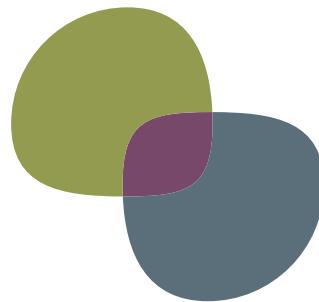


**STRATEGIES FOR PROTECTING AND EXPANDING ACCESS TO
MISOPROSTOL IN THE UNITED STATES:
A WHITE PAPER**

DECEMBER 2018



CAMBRIDGE
REPRODUCTIVE
HEALTH
CONSULTANTS

STRATEGIES FOR PROTECTING AND EXPANDING ACCESS TO MISOPROSTOL IN THE UNITED STATES: A WHITE PAPER

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ABOUT THE AUTHORS: Cambridge Reproductive Health Consultants (CRHC) is a non-profit organization dedicated to improving reproductive health and fostering reproductive justice worldwide. By leveraging the skills of professionals from a variety of fields, CRHC focuses on increasing access to safe, legal, high quality, and affordable abortion care, reducing harm from unsafe abortion, increasing access to emergency contraception and long-acting reversible contraceptive methods, and advancing new reproductive health technologies in low resource and protracted refugee and conflict settings. CRHC accomplishes its mission by conducting action and intervention oriented research, creating and incubating new and innovative programs, and developing and delivering evidence-based reproductive health information, resources, and trainings.

ACKNOWLEDGEMENTS: This project was supported by an anonymous funder. The conclusions and opinions expressed in this report are those of the authors and do not necessarily represent the views of the organizations with which the authors are affiliated, the individuals and organizations acknowledged in this report, or the funder.

The authors thank Professor Mindy Roseman of Yale Law School, Professor Jeannie Suk-Gersen of Harvard Law School, and Professor Yvonne Lindgren of the University of San Francisco School of Law, as well as Dr. Angel M. Foster, Principal at CRHC and Associate Professor in the Faculty of Health Sciences at the University of Ottawa, and Nora Dye for their contributions to this report.

SUGGESTED CITATION: Sietstra C, Lint S, Rodriguez, S. *Strategies for Protecting and Expanding Access to Misoprostol in the United States: A White Paper*. Cambridge, MA: CRHC, 2018.

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I. EXECUTIVE SUMMARY

Reproductive health and justice advocates in the United States continue to search for paths forward during a time when legislative restrictions in many states¹ have dramatically curtailed access to legal, safe, clinic-based abortion, and when documented cases of clinic-based abortion are decreasing markedly, without a clear explanation that does not include, at least in part, an increase in self-management of abortion.² Their efforts include broad and sustained work to decriminalize self-managed abortion and to defend people charged with crimes related to pregnancy loss,³ as well as coordinated endeavors to look beyond current, clinic-based models for safe abortion services. Advocates and researchers are exploring options such as telemedicine and online provision of medication abortion drugs,⁴ and devoting sustained attention to improving access to mifepristone.⁵

With a narrowing of abortion rights expected under the new Supreme Court, organizations and leaders are also beginning to strategize for a future when legal abortion may be explicitly or effectively banned in parts of the US, and when self-management of abortion will likely increase, as will the possibility of forced pregnancies. Because misoprostol is already the linchpin for safer abortion in legally restricted settings around the world, this paper argues that these forward-looking efforts should include focused work to protect and expand access to misoprostol in the US – not only in conjunction with mifepristone, but also and to an even greater extent, alone.

In order to evaluate possible strategies to protect and expand misoprostol access, the authors of this paper undertook two main forms of research. First, we explored current law and policy related to misoprostol access at both the state and federal levels, analyzing Food and Drug Administration (FDA) regulations, liability related to off-label prescriptions of drugs, laws related to importation of prescription medicines, physician malpractice laws, and legal standards regarding standard of care. We also focused particular attention on regulations in two progressive states, California and Oregon, where misoprostol prescriptions might be expanded for a novel indication, to ensure a state of non-pregnancy when pregnancy is

¹ S.C.M. Roberts, K. Kimport, R. Kriz, et al, *Consideration of and Reasons for Not Obtaining Abortion Among Women Entering Prenatal Care in Southern Louisiana and Baltimore, Maryland*, Sexual Research and Social Policy (2018), <https://doi.org/10.1007/s13178-018-0359-4>.

² Diana Greene Foster, *Restricting Access to Abortion Makes Poor Women Poorer*, Seattle Times, (Jan. 24, 2018), https://www.seattletimes.com/opinion/restricting-access-to-abortion-makes-poor-women-poorer/?utm_source=RSS&utm_medium=Referral&utm_campaign=RSS_all.

³ See for example, SIA Legal Team, (accessed on Nov. 13, 2018), <https://www.sialegalteam.org/about-us>; National Advocates for Pregnant Women, (accessed on Nov. 13, 2018), http://advocatesforpregnantwomen.org/main/programs/legal_advocacy/.

⁴ See E.G. Raymond, E. Chong, P. Hyland, *Increasing Access to Abortion With Telemedicine*, *JAMA Intern Med.*, 176(5):585–586 (2016); also Aid Access,(accessed on Nov. 13, 2018), <https://aidaccess.org/en/page/561/about-us>.

⁵ Researcher 3, *Stakeholder Interview* (2018); FDA Policy Expert 1, *Stakeholder Interview* (2018).

suspected but not established (i.e. menstrual regulation (MR)). And finally we looked closely at practice barriers that clinicians face, both actual and perceived.

In general, our legal research identified almost no formal barriers to increasing prescriptions of and access to misoprostol beyond generalized abortion regulations, though questions around standard of care and informed consent regarding the novel indication of MR may be potential hurdles for increasing access to the medicine for that purpose. Some states, including California, have existing but unenforced laws regarding disposal of fetal remains that could be resurrected to make self-management of either abortion or MR legally risky for individuals. And the perception among clinicians of an increased risk of liability related to off-label use of misoprostol, while exaggerated, is also a potential barrier to expanded prescriptions. This is why the authors argue for a strategy of online provision of prescriptions for a novel indication, rather than pushing for an across the board increase in prescriptions from clinicians. If many or most clinicians worry about increased liability from off-label or novel usage of misoprostol, it is unlikely that widespread prescriptions for a novel indication will be possible in the near future. However, online provision requires only a small number of progressive clinicians to generate increased access for pregnant and/or potentially pregnant people.

In addition to legal research, the lead author conducted more than three dozen stakeholder interviews with advocates, health researchers, abortion providers, FDA policy experts, academics and funders to establish the landscape of ideas related to increasing access to misoprostol and to evaluate the potential strategies that stakeholders identified. The lead author sought to determine whether or not consensus regarding future actions already exists, and if not, what options receive the most consistent support, and what criticism each idea generates. In this paper, the authors attempt to elevate the voices of stakeholders who represent communities already facing barriers to abortion access, including people of color, people who identify as LGBTQ, immigrants, and poor people.

Within the constraints of the paper, four main strategies emerge with either strong or moderate enthusiasm among stakeholders. These include two options with strong, consistent stakeholder support: 1) Evolving standard of care guidelines such that clinicians routinely prescribe or provide misoprostol for patients after any uterine bleeding event including miscarriage, abortion, and birth for the purpose of treating potential excessive bleeding at home; and 2) Increasing targeted education and efforts to ensure independent prescriptive authority for certified nurse midwives (CNMs) as well as supporting access to misoprostol for all midwives.

Recommended strategies also include a third option with qualified support and many questions, but also an enormous potential impact: 3) Exploring a novel indication for prescriptions of misoprostol for MR (i.e. “bringing down a period,” “pushing a period,” or “inducing a chemical pregnancy”) in progressive laboratory states. If realized, this strategy would mean potentially pregnant people in some states could regularly obtain misoprostol for self-use without a positive pregnancy test. And finally, a fourth strategy received more positive feedback than not, and could have limited but positive impact on access to misoprostol: 4)

Regularly testing medicines sent from extralegal, foreign pharmacies labeled “misoprostol” and/or “mifepristone and misoprostol” and continuously updating a central, online source of information about the reliability of these pharmacies regarding both quality of product and shipping.

Two other strategies received mixed reviews from stakeholders, and as such the authors neither recommend nor discourage them: 1) Advocating for prescriptions of misoprostol alone for abortion, either generally or through telemedicine. The mixed reactions to this strategy represent ongoing philosophical differences within the reproductive health and justice movements that may be resolved through future targeted conversations or increased research establishing the improved efficacy of misoprostol alone with repeat doses and longer timeframes; 2) Expanding education for patients and doctors regarding the use of Arthotec, a combined non-steroidal anti-inflammatory drug (NSAID) and misoprostol medicine indicated for arthritis and rheumatoid arthritis pain with the potential to manage many other types of chronic pain.

Finally, stakeholders argue persuasively that three proposed strategies should not be pursued, either because they are unlikely to succeed or because they carry enormous risks of unintended consequences that could restrict access to misoprostol or harm pregnant people: 1) Expanding use of misoprostol as a preventative treatment for ulcers (the original, approved medical indication for misoprostol in the US); 2) Seeking changes to FDA labeling of misoprostol to include a new, black-box “abortifacient” warning or pushing for FDA approval of a misoprostol alone protocol for abortion; and 3) Evolving standard of care guidelines to include the assertion of prior misoprostol use as an indication for active miscarriage management or therapeutic abortion.

This paper begins by discussing the key reasons to advocate for better access to misoprostol, its background in the US, and legal questions related to expanding access. The paper then turns to potential strategies, analyzing each in turn, and describing the reasons why stakeholders do or do not support concentrated action, funding, or further steps to bring a given idea to fruition.

SUMMARY OF PROPOSED STRATEGIES TO PROTECT AND EXPAND ACCESS TO MISOPROSTOL

PROPOSED STRATEGY	POTENTIAL IMPACT	CRITICISM OR QUESTIONS	ASSESSMENT
Evolving the standard of care for uterine bleeding events.	This strategy could increase the amount of misoprostol in the hands of potentially pregnant people and give clinicians a way to support harm reduction.	Stakeholders express very little criticism of this approach.	Strongly recommend.
Expanding education and ensuring independent prescriptive authority for CNMs.	This strategy could improve access to misoprostol for CNMs and their patients.	Stakeholders express very little criticism of this approach.	Strongly recommend.
Exploring online provision of misoprostol to ensure a state of non-pregnancy when pregnancy is suspected (MR).	This strategy could dramatically expand prescriptions of and access to misoprostol without a positive pregnancy test.	Stakeholders express both questions around efficacy and philosophical concerns.	Recommend further exploration.
Supporting ongoing quality assurance work related to online, foreign pharmacies.	This strategy has limited potential to increase the number of pregnant people comfortable with ordering misoprostol online.	Stakeholders note this approach is fundamentally limited in size and scope.	Recommend.
Promoting misoprostol alone for abortion, particularly through telemedicine.	This strategy could expand access to medication abortion and lower its cost.	Stakeholders are deeply split on whether this strategy represents an additional choice for patients or substandard care.	Neither recommend nor discourage.
Exploring expansion of Arthotec, a combined NSAID/misoprostol medicine.	This strategy has unclear potential, due in large part to uncertainty regarding implementation.	Stakeholders express concerns regarding risk of overdosing on the NSAID and express uncertainty about the strategy overall.	Neither recommend nor discourage.
Improving education about misoprostol as a drug to prevent and treat ulcers.	This strategy has low potential because clinicians are unlikely to increase prescriptions for ulcer prevention.	Stakeholders believe that this will not expand access to misoprostol.	Discourage.
Approaching the FDA for either a black box “abortifacient” warning or to approve misoprostol as a stand-alone abortifacient.	These strategies are unlikely to improve access to misoprostol even if successfully implemented.	Stakeholders strongly caution that these strategies could open up the possibility that the FDA moves to restrict access to the medicine.	Discourage.
Working to change the standard of care for miscarriage management or therapeutic abortion in cases of prior use of misoprostol.	This strategy is unlikely to improve access to misoprostol given clinicians' wide latitude in managing miscarriage and participating in abortion.	While stakeholders are mixed, many believe this strategy will not work and will result in pregnant people being punished by clinicians or other authorities.	Discourage.

II. MISOPROSTOL: BACKGROUND, LEGALITY, AND BARRIERS TO EXPANDED ACCESS

A. WHY FOCUS ON MISOPROSTOL ALONE?

The vast majority of current efforts to increase access to medication abortion in the US focus on the “gold standard” of medication abortion, or protocols which rely on both mifepristone and misoprostol. There have been strong reasons for this prioritization: the combination has been extensively documented as being more effective than misoprostol alone,⁶ and the combination is explicitly approved for medication abortion by the FDA while misoprostol alone protocols are not.⁷ In addition, because approval of mifepristone was highly politicized due to the medicine’s sole indication as an abortifacient,⁸ mifepristone carries additional regulatory restrictions from the FDA called REMS,⁹ and as a result its distribution is more restricted than misoprostol. Given the constraints on access to mifepristone, reducing regulations on this medicine has been a key priority for advocates working to increase access to medication abortion.

Though the lack of a specific focus on the use of misoprostol alone has been understandable, it is important to note that misoprostol works quite well to induce abortion without mifepristone.¹⁰ Extensive peer reviewed research documents that misoprostol alone is at least 75-90% effective at inducing uterine contractions and expelling the contents of the uterus through 12 weeks after a last menstrual period (LMP).¹¹ Moreover, more recent research suggests that misoprostol alone may show efficacy closer to that of the combination protocol when repeat doses are given until an abortion is completed.¹² Misoprostol is relatively cheap, available worldwide, and is used for a variety of indications beyond abortion.¹³ Unlike

⁶ See for example, M. Gatter, K. Cleland, D.L. Nucatola, *Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days*, Contraception 91, 269-273 (2015).

⁷ Jennifer Templeton Dunn et al, *Abortion in California: A Medical-Legal Handbook*, Abortion in California, 23 (2012) <http://californiaabortionlaw.com/wp/wp-content/uploads/2012/03/AIC-Handbook1.pdf>.

⁸ K. E. Simmonds, M. W. Beal, and M.K. Eagen-Torkko, *Updates to the US Food and Drug Administration Regulations for Mifepristone: Implications for Clinical Practice and Access to Abortion*. Journal of Midwifery & Women's Health, 62: 348, 352 (2017); *Mifeprex Label* (accessed Dec 10, 2018), https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/020687s010-lbl.pdf.

⁹ *FDA Basics Webinar: a Brief Overview of Risk Evaluation and Mitigation Strategies*, (accessed on Dec 10, 2018), <https://www.fda.gov/aboutfda/transparency/basics/ucm325201.htm>.

¹⁰ See *Safe abortion: technical and policy guidance for health systems*. World Health Organization, 4 (2012), http://apps.who.int/iris/bitstream/handle/10665/70914/9789241548434_eng.pdf?sequence=1.

¹¹ *Id.*

¹² A. M. Foster, G. Arnott, M. Hobstetter, *Community-based distribution of misoprostol for early abortion: Evaluation of a program along the Thailand-Burma border*, Contraception 96, 242–247 (2017); also Researcher 2, Stakeholder Interview (2018). (Full disclosure, Dr. Foster is a colleague of the author at Cambridge Reproductive Health Consultants.)

¹³ *Cytotec*, GoodRX.com (accessed Aug 1, 2018) <https://www.goodrx.com/cytotec>; Rebecca Allen and Barbara M. O'Brien, *Uses of Misoprostol in Obstetrics and Gynecology*, 2 Reviews in Obstetrics & Gynecology 159, 165 (2009).

mifepristone, misoprostol has no additional FDA restrictions beyond its status as a prescription drug.¹⁴

In legally restricted and low resource settings where safe, legal, clinic-based abortion is inaccessible, misoprostol alone is, without a doubt, the best practical option for pregnant people to induce pregnancy loss. Nothing else provides close to the same level of efficacy and safety; there is no other reasonable option for widespread, safe, self-managed abortion in restricted or illegal settings if misoprostol becomes difficult or impossible for pregnant people to obtain. Ensuring that pregnant people can obtain misoprostol when they need it may well be the linchpin of ensuring access to safe abortion in the future if and when abortion rights in the US are further restricted by de facto or de jure bans in many states.

Misoprostol is fundamentally important as a harm reduction tool in restricted and illegal settings. In addition, widespread access to misoprostol may have the potential to transform the broader cultural and legal context of abortion in the US. For more than five decades, advocacy for safe, legal abortion has rested on the assumption that ensuring access to abortion procedures provided by qualified clinicians is a necessary but insufficient condition for ensuring that individuals can safely control their own fertility. Historically, in the absence of access to qualified clinicians who could provide legally sanctioned procedures, a significant number of people seeking to induce pregnancy loss took matters into their own hands and relied on poisons, blunt force trauma, or insertion of sharp objects into the cervix to end pregnancies, with resulting risks of morbidity and mortality. But widespread, normalized access to misoprostol could fundamentally shift this underlying assumption.

With access to misoprostol, individuals can safely and effectively take matters into their own hands. With access to misoprostol, pregnant people do not need to brave the gauntlets of protestors at clinics, nor submit to recitations of inaccurate information about disproven health risks from abortion in order to ensure that they are no longer pregnant. Instead, with the technological advance of misoprostol, pregnant people can safely induce abortion at home, outside of a clinical setting. This democratization of safe abortion could radically shift the cultural and legal landscape around abortion by both normalizing the use of pills to induce pregnancy loss, and by moving fertility control out of the public view and into the privacy of the home – a more protected space for personal actions under the Constitution.

Researchers and advocates already suspect that women in the United States are beginning to follow the global trend of self-managed abortion using misoprostol or the mifepristone/misoprostol combination.¹⁵ In the absence of a profound, positive change in access to and costs associated with clinical abortion, if people can access misoprostol this trend

¹⁴Cyctotec (misoprostol), Food and Drug Administration, https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/19268s1r037.pdf; *Approved Risk Evaluation and Mitigation Strategies (REMS)*, Food and Drug Administration, <https://www.accessdata.fda.gov/scripts/cder/REMS/index.cfm>.

¹⁵ Physician/Researcher 1, *Stakeholder Interview* (2018); Physician/Researcher 2, *Stakeholder Interview* (2018); Researcher 5 *Stakeholder Interview* (2018).

is likely to continue as information about self-managed medication abortion spreads. If home use of misoprostol becomes common, the legal landscape around abortion may transform such that the key question no longer will be whether and how to regulate clinicians who have the skills to perform abortion procedures, but whether or not society will prosecute individuals who are experiencing heavy menstrual periods, miscarrying, or going into early labor. Widespread uptake of misoprostol at home has the potential to make self-managed fertility control so commonplace and ubiquitous that self-managed pregnancy loss will become, quite simply, too big to fail.

Sometimes law drives access to fundamental rights and the expression of those rights, shifting culture and empowering individuals. But at other times, such as when groups of Americans launched sit-ins at lunch counters, or fought for the right to vote, or insisted on living LGBT love publicly, individual actions, writ large, have changed culture and opened up space for accessing fundamental rights. Widespread use of misoprostol by individuals who are pregnant or at risk of pregnancy has the potential to be the kind of action that shifts access to the right to abortion in a similar way, democratizing abortion by normalizing and privatizing reproductive health decisions, changing the legal battleground around reproductive healthcare in the US.

B. BACKGROUND

Misoprostol was first approved in the US in 1988, for the prevention and treatment of gastric and duodenal ulcers.^{16,17} Misoprostol is sold in the US as Cytotec by GD Searle & Co,¹⁸ and by Pfizer Pharmaceuticals as Arthrotec, in which misoprostol is combined with an NSAID to treat arthritis and rheumatoid arthritis pain and prevent NSAID-induced ulcers.¹⁹ In the US the medicine is also sold as a generic drug by several companies, including Ivax Sub Teva Pharms and Novel Labs.²⁰

Misoprostol is inconsistently labeled in the US. The medicine carries warnings that it should not be given to pregnant women because it increases the risk of abortion, premature birth, and birth defects.²¹ But it is approved by the FDA for use with mifepristone for medication abortion.²² This inconsistency in labeling resulted from political considerations related to religious objections to abortion on the part of a key executive at GD Searle & Co. when

¹⁶ See *Cytotec (misoprostol)*, Drugs.com (accessed October 3, 2018), <https://www.drugs.com/availability/generic-cytotec.html>.

¹⁷ See *Cytotec (misoprostol)*, Food and Drug Administration, *supra*, at 6; *Arthrotec (diclofenac sodium/misoprostol) Tablets*, Food and Drug Administration, 6, https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020607s016lbl.pdf (Note: the misoprostol in Arthrotec is used to prevent ulcers that might otherwise be caused by the diclofenac sodium that treats osteoarthritis/rheumatoid arthritis. NSAIDs are also used to treat other pain such as menstrual cramps.); See also *Misoprostol*, Pharmacodia.com (accessed October 3, 2018), <https://www.pharmacodia.com/yaodu/html/v1/chemicals/2f58929950c0c51f338ad911e492ec8e.html>.

¹⁸ *Cytotec*, GoodRX.com, *supra*.

¹⁹ *Arthrotec*, GoodRX.com (accessed Aug 1, 2018) <https://www.goodrx.com/arthrotec>.

²⁰ *Cytotec (misoprostol)*, Drugs.com, *supra*.

²¹ See, e.g., *Cytotec (misoprostol)*, Food and Drug Administration, *supra*, at 1.

²² Dunn, *supra*, at 23.

mifepristone and the combined mifepristone/misoprostol medication abortion regimen were approved by the FDA.²³ Misoprostol carries a warning of possible birth defects when used by pregnant women whose pregnancies continue,²⁴ and indeed the possibility that misoprostol may be a mini-teratogen²⁵ when used at a suboptimal dose with resulting ongoing pregnancy is likely.²⁶

Misoprostol is widely available in US pharmacies²⁷ and has a shelf life of 18-36 months.²⁸ The medicine is inexpensive worldwide, and even in the US it is relatively cheap with a final consumer price of \$6-\$24 for 4 tablets.²⁹ Although several stakeholders reported a belief that a barrier to Arthrotec access is its expense, online research indicates it is similarly priced.³⁰

Globally, misoprostol is used widely for a number of gynecological indications, including the prevention and treatment of post-partum hemorrhage (PPH), cervical ripening, induction of labor, miscarriage management, abortion and MR.³¹ In the US it is commonly used off-label for cervical ripening, induction of labor, miscarriage management, and prevention or initial treatment of PPH at home births.³²

²³ FDA Policy Expert 1, *supra*.

²⁴ See, e.g., *Cytotec (misoprostol)*, Food and Drug Administration, *supra*, at 1.

²⁵A “mini-teratogen” can be defined as an agent that causes less than 10 defects per 1,000 exposures. See Neena M. Philip, Caitlin Shannon, and Beverly Winikoff, ed., *Misoprostol and Teratogenicity: Reviewing the Evidence*, Report of a Meeting at the Population Council, 15 (May 22, 2002), <https://pdfs.semanticscholar.org/85f4/fc629e3cbd0fc384b9c8a299b851da3e540e.pdf> (accessed 10/30/18).

²⁶ FDA Policy Expert 1, *supra*; Physician/Researcher 2, *supra*; Human Development and Teratogen Expert 1, *Stakeholder Interview* (2018); Human Development and Teratogen Expert 2, *Stakeholder Interview* (2018).

²⁷ Physician/Researcher 2, *supra*.

²⁸ See *Misoprostol for Maternal Health*, Reproductive Health Supplies Coalition 1 (2013), https://www.rhsupplies.org/fileadmin/uploads/rhsc/Working_Groups/New_Underused_RH_Technologies_Caucus/Documents/Technical_Briefs/rhsc-brief-misoprostol_A4.pdf.

²⁹ *Cytotec*, GoodRX.com, *supra*.

³⁰ *Arthrotec*, GoodRX.com, *supra*.

³¹ Rebecca Allen and Barbara M. O’Brien, *Uses of Misoprostol in Obstetrics and Gynecology*, 2 *Reviews in Obstetrics & Gynecology* 159, 165 (2009); *Safe abortion: technical and policy guidance for health systems*. World Health Organization, 5 (2012), http://apps.who.int/iris/bitstream/handle/10665/70914/9789241548434_eng.pdf?sequence=1; and Dunn, *supra* at 30. But see *Misoprostol (marked as Cytotec) Information*, Food and Drug Administration (Jul 2015) <https://www.fda.gov/Drugs/DrugSafety/ucm111315.htm> (“Misoprostol is sometimes used to decrease blood loss after delivery of a baby. These uses are not approved by the FDA. No company has sent the FDA scientific proof that misoprostol is safe and effective for these uses.”), Fauzia Akhter Huda et al. *Provision of menstrual regulation with medication among pharmacies in three municipal districts of Bangladesh: a situation analysis*, 97 *Contraception* 144, 146-47 (Feb 2018), <https://doi.org/10.1016/j.contraception.2017.11.006>; See also Andil Alam et al., *Acceptability and Feasibility of Mifepristone-Misoprostol for Menstrual Regulation in Bangladesh*, *International Perspectives on Sexual and Reproductive Health*, 79-87 (Jun 2013), <https://www.guttmacher.org/journals/ipsrh/2013/07/acceptability-and-feasibility-mifepristone-misoprostol-menstrual-regulation>; M.L. Swahn et al, *Once-a-Month Treatment with a Combination of Mifepristone and the Prostaglandin Analogue Misoprostol*, *Human Reproduction*, 485-488 (Feb 1, 1999), <https://academic.oup.com/humrep/article/14/2/485/614121>.

³²Allen, *supra*, at 165.

For pregnancy termination, the World Health Organization (WHO) provides usage and dosage guidelines for misoprostol plus mifepristone for terminating pregnancies up to 9 weeks; 12 weeks; and beyond 12 weeks.³³ The WHO also provides guidelines for safe abortion using misoprostol alone in settings where mifepristone is unavailable.³⁴

C. REGULATIONS AND LEGAL RESTRICTIONS OF MISOPROSTOL

The paper's scope is limited to legal options for expanding access to misoprostol. The authors did not analyze strategies for improved access to misoprostol that involve illegal acts such as encouraging people to lie to clinicians as to the reasons they are requesting a prescription, or to purchase the medicine from a pet store as a canine ulcer prevention medicine, or to commit civil disobedience by visibly importing or ingesting misoprostol to draw attention to the drug and its use in harm reduction for self-managed abortion. While these strategies should be explored, the mandate of this research is restricted to possible ways forward which do not involve legal risk to the individuals attempting to implement them. As a result, understanding the current legal environment is an important precursor to analyzing potential avenues for change.

On a basic level, the federal government restricts access to misoprostol to those possessing a valid prescription for the medicine from a licensed clinician.³⁵ There are no additional federal government restrictions on misoprostol per se, but when used as an abortifacient, misoprostol is subject to generalized federal abortion regulations such as the Hyde Amendment.

The only direct state laws targeting misoprostol thus far are those such as Oklahoma's that would explicitly prohibit using a misoprostol alone protocol for abortion by seeking to enforce the original, FDA approved protocol for the mifepristone/misoprostol combination instead of the less risky, more comfortable updated combination protocol.³⁶ Indeed, while this paper originally sought to identify state-level legal barriers to increasing off-label indications of misoprostol, in general these do not exist.³⁷ To the extent state laws impact misoprostol usage off-label, it is because they restrict abortion in general, they restrict access to abortion medication via telemedicine, or they restrict prescriptive authority for advanced practice clinicians. Each of these potential issues is addressed below to the extent they impact potential strategies, but importantly these regulations do not limit the prescription of misoprostol for an off-label use in general.

In addition to looking at state laws around misoprostol generally, this paper also looks at two potential laboratory states, California and Oregon, and examines possible restrictions to the expansion of prescriptions of misoprostol online for the innovative indication of ensuring a state of non-pregnancy when pregnancy is suspected. Both states were chosen for their

³³ *Safe abortion: technical and policy guidance for health systems*. World Health Organization, *supra*, at 3.

³⁴ *Id.* at 4.

³⁵ See *Cytotec (misoprostol)*, Food and Drug Administration, *supra*, at 6.

³⁶ For example, see *Cline v. Okla. Coal. for Reprod. Justice*, 570 U.S. 930, 133 S. Ct. 2887 (2013).

³⁷ Physician/Researcher 1, *supra*.

progressive laws and politics related to abortion. Neither state has laws that would directly restrict the expansion of prescriptions of misoprostol for a new, off-label indication like menstrual regulation.

1) CALIFORNIA

Misoprostol use is likely to be relatively unhindered in California, where there is a friendly legal and regulatory environment. California's constitution explicitly protects a right to privacy, providing greater protections for abortion rights than the federal Constitution.³⁸ Authorized abortions are relatively unrestricted,³⁹ without the obstacles present in many states such as waiting periods or parental consent requirements.⁴⁰ While self-induced abortion violates the Health and Safety Code and Business Code requirements that abortions be provided by a health care provider, and is therefore unauthorized,⁴¹ it is not punishable so long as there was no intent to produce a live birth. Interestingly, in California, there are statutory requirements for reporting fetal death beyond 20 weeks LMP and for disposing of fetal remains (including those less than 20 weeks LMP),⁴² neither of which comply with the newer Reproductive Privacy Act.⁴³ These regulations might be used to regulate either providers or pregnant people who use misoprostol to self-manage abortion or MR, though that it is highly unlikely in the foreseeable future given California's deeply progressive majorities in the state legislature. Our legal research found no mention of MR under any of its various descriptions in CA statutes or case law.

In regard to novel indications of misoprostol, such as MR, the state generally defers to providers to determine the appropriateness of off-label uses of medications. In cases of medical malpractice, a court will look to whether the provider followed the standard of care. In assessing the reasonableness of the provider's prescription of an off-label use as it relates to standard of care, a court will look to: civil statutes,⁴⁴ community standards of

³⁸ 1 *California Forms of Pleading and Practice--Annotated* § 4.11 (2018) [citing Cal. Const., art. 1, § 1; Committee to Defend Reproductive Rights v. Myers (1981) 29 Cal. 3d 252, 261–263, 172 Cal. Rptr. 866, 625 P.2d 779; American Academy of Pediatrics v. Van de Kamp (1989) 214 Cal. App. 3d 831, 839–842, 263 Cal. Rptr. 46; § 4.15]; See also Dunn, *supra*, at xiii.

³⁹ The main regulations fall under the Reproductive Privacy Act, Cal. Health & Safety Code §§ 123460-68.

⁴⁰ Parental consent requirements declared unconstitutional under the California State Constitution in *Am. Acad. of Pediatrics v. Lungren*, 16 Cal. 4th 307 (1997).

⁴¹ Cal. Bus. & Prof. Code § 2253 (Deering 2018).

⁴² Cal. Health & Safety Code § 7054.3 (2011), (“[A] recognizable dead human fetus of less than 20 weeks uterogestation not disposed of by interment shall be disposed of by incineration.”) and Cal. Penal Code § 643 (2011) (“No person knowingly shall dispose of fetal remains in a public or private dump, refuse, or disposal site or place open to public view”).

⁴³ Cal Health & Safety § 102950 (Deering 2018).

⁴⁴ See, e.g., 1 CACI 501 (2018); 16 CCR § 1443.5 (Barclays 2018) (outlining general “standards of competent performance” for nurses); 16 CCR § 1356.6 (Barclays 2018) (specifying procedures for physicians to follow in liposuction); CACI No. 513 (2018) (specifying that provider should inform pregnant woman of fetal abnormalities).

practice,⁴⁵ robust professional literature,⁴⁶ and possibly the opinions of local colleagues, though the emphasis on local standards has decreased.⁴⁷ Medical malpractice case law protects providers who prescribe a medicine for an off-label use if they do so based on medical knowledge and with the interest of the patient in mind.⁴⁸ Clinicians' perceptions of risk as well as any actual heightened malpractice risks of off-label prescriptions are discussed in section D, below.

Without a doubt, most gynecological, off-label uses of misoprostol clearly fall within acceptable standards of care, because of robust professional literature and/or statements of professional organizations. The one exception may be MR, which may meet the standard of robust professional literature (primarily in peer-reviewed journals citing studies from Bangladesh), but is novel enough in the US that a court might view prescriptions for it as deviating from normal standard of care, especially without a clear statement from a professional organization like the American College of Obstetricians and Gynecologists (ACOG). And while both clinicians and advocates believe that a malpractice suit would be highly unlikely for a doctor who prescribes misoprostol off-label, some agree that they could see a state licensing organization revoke a doctor's license for a novel use without well-documented support from a professional organization.⁴⁹

2) OREGON

State law in Oregon is similarly supportive of abortion rights and the off-label uses of medicine. The Oregon Constitution protects the right to choose abortion to a greater extent than the U.S. Constitution, specifically protecting the right of all Oregonians to "freedom from unreasonable government intrusion into their private lives, and specifically the right of consenting individuals to obtain and use methods of contraception without

⁴⁵ Community practice or custom was the first way standard of care was established in malpractice suits historically, see Peter Moffett and Gregory More, *The Standard of Care: Legal History and Definitions: the Bad and Good News*, 12 West J Emerg Med 109 (2011). But see *Id.* at 110 ("while great weight is given to customary practices with regard to the standard of care, custom is not the definitive factor in determining negligence. In essence... what is commonly done (i.e. custom) may not be enough, and that there are some things that may not be standard, but are still reasonable for the physician to perform.").

⁴⁶ Scientific advances as outlined in textbooks or medical literature are part of ever-evolving standards of care. See Gordon L. Ohlsson, Louisell & Williams Medical Malpractice, § 8.04 (2018), citing *Smethers v. Campion*, 108 P.3d 946, 949–950 (Ct. App. 2005). For example, the Supreme Court of California reversed a lower court's dismissal of a complaint against a doctor who failed to identify battered-child syndrome, noting numerous studies on the topic over a 20-year period, see 22 Personal Injury--Actions, Defenses, Damages § 106.02 (2018) citing *Landeros v. Flood*, 551 P.2d 389, 394 (1976). The court remanded to a jury to determine whether a reasonable physician would act in accordance with these studies, see *id.* citing *Landeros v. Flood*, 551 P.2d 389, 394 (1976).

⁴⁷ Riley, Jr. and P. Aaron Basilius, *Physicians' Liability for Off-Label Prescriptions*, Hematology & Oncology News & Issues 24 (May/Jun 2007), https://www.mcguirewoods.com/news-resources/publications/health_care/Off_Label.pdf.

⁴⁸ In one instance where a provider was sued for off label Misoprostol prescription, the situation concerned use to induce labor during which the baby lost oxygen and suffered serious harm. The case ended in a \$70 million arbitration award. See *Birth Injury Case - Largest Arbitration Award in U.S. History*, AVVO, (2011), https://www.avvo.com/attorneys/80237-co-david-woodruff-1412913/legal_cases/72634.

⁴⁹ Physician/Entrepreneur, *Stakeholder Interview* (2018); Physician/Researcher 1, *supra*.

governmental interference.”⁵⁰ The state has no significant abortion restrictions as of May 1, 2018.⁵¹

Legal changes do not appear to be necessary for providers to prescribe misoprostol for MR given the liberal legal framework surrounding abortion in the state. That said, in Oregon, as in California, the lack of an accepted cultural or medical framework around ensuring a state of non-pregnancy when pregnancy is suspected could mean that providers, people at risk of pregnancy, and prosecutors may all be unsure about how to approach MR, which could open up room for unexpected legal responses.

3) MEDICAL MARIJUANA AS A MODEL FOR MISOPROSTOL EXPANSION IN LABORATORY STATES

The legalization of medical marijuana may provide an instructive example related to novel indications of misoprostol, by demonstrating what can happen by expanding legal access to a novel therapy or stigmatized medicine, and by showing examples of how clinicians can be protected from liability. Decriminalization and legalization of medical and recreational marijuana in progressive states has shifted cultural views and increased access to quality, regulated product – something that could also result from state-level expansion of misoprostol alone for either abortion or ensuring a state of non-pregnancy when pregnancy is suspected. Some states, including California and Oregon, have enshrined in law some degree of civil and criminal immunity for health care providers and dispensaries that comply with state law regarding medical marijuana.⁵² But, as with off-label prescription of misoprostol, liability for misuse or harm from prescription marijuana products likely transcends these statutory frameworks and rests on whether practices conform to medical standards of care.⁵³

In Oregon, the legislature convened a group of physicians and medical experts to develop guidelines for attending physicians to follow when recommending the medical use of marijuana.⁵⁴ Failure to abide by these requirements likely provides a strong case for malpractice liability and negligence per se.⁵⁵ In addition to guidelines issued by a professional medical organization like ACOG, a convened panel of experts who explicitly develop guidelines for either misoprostol alone abortion, or for ensuring a state of non-pregnancy when pregnancy is suspected, could also be an avenue for protecting clinicians from possible increased malpractice liability for a novel indication like MR.

⁵⁰ Or. Rev. Stat. Ann. § 435.200.

⁵¹ *State Facts About Abortion: Oregon*, Guttmacher Institute (Aug. 2018), <https://www.guttmacher.org/factsheet/state-facts-about-abortion-oregon>.

⁵² OAR 475B.483.

⁵³ See American Bar Association, Section on Health Law, Malpractice Liability and Medical Marijuana, https://www.americanbar.org/content/dam/aba/administrative/healthlaw/10_paper_3.authcheckdam.pdf.

⁵⁴ 2016 Bill Text OR D. 145.

⁵⁵ See Black’s Law Dictionary 847 (7th ed., 2000) (defining negligence per se); Law and Physician Health Law Web Site, Negligence per se (1993), at <http://biotech.law.lsu.edu/Books/lbb/x133.htm>.

D. PRACTICE AND PERCEPTION BARRIERS FOR EXPANDED OFF-LABEL PRESCRIPTIONS

Misoprostol is widely used and prescribed for off-label gynecological indications. To the extent that perceptions of liability for off-label prescriptions are barriers to writing prescriptions for misoprostol, physicians are likely to be particularly worried about increased risk of malpractice claims. Importantly, from a legal standpoint off-label usage does not implicate a heightened risk of malpractice liability per se.^{56,57} Legally, prescribing a medicine off-label does not show negligence on the part of a provider, and a claimant would need to show harm or injury from the use of the medicine.⁵⁸ Given the very low risk of serious injury or harm from use of misoprostol, that is unlikely. In addition, a malpractice claim would need to establish that the physician deviated from generally accepted standards of care.⁵⁹

There is generalized protection for clinicians around off-label prescriptions, and ways exist to create greater protections (including the creation of more professional literature, professional organization statements, and state panel recommendations). Even so, perception of liability may be a potential barrier to expanded off-label prescriptions of misoprostol for either abortion or ensuring a state of non-pregnancy when pregnancy is suspected. Stakeholders disagree as to whether or not the perception of increased risk of liability from off-label prescriptions by physicians or other clinicians is a significant barrier to increasing prescriptions of misoprostol for off-label indications, particularly for a novel indications like MR.⁶⁰ Some believe the

⁵⁶ *Id.* at 17 (“Since 1982, the FDA has acknowledged that physicians may prescribe a drug to serve any legitimate medical purpose, regardless of whether the agency has approved the drug for that use”); Laura Britton and Amy Bryant, *When Off-label is Illegal: Implications of Mandating the FDA-approved Protocol for Mifepristone-induced Abortions*, *Women’s Health Issues*, 433 (2015), (“FDA has the authority to regulate the entry of prescription drugs into the market but the FDA cannot regulate the practice of medicine, which is how off-label drug prescribing is categorized.”); Benjamin A. Hooper, *The Negative Effects of Cumulative Abortion Regulations: Why the 5th Circuit Was Wrong in Upholding Regulations on Medication Abortions (Planned Parenthood of Greater Texas Surgical Health Services v. Abbott)*, 83 U. Cin. L. Rev. 1489, 1495 (2015), (“Though the FDA approves only the on-label use of drugs, it is commonly expected that many drugs will be used off-label at the discretion of medical doctors”); *FDA Drug Bulletin* 4 (Apr. 1982); *FDA Proposed Rule*, 37 Fed. Reg. 16,503 (1972); David Kessler, *Regulating the Prescribing of Human Drugs for Nonapproved Uses Under the Food, Drug and Cosmetic Act*, 15 Harv. J. Legis. 693, 698 (1978); William S. Comanor and Jack Needleman, *The Law, Economics, and Medicine of Off-Label Prescribing*, 91 Wash. L. Rev. 119 (2016).

⁵⁷ Certainly prescribing misoprostol as an abortifacient carries potentially higher malpractice insurance costs for physicians, namely pricey “abortion riders,” that may prevent family practice clinicians in particular from offering abortions. See Christine E. Dehlendorf and Kevin Grumbach, *Medical Liability Insurance as a Barrier to the Provision of Abortion Services in Family Medicine*, Am. J. Public Health, 1770 (Oct. 2008) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2636480/>.

⁵⁸ See e.g., *Watson v. Gish*, 2011 U.S. Dist. LEXIS 58317 (N.D. Cal., 2011); James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 Food Drug L.J. 71, 81, 86 (1998).

⁵⁹ 1 Medical Malpractice § 8.04 (2018); Riley, *supra*, at 27; 1 CACI 501 (2018); Maxwell Mehlman, *Professional Power and the Standard of Care in Medicine*, 44 Ariz. St. L.J. 1165 (2012).

⁶⁰ Physician/Entrepreneur, *supra*; Physician/Researcher 1, *supra*; Provider/Researcher 1, *Stakeholder Interview* (2018).

perception of liability for off-label prescribing absolutely stops clinicians from writing prescriptions, especially for abortion, while other stakeholders think that statements around perceived risks of malpractice liability simply stand-in for actual opposition to abortion and/or fear of being involved with abortion more generally.⁶¹

One more avenue for liability for doctors for off-label prescriptions that did not come up in clinician interviews, but was raised by legal research, relates to informed consent. While off-label use does not require more robust informed consent than the common standard,⁶² medical malpractice claims related to misoprostol would likely center on live or near at-term births that result in serious complications to the person who has given birth or to their child.⁶³ Given the potential for misoprostol's mini-teratogenicity in suboptimal doses, there is a very small chance that either a doctor or a manufacturer could be sued for malpractice relating to birth defects in a baby born to a person who had unsuccessfully taken misoprostol for either abortion or MR who then went on to sustain a pregnancy until term or near-term. Though the success of such a suit would be mitigated by warnings on the misoprostol label clearly indicating its possible role in birth defects, establishing robust informed consent for any novel use could be an important part of a legal defense regarding a claim of malpractice.

For manufacturers, liability for foreseeable misuse of a drug – for instance from self-management of an abortion using misoprostol prescribed for a different indication – is much greater than that for physicians, though clear warnings mitigate manufacturer liability.⁶⁴ Even so, one possible route to *restricting* access to misoprostol would be fallout from a rare death from an attempted self-managed abortion that implicated even a claim of manufacturer liability. Extensive negative press might cause manufacturers to either pull the drug themselves or ask the FDA to more strictly limit access to misoprostol with REMS similar to those on mifepristone. Again, this is unlikely given that warnings against misuse mitigate manufacturer liability, and misoprostol has clear warnings related to potential birth defects and/or pregnancy complications and loss from use.⁶⁵

⁶¹ Physician/Entrepreneur, *supra*; Researcher 1, *Stakeholder Interview* (2018); Physician/Researcher 1, *supra*; Provider/Researcher 2, *Stakeholder Interview* (2018).

⁶² Beck, *supra*, at 86.

⁶³ See, e.g., *Jane Doe v. Unnamed Hospital*, WL 2559801 Cal. Superior (2006) (awarding a \$5 million to Baby Doe, who was born with severe hypoxic-ischemic encephalopathy after his mother was given misoprostol to induce labor, and other drugs); *Hernandez v. Sutter Med. Ctr. of Santa Rosa*, LEXIS 109633 (N.D. Cal. 2008); *Hypolite v. Columbia Dauterive Hosp.*, 968 So. 2d 239, 07-357, (La. App. 3 Cir. 2007), (in this case the court found for the defendant providers, because there was no breach of the standard of care and the patient, who experienced uterine rupture, gave informed consent, at 246-47).

⁶⁴ Kaspar J. Stoffelmayr, *Comment: Products Liability and 'Off-Label' Uses of Prescription Drugs*, 63 U. Chi. L. Rev. 275, 299 (1996).

⁶⁵ Law Professor 1, *Stakeholder Interview*, (2018); Self-Managed Abortion Advocate 1, *Stakeholder Interview* (2018).

III. POTENTIAL STRATEGIES FOR PROTECTING AND EXPANDING ACCESS TO MISOPROSTOL

A. RECOMMENDED STRATEGIES

Four strategies received overwhelmingly positive or mostly positive feedback from stakeholders. Two are highly recommended – evolving standard of care guidelines for uterine bleeding, and funding education and advocacy for the independent prescriptive authority of CNMs. A third strategy of pursuing online access to misoprostol for MR is recommended because of its enormous potential to increase access to the medicine, though there are significant questions to be answered before directly pursuing pilot projects in laboratory states. Finally, a fourth strategy is also recommended – monitoring and evaluating online, extralegal, foreign pharmacies that provide misoprostol with or without mifepristone for self-managed abortions. Each recommended strategy is explored in turn.

1) EVOLVING THE STANDARD OF CARE FOR UTERINE BLEEDING EVENTS

This is the only proposed strategy that can be directly attributed to an individual stakeholder. Dr. Lisa Harris at the University of Michigan first suggested changing the standard of care around any uterine bleeding event – miscarriage, abortion, birth – such that caregivers provide women with a prescription for misoprostol, or actual misoprostol tablets, to use at home to treat potential excessive bleeding, thus ensuring that women have the medication or a prescription for it on hand. According to Professor Harris, in some institutions, women in the past routinely were sent home after birth or abortion with a prescription for methergine, an ergot alkaloid commonly used to prevent or treat excessive bleeding after childbirth, miscarriage or abortion.⁶⁶ But due to increased costs and supply chain issues for hospitals, as well as contraindications to its use in women with hypertension or some other medical conditions, this standard of care gradually fell out of favor. As a general practice, women currently are not sent home with any medicines to treat delayed excessive bleeding. While there are anecdotal reports that some abortion clinics send post-abortion patients home with 800mcg of misoprostol,⁶⁷ it is not currently standard of care to do so after any uterine event.

There is widespread stakeholder support for increasing the availability of misoprostol by changing standard of care for follow up of uterine events to include either prescriptions for misoprostol or, even better, actual misoprostol tablets to take as-needed for excessive bleeding at home.⁶⁸ Only one stakeholder opposes the idea, due to a belief that excessive bleeding is rare enough that doctors are unlikely to prescribe any medicine prophylactically to treat it.⁶⁹ But another physician researcher who specifically

⁶⁶ Provider/Researcher 2, *supra*.

⁶⁷ *Id.*

⁶⁸ Provider/Researcher 1, *supra*; Researcher 4, *Stakeholder Interview* (2018); Provider/Researcher 2, *supra*; Law Professor 2, *Stakeholder Interview* (2018); Physician/Researcher 2, *supra*.

⁶⁹ Provider/Researcher 1, *supra*.

works with low-access communities strongly disagrees, and contends that increases in maternal mortality in African American communities strongly argue for more measures to prevent excessive, delayed bleeding, especially after birth.⁷⁰ All other researchers and clinicians surveyed respond positively to the idea of this general strategy.

Several approaches are suggested by stakeholders, including provision of a prescription for 800mcg or 1600mcg of misoprostol, or a refillable prescription for 800mcg x 3 doses. The only caveat supportive stakeholders raise is whether an individual prescription would be sufficient to help women self-manage a later abortion,⁷¹ and this is answered best by the refillable prescription of 800mcg x 3, which has the clearest support from clinicians and researchers. Direct provision of 2400mcg misoprostol would be an even better option as this would ensure that patients have the pills on-hand in the event of excessive bleeding; this is especially important for individuals who live far away from either clinics or hospitals or who live in regions where pharmacists are known to raise conscience-based objections to filling prescriptions of misoprostol for reproductive indications.

This strategy has the potential to increase availability of misoprostol on-hand for people at risk of pregnancy, and it allows for the possibility that physicians can offer a harm reduction approach to abortion care in restricted settings, while still meeting the requirements of the profession and only prescribing a medicine for a valid need.

While clinicians and researchers reject any projects that involve splashy, public campaigns as being counter-productive and engendering anti-abortion backlash, stakeholders propose two main ways for moving this idea forward. First, there is agreement that quietly discussing the idea in residency training programs and informally at professional meetings will be excellent initial steps. Second, for broader national acceptance, key professional organizations like ACOG may need to be persuaded to issue statements of support for the standard of care change, though it is unclear if this will be possible. Given that many individuals manage miscarriages with family physicians and in emergency rooms, and manage childbirth with family physicians as well as obstetricians, other professional organizations such as the American Academy of Family Physicians and the American Academy of Emergency Medicine may also be important to approach. One stakeholder who works with low-access communities persuasively argues that proposals for standard of care change proposals will benefit from research on delayed bleeding after uterine events, and that the standard of care changes should be rooted in arguments for access to care, especially for rural populations or other populations that may have difficulty quickly reaching responsive emergency care in the event of delayed, excessive bleeding.⁷² Researchers are clear

⁷⁰ Provider/Researcher 3, *Stakeholder Interview* (2018).

⁷¹ Researcher 6, *Stakeholder Interview* (2018); Physician/Researcher 2, *supra*.

⁷² Provider/Researcher 3, *supra*.

that harm reduction arguments regarding extralegal and/or self-managed abortion should not be explicitly broached.⁷³

This paper recommends that funders and advocates explore the possibility of funding and coordinating informal outreach among supportive physicians to peers and residents, abortion clinics, and professional groups to gradually change practice around misoprostol and uterine events. In addition, research on delayed, excessive bleeding, and the potential benefit of misoprostol to treat it, would be supportive and an important way to build momentum at professional organizations, as would outreach to leading influencers at ACOG and other professional medical organizations.

2) EXPANDING EDUCATION AND ENSURING INDEPENDENT PRESCRIPTIVE AUTHORITY FOR CERTIFIED NURSE MIDWIVES

Key stakeholders agree that midwives are important actors for expanding access to misoprostol.⁷⁴ Globally, midwives are often critical providers who ensure expanded access to safe abortion in restricted or illegal settings, and there is no reason to expect this will be different in the US if clinic-based, legal abortion is further restricted. As a caveat, at least one stakeholder mentions that midwives still account for only a small percentage of US births, though even this potential criticism was met with the acknowledgement that midwives' impact on self-management of abortion in restricted settings is often disproportionate to their numbers overall.⁷⁵

Academic midwives interviewed for this paper agree that both Certified Professional Midwives (CPMs or "direct entry midwives") and CNMs – that is, midwives with nursing credentials, all generally have access to misoprostol.⁷⁶ While some CPMs may not be authorized to carry misoprostol for the purposes of preventing or treating PPH at homebirths, it is widely acknowledged that essentially all of them do carry the medicine because of its lifesaving benefits.⁷⁷ As far as academic midwifery stakeholders know, there are generally no specific reporting requirements on the use of misoprostol during homebirths,⁷⁸ though this was widely suspected as a barrier to broader access to misoprostol by stakeholders who are not deeply familiar with midwifery education and practice.⁷⁹

⁷³ Physician/Researcher 2, *supra*.

⁷⁴ Self-Managed Abortion Advocate 4, *Stakeholder Interview* (2018); Academic Midwife 1, *Stakeholder Interview* (2018); Academic Midwife 2, *Stakeholder Interview* (2018); Physician/Researcher 2, *supra*.

⁷⁵ Self-Managed Abortion Advocate 1, *supra*.

⁷⁶ Academic Midwife 1, *supra*; Academic Midwife 2, *supra*.

⁷⁷ *Id.*

⁷⁸ *Id.*

⁷⁹ Self-Managed Abortion Advocate 1, *supra*; Self-Managed Abortion Advocate 2, *Stakeholder Interview* (2018); Self-Managed Abortion Advocate 3, *Stakeholder Interview* (2018).

Academic midwives caution that knowledge of misoprostol outside of its uses for prevention and treatment of PPH is low among all midwives, including CNMs.⁸⁰ This is in part due to the history of politics within the main US midwifery professional body, the American College of Nurse Midwives (ACNM). Modern midwifery in the US has been strongly associated with fundamentalist Christianity and has often been stridently opposed to midwife involvement in abortion.⁸¹ Though ACNM put forward a new statement on abortion in March of 2018 that is remarkably supportive (it includes language opposing restrictions, and supporting abortion provision as well as conscientious refusal),⁸² in practice educators find that it remains a roadblock to increased education.

Stakeholders agree that continuing medical education units that educate CNMs on misoprostol as a stand-alone or combination abortifacient and/or as an abortifacient in low resource settings likely will continue to be rejected by ACNM.⁸³ As a result, there is a clear need for stand-alone educational materials related to misoprostol for both CNM students and for CNMs seeking continuing education.

There are also ongoing issues with prescriptive authority for CNMs. According to midwifery academics, CNMs in forty-five states currently have the ability to prescribe misoprostol (though many states have restrictions on their ability to perform abortions either using procedures or medications).⁸⁴ However, in almost half of those states CNMs' prescriptions must be supervised by a physician, and in some states CNMs must have a collaborative relationship with a physician such that they are writing prescriptions directly under that physician's license.⁸⁵ Stakeholders caution that such physician supervision has the potential to limit CNMs' future ability to prescribe misoprostol for gynecological uses, especially if the medicine becomes more of a flash point regarding self-managed abortion.⁸⁶ In addition, CNMs' practical ability to prescribe misoprostol can be impacted by conflicting pharmacy regulations that limit fulfillment of prescriptions in pharmacies to those written by physicians, making misoprostol access in hospitals easier for midwives than in outpatient settings.⁸⁷ In states where CNMs do not have unlimited prescriptive authority, they are generally constrained to prescribing drugs on state formulary lists.⁸⁸ Academic midwife stakeholders report that because misoprostol is on the WHO essential drug list, they believe misoprostol is currently on every state formulary list. However, at least one

⁸⁰ Academic Midwife 1, *supra*; Academic Midwife 2, *supra*.

⁸¹ *Id.*

⁸² See *Position Statement: Midwives as Abortion Providers*, (accessed on November 30, 2018), <http://www.midwife.org/acnm/files/acnmlibrarydata/uploadfilename/00000000314/ps-midwives-as-abortion-providers-final-19-mar-18.pdf>.

⁸³ Academic Midwife 1, *supra*; Academic Midwife 2, *supra*.

⁸⁴ Academic Midwife 2, *supra*.

⁸⁵ *Id.*

⁸⁶ *Id.*

⁸⁷ *Id.*

⁸⁸ *Id.*, Academic Midwife 1, *supra*.

stakeholder cautions that these lists are created by appointed, unelected commissions that report only to governors, and as such they are potential choke points should an emboldened, anti-abortion group decide to target access to misoprostol.⁸⁹

The essential takeaways in terms of regulation of midwives is that access to misoprostol is currently widespread, but has potential points of restriction including physician supervision and formulary lists that could easily be used to limit future accessibility. Supporting independent licensure for prescriptions and keeping a close eye on unelected commissions that determine formulary lists are both important for ensuring continued access to this critical drug within the nurse midwife community.

This paper recommends that funders and advocates work with academic midwives to create stand-alone online and classroom curriculum units on misoprostol for nurse midwifery programs and, even more importantly, for continuing medical education. Professors in CNM programs who have interest should be provided with curricula on misoprostol that includes power points, online resources, hard copies of handouts and notes. Topics should include miscarriage management and either focus on use of misoprostol as a safe abortifacient in low resource and legally restricted settings, or contain add-in components that specifically address abortion with misoprostol alone and with mifepristone in the US.⁹⁰ Continuing medical education units should also be developed. These courses could be certified by a state body as opposed to the ACNM for easier approval. Ideally these continuing medical education units will be available online, for free, and cover gynecological uses of misoprostol including abortion, as well as information on uses of misoprostol in low-resource settings, which may be a more politically palatable entry point for some midwives.⁹¹

In addition, this paper strongly recommends that funders and advocates assess current political efforts to establish independent licensure and prescriptive authority for CNMs, in conjunction with other advanced practice clinicians, and support efforts to move this work forward. Efforts should concentrate on arguments unrelated to abortion, including the trustworthiness of nurses and the shortage of primary care providers, particularly in rural states.⁹² Finally, it would be ideal for an organization already working to ensure access to methods of self-managed abortion, like the SIA Legal Team, to routinely check state commissions that establish formulary lists of medicines for potential changes and new restrictions related to misoprostol.

A third strategy receives qualified support from stakeholders, but it is included on the list of recommended strategies because if successful, it has the potential to dramatically expand prescriptions of and access to misoprostol.

⁸⁹ Academic Midwife 2, *supra*.

⁹⁰ *Id.*

⁹¹ *Id.*; Academic Midwife 1, *supra*.

⁹² Academic Midwife 2, *supra*.

3) PILOTING ONLINE PROVISION OF MISOPROSTOL IN PROGRESSIVE LABORATORY STATES FOR A NOVEL INDICATION – TO ENSURE A STATE OF NON-PREGNANCY WHEN ONE IS SUSPECTED BUT NOT CONFIRMED

Access to prescriptions of misoprostol, with or without mifepristone, for people who suspect but have not confirmed a pregnancy (either when their menses are already late or in anticipation of possible late menses), could vastly expand the scope of access to misoprostol for a legitimate, valid medical indication. Online provision of misoprostol in progressive laboratory states for this indication has particular promise since the expansion of online prescriptions could radically open up access to misoprostol with the support of only a small number of prescribing clinicians. But significant questions – both philosophical and practical – need to be answered before a pilot project can be undertaken.

The various frameworks around ensuring a state of non-pregnancy when pregnancy is suspected may be new to readers, so a quick introduction may be useful. Regulating menses, or MR, is both a traditional Anglo-American framework for fertility control and a modern framework for ensuring a state of non-pregnancy and pregnancy loss promoted in other countries.⁹³ In both historical and contemporary contexts, MR provides time and space for potentially pregnant people to ensure they are not pregnant, without first confirming the existence of a pregnancy. Consequently, the intervention is quintessentially liminal in that it lies somewhere between pregnancy prevention (contraception) and pregnancy termination (abortion).

Today, people in the US who suspect a pregnancy generally perform a urine pregnancy test, often at home, on or beyond 28 days LMP. These pregnancy tests are typically followed by in-clinic confirmation, through urine tests, bloodwork, and/or ultrasound, processes that often begin in the 35-42 day LMP window. Although these timeframes may appear to leave very little possibility of a gray area between suspected and established pregnancies, researchers and advocates understand that patients' lived realities often do not conform neatly to idealized medical and scientific timelines. Indeed, people who suspect they are pregnant but do not want to be may deliberately delay taking an at-home pregnancy test in the hope that their periods are simply late or that if a pregnancy is developing, they will miscarry early.⁹⁴ Recent research conducted by Gynuity Health Projects suggests that a sizeable proportion of women presenting for a pregnancy confirmation in clinics would be interested in a "missed period pill" that would bring on menses, including 70% of those who reported they would not want to be pregnant.⁹⁵

⁹³ The lancet, *Menstrual regulations*, The Lancet, 7966 (307): 947 (1976).

⁹⁴ J. Wessel, U. Buscher, *Denial of pregnancy: Population based study*, BMJ: British Medical Journal, 7335:324 (2002).

⁹⁵ W. R. Sheldon, M. Tarnagada, E. Talmont, L. Harris, K. Starr, B. Winikoff, *Is there a role for medical menstrual regulation in the US? Assess potential interest among women in New Jersey and Michigan*, Poster presentation, National Abortion Federal Annual Meeting, (April, 2018).

Overall, stakeholders are generally either curious or supportive about exploring efforts to use misoprostol for MR, though they disagree about whether the medicine should be prescribed alone or in combination with mifepristone.⁹⁶ To the extent stakeholders express philosophical concerns, the first is that people “should” know that they are inducing an abortion as opposed to operating within a more uncertain context in which they *might* be inducing pregnancy loss.⁹⁷ While descriptions of MR for potentially pregnant people must clearly articulate that if a patient *is* pregnant, MR will end a pregnancy, the worry that patients *should* know and make a definitive choice to induce pregnancy loss is, upon deeper questioning, tied to concern that MR could increase stigma around abortion, a more broadly expressed worry among stakeholders. Though this concern is rooted in real and deep-seated stigma around abortion in the US, it is unlikely that reproductive health advocates working to promote MR would ever frame it as oppositional to abortion, or advocate for it in ways that would serve to further stigmatize the choice to end an established pregnancy. And there is no chance that the current Pro-Life movement would encourage Americans to adopt fertility control frameworks like MR while drawing a line at abortion, given that anti-abortion advocates oppose even contraceptives like IUDs as abortion by another name. Thus, increased stigma is an unlikely outcome of advocacy for this novel indication.

Other concerns from stakeholders include whether support for an early intervention would further medicalize pregnancy, and whether advocacy for medicines that carry a low but real risk of excessive bleeding is appropriate, especially when so many very early pregnancies are lost naturally.⁹⁸ Other stakeholders respond that MR could actually contribute to de-medicalizing early pregnancy by embracing liminality and ideally at-home use of medications for pregnancy loss. Finally, one researcher wondered if patients would have more difficulty predicting their next ovulation if they used misoprostol for MR regularly.⁹⁹ Years ago this was a concern around the use of emergency contraception (EC) as well, one which has not been proven to be problematic. It is unlikely that misoprostol use would have significantly different impacts.

In addition to these overarching questions, more research needs to be undertaken before online provision of misoprostol in this liminal frame can be responsibly piloted. Key questions to answer include how early current medication abortion protocols can be effectively used. A recent, unpublished scoping review finds that there is strong evidence that medication abortion regimens work well by day 35 LMP, but that very

⁹⁶ Law Professor 1, *supra*; Medication Abortion Advocate 3, *Stakeholder Interview* (2018); Provider/Researcher 1, *supra*; Researcher 1, *supra*; Physician/Researcher 1, *supra*; Researcher 6, *supra*; Law Professor 2, *supra*; Researcher 7, *Stakeholder Interview* (2018); Physician/Researcher 2, *supra*.

⁹⁷ Physician/Researcher 1, *supra*.

⁹⁸ Academic Midwife 2, *supra*.

⁹⁹ Physician/Researcher 1, *supra*.

little data exists earlier.¹⁰⁰ Some researchers express doubt about whether the combination protocol of mifepristone and misoprostol or misoprostol alone will work well on or just after day 28 LMP.¹⁰¹ In contrast, three recent studies from China indicate strong probabilities that the medicines may work earlier than day 35 LMP, and at least one researcher who has worked with prostaglandins for over four decades believes strongly that there is no reason to question efficacy rates when menses are even just one or two days late.¹⁰² A number of stakeholders support a clinical trial, but there is disagreement on whether or how an effective trial could be designed.¹⁰³ Others suggest simply recommending potentially pregnant people wait to take the medicines at or beyond day 35 LMP.¹⁰⁴

Another outstanding question is the efficacy needed for the intervention to be acceptable for potentially pregnant people and clinicians, who may have very different perceptions of how well the intervention would need to work to be useful. We do not know whether or not potentially pregnant people would be willing to take repeat doses of misoprostol until the medicine works, something that would likely dramatically improve overall efficacy rates.¹⁰⁵

We also still need to understand what frames resonate with potentially pregnant people to describe intervening in this this liminal period. Before creating an online model for provision of misoprostol without a positive pregnancy test, qualitative research will be helpful to understand which frames, if any, resonate with potential users. And finally, there are limited but real questions around standard of care and informed consent related to both actual and perceived risk for clinicians. Would advocates want to seek letters of support for standards of care from a major medical organization like ACOG before moving forward with large scale provision in a progressive state? Or is current, peer reviewed research sufficiently protective? Would rigorous informed consent be enough to limit liability regarding the potential risk of maintaining an ongoing pregnancy in this context? And finally, is there a significant chance that pursuing this novel indication might spur the FDA to respond and restrict the medicine in some form?

Making misoprostol widely available for MR (or other theoretical frames that ensure a state of non-pregnancy without a positive pregnancy test), through online prescription in one or more progressive states, especially one as large as California or as protective of reproductive choices as Oregon, could dramatically shift access to misoprostol by making the medicine far easier to obtain in some areas of the country. Such a strategy could also shift culture toward normalizing at-home use of medications to ensure a state of non-pregnancy or to end an established pregnancy. It could also help re-privatize

¹⁰⁰ Physician/Researcher 2, *supra*.

¹⁰¹ *Id.*

¹⁰² *Id.*

¹⁰³ *Id.*, Physician/Researcher 3, *Stakeholder Interview* (2018).

¹⁰⁴ Researcher 2, *supra*.

¹⁰⁵ Physician/Researcher 2, *supra*.

fertility control, including induction of miscarriage and abortion, and thus change the legal landscape of abortion rights. Such expansion might also shift culture in the same way that state-based legalization of medical marijuana and gay marriage led the expansion of access to a drug or civil right, and in so doing contribute to national changes in acceptance and normalization.

Given these potential outcomes, this paper recommends moving forward with research on efficacy, on framing, and on legal protections to explore the possibility of establishing online provision of misoprostol for MR, either with or without mifepristone. Work could also begin on the creation of an advisory board of experts and/or the creation of state coalitions in laboratory states like California and Oregon to build support for moving forward with studies and pilot projects.

One further strategy receives substantial stakeholder support and could have limited but positive impact on misoprostol access – engaging in ongoing quality assurance work related to online foreign pharmacies.

4) SUPPORTING ONGOING QUALITY ASSURANCE WORK RELATED TO ONLINE FOREIGN PHARMACIES

Early on in the process of stakeholder interviews, a researcher mentioned her belief that the best way to ensure a high-quality supply of misoprostol would be to support foreign-based, online pharmacies that currently supply both misoprostol and, more recently, the mifepristone/misoprostol combination.¹⁰⁶ This researcher suggests support could include regularly testing product coming into the US from these pharmacies for quality, and maintaining an online site to rate pharmacies for cost, shipping, and quality.¹⁰⁷ The site could also provide consumer education around legal liability and risks. The researcher further advocates for communicating with pharmacies about their shipping protocols so as to better ensure that medicines arrive intact.¹⁰⁸

Other stakeholders express mixed reactions to this idea, with some agreeing it would be useful,¹⁰⁹ including one researcher who had recently surveyed women and found that they easily located online pharmacies but were deeply skeptical that they would receive quality medicine.¹¹⁰ Other researchers and advocates question the strategy, noting its overall impact is at best limited¹¹¹ and that it doesn't fully address what is anticipated to be a very large public health problem if safe, legal abortion becomes even more difficult to procure in many areas of the US.¹¹²

¹⁰⁶ Physician/Researcher 1, *supra*.

¹⁰⁷ Medication Abortion Advocate 1, *Stakeholder Interview* (2018); Medication Abortion Advocate 2, *Stakeholder Interview* (2018).

¹⁰⁸ Physician/Researcher 1, *supra*.

¹⁰⁹ Researcher 1, *supra*.

¹¹⁰ *Id.*; Researcher 1, *supra*.

¹¹¹ Researcher 6, *supra*; Provider/Researcher 2, *supra*.

¹¹² *Id.*

After extensive legal research, our team concludes that while it is a felony for an unregistered pharmacy to import medicine to the US¹¹³ and that a person who purchases a non-FDA approved version of misoprostol online which is then shipped from outside the US would technically violate federal drug import regulations,¹¹⁴ that mere possession of misoprostol without a prescription is generally not criminalized,¹¹⁵ and the DEA has suggested their enforcement efforts do not target individual consumers.¹¹⁶ We could find no evidence that rating the quality of abortion medicines available for importation to the US would itself break laws, though importing them would.

While the outcomes may be incremental, this paper recommends pursuing the strategy of funding ongoing testing and quality assurance for product coming into the US from foreign pharmacies. To ensure legality, the medicines could be ordered outside of the US. Regularly updating an online site where the pharmacies are rated and making sure the site appears prominently in online searches would have a limited but likely positive impact on pregnant people's certainty of obtaining quality medicine, and would likely carry an investment cost for funders commensurate with results. Though communicating with online pharmacies that experience breakage of pills in shipment regarding better packaging and blister packs could also have a limited but positive impact on the amount of quality misoprostol arriving in the US intact, this could potentially be viewed by a zealous prosecutor as conspiring to import pills and so is not included in recommended actions.

B. STRATEGIES NEITHER RECOMMENDED NOR DISCOURAGED

1) PROMOTING MISOPROSTOL ALONE FOR ABORTION, PARTICULARLY THROUGH TELEMEDICINE

Advocates and clinicians have had previous discussions about whether or not to support the use of misoprostol alone for abortion in the US, given that mifepristone access is more restricted, and mifepristone is significantly more expensive than misoprostol. Some advocates whose work centers on protecting access to and safety of self-managed

¹¹³See *Consumer Alert*, (accessed on October 8, 2018), https://www.deadiversion.usdoj.gov/consumer_alert.htm.

¹¹⁴ The United States Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. section 331) prohibits the interstate shipment (which includes importation) of unapproved new drugs; *also see id.*; Phil Ayers, *Comment: Prescribing a Cure for Online Pharmacies*, 72 Tenn. L. Rev. 949, 962-63 (2005), (citing Yoo at 78 and see 21 U.S.C. § 331 (2000) ("If the patient does not have a valid prescription, then the drug is considered misbranded" and the "introduction or distribution of misbranded drugs into interstate commerce violates the FDCA.")).

¹¹⁵ 6 California Criminal Defense Practice § 145.01 §§ 1(a)(1) (2018).

¹¹⁶ See Marvin A. Blumberg, *Information on Importation of Drugs Prepared by the Division of Import Operations and Policy*, Food and Drug Administration (Apr. 3, 1998),

<https://www.fda.gov/forindustry/importprogram/ucm173751.htm>; *see also People v. Duke*, No. A134692, 2012 Cal. App. Unpub. LEXIS 7453, 5-6 (Oct. 16, 2012) (case against defendant who ordered large quantity (957) of valium online from Thailand, a quantity not comparable to a woman ordering 4-8 misoprostol tablets for personal use).

abortion believe that, due to misoprostol's lower cost and better accessibility, advocating for misoprostol alone for abortion, particularly through telemedicine, is a potentially useful strategy.¹¹⁷ At least one advocate for low-access communities, particularly communities of color, also strongly believes that misoprostol alone should be an option for pregnant people considering abortion.¹¹⁸ Given the easy access to misoprostol for most physicians, as well as its lower cost, misoprostol alone abortion regimens could offer pregnant people an alternative for medication abortion that is less susceptible to possible stricter, future interpretations of the REMS in relation to provision of mifepristone outside of a clinical setting.

However, many stakeholders do not agree with a strategy of advocating for access to misoprostol alone abortion.¹¹⁹ Most of the researchers and clinicians interviewed for this paper believe that, to the extent medication abortion is formally promoted and made more available, the likelihood of increased efficacy and the clear benefits in terms of physical comfort argue persuasively for a combined misoprostol/mifepristone regimen as opposed to misoprostol alone.¹²⁰ Some of those who oppose the promotion of misoprostol alone cite ethical concerns related to advocating for a less effective option, especially for communities that are marginalized and already face barriers to access. Additionally, they note that new studies related to telemedicine options using the combination protocol are being tolerated by the FDA including Gynuity's current six-state telemedicine study and ANSIRH's upcoming study on telemedicine abortion in California, both of which demonstrate that the FDA is currently willing to let telemedicine abortion with mifepristone move forward even with the ongoing restrictions on its use and delivery as per the REMS.¹²¹

This is an area of discussion within the reproductive health and justice movements that continues to evolve. Future conversations, especially among leaders and organizations who represent marginalized and low-access communities, could help create space for those who want to explore misoprostol alone for abortion. And continuing research into misoprostol alone efficacy with repeat doses and longer timeframes may help alleviate some concerns about offering a substandard or unethical option to low access communities. Divisions are currently too deep to recommend pursuing medication abortion with misoprostol alone, while its potential for increased access makes it too important a potential strategy to discourage out of hand.

¹¹⁷ Self-Managed Abortion Advocate 1, *supra*; Provider/Researcher 3, *supra*.

¹¹⁸ Provider/Researcher 3, *supra*.

¹¹⁹ Provider/Researcher 1, *supra*; Physician/Researcher 1, *supra*; Medication Abortion Advocate 1, *supra*; Medication Abortion Advocate 2, *supra*.

¹²⁰ *Id.*

¹²¹ Researcher 2, *supra*; Researcher 4, *supra*; Provider/Researcher 1, *supra*; Physician/Researcher 1, *supra*; Reproductive Rights/Justice Legal Advocate 4, *Stakeholder Interview* (2018).

2) EXPLORING EXPANSION OF ARTHOTEC

A final strategy that received mixed responses involves investing in educating patients and clinicians about Arthotec for managing arthritis and rheumatoid arthritis pain, and/or to explore off-label uses for Arthotec for other chronic pain conditions.

Arthotec, a combination of diclofenac sodium, a prescription NSAID, combined with 200mcg of misoprostol to prevent NSAID-induced ulcers, can be taken as a daily drug. A typical three-month prescription of Arthotec has enough misoprostol to self-manage seven or eight safe, early abortions.

Stakeholders are mixed about a strategy of encouraging more Arthotec prescriptions for other chronic pain medications and/or educating arthritis patients about the drug.

While some support the idea¹²² and suggest that there is no reason to think physicians wouldn't be willing to prescribe this instead of other NSAIDs,¹²³ others note that even so, the strategy should not be pursued because there is a risk of overdosing on the NSAID component of the medicine if pregnant people use too much of the combination pill.¹²⁴ Another stakeholder responds that such concerns are overblown, because the pills can be cut apart into distinct NSAID and misoprostol segments, and overdosing on NSAIDs is actually quite difficult and would require a much higher dose than pregnant people would use to self-manage an abortion.¹²⁵ Some stakeholders are concerned that Arthotec is significantly more expensive than misoprostol alone, but this was not borne out by our research.¹²⁶

This paper declines to recommend either pursuing or discouraging this strategy. There is certainly potential in quietly studying and promoting Arthotec for chronic pain indications. More prescriptions for Arthotec would amplify the amount of misoprostol in medicine cabinets throughout the US. But this is not a straightforward approach. Certainly there is at least some risk of blowback and negative attention to self-managed abortion in general if abortion rights groups are seen as involved in patient education around an arthritis drug, and it is not clear what the actual funding strategy to move forward would be, especially within legal lines. This strategy may fit much better within a broader analysis of civil disobedience than with other above-board, legal actions that funders and organizations might take.

C. DISCOURAGED STRATEGIES

Three other strategies do not receive overall positive feedback from stakeholders, either rejected as unworkable, or too risky, or both. Each of these discouraged strategies is discussed in turn below.

¹²² Physician/Entrepreneur, *supra*; Researcher 3, *supra*; Academic Midwife 2, *supra*.

¹²³ Physician/Entrepreneur, *supra*.

¹²⁴ Physician/Researcher 1, *supra*.

¹²⁵ Academic Midwife 2, *supra*; Physician/Researcher 2, *supra*.

¹²⁶ Physician/Researcher 1, *supra*; Cytotec, GoodRX.com, *supra*; Arthrotec, GoodRX.com, *supra*.

1) IMPROVING EDUCATION ABOUT MISOPROSTOL AS A DRUG TO PREVENT AND TREAT ULCERS

As noted above, misoprostol's original, approved use in the US is for the prevention of gastric and duodenal ulcers. Like Arthotec, prescriptions for misoprostol as an ulcer prevention drug often are for daily use, and so involve large quantities of the drug over time. But with just one exception¹²⁷ stakeholders firmly reject as unworkable efforts to educate doctors around this indication for the medicine, or to educate patients about their capacity to request ulcer prevention prescriptions for misoprostol should they be at risk of developing ulcers.¹²⁸ Clinicians especially are convinced that doctors will not prescribe misoprostol when other, more efficacious drugs for ulcer prevention are now available.¹²⁹ They also note that such requests from patients, especially in large numbers, could bring attention to the medicine in ways that could lead to physician backlash or increased scrutiny.¹³⁰ As a result, this strategy is not recommended.

2) APPROACHING THE FDA FOR EITHER A BLACK BOX “ABORTIFACIENT” WARNING OR TO APPROVE MISOPROSTOL AS A STAND-ALONE ABORTIFACIENT

Approaching the FDA for changes around labeling or to approve a new indication for misoprostol are two other potential ideas not originally considered by the authors of this paper, but suggested early on in stakeholder interviews.¹³¹ Though these ideas receive some positive feedback from clinicians and researchers¹³² they were ultimately dismissed as too risky after speaking to advocates for self-managed abortion¹³³ and exploring the ideas in-depth with FDA experts who spent some or much of their careers with the administrative agency.¹³⁴

While changing the labeling of misoprostol to carry a black box warning that the medicine is an abortifacient might raise the profile of its potential for self-managed abortion, it would not by itself increase access to the medicine. Advocates suggest this strategy in part because prominent labeling of misoprostol as an abortifacient in South America was anecdotally responsible, at least in part, for its widespread uptake as a method of self-managed abortion throughout the continent. However, FDA experts caution that asking the agency to take up this labeling change could create a situation in which the agency goes further and moves to restrict the medicine, potentially by adding REMS, which could limit access to misoprostol.¹³⁵ Self-managed abortion advocates also argue that such a clear warning label could impact assumption of mens rea, the element

¹²⁷ Academic Midwife 2, *supra*.

¹²⁸ Physician/Entrepreneur, *supra*; Provider/Researcher 1, *supra*.

¹²⁹ *Id.*

¹³⁰ *Id.*

¹³¹ Researcher 3, *supra*.

¹³² Researcher 6, *supra*; Provider/Researcher 2, *supra*.

¹³³ Self-Managed Abortion Advocate 1, *supra*; Self-Managed Abortion Advocate 2, *supra*; Self-Managed Abortion Advocate 3, *supra*.

¹³⁴ FDA Policy Expert 1, *supra*.

¹³⁵ *Id.*

of intent, when women are prosecuted for self-induction.¹³⁶ Given that the misoprostol label already warns that the medicine can increase the risk of abortion, it is not clear how realistic the mens rea concern is, but it does exist.

Similarly, some stakeholders propose asking the FDA to consider registering a misoprostol alone protocol for abortion, even though it may not be as efficacious as the mifepristone/misoprostol combination.¹³⁷ The FDA does approve medicines that are less effective than other alternatives if there are compelling reasons why the new medicine or protocol would be better for some populations or in some circumstances. In general, easier access to a medicine might argue in favor of its registration for a given indication even if another regimen or medicine is more effective.¹³⁸ And while cost is not considered a persuasive argument, it may have some influence on the FDA's considerations.¹³⁹

However, stakeholders with direct FDA backgrounds strongly caution against this approach. Asking the FDA to register misoprostol alone as an abortifacient would require spending extensive political capital, and while it may raise the profile of the medicine as an abortifacient, bringing more education to potential users, it absolutely risks the FDA deciding to restrict the medicine in the same way it restricts mifepristone, with REMS. This could dramatically impact availability of misoprostol not only for abortion, but also for the wide array of important gynecological indications for which it is currently used.¹⁴⁰

Given the enormous risks of these strategies, combined with their low or unknown probability to dramatically increase access to this medicine, the authors strongly recommend avoiding new efforts to approach the FDA to change labeling or approved indications for misoprostol.

3) WORKING TO CHANGE THE STANDARD OF CARE FOR MISCARRIAGE MANAGEMENT IN CASES OF PRIOR USE OF MISOPROSTOL

Very early in the process of interviews, a legal academic pondered whether or not the assertion of prior use of misoprostol to induce a miscarriage might change physicians' treatment of a potential or ongoing miscarriage and make them more likely to actively manage it with additional misoprostol or other interventions.¹⁴¹ This is an idea that has circulated at times within the reproductive health movement more generally, especially in relation to misoprostol's potential as a mini-teratogen. If misoprostol has the potential to cause birth defects when it is used at sub-optimal doses, could assertion of

¹³⁶ Self-Managed Abortion Advocate 1, *supra*; Self-Managed Abortion Advocate 2, *supra*; Self-Managed Abortion Advocate 3, *supra*.

¹³⁷ Researcher 3, *supra*; Researcher 6, *supra*.

¹³⁸ FDA Policy Expert 2, *Stakeholder Interview* (2018).

¹³⁹ *Id.*

¹⁴⁰ *Id.*

¹⁴¹ Professor 1, *supra*.

prior use be reason enough for women to receive a therapeutic abortion or active miscarriage management?¹⁴²

Clinicians and researchers strongly disagree about whether an assertion of prior use of misoprostol would lead to different outcomes for miscarriage management, or lead to more normalization of and access to misoprostol.¹⁴³ While at least one prominent researcher believes this strategy may work, many fear the opposite effect – that assertion of prior use might lead clinicians to punish patients and withhold care. It might also create backlash around the medicine by highlighting its potential as a mini-teratogen if taken in sub-optimal doses.¹⁴⁴ Clinician researchers argue that doctors have wide latitude in choices for miscarriage management that range from watchful waiting to active management, which could include a procedure or medications like misoprostol to complete a miscarriage.¹⁴⁵ Clinician researchers generally agree that the state of a miscarriage and doctors' values around abortion would remain deciding factors in choices regarding how a miscarriage or potential miscarriage is managed, whether or not a person asserts prior misoprostol use.¹⁴⁶

Moreover, at least one researcher who has had experience conducting studies in international settings where abortion is restricted mentions that in other contexts, when women disclose prior efforts to end a pregnancy, they have been punished by clinicians more often than they have been helped.¹⁴⁷ Contrastingly, another researcher argues the strategy of disclosing misoprostol use *has* worked as an indication for therapeutic abortions in some restricted settings in South America.¹⁴⁸ And an advocate for self-managed abortion points out that at least one person in the US is currently being prosecuted after telling her physician she tried to induce an abortion by taking misoprostol.¹⁴⁹ Thus serious questions exist as to whether or not this would work for as a strategy for people to acquire misoprostol to manage a miscarriage or abortion, or to obtain an otherwise inaccessible abortion procedure.

Beyond questions of effectiveness, stakeholders express worry that exaggerating or leveraging the potential but inconclusive risks of misoprostol as a mini-teratogen would unreasonably and without scientific justification raise the profile of the medicine as something dangerous that should be restricted.¹⁵⁰ As a result, this paper concludes that the risks of attempting to change standard of care around miscarriage management

¹⁴² Physician/Researcher 2, *supra*.

¹⁴³ *Id.*; Physician/Researcher 1, *supra*; Researcher 6, *supra*.

¹⁴⁴ *Id.*

¹⁴⁵ Physician/Researcher 2, *supra*; Physician/Researcher 1, *supra*.

¹⁴⁶ *Id.*

¹⁴⁷ Researcher 6, *supra*.

¹⁴⁸ Provider/Researcher 1, *supra*.

¹⁴⁹ Self-Managed Abortion Advocate 5, *Broader Stakeholder Conversation* (2018).

¹⁵⁰ Physician/Researcher 2, *supra*.

such that assertion of prior use of misoprostol justifies either active miscarriage management with misoprostol or abortion care are higher than the potential benefits.

Although the authors discourage efforts to change the standard of care in this regard, additional research on the actual risk of suboptimal doses of misoprostol may be useful. Two researchers who have done extensive work (one for over four decades) exploring teratogenicity and human development argue for developing more clarity around the potential risks in pregnancies when misoprostol is taken but does not work as an abortifacient, either due to variation in prostaglandin receptivity or because the medicine has been ingested at a suboptimal dosage.¹⁵¹ Understanding these risks would be helpful for purposes of informed consent, as well as for advocacy and education around self-managed abortion.

Because a human study to examine these risks would be unethical, the two researchers propose a well-designed study using either rats or rabbits, both of which react to prostaglandins in analogous ways to humans, as the appropriate way to move forward.¹⁵² Such a study, which would ideally involve three groups of pregnant animals – one given doses of misoprostol that would be sufficient to induce abortion, and two groups given doses that are suboptimal, one lower than the other – and then examining fetuses half-way through gestation would be the best way to learn more about the potential impact of pregnant people taking too little misoprostol and maintaining pregnancies.¹⁵³ Such a study would likely cost around \$200,000 and take approximately six months.¹⁵⁴ It is unclear if various funders and leaders within the reproductive health and justice movements would want to explore this question, but should leaders decide to look into the issue further, this is type of study the authors recommend.

IV. CONCLUSION

Globally, misoprostol is the critical linchpin for harm reduction from unsafe abortion when clinic-based legal procedures are restricted or banned. As we look into a future where these conditions may become much more common in large parts of the US, assessing strategies for protecting and expanding access to misoprostol is one important piece of broader work to ensure access to safe abortion. A number of ideas, including changing the standard of care around uterine bleeding events, educating and supporting CNMs, exploring the possibility of prescriptions for MR, and evaluating products from online foreign pharmacies all hold potential to increase access to this life-saving medicine. At least two other ideas - exploring advocacy of misoprostol alone abortion regimens and thinking through possibilities for expanding education and indications for Arthotec, may merit further work and should not be actively discouraged.

¹⁵¹ Human Development and Teratogen Expert 1, *supra*; Human Development and Teratogen Expert 2, *supra*.

¹⁵² *Id.*

¹⁵³ *Id.*

¹⁵⁴ *Id.*

Three other ideas currently circulating are best discouraged, due to their lack of impact or risk of harm.

Ensuring access to misoprostol is a proactive, constructive strategy that lays the groundwork for a safer future for pregnant people in the US. Advocates for abortion rights often have been forced to play defense as state legislatures have enacted new, increasingly creative laws that limit access to reproductive healthcare. Expanding access to misoprostol represents a positive path forward for reproductive health and justice leaders that could help ensure options for safe abortion in a more difficult future, and give individuals safe options to ensure a state of non-pregnancy or induce pregnancy loss. Widespread access to misoprostol has the potential to transform the broader cultural and legal context of abortion in the US, empowering people who are pregnant or at risk of pregnancy, normalizing and privatizing choices around pregnancy loss, and moving the legal battles about abortion rights away from clinics and into the intimacy of the home. Advocates and leaders should devote time, energy and resources now to protect and expand access to misoprostol in the future.