants identified as women and four as men. There existed a range in professional experience and expertise, including eight obstetricians and gynecologists, two public health physicians, six public health non-physician providers, and five participants with a research, or advocacy background with advanced degree(s) (i.e. MPH, MA, JD, PhD, DPhil). Medical experts provided insights on their use of misoprostol in the field and use of clinical guidelines and protocols. Perspectives from informants involved in reproductive

health advocacy and research focused on their work promoting and piloting misoprostol both at international and national levels. However, often there were overlapping experiences between a participant's role in policy-making and programming. There was extensive geographical coverage of countries where participants provide technical assistance, or on the ground reproductive health service delivery, including a range of areas that have experienced conflict, crisis, emergency, or large refugee populations within the last ten years.

6.4 Perceived situation of misoprostol use in humanitarian settings

All participants agreed that misoprostol is a highly relevant medication for use in humanitarian settings. During the interview many used the term “natural fit” while describing its characteristics in relation to applications in low-resource settings. Stakeholders from implementing agencies currently located in active conflict and emergency settings expressed this especially. One policymaker stated that “[misoprostol] is a logical thing. It is easy to transport, it doesn't have very strenuous storage requirements and it is just generally likely to be available where nothing else is.” Indeed, some discordance existed between the indication for which misoprostol is implemented, or advocated for among participants. More than half of all informants were involved in policy-making, or programming with all four misoprostol indications. The remaining six participants were evenly split between work focused on PPH prevention, PPH prevention and PPH treatment, or incomplete abortion management and early induced abortion. The extent to which participants reported on implementation directly relates to the programmatic level wherein they are situated.

6.4.1 Misoprostol for PPH Prevention

Participants unanimously accepted that oxytocin is a clinically superior agent for PPH prevention, but that it is often not feasible to procure and use in humanitarian contexts. Several clinicians concurred that although WHO approves other uterotonics to be used in the absence of oxytocin, misoprostol is the best alternative. Not all key informants with field experience had access to first-line oxytocin within hospital settings. A participant from a country-level NGO working in an active conflict area described how their affiliate hospital exclusively seeks misoprostol for PPH prevention due to the unreliability of the oxytocin that they have access to. However, five participants from large humanitarian organizations confirmed that their established field hospitals are staffed with highly trained medical professionals with access to more advanced medications and commodities to prevent and treat PPH. In these contexts oxytocin is the primary drug of choice, but one of these five participants pointed out an area in which he sees misoprostol's use:

Misoprostol is stable- it does not require a kind of care like oxytocin and could be given orally by the lay health worker. Its applicability would be more at the community level. So in emergency response it might have its application... There might be a role for misoprostol if health services are fragmented in the emergency response, or a situation where access is not readily available. There are issues where misoprostol can have a significant role in my opinion, to be administered at the community level and then do a referral.

The majority of stakeholders involved in programming PPH prevention strategies outside of the field hospital setting discussed the potential of misoprostol use for PPH prevention at the community level. Several participants believed scaling up community based distribution and training unskilled community health workers represents the next stage of misoprostol programming in low-resource settings for PPH prevention. However, only two participants were able to comment on such efforts taking place in emergency settings.

6.4.2 Misoprostol for PPH Treatment

Participants widely acknowledged that WHO recommendations currently do not support misoprostol for PPH treatment. Yet most stakeholders from implementing organizations using misoprostol for prevention stated they also use the medication for PPH treatment. One participant from a global non-profit organization felt that using the drug for PPH treatment was a “no-brainer” and that in the field “everybody uses it” for this purpose. A few participants gave suggestions that misoprostol be administered for PPH treatment exclusively in a facility setting. As highlighted by one informant, evidence for effective community level use for treatment is not as strong at the current research available for PPH prevention:

I think in the field almost everybody agrees that it should be a facility-based treatment. WHO pushed [For PPH prevention], and understandably of course, for facility deliveries and were concerned whether it will detract women from going to facilities if they had the drug et cetera [sic]. Those were all very valid concerns, but you know women did not react that way and a few studies did show that women actually used facilities more after they were given misoprostol. So that was kind of understandable, but with treatment I don't think there is that... right now everybody is pretty much on the same page that it should be available for treatment. So if your message is go to the facility to take misoprostol, it doesn't really become controversial in that sense.

6.4.3 Misoprostol for incomplete abortion management

Participants with experience working with survivors of sexual assault in refugee, conflict, crisis, or emergency settings were especially familiar with misoprostol for PAC when compared with other indications. A participant from a global non-profit organization reasoned that this indication is the most widely programmed because incomplete abortion management is the only indication for which misoprostol is available in the Inter-Agency RH Kits:

It seems like it is such a natural fit. I mean the low hanging fruit is using it for PAC of course and that is what it is in the Kits for, under that rubric, under treatment of incomplete abortion.

So that is the low hanging fruit and even just getting it used for that in humanitarian settings is thought to be natural and easiest.

However, many health practitioners noted that although PAC is well managed in humanitarian contexts, it is performed in some settings using D&C rather than misoprostol. One participant claimed that there exists a large training gap among international NGOs to train personnel on using misoprostol for incomplete abortion management. These participants commonly attributed the challenge of shifting provider knowledge and behaviour towards a new technology.

6.4.4 Misoprostol alone for early induced abortion

Several medical experts discussed the barriers associated with being able to provide the gold standard regimen for medication abortion in humanitarian contexts. Participants from international medical NGOs discussed the challenges associated with accessing mifepristone. Access barriers were primarily due to the fact that mifepristone is not registered in most of the countries they work in. A medical practitioner remarked that in the field misoprostol is most often being used as a solo agent:

Most of the places where we do it, we do it with only misoprostol and not mifepristone. This is what people are doing in the field. And this is with the fact that misoprostol is available and mifepristone is more difficult. On top of that everybody knows that it [mifepristone] is for abortion and misoprostol you can use for other things.

Five participants described misoprostol as an important commodity when considering ways in which to reduce harm from unsafe abortion in fragile settings. Many reported having witnessed this taking place in the conflict or crisis settings they have worked in. As suggested by a participant affiliated with a research institute:

Misoprostol as a single abortifacient for early induced abortion is not nearly as good as mife [mifepristone] and miso [misoprostol] [together]. I think that we have good evidence that

misoprostol works much better than many things that people do, and causes much less harm and negative outcomes.

Although misoprostol programming was discussed with all informants, the majority commented on clinical and policy guidelines; only one quarter of participants could comment on direct provision of misoprostol during a crisis, or emergency. Given participant knowledge and experience, discussions surrounding implementation practices were primarily focused on the post-conflict and recovery phases of emergencies. Several participants expressed limited knowledge regarding how misoprostol is currently built into programming taken on by humanitarian agencies. Many participants expressed interest in learning about the activities of other implementing agencies. It was commonly mentioned that outside of one's own implementing agency's clinical guidelines, field hospital functions, or ordering of RH Kits, they had limited knowledge of how the rest of the field applies misoprostol on the ground. One advocacy oriented informant claims that limited knowledge about how misoprostol is being used stems from a "lack of interest and education," leading to underutilization in humanitarian contexts. Contradicting this view, a researcher suggested that the misoprostol-related policy environment is exceptionally strong and that there exists no reason for actors and agencies to not be aware of the evidence. For this reason he suggests that gaps in humanitarian settings are not related to lack of knowledge, but rather the uncertainty of integration among international NGOs:

I think there is a bit of a program gap – it's not a knowledge gap because they are fully aware, I think they have yet to determine the best way for them to integrate the programmatic aspects into their work.

After exploring reasons for participants' limited knowledge regarding misoprostol use in the field, eight informants highlighted the need to expand dialogue about how misoprostol is being used for each indication among different humanitarian actors. A subset of these

interviewees discussed issues surrounding humanitarian and development agencies be “siloes” from one another. They suggested that collaboration to address current reproductive health issues is lacking, but that joint efforts could be of importance for advancing misoprostol use in humanitarian contexts. These informants called upon integrated discussion between development and humanitarian agencies to share what is known and improve practice. As expressed by one participant from an international advocacy organization “I do hope that dialogue between development and humanitarian agencies continue, so that there is mutual learning and mutual improvement in both spheres for service provision.”

6.4.5 Availability and accessibility of misoprostol in humanitarian settings

Almost all participants discussed the role of misoprostol in the RH Kits distributed by UNFPA. For stakeholders involved with MOHs at the country-level during crisis response, this Kit system is a primary channel for accessing health commodities. Several mentioned that the RH Kit process can be complicated in terms of knowing where misoprostol is nationally approved and registered. One participant stated that this is especially relevant when trying to make misoprostol available within refugee camps. Given this challenge, a few participants from international NGOs acknowledged that during their crisis response activities in the last five years, misoprostol has not been included in their health kits, or health response packages. Some participants reported having tried to incorporate oxytocin into their Kit system, but that generally this drug does not make it into a country’s emergency response Kit due to challenges with establishing a cold chain. A policymaker reported that this was occurring in a current conflict and crisis area and expressed great

concern given RH Kits would not include a uterotonic agent for facilities to prevent and treat PPH. Many participants followed these accounts with comments similar to one policymaker who stated, “when you hear things like that it makes me realize the potential of misoprostol.” Many participants commented on the potential for misoprostol to be integrated into the RH Clean Delivery Kits for PPH prevention, and stated they would support its inclusion.

Aside from the RH Kits, the second most identified access channel for misoprostol was local pharmacies, followed by field hospitals, and finally the national health system. Several participants stated that misoprostol is readily available from community pharmacies in conflict and crisis-affected settings around the world. Many actors from implementing agencies reported that women are increasingly presenting at pharmacies requesting misoprostol to induce abortion. A nurse midwife from a humanitarian agency remarked that this trend made sense given the “first port of call” in most conflict settings is often the local pharmacy, or traditional healers followed by their field hospital and the health system.

Several participants expressed concern regarding women accessing misoprostol in pharmacies without adequate counseling, or education from the supplier. Five NGO participants described experiences in countries where pharmacies and marketplace vendors were selling misoprostol at “jacked up prices” based on what the woman said she could afford. One nurse midwife discussed the “economic incentive to gouge women” and its impact on not providing women with an exact dosage, or a high quality drug. One gynecologist recounted being in a post-conflict country local marketplace and asking a pharmacist for misoprostol. After showing her numerous shelves stacked with misoprostol the pharmacist responded, “How much do you want?” As stated by one researcher, the availability of misoprostol on the black market and in pharmacies necessitates a response to educate and train:

There are certain NGOs in countries that feel misoprostol can be used for abortion and therefore it should not be permitted to be used at all; but they deny the fact that it is already available on the market. You can go into a pharmacy in many countries and just purchase it and so if a drug is widely available and can be purchased I think the health community has an obligation to teach people how to use it correctly. If you just ignore it, that is when problems come up.

Besides training pharmacists and providers on misoprostol use and its indications, some participants considered the impact that social marketing could have when directed toward women in emergency settings with intact media structures (i.e. radio, internet). One medical expert suggested social media could be used to explain the following:

If you take it [misoprostol], this is the brand you should take; these are the pharmacies where there is quality material available. This is the price you should be paying, this is the quantity, and this is what you should expect afterwards. If you're bleeding more than 48 hours this is where you go, and if you go there nobody is going to denounce you because post abortion care is not illegal.

6.5 Policies perceived to influence misoprostol use in humanitarian settings

6.5.1 International policies

Nearly all participants cited normative body policy and guidelines as influential for carrying out their work. The most commonly mentioned normative body discussed were those of the WHO, followed by IAWG, and UNFPA. WHO and IAWG's role has been addressed in the normative body policy and recommendations discussed above. Interviewees consider UNFPA to be influential due to their involvement in developing and distributing the RH Kits during emergencies. There was consensus among all participants that it is fundamentally important to include misoprostol in WHO recommendations and supported its listing on the WHO EML for most indications. Most participants considered the EML to be an important tool for expanding access and information about misoprostol in all country settings. As suggested by one participant:

I think the EML has been the single greatest policy change that has opened up channels for access for our work with misoprostol. I mean there [are] certainly norms and standards by other bodies and organizations that are important, but I think that one is really key.

Some medical experts also commented on the EML's significance when working with MOHs, pharmaceutical regulatory bodies, and procurement officers. The EML was also considered to be of importance when training national health providers, and community health workers. It was noted by one participant that the EML serves as necessary first step:

It's kind of like a situation of exclusion. Just because misoprostol is on the EML doesn't mean it is automatically going to be used in countries, but if it is not on the EML it is very unlikely to be used in countries.

Several participants agreed that the EML is not sufficient for expanding access, and that secondary efforts to "actively and then proactively" promote, monitor, and evaluate misoprostol implementation are needed. A few interviewees concluded that the EML has likely had more of an effect from a policy and advocacy perspective than on direct implementation.

In contrast, some participants agreed that while WHO's EML inclusion is a significant first step for registering a drug in country, and is key for including misoprostol in emergency response RH Kits, it does not necessarily impact all settings equally. This point of view was held especially by participants working among community-based organizations, or in countries where misoprostol remains challenging to access for reproductive health indications.

The IAFM was often referred to as the "authoritative guidance" or "bible" for reproductive health programming in conflict and crisis areas. Seven participants stated that they use this document to guide misoprostol advocacy, or for training and use in the field. Some participants stated they became aware of the IAFM through promotion of the MISIP.

Several claimed they were supportive of the guidelines because they are the only ones currently tailored for humanitarian settings. Some key informants from NGOs not working exclusively in humanitarian settings claimed the IAFM is their first reference point for implementing reproductive health interventions in a crisis affected country. The IAFM and MISIP were updated in 1999 following extensive field-testing. However, a number of participants suggested components of the most recent IAFM edition require revisions, which have not yet been completed.

Other global policies identified as important for misoprostol related programming were technical guidance and toolkits originating from FIGO, Gynuity Health Projects, Ipas, and the Misoprostol for PAC Consortium. A number of additional WHO documents were referenced by participants and named important tools for programming. In order of most frequently discussed: *Recommendations for the prevention and treatment of PPH*, *Safe abortion: technical and policy guidance for health systems 2nd edition*, and *Optimizing health worker roles for maternal newborn health*.

Global normative body policy was recurrently referred to as “validating” by interviewees. This phenomenon was expressed by both participants claiming to align their misoprostol programming with normative body recommendations, and those who do not. As suggested by one international NGO participant, normative body endorsement provides her with “more strength in convincing policy makers.” Another claimed that international policy supporting misoprostol use, especially the EML, is useful when the drug is being used in settings where the regulatory status conflicts with community use. In this case, many participants cited that inclusion on the EML for PPH prevention has significantly helped distribution of misoprostol.

Several participants discussed the importance of a WHO stance for donor relationships, especially when funds are used to procure medication. As interpreted by one participant:

Donors are worried when you are not following international policies, but they don't want to sit down and listen to the data and the research. So I think it is more helpful in that setting.

6.5.2 National policies

Four participants expressed that national policies influence their work far more than global policies. A participant working for a normative body explained that global policies hold less weight than national policies, or laws since advocacy can only center on whether a drug is available in a country. Several participants expressed the need for governments to register misoprostol; they consider the MOH to be the main actor responsible for advancing availability and accessibility. Many participants stated the importance of countries using the WHO EML as a foundation for their national medicines list. Listing and registering misoprostol was explained in many cases to have occurred in “global increments” following WHO EML inclusion. A few informants explained that once misoprostol is on the national list, they have been able to move forward with the MOH to establish further policy guidelines including, registration, importation, and clinical guidelines.

Stakeholders from international NGOs and normative bodies operating within the RH Kit system attested to the importance of a drug being registered in-country. Several participants stated that knowing whether misoprostol is registered in-country, and for which indications can be a challenge. Sometimes those ordering the Kits do not know whether they would, or would not be receiving misoprostol. Although availability in times of crisis was often described as “sporadic” and “unknown,” some participants described their experiences

in countries without misoprostol registration where the drug was readily available at the street level.

Some participants discussed the influence international conferences and meetings had on integrating misoprostol into national policy. A participant from an NGO elaborated on how the reproductive health movement changed once countries began signing onto international declarations to reduce global maternal mortality. Following increased government attendance at meetings and MOH commitment, this participant noted that governments could not deny maternal deaths were an issue in their countries and could see that misoprostol was a commodity of great benefit.

6.5.3 Internal NGO/organization level policies

A number of participants from medical NGOs discussed the importance of their own policies and clinical guidelines related to misoprostol and its indications. All participants working in a medical capacity agreed that their organizational policies are clear and that it is well understood how misoprostol should be used. Clinical policies were often described as being “laminated and presented on all the clinic walls,” and supplemented by the normative body and national level policy relating to misoprostol use. Two providers claimed policies surrounding PPH were made extremely visible and “constantly coached” within the health care setting; misoprostol for the termination of pregnancy was identified as a more “tricky issue,” and was communicated using more “restricted strategies” in order to protect host national staff. In this case, the decision to publicly display misoprostol clinical guidelines was dependent on the national abortion laws, cultural norms, and provider values within their facilities.

Conversely, some providers described how clinic-level policies have restricted access to misoprostol. Most notable were reports from a few medical providers about clinical settings “locking up” misoprostol. A provider discussed the challenges of coming into the field facility in the middle of the night to treat a case of PPH and incomplete abortion and not having access to the drug:

You always want to have it close to you- always. Sometimes people don't realize the importance of having it available anytime, and then they think about the risk of increasing the black market and all that and they lock the misoprostol – that has happened in a few fields. No, misoprostol has to be available for anyone in the staff, anytime ... you have to assure the misoprostol is absolutely available in any maternity 24/7.

6.6 Perceived adherence to misoprostol related policy in humanitarian settings

Many participants agreed that the policy environment surrounding misoprostol can be complicated due to its multiple indications for use. However, most concurred that clinical guidelines and normative body policy are explicit and many stated that it is clear what implementation should be. Many participants concurred that there exists a conscious effort to adhere to policy set by normative bodies. It was suggested that alignment generally occurs to varying degrees because groups adhere for a variety of reasons; often implementing organizations are more reliant on internal technical advice rather than interested in complying with WHO or other agencies.

Nevertheless, some participants expressed that they do not think misoprostol is being used to its full extent in humanitarian contexts despite comprehensive policy. The drug was often referred to as “underutilized” or “departmentalized” among key informants. Many participants openly acknowledged that their organization does not adhere to global misoprostol policy for several reasons. Commonly cited was that some agencies in the humanitarian relief sector cannot conform to WHO safe abortion guidelines due to

restrictions on their programming set by specific donors. Participants state that due to their funding structures they remain unable to provide safe abortion care, or training even in countries where abortion is legally permitted for specific reasons. Others explained that their work with community-based organizations involves distributing and piloting misoprostol at the community level, which is not currently endorsed in WHO's recommendations for the prevention and treatment of PPH. The time lapse between policy reflecting new findings in the literature was suggested by a participant from a global non-profit organization as the main reason for not adhering to standards:

We try to align those with WHO or international policy when appropriate, but there are times when it is not appropriate to following international guidelines, which are usually several years behind the current research because it takes quite a while for new policy to get approved. So when we started seeing the utility of misoprostol and started recommending to our partners to use it, we very carefully documented any instance when we [were] deviating from international standards in terms of best practices. So we documented the literature and the studies that those recommendations were based on, and shared information with our partners.

Advocacy based participants unanimously expressed building normative body policy into their programming activities. Conversely implementing agencies described a lack of document uptake with specific mention given to refugee camp settings. A medical expert indicated that over the last five years working in three large UN recognized refugee camps she has never witnessed any international actors communicate, or inquire about reproductive health policy guidance. Despite access to policy documents and using them for training, she does not think they are part of the conversation when agencies are deciding on a course of action at the onset of an emergency that ensures quality reproductive health inside the camp. While she attests her international NGO operates within clinical guidelines based off the WHO recommendations and IAFM, she does not think discussion around these policies or their implementation are adhered to in the field and states that this a “real problem.”

6.7 Perceived barriers to addressing misoprostol policy and practices in humanitarian settings

Participants identified several barriers they face when working in a professional capacity to integrate misoprostol into policy and practice. Collectively, the challenges discussed can be located at four distinct levels: individual, national or international NGO, national government, and international bodies at the global level. The study findings are presented using this structure.

6.7.1 Individual level

A few participants experienced resistance from women and their family members to the use of misoprostol for PPH prevention. Barriers at this level were regarded as “minimal” and easy to overcome since women are “very cognizant” of the risk associated with pregnancy and home birth. As expressed by a medical expert, “women are invested in their own survival.” When family members deter a woman from taking misoprostol it is often because they were not adequately educated on the purpose, or benefits of the drug. It was suggested by some participants that although there can be “initial skepticism” among family members, it becomes a non-issue with dedicated counseling and education.

Another issue that was raised was how health provider behaviour can influence whether reproductive health practices include misoprostol. A member from a university affiliated NGO believed the situation is not specific to misoprostol, although he has seen it occur, and that often “doctors and specific health practitioners are not terribly amenable to practice change globally.” Some participants expressed frustration in describing going through the process of identifying knowledge gaps among health care practitioners, and then educating and disseminating updated material among them, only to witness no clinical or

behaviour change. A few participants claimed provider preference to perform alternative procedures for incomplete abortion management has posed challenges in the field:

We are very much pushing for miso [misoprostol], from a teaching point of view and policy guidance point of view, to use the less invasive. I mean every time you go to the field you check and see the statistics... because obviously you have medical officers in some countries who are enabled and who have had training to do a D&C [dilation and curettage] for a retained placenta and they are very good at it. So I understand, they are very good at it they wouldn't perforate a uterus, but it is still invasive you have a higher risk of infection than doing it with medicals. So internally we continue [to] push the views of misoprostol for uncomplicated incomplete abortion and termination of pregnancy as first choice, but it is a continuous process.

6.7.2 National and international NGO level

A few participants from national and international NGOs indicated internal tension related not specifically to misoprostol, but with early induced abortion. Notably, four participants from international NGOs with their own abortion guidelines emphasized issues arising when their staff face requests for safe abortion in the field. These participants all claimed midwives and obstetricians are screened, informed of the policy, and sign a statement of support of the abortion policy before sending them into the field. However, once they are in the field they can serve as a barrier if they refuse care. They stated that this becomes a problem when the NGO's staff member is an expatriate, given they encourage expatriate professionals to perform safe abortion in restrictive or unstable contexts to protect national level staff:

It's no use sending an obstetrician if she's going to be the main person doing the MVAs, or curettage and then basically because of personal beliefs refuses to do it. Then she can't work in this kind of context where we are going to be providing [termination of pregnancy] TOP.

A number of participants believed that religiously affiliated NGOs are resistant to the use of misoprostol. Several participants stated that this is due to misoprostol being able to be used for a number of indications including abortion. However, some participants noted that they have witnessed opposition from non-religiously affiliated organizations in the

humanitarian relief sector. This was demonstrated by a participant from an NGO providing misoprostol exclusively for PPH prevention in conflict settings, “we don’t want to be tied to it at all... it is dangerous to have it in the same sentence, it creates too many problems.” A few participants recounted meetings where international NGO stakeholders became guarded during misoprostol-related discussions. A medical expert perceived that groups stay away from it because of the uncertainty of indications being discussed, “are you talking about induction, are you talking about hemorrhage? I mean what are you really talking about in a room full of people?” An advocate from an NGO agreed that tension regarding the use of misoprostol is present in international meetings and workshops. She condemned establishing restrictions for the drug’s use at the NGO policy level, and suggested that it should only be done in-country and by health care providers. Other members from international NGOs agreed that the global health community must acknowledge misoprostol’s availability at the street level and ensure women access and administer it safely.

6.7.3 National level

Fifteen participants reported having worked on reproductive health programming with a MOH in less fragmented settings, or with those from nations with large refugee populations. Comparably, participants expressed that governments can serve as barriers in similar ways and commonly express fear of “misuse” of misoprostol for abortion. In cases of misoprostol for the prevention and treatment of PPH, a few participants revealed that MOHs have expressed concern over whether women take the correct dosage of misoprostol, administer at the right time, or confuse the drug with additional medication or prenatal vitamins. Moreover, a few participants reported that a MOH could be hesitant to endorse the drug for home births because it contradicts national health policy encouraging women to

seek facility-based deliveries. A participant suggested that MOHs also fear if misoprostol fails to prevent hemorrhage, women will not self refer to a clinical setting afterwards. A number of participants discussed establishing supportive partnerships with MOHs and being able to quell concerns at the government level by “helping them look at research and evidence from other countries,” or pilot a “learning phase intervention to acquire local evidence,” and confidence in the intervention.

Another issue raised was limited advocacy for misoprostol use and registration at the national level. Some participants claimed without a committed source building an “advocacy profile” for misoprostol among national policymakers and MOHs, it is hard to move the drug into mainstream national practice. A policymaker recounted a number of “isolated misoprostol experiments” he had seen being programmed in different parts of the country. He claimed there was no effort to share and integrate findings into a comprehensive national strategy. From a policy perspective he believes that pocketing misoprostol advocacy in select regions and operating outside of the national reproductive health strategy is not productive. A participant from an international research and advocacy organization argued that when local governments or ministries create “bottlenecks” and resist integrating misoprostol, normative body policy serves as the means to overcome barriers:

I do feel that a lot of the time bottlenecks can be [created] by local governments or ministries that say ... we don't really want to abide by [international guidelines]. But when it has the WHO approval it really brings that weight and credibility for procurement and advocacy... [WHO policies] serve as advocacy tools to make the case for why it is important, even if it is counter to their personal belief system.

Participants from medical international NGOs who establish a cold chain in country, or operate using the RH Kit system agreed that bottlenecks at the national level impede their work in many ways. A medical expert discussed how convincing ministries to allow a certain

drug into the country is one of her agency's foremost challenges. Several participants named mifepristone and its lack of national registration as a prominent barrier to providing the gold standard medication abortion regimen. Many participants from medical international NGOs claimed that if neither drug is registered they focus their efforts on getting misoprostol into their supply chains since it can be used for multiple indications. Regarding the RH Kits, a medical expert explained that although ordering the RH Kits goes through a global procurement office and there is less involvement from the national government, the procurement office will rarely send a commodity if it is not listed on the national EML.

6.7.4 Global level

Several participants suggested that a number of gaps exist within the current global policy climate that do not promote the advancement of misoprostol in humanitarian settings. Some participants voiced concern that advocacy within the humanitarian relief sector has not championed misoprostol nearly as successfully as in development fields. Many participants cited IAWG as the guiding authority in these settings and referenced misoprostol's inclusion in the IAFM, but felt advocacy was lacking from larger global bodies external to IAWG. A participant from an humanitarian relief NGO claimed that discussions on what elements of a project to implement at the global policy level frequently forget to consider what will best support a government from "adopting or not adopting" such practices. As suggested by a researcher from an academic institute, failure to integrate misoprostol into national policy and scale-up programming can be linked to limited support at the global level:

The primary reason that they said it wasn't being scaled up is because there is no global support for it. There is no policy that says we should do this. So the government's willing to try something but not willing to commit to something if there isn't global policy support.

A medical provider argued that it is easy at the global policy level to “get caught up with smaller issues and forget the greater impacts” that she witnesses in the field. She concurred that what is currently required at the global level is commitment to scale-up:

Misoprostol is effective in prevention of post-partum hemorrhage, I think that has been documented. Everyone knows it and oxytocin is unfortunately not available where we want it to be and in most of the places where we work. Also for treatment of post abortion care it is a much safer option; it is available and it is in the guidance of the World Health organization. I think if we then look into indications and start engaging how we as a global community can support countries use, scale up and make this available to communities, I think we will move much faster.

Some participants claimed that the current WHO positioning around misoprostol at the community level has served as a barrier for their PPH prevention and treatment programming. Despite WHO endorsement for misoprostol at home birth, three participants state that without a normative body recommendation in favor of advanced distribution of misoprostol in the community, components of their programming and implementation objectives remain challenging.

7. Discussion

Over the last 20 years there has been steady integration of misoprostol for PPH prevention and treatment, incomplete abortion management, and early induced abortion within global health policy environments. However, other than the IAFM and MISP, there exist few specific policy guidelines from normative bodies for refugee, conflict, crisis, and emergency settings. It appears that in these contexts, IAWG and agencies advocating for use of the MISP are leading the improvements being made for women's reproductive health. Although some participants expressed concern that components of the most recent edition of the IAFM have not gone through revision, field-testing is underway and will be undertaken for all future versions.

Results from the policy analysis suggest misoprostol policies for PPH prevention are fairly coherent, which is largely due to its inclusion following the 2011 EML Expert Committee meeting. This is corroborated by data from the key informant interviews in which many participants agreed that prior to its 2011 inclusion for PPH prevention on the EML, normative body positioning around the drug was ambiguous. Policies regarding misoprostol for incomplete abortion management were also well defined; they aligned among normative body policies, including WHO's EML, and the IAFM, as well as within NGO internal policy. This may be associated with misoprostol's availability for incomplete abortion management in the RH Kits. However, for other indications it appears normative body policy is not always in alignment, and discrepancies do exist. Although misoprostol is not currently listed on the EML for PPH treatment it appears NGO level policies and implementers are routinely using the drug for this indication. There are many caveats within the IAFM and WHO guidance for providing early induced abortion in refugee, conflict, crisis, and emergency affected settings, since such contexts commonly have legal restrictions on abortion. However,

there is discrepancy among WHO normative body policies given misoprostol is included in the WHO's Safe abortion: technical guidance for health systems 2nd edition as a solo agent to induce early abortion in contexts where mifepristone is not available; yet misoprostol is not recommended as a solo agent on WHO's EML.

That normative body policy is not uniformly considered and implemented among all actors and organizations is intriguing, given the support that was expressed among a number of informants to align their agency policies with normative body guidance. Granted, misoprostol guidelines are not used in the same capacity among all and many indicated that the peer-reviewed literature played a larger role in informing their practices. However, the validation and influence that WHO and other UN agency policies have on the work of actors, NGOs, and researchers is apparent.

The importance of the policy-making process at WHO and country-levels is the impact it has on procuring RH Kits during an emergency. The findings indicate that in-country registration of misoprostol is important for facilitating entry of the Kits, thus MOHs should be encouraged to register misoprostol in their counties. Without steady international support for governments to include misoprostol on national essential medicines lists, to integrate it into regional health centers, and train health care providers, it is not possible for the drug to be mobilized through the RH Kit system. Therefore, it would be valuable for humanitarian-based agencies with experience working with or providing technical assistance to MOHs to consider integrating misoprostol into projects. Research conducting pilot studies in specific regions with MOH approval is another way to encourage governments to support misoprostol registration and has been successful in some development projects in post-conflict settings. The potential to have commodities registered in-country prior to an emergency can significantly improve response and recovery phases.

The study findings suggest that current challenges regarding misoprostol use in fragile settings exist at both global policy and programmatic levels. To date, global advocacy for misoprostol has largely focused on developing guidance and encouraging its inclusion in health policy. Although misoprostol-related policy may be coherent at some levels, there remains inconsistency between certain normative body guidelines and challenges with translating policy into practice among implementing agencies. There also remain gaps regarding misoprostol's lack of inclusion in the RH Kits for PPH prevention and early induced abortion, despite being listed on the EML and within other WHO guidelines. Discovery of implementation gaps are common phenomena in health policy research. Implementation gaps can be the result of poor communication between researchers and policy makers, limited dissemination of new guidelines, or lack of consideration given to knowledge translation techniques and practices. The gap is identifiable when we consider how limited training and documented misoprostol use was reported on by actors who are implementing within crisis affected areas. This was true for all indications, but especially for early induced abortion misoprostol regimens; for this indication it appears NGO staff may be a continuous barrier to using the drug due to personal values. Lack of training taking place after launching global guidance, suggests implementation is somewhat removed from what was intended. It appears warranted to call upon the global health community to concentrate efforts surrounding misoprostol use at implementation levels rather than through continuing to assess its physiology and efficacy. Additionally, training on misoprostol regimens for PPH prevention, PPH treatment, incomplete abortion management, and early induced abortion, and other updates made to the IAFM once field-testing of the new version is completed, should be undertaken.

Pilot studies and implementation research surrounding misoprostol use in humanitarian contexts may be a useful next phase inquiry. Few informants could comment on the pathways through which misoprostol is being programmed in humanitarian settings. Even the participants who work in field hospitals, or supply medications in-country lacked knowledge about implementation systems outside their provision. In the last five years, misoprostol programmatic research has been highly focused on development contexts and to some degree post-conflict settings. In terms of implementation, a unique body of programmatic evidence should be generated for refugee, conflict, crisis, or emergency settings. Spill-over of recommendations from development to humanitarian sectors (and vice versa) is accepted and has frequently occurred for other drugs and commodities. However, there has been limited effort in humanitarian circles to understand where the successes, challenges, and barriers are for translating misoprostol policy into practice in such contexts. Without a comprehensive process of mapping misoprostol use to better understand channels of provision and successful training efforts, it remains challenging to understand these important questions. In order to improve misoprostol programming during complex emergencies, a collective discussion between development and humanitarian actors is needed.

To date, most research that guides our knowledge surrounding misoprostol practices originates from research focused in low-resource settings. This is not uncommon as there is often overlap between the two fields, and yet there does not appear to be on-going dialogue to share lessons learned and ensure misoprostol remains part of reproductive health services. Given that development agencies and researchers are often well established in countries and regions before the onset of a crisis or emergency, they have critical knowledge of local contexts and availability of medications. Phenomena of siloing development and humanitarian actors emerged as an existing barrier for advancing misoprostol use, and given

the drug's wide use and current evidence base in development scopes, it would be an advantage for knowledge sharing, coordination, and collaboration to take place. This knowledge will be country specific and distinct to the contextual dynamics at play. Based on the nature of the questioning and the strong policy focus of the in-depth interviews, it is beyond the scope of this research to map regionally specific, or programming activities at the country level among implementing agencies in refugee, conflict, crisis, and emergency settings.

Issues of religion influencing misoprostol policy and programming did not emerge as an explicit construct during analysis. However, it is apparent that religion is infused into larger policy issues, which is demonstrated in the results by conscientious objection to abortion among health providers and NGO organizational policies. Indeed, religious motivations may be subtly removed from the discourse surrounding the policy-making process, but can shape the way policies are interpreted and serve as a barrier for implementation. The interview data indicates that this is especially the case among established funding structures and influential humanitarian agencies.

As suggested from the qualitative interview findings, the phenomenon of fear that misoprostol is being "misused" is present. However, it appears that over the years this dominant concern has been able to be mitigated. It was suggested that "misuse" is more of a "hypothetical" concern and that within global health communities the drug is slowly being embraced for its multi-purpose use. Addressing concerns that misoprostol can be used to induce abortion remains a challenge at government levels. Mitigating perceptions around "misuse" at this level should be considered through a number of different strategies. For example, modifying semantics to focus on reducing the potential for maternal mortality and the value of having a drug with multiple safe uses. Given local provider interest in

misoprostol and country-level governments supporting its use for PPH prevention, using an integration approach appears to be warranted and shows potential success for using the drug for other indications. Using the same integration approach moving forward, consideration should be given to integrating misoprostol as part of greater emergency response packages of commodities rather than the drug on its own. A participant from a global normative body discussed that health agencies operating in refugee, conflict, crisis, and emergency settings are researching the potential for collections of commodities that can be combined into reproductive health packages. Embedding the drug within a greater scope of reproductive health services and packages may reduce the stigma associated with its use for abortion, and advance its integration on the ground following a crisis or emergency.

WHO global guidance states a uterotonic agent must be available at every childbirth for the prevention of PPH. On the contrary, in the UNFPA RH Kits oxytocin is the only uterotonic made available. As discussed, an injectable and non-heat stable medication like oxytocin that requires a cold chain supply is not feasible in many humanitarian contexts. Without an RH Kit with alternative uterotonics to prevent PPH, it cannot be assumed that a uterotonic will be present at all births. The RH Kits are established using WHO policy recommendations and WHO's EML, and undergo expert revision every two years. Granted, the misoprostol for PPH prevention recommendation was issued by WHO after the Kits underwent the 2012 revision, but given misoprostol's presence on the current EML future revisions should consider its inclusion. In 2014 the RH Kits are expected to undergo a multi-agency review process wherein consideration for including misoprostol in the Clinical Delivery Assistance Kit (Kit 6) and other safe delivery kits should be considered.

There exists an overwhelming lack of knowledge regarding misoprostol's inclusion for incomplete abortion management in Kit 8. This is possibly attributed to limited

awareness raising around the RH Kits and encouragement from distribution agencies about its potential benefits. Given almost all countries permit abortion for some indications, an RH Kit dedicated to providing safe abortion care in emergency settings should be considered. The Kit should follow the WHO established gold standard for medication abortion, which could include the Medabon® packet of 200mcg mifepristone tablet and four 200mcg misoprostol tablets. However, since mifepristone is not widely registered, a secondary kit containing the recommended misoprostol alone regimen could be created to prevent importation barriers. Creating a kit that includes MVA could also be of consideration for providing safe early abortion in refugee, conflict, crisis, or emergency settings. Developing and proactively raising awareness about a new Kit for medication abortion may potentially reduce morbidity and mortality associated with unsafe abortion that takes place in emergency settings. This strategy aligns with the mandates of WHO and UNFPA who approach reproductive health comprehensively, and are committed to scaling up strategies to prevent and treat the consequences of unsafe abortion globally. Moreover, given the systematized process of ordering the Kits through UNFPA, the procurement center would only be able to issue an order for a medication abortion RH Kit in countries where there are legal exceptions for abortion.

Policy framing is a key element to consider when exploring ways in which to register, or expand access to misoprostol in all global settings. Normative bodies, namely UN agencies, center most of their reproductive health recommendations in HRBA and frames. HRBA operates within the principles of human dignity, empowerment, anti-discrimination, equality, and freedom; it claims governments have an obligation to respect, protect, and fulfill human rights (180). However, using this normative approach within policy-making processes in order to influence drug registration may not be pragmatic in all settings. Drug

registration processes can be compounded by dynamics of limited transparency, closed decision making that rarely includes public discussion, and the influence of national laws and policies surrounding abortion. In contexts where HRBA may not be feasible or widely accepted, alternative strategies have proven to be successful.

Globally, harm reduction has shown to be an important frame rooted in evidence-based public health approaches to explore misoprostol policies and programmatic advancements. Research indicates it has been successful in encouraging safer practices and reducing the rate and severity of complications from unsafe abortion in complex contexts (144). In this case, harm reduction frames provide ways in which to circumvent prohibitive abortion policies by providing women with safe alternatives and medically accurate information without reforming national abortion law. Following a complex emergency or during active-conflict, using misoprostol to reduce harm given high rates of unintended pregnancy and sexual violence may be a significant public health intervention. Currently, there are few studies exploring harm reduction practices using misoprostol in conflict, or crisis affected contexts. This may in part be due to its exclusion from the RH Kit system and challenges with conducting research in said settings. Often harm reduction and HRBA are discussed as being exclusive frameworks and opposite to one another. However, it is important to consider their convergence given both approaches act as mechanisms for institutionalized change; harm reduction provides an evidence-base for intervention in contexts where human rights are violated, and human rights can eventually be used as a normative base for legal reform (147). Considering how to work within each of these frames and strategize their convergence at a given point in time may prove successful for improving future misoprostol policy and practices.

Identifying misoprostol implementation gaps in this study aligns with acknowledgement among external working groups that although reproductive health technical guidance and policy has become well institutionalized in crisis and emergency settings, there remains limited understanding regarding how programming is taking place on the ground. To address this gap in research, over the last year IAWG has been conducting a multi-methods evaluation to document and critically assess current global reproductive health interventions. The study sampled from a wide range of governmental and non-governmental informants from crisis affected countries, and aims to guide future implementation practices, decision-making, and advocacy (181). Whether mapping misoprostol-related programming has been explored in this global evaluation remains unknown, but it can be inferred that activities surrounding deployment of the MISIP and emergency preparedness were considered, which may have implications for future misoprostol implementation.

7.1 Limitations and Future Directions

The qualitative research methods used in this study were essential in order to explore the policy and practices surround misoprostol use in refugee, conflict, crisis, and emergency settings. The methodology allowed for professional experiences, perceptions, and opinions of key informants to be explored without restriction. The policy analysis and interviews were explored iteratively, which informed one another and the overall findings. However, the methodology is not intended to yield representative or generalizable results. The sample was not randomized and ultimately relied on key informants' interest in the study and willingness to participate in an interview. It cannot be assumed that the interviewees represent a

complete contingent of policymakers, advocates, and implementers working with misoprostol in fragile settings. Most notably, this study does not explore specific regions or countries in-depth, and thus does not include informants from governmental bodies, or MOH representatives. The role of country-level governments is clearly of great importance when considering how commodities make it into countries and the emergency response. Granted, this research takes on a global review of misoprostol policy and programming, but it should be noted that the policy-making processes at national levels were not considered in depth. Finally, it is essential that the unique nature of emergency affected settings be considered independently. To adhere to the global scope of this thesis, I use the term “refugee, conflict, crisis, and emergency settings” throughout. This models the language used by international-level agencies and advocacy groups given the recurring trends that are present in such contexts. However, the diversity and complexity of distinct crises or emergencies, and the lived or professional experiences of persons in refugee or conflict affected areas is not intended to be representative in this thesis. Indeed, subjectivity is inherent of qualitative research and the reflexivity of the researcher was discussed throughout the thesis. To minimize subjectivity this study adhered to rigorous standards outlined in the methods section to ensure credibility, confirmability, and trustworthiness. Given the multi-method assessment and diverse cadres of professionals who participated, I am confident that the identified themes are significant, but am unable to assess the degree to which these perceptions and opinions represent broader trends.

In this study I explore established normative body misoprostol policy and discuss the global dynamics that impact programming and potentially lead to implementation gaps. Moving forward, additional research assessing country or region specific misoprostol programming is required, and strategies for improving translating policy to practice should

be explored. Mapping misoprostol programming for all four indications in refugee, conflict, crisis, and emergency settings would be instrumental in identifying additional mechanisms for advancing availability and accessibility, given it appears that there are numerous undocumented channels through which women are accessing the drug. Future research should also be conducted to field test and update current policies specific to crisis settings, most importantly the IAFM. The previous edition of the IAFM had been field-tested and this is expected to take place for all future manuals. This study also demonstrates inclusion of misoprostol in the RH Kits for indications other than incomplete abortion management may be warranted. Thus, moving forward actors and agencies from the global reproductive health community should explore its inclusion further and engage in discussion with UNFPA and committee experts regarding revising and updating RH Kits. Finally, strengthening advocacy efforts surrounding the registration of misoprostol at the country level appears warranted, especially given these efforts have not focused on countries prone to conflict or crisis.

8. Conclusion

This study aimed to identify misoprostol-related policies set by normative bodies and to understand better how they are implemented in refugee, conflict, crisis, and emergency settings. The findings suggest there exists coherent normative body policies for PPH prevention and incomplete abortion management, but that misalignment occurs among misoprostol for PPH treatment and early induced abortion guidelines. In most cases, the IAFM and WHO policies appear to serve as authoritative guidance and provides validation for on-going programming. However, this research concludes that a number of barriers remain for misoprostol implementation in complex contexts. The implementation gaps identified in this study are significant, and may be compounded by the complexity of fragmented health systems, or unmet reproductive health needs. Data from key informant interviews reveal barriers existing at all levels of intervention beginning with individual patient misconceptions of the drug and NGO health staff who are reluctant to administer the medication. Challenges associated with registering the drug at national levels and the impact registration has on ordering the RH Kits were identified. Moreover, lack of global support for misoprostol scale-up projects and inconsistency surrounding policies requiring a uterotonic agent at all births were both highlighted.

While this research has shown the benefits of working within HRBA, harm reduction approaches become import when considering how to advance misoprostol policy and programming, especially in contexts where HRBA may not be realistic or feasible. As such, it may be beneficial to revise misoprostol policy and encourage its use through public health based approaches. This study documented multiple channels through which women access misoprostol. Given that this phenomenon is occurring in global crisis settings it is essential that the global health community ensure women receive counseling and medically accurate

information when given misoprostol. Further, a commitment to train community-level health professionals on misoprostol, as a way to reduce maternal morbidity and mortality should be encouraged. This study aims to be an applied contribution to the literature and provides recommendations for advancing misoprostol policy-making and programming. However, this research may serve as an interesting case study for further theoretical considerations. Moving forward there may be an opportunity to explore in-depth the dynamics associated with policy continuity and change in a time where the rise of expertise and evidence-based practice has changed the policy-making process.

Based on the findings from this multi-methods study the following recommendations are suggested for stakeholders involved in misoprostol policy and programming in global humanitarian settings:

1. Update the RH Kits to include two new packages with misoprostol for PPH prevention and early induced abortion. Early induced abortion RH Kits could include the combination mifepristone and misoprostol regimen (Medabon® packets). Additional Kits including misoprostol alone, or MVA for early induced abortion should also be considered.
2. Include misoprostol on the WHO EML for PPH treatment and early induced abortion as a single agent.
3. Conduct rigorous field-testing of the IAFM and other guidelines in an effort to provide updates according to the current evidence-base.
4. Map misoprostol use in refugee, conflict, crisis, and emergency settings and assess the drug's success, failures, and barriers at programmatic levels.
5. Support relationship-building efforts between development and humanitarian actors in order to effectively introduce misoprostol into crisis response and recovery plans.

Global maternal morbidity and mortality from PPH, incomplete abortion, and unsafe abortion continues to be of significant consequence in fragile settings. Given the current body of evidence and this additional study, it is clear that policies require alignment and programmatic response demands innovation and alternative approaches. The role of misoprostol for reproductive health indications in refugee, conflict, crisis, and emergency settings has the potential to address unmet need and become an integral medication among the various toolkits of the humanitarian response. Developing policy and implementing misoprostol requires collaborative support from policymakers, governments, international agencies, and humanitarian actors; a dialogue between actors should be coordinated and will require engagement among conventionally siloed stakeholders. More research is required in order to rigorously map, monitor, and evaluate misoprostol use in fragile settings. Along with policy change for misoprostol inclusion on the EML and in RH Kits, future implementation research will generate a better understanding of successful programming, and support transitioning from policy to practice.

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Appendix

Appendix A: REB approval letter

File Number: H02-13-01

Date (mm/dd/yyyy): 02/22/2013



Université d'Ottawa **University of Ottawa**
Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

Ethics Approval Notice Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

<u>First Name</u>	<u>Last Name</u>	<u>Affiliation</u>	<u>Role</u>
Angel	Foster	Health Sciences / Others	Supervisor
Grady A.	Arnott	Health Sciences / Others	Student Researcher

File Number: H02-13-01

Type of Project: Master's Thesis

Title: Mobilizing Misoprostol: A multi-methods analysis of the policies and practices of normative bodies.

Approval Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
02/22/2013	02/21/2014	Ia

(Ia: Approval, Ib: Approval for initial stage only)

Special Conditions / Comments:

N/A

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Université d'Ottawa **University of Ottawa**
Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

This is to confirm that the University of Ottawa Research Ethics Board identified above, which operates in accordance with the Tri-Council Policy Statement and other applicable laws and regulations in Ontario, has examined and approved the application for ethical approval for the above named research project as of the Ethics Approval Date indicated for the period above and subject to the conditions listed the section above entitled "Special Conditions / Comments".

During the course of the study the protocol may not be modified without prior written approval from the REB except when necessary to remove subjects from immediate endangerment or when the modification(s) pertain to only administrative or logistical components of the study (e.g. change of telephone number). Investigators must also promptly alert the REB of any changes which increase the risk to participant(s), any changes which considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project and safety of the participant(s). Modifications to the project, information/consent documentation, and/or recruitment documentation, should be submitted to this office for approval using the "Modification to research project" form available at:
<http://www.research.uottawa.ca/ethics/forms.html>

Please submit an annual status report to the Protocol Officer four weeks before the above-referenced expiry date to either close the file or request a renewal of ethics approval. This document can be found at:
<http://www.research.uottawa.ca/ethics/forms.html>

If you have any questions, please do not hesitate to contact the Ethics Office at [REDACTED]

Signature:

[REDACTED SIGNATURE]