KEEP LEARNING

for pregnant and lactating people

Towards an ethically responsible learning healthcare system

Marieke J Hollestelle

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BLIJVEN LEREN

Op naar een ethisch verantwoord lerend zorgsysteem voor zwangere en lacterende mensen

(met een samenvatting in het Nederlands)

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CHAPTER 1

General introduction & thesis outline

Background

Throughout history, there has been a consistent hesitancy to include pregnant people in clinical research, mainly having to do with the fear of potential harm to the fetus.[1-4] As a result, there is little information available about the safety and efficacy of medications taken during pregnancy. At the same time, certain medications have been associated with birth defects and adverse pregnancy outcomes. Often mentioned examples in this context are medicines diethylstilbestrol (DES) and thalidomide.[1, 5] DES was prescribed to an estimated 1.5 to 3 million pregnant persons during the 1940s, 1950s, and 1950s to protect against miscarriages. The drug was eventually (30 years later) discovered to be ineffective and identified as a cause for harmful reproductive complications for the offspring (both male and female).[1, 6, 7] Thalidomide was prescribed, without prior testing, for treating nausea and vomiting during the first weeks of pregnancy, resulting in teratogenic effects and severe birth defects in over 10.000 children.[1, 8] While neither of these tragedies involved clinical research, they notably increased the research community's already protectionist approach towards including pregnant people in clinical research.[1] The thalidomide disaster, on the one hand, prompted the Food and Drug Administration (FDA) in the United States to expand clinical trial studies. On the other hand, simultaneously, these disasters led to the emergence of numerous barriers to the inclusion of pregnant people in clinical research. These barriers were introduced as a measure to safeguard pregnant people, and more specifically, their fetus from potential research-related risks.[9] While the concerns about potential risks for pregnant people and their fetuses are valid, there is a simultaneous need for evidence-based information on medications and treatments for pregnant people. These medications include prescription and non-prescription medications for obstetric and non-obstetric conditions, but also vaccines, medical devices, and natural health products.[10] Currently, approximately 5% of all medications include information about safety during pregnancy in their labels, and the process of updating drug labels, if done at all, takes a relatively long time.[11-14] Furthermore, sources that are available are oftentimes not up to date, contradictory, and difficult to interpret.[15] The limited available evidence-based information affects a very large population as more than 200 million people worldwide become pregnant every year,[16] the majority of whom takes at least one medication during pregnancy.[17-19] In the absence of evidence-based knowledge, clinicians are sometimes compelled to prescribe medications without sufficient supporting evidence or based on conflicting information. This situation may also prompt clinicians and pregnant people to discontinue medically important medications or treatments. Pregnant people might be under-dosed to minimize exposure, resulting in inadequate treatment and potential harmful consequences for both the pregnant person and the developing fetus.[20-22] Although unnecessary medication use during pregnancy should be limited, there are instances when treatments should not be avoided due to acute or chronic diseases, both for

pregnancy-related (e.g., preeclampsia or gestational diabetes) and nonpregnancy-related conditions (e.g., epilepsy, hypertension, diabetes, cancer, or depression). These challenges also extend to medication use during nursing, as there is even less available and conclusive information concerning the impact of medication exposure on newborns through lactation.[14, 22-24]

Over the past decades, much has been written about the widespread reluctance to include pregnant people in clinical research. Regulators, researchers, and bioethicists seemed to have reached consensus that the inclusion of pregnant people in clinical research should be promoted.[25] Some researchers suggest new research designs to promote the fair inclusion of pregnant people as research subjects. Separate trials with pregnant people can start, for example, at a later stage when the first results on the safety have been studied in the general population. Alternatively, pregnant people can be included in phase III trials after a drug has passed safely through phases I and II.[10, 26, 27] An important point to consider is that including only a few pregnant people in clinical trials may not produce meaningful results. In such cases, a study with sufficient statistical power is essential. Despite available promising alternative research designs, the current research infrastructure does not support these alternatives, because solid methodology is lacking and there is limited insight into the advantages and disadvantages of alternative designs to study medication impact in pregnancy.[28, 29] Another suggestion has been to reclassify pregnant people from being categorized as "vulnerable" to "medically complex" populations, demanding special scientific and ethical considerations.[30] In ethical guidelines on medical research, such as the Council for International Organizations of Medical Sciences (CIOMS) *International Research Ethics* guidance (2016), groups are considered vulnerable when they have a compromised ability to safeguard their interests and provide informed consent.[31] Pregnant people are generally capable of protecting their own interests and giving their own informed consent. Van der Zande and colleagues have studied the vulnerability of pregnant people as research subjects and concluded that they are potentially vulnerable to the extent that they are increasingly exposed to higher risks due to a lack of scientific knowledge.[32] To overcome this state of vulnerability, the frequent inclusion of pregnant people in clinical research is required.[32] Researchers and international ethical guidelines, such as CIOMS, adopted this understanding of vulnerability, presuming pregnant people eligible for participating in clinical research.[28, 31] Moreover, numerous scholars and guidelines have advocated for a shift in the presumption of excluding pregnant people, arguing that researchers should be obliged to justify the exclusion of pregnant people from research by providing compelling "scientific reasons" for their exclusion.[25, 30, 31, 33] It should be acknowledged that the call for fair inclusion does not align with the tendency of stakeholders to avoid *any* potential risks to the fetus in research.[34] The precautionary principle, oftentimes interpreted

as “better safe than sorry”, continues to be a guiding principle in pregnancy care and research.[3,4] However, it is important to recognize that although this sentiment is not unusual or even logical, the precautionary attitude also carries the risk of serious harm. This precautious approach may leave pregnant people vulnerable to potentially avoidable therapeutic incidents.[3]

Although (inter)national ethical guidelines for clinical research increasingly provide clarity on the conditions under which pregnant and lactating people can be included (see Box 1), pregnant and lactating people are still being excluded regularly. The COVID-19 pandemic is a perfect example, which showed how: 1) scientific research into the impact of treatment on health outcomes often lags in pregnant people and 2) a lack of scientific evidence on the safety and efficacy of treatments can lead to fear, distress, and contradictory information and policies.[35] Early in the COVID-19 pandemic, it became clear that pregnant people are at elevated risk of harm from SARS-CoV-2 infection compared to non-pregnant people of reproductive age. Furthermore, people with a SARS-CoV-2 infection during pregnancy also had an increased risk of negative birth outcomes including preterm birth, stillbirth, small for gestational age and decreased birth weight.[35] Despite these insights, policies and recommendations from international organizations were contradictory and presented different conclusions and evidence. Furthermore, the lack of safety and efficacy data on COVID-19 vaccines during pregnancy led to mixed messaging on the vaccination policy regarding

Box 1. Overview of initiatives and guidelines on the inclusion of pregnant people in clinical research

The Second Wave Initiative (2009)
The Second Wave Initiative is a collaborative academic effort from the United States that aimed to identify, develop, and advance ethically and scientifically responsible solutions for increasing the knowledge base for the treatment of pregnant people who have medical conditions. (https://www.secondwaveinitiative.org).

PHASES (2016)
Pregnancy and HIV/AIDS: Seeking Equitable Study (PHASES) seeks ethical solutions to advance research at the intersection of people’s reproduction and HIV prevention, treatment, and management. PHASES is an interdisciplinary, research-driven project funded through the U.S. National Institute of Allergy and Infectious Diseases of the National Institutes of Health and collaborates with international leaders in different fields across the world. (http://www.hivpregnancyethics.org).

US Task Force on research specific to pregnant and lactating women (PRGLAC) (2018)
The 21st Century Cures Act established PRGLAC to advise the Secretary of Health and Human Services (HHS) on gaps in knowledge and research on safe and effective therapies for pregnant and lactating people. (https://www.nichd.nih.gov/about/advisory/PRGLAC).

Box 1. *Continued*

PREVENT (2018)
Pregnancy Research Ethics for Vaccines, Epidemics and New Technologies (PREVENT) has developed concrete, actionable, consensus-driven ethics guidance on how to equitably include the interests of pregnant people and their offspring in vaccine research and development for priority pathogens and emerging epidemic threats. PREVENT is led by researchers from the United States, with external contributions from international experts. (https://bioethics.jhu.edu/research-and-outreach/projects/prevent/).

CIOMS international Research ethics guidance (guideline 19) (2016)
The Council of International Organizations and Medical Sciences (CIOMS) provides guidance to a number of pressing issues in research ethics, including research with pregnant people. CIOMS represents a substantial proportion of the international medical scientific community through its member organization across the world. (https://cioms.ch).

pregnant people by many important health organizations,[35] leading to global vaccine hesitancy in pregnancy. Because pregnant people were initially excluded from all clinical trials for COVID-19 vaccinations, an alternative approach to study the effects of the COVID-19 vaccines was pursued through observational studies. These studies relied on the secondary use of health care data, primary care data, and on self-reported pregnancies from people.

The COVID-19 pandemic highlights the necessity for both a ready-to-use data infrastructure and reliable methods for data-intensive analyses that can be used effectively in emergency scenarios, such as a pandemic. A similar argument was made in the literature, advocating for the restructuring of healthcare systems to improve the evidence base for treatments for people affected with COVID-19 and to optimize the potential of health systems to create meaningful outcomes, by for example: supporting a Learning Healthcare System (LHS).[36, 37]

Learning healthcare systems

An LHS is a system in which the clinical practice is more aligned with research in such a way that it can accelerate research and outcomes for patients.[38] In 2007 the Institute of Medicine (IoM), now the National Academy of Medicine (NAM), introduced the concept LHS with the aim to mend the disconnect between research and the clinical practice, and moreover, to overcome the gaps left by Randomized Controlled Trials (RCTs). RCTs oftentimes do not capture the complex and heterogenic clinical practice and do not always study the questions or provide answers that are most relevant to the patients and clinical practice.[39, 40] To this date, more organizations and research projects aim to develop an LHS for different purposes. For instance, an LHS for the purpose of improving patient outcomes and experiences through the dissemination of actionable knowledge at the point of care. It could also involve expanding the education, training, and

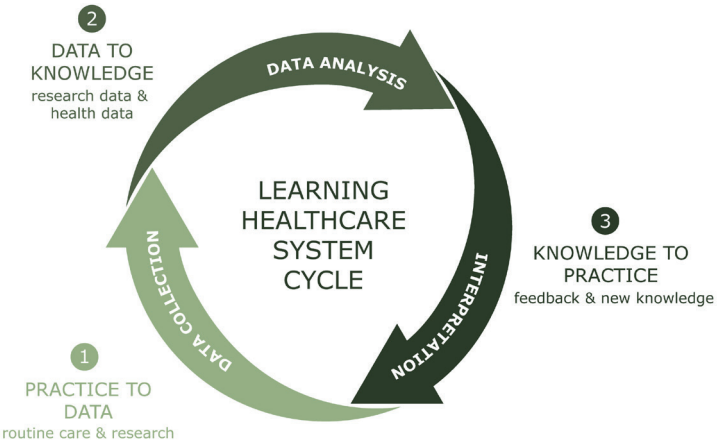

Figure 1. Simplified illustration of an LHS cycle
In an LHS, the process typically starts (1) with collecting or structuring data from routine care or from research. These data can be analyzed for different purposes and various research questions (2). After analysis, results are interpreted (3) and can provide feedback to improve the clinical practice, offer new insights to change the clinical practice, or inform new research questions. This iterative process is ongoing.

performance of clinicians by means of performance feedback based on routinely collected clinical data. Additionally, the aim might be to generating generalizable knowledge by, for example, hosting prospective pragmatic trials or retrospective observational studies.[39, 41] LHSs can take various structures, but at their core, each follows a comparable cycle involving data collection, analysis, and interpretation, followed by feeding new insights back into the clinical practice to stimulate change and improvements.[39, 41] Figure 1 shows a simplified LHS cycle.

An LHS might also be the much-needed approach to a fundamental change in the way knowledge is generated for the group of people who take medications during their pregnancy or during lactation. In 2019, van der Graaf and colleagues suggested to transform the field of pregnancy and lactation into an LHS. An LHS holds great promise in addressing the existing paradoxical situation where pregnant people are overly protected from inclusion in RCTs due to concerns about fetal well-being and physiological changes, while simultaneously being under-protected from high risks in routine practice with potential learning outcomes.[28] The adoption of an LHS approach can be supported by strong moral arguments, as these systems seem to offer value to patients, improving both the quality and efficiency of care, and stimulating research activities that use the real-world clinical practice to target real-world needs.

An LHS leaves the sharp distinction between care and research behind and acknowledges that traditional RCTs are not suited to maximize the desired output for, in this particular setting, pregnant people who use medications. It

emphasizes the need to learn from data gathered during routine clinical care. Lastly, transforming the field of medicines safety during pregnancy and lactation into an LHS could also restore the lack of ownership of the problem. The progress of drug research for pregnant people is a shared problem, with no single stakeholder bearing ultimate responsibility for progress in the field. Addressing the lack of scientific knowledge calls for collaboration among all relevant stakeholders. In the context of an LHS a co-creationistic approach is required. Co-creation is crucial for both the creation of health knowledge that leads to meaningful outcomes and for the transformation towards an LHS. The transformation towards an LHS requires that all relevant stakeholders, including clinicians, patients, funders, regulators, pharmaceutical companies, and others, support the idea of changing the paradigm of knowledge generation in the field of pregnancy and lactation.[28]

Given the widespread medication usage by pregnant and lactating people[17, 18] and the lack of a systematic approach to understand the impact of current medication exposure, transitioning to an LHS seems a promising way forward. In April 2019, the Innovative Medicines Initiative (IMI) ConcePTION* project was launched to investigate the potential of utilizing various data sources, including electronic health records, registries, and claims data, to generate new knowledge on the impact of medications during pregnancy and lactation.[42] IMI ConcePTION aims to build a European LHS that can generate reliable information through a large European network, consisting of already established networks such as the European system for the evaluation of safety of medication use in pregnancy in relation to risk of congenital anomalies (EUROmediCAT), European Network of Teratology Information Services (ENTIS), and Biobanking and BioMolecular resources Research Infrastructure Europe (BBMRI-ERIC), but also with patient and healthcare providers (HCPs) organizations, as well as (inter)national regulators and public health organizations.[43]

As the IMI ConcePTION project takes shape and the imperative for a paradigm shift in understanding the impact of medical treatments on pregnant and lactating people and their offspring becomes apparent, a sense of promise emerges. However, the development of an LHS is a complex endeavor, as there is no one-size-fits-all blueprint for LHS development and implementation. Moreover, the interpretation of LHSs widely varies, leaving room for personal interpretation and implementation.[44, 45] Additionally, the implementation of an LHS introduces ethical challenges that require careful reflection.

Open questions

Although an extensive body of literature exists on LHSs and on research involving pregnant people, there remain certain open ethically relevant questions that

* ConcePTION stands for: Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now

require consideration to facilitate the development of an ethically responsible LHS for pregnant and lactating people.

First, what constitutes as an LHS? Currently, the design of an LHS tailored to pregnancy and lactation lacks comprehensive guidelines. While literature on LHSs cover different LHS-models, conceptualizations, and some examples of LHS projects,[41, 44, 45] it is worth noting, as previously mentioned, that the interpretation of LHSs varies, allowing for personal customization of these models and components. Should research projects, like the IMI ConcePTION project, aspire to transition into operational LHSs, a design customized for pregnancy and lactation becomes imperative. Such a design should encompass vital elements for an LHS framework, aligned with the realm of available real-world data pertaining to pregnancy and lactation, along with ethical considerations critical for project development.

Second, what do stakeholders think of an ethically responsible LHS? An LHS requires a process of stakeholder involvement, implying active engagement with relevant stakeholders in the development phase and in LHS activities. Empirical data concerning the views of stakeholders regarding LHS development remains scarce, particularly within the realm of pregnancy and lactation research. Given that the concept of an LHS, together with the utilization of real-world data in pregnancy research is relatively new, empirical research to stakeholder perspectives should inform the development of an ethically responsible LHS.

Third, what could be the role of pregnant people in addressing the knowledge gap? Despite various attempts to catalyze change for pregnant and lactating people (see Box 1), the situation has not significantly changed. It is imperative to set a course that can truly revolutionize the field and foster the necessary momentum for transitioning to an LHS. Notably, most literature has predominantly focused on the roles of individual stakeholders, including research ethics committees, researchers, funding agencies, manufacturers, pharmacologists, and guidelines committees, in safeguarding the interests of pregnant people in clinical research.[32] However, pregnant people seemed to have been overlooked as significant and influential contributors to driving change. One of the first LHS ethics frameworks, developed by Ruth Faden and colleagues (2013), underscores the obligation of patients to contribute to the common purpose of improving the quality and value of clinical care and the health care system.[46] While exploring a potential obligation for pregnant people to contribute could be interesting, it might be formulated too strong. The lack of scientific evidence transcends the confines of just the clinical practice or a health care system. Instead, it encompasses the international research community and legislative domains as well. Furthermore, it is important not to place the responsibility of changing the status quo solely on pregnant people, considering that the lack of knowledge is not their fault. Nonetheless, exploring the question what their role in addressing the knowledge gap could be is essential, as they may hold the key to driving progress.

Fourth, what are important ethical requirements for transitioning into an operational and sustainable LHS? The development of an LHS starts with, among other things, the establishment of a functioning infrastructure and strategic collaborations. This process may extend over several years. Subsequently, attention is directed towards the establishment of a sustainable LHS, capable of offering an enduring resolution to the current knowledge gap. Interestingly, a notable gap exists in terms of a robust ethics framework for research projects that have invested substantial time and effort in constructing the foundational elements of an LHS, yet have not completed the transition to an operational LHS.

As such, the main objective of this thesis is to help enable the shift in knowledge generation in the field of pregnancy and lactation by addressing at least these four open ethically relevant questions.

Central aim and research questions

Central aim

This thesis aims to reflect on the development of an ethically responsible learning healthcare system for pregnant and lactating people.

Research questions

The research questions can be categorized into four themes, aligning with the four aforementioned open ethically relevant questions:

Design of an LHS for pregnant and lactating people

1. What constitutes an LHS that aims to study the safety and efficacy of medications used during pregnancy and lactation?

Stakeholder views

2. What are the views of pregnant people on an LHS for pregnant and lactating people?
3. What are the views of data access providers within an LHS?

Solidarity

4. Can the enactment of solidarity among pregnant people be stimulated to help address the poor evidence base on medications used during pregnancy?

The transition to an operational LHS

5. What are the necessary ethical requirements for guiding the transition of research projects to an operational LHS?

Research approach

Wide reflective equilibrium

In this thesis we will use the wide reflective equilibrium as a model for moral reasoning. Using wide reflective equilibrium allows us to combine empirical data with ethical analysis and argumentation.[47] Wide reflective equilibrium requires an iterative process which means that the so-called 'thinker' (our research group in this case) goes back and forth between morally relevant facts, moral intuitions, and ethical principles and theory until a coherent normative view is reached, i.e. the 'reflective equilibrium'. The term wide reflective equilibrium encompasses both the process and the outcome of moral reasoning. Unlike narrow reflective equilibrium, it includes background theories to offer critical input.[47, 48]

The empirical elements of this thesis comprise of qualitative interview studies to collect the perspectives of pregnant and lactating people, as well as people working for organizations that have access to relevant pregnancy and lactation related data (data access providers). For the analysis of these interview studies, we use an inductive thematic analysis. The normative elements of this thesis are normative reflections on the concept of solidarity and on ethical requirements to guide the transition towards an operational LHS in the field of pregnancy and lactation.

The background theories and principles that we incorporated in our moral reasoning stem from various ethical theories. Historically, there is a distinction between the ethical guidance of research and care. However, an LHS is characterized by the intertwinement of clinical care and research, which could challenge the traditional ethics frameworks of research ethics and clinical ethics. It has been argued that LHSs need a different ethics framework to guide the activities that fall both under research and care, namely by incorporating appropriate principles from both research and clinical ethics or by adopting a public health ethics framework.[46, 49] In this thesis, we will reflect upon these ethics frameworks and reflect on the appropriateness of their principles in relation to various aspects of an LHS in the context of pregnancy and lactation.

Definitions

In this thesis we are concerned with people who want to become pregnant or are pregnant, but also who recently gave birth, and who are nursing. Although the lack of knowledge on medication safety and efficacy mostly affects women, it also affects transgender and gender diverse people. In fact, even less knowledge is available on the safety of hormone therapy, let alone in combination with a chronic disease or illness for pregnant transmen and their developing fetus. For transwomen it is not (yet) possible to become pregnant, however, there are ways for transwomen to develop breast tissue and to start hormone therapy to mimic the natural postpartum process. The risks of these therapies for the

infant also remain unknown.[50] Therefore, during the course of our research, we have chosen to refer to pregnant and lactating people in this thesis. Additionally, we use the term 'lactation' instead of 'breastfeeding', aligning with argument favoring inclusive language. It is worth mentioning that Chapter 3 deviates in terms of wording, as this was one of our initial research projects and the decision for inclusive language had not yet been established. We do want to emphasize that terminology remains a subject of ongoing debate, with little consensus on the definitive wording. Nonetheless, prioritizing inclusivity, which we consider a significant value in research, we have chosen to align with references to people and lactation, a choice observed by multiple researchers and organizations.

Furthermore, it is important to clarify that we consider pregnant people and their fetuses as a whole entity. While there is ongoing debate regarding the moral status of the fetus and varying perspectives on the extent to which the interests of the pregnant person and their fetus are intertwined, we assume that the well-being or harm to the pregnant person is almost always connected to the well-being or harm to the fetus.

IMI-ConcePTION

The research presented in this thesis was part of the IMI-ConcePTION consortium, however, a distinction must be made between the two roles we had during the project phase. As ethicists, we contributed by providing ethical guidance on the ethical issues relevant to an LHS in de field of pregnancy and lactation, formulating important elements for a governance structure for the ConcePTION ecosystem, addressing the involvement of pregnant people and the engagement with other stakeholders, and thinking along with a sustainability plan for ConcePTION. These results were published in several deliverables or presented during project meetings.[51] As researchers, we aimed to analyze the project from a distant perspective and independently conduct our ethical reflection. These results are presented in this thesis. Nonetheless, given that IMI ConcePTION is laying the groundwork for an LHS tailored to pregnant and lactating people, this thesis will use the project as an example of an LHS-project to provide the necessary context.

Structure of this thesis

The chapters of this thesis consist of articles that have been published or submitted for publication and each explore one of the sub-questions stated above.

In **Chapter 2** we offer an overview of the building blocks essential to an LHS aimed at studying the impact of medications used during pregnancy and lactation. Despite the substantial literature on LHSs, a universal blueprint for developing an LHS does not exist. Moreover, the interpretation of LHSs widely varies, and its design is often considered context depended. To guide the progression towards a European LHS for pregnant and lactating people, this chapter leverages insights

from the existing literature on LHS conceptualization and ethical challenges, and from the IMI ConcePTION project. Our design exists of three building blocks: 1) the (data) infrastructure, 2) the learning cycle, 3) stakeholder involvement. While presenting these elements, we also discuss their ethical challenges and the approach the IMI-ConcePTION is adopting.

Chapter 3 presents empirical insights from a qualitative interview study with Dutch women during preconception, pregnancy, and nursing to understand their views on an LHS for pregnant and lactating people. To offer the essential context, we gave our respondents additional information on the concept of an LHS, presenting them with a design similar to that described in Chapter 2.

Chapter 4 gives an overview of the results of our qualitative interview study with data access providers from the IMI-ConcePTION project. We examine their views on a sustainable LHS. Additionally, we examine whether data access providers themselves perceive and articulate their moral responsibility regarding ethical data handling and dissemination of research findings.

In **Chapter 5** we challenge the concept of solidarity and aim to understand whether and how enactment of solidarity among pregnant people can be stimulated to help the shift in the way knowledge is being generated. Here we propose that in order for solidarity to take effect, we need to empower pregnant people. The process of empowerment starts by raising awareness about the lack of evidence on medications used during pregnancy, and by explaining to pregnant people how they can contribute to changing the way knowledge is being generated.

Chapter 6 presents an ethics framework that contains ethical requirements to guide the transformation of projects to an operational LHS. In this chapter, our focus shifts to the crucial phase of transitioning from a research project to an operational LHS, where we provide ethical guidance.

In the final chapter, **Chapter 7**, we look back at the main results, conclusion, and limitations of this thesis and place our findings in the broader context of LHSs and the field of pregnancy and lactation.

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CHAPTER 2

A European comprehensive data learning healthcare system to study the impact of medications used during pregnancy and lactation

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Abstract

The majority of medications lacks clear guidance on their potential risks and benefits in pregnancy and lactation. To change the way knowledge is currently generated, it has been proposed to transform the field into a learning healthcare system. In a learning healthcare system, care and research are becoming more aligned to accelerate improvements and patient outcomes by examining real-world experiences and integrating new insights into the clinical practice. An LHS offers an opportunity to streamline the use of real-world data from routine healthcare and to continuously study current medication experiences to generate evidence regarding the safety and efficacy of medications used in pregnancy and lactation. Despite the substantial literature on LHSs, a universal blueprint for developing an LHS does not exist. By drawing insights form existing literature on LHS conceptualization and ethical challenged related to LHS development, this paper discusses three essential LHS building blocks, namely: 1) the data (infrastructure), 2) the learning cycle, and 3) stakeholder involvement. Additionally, the IMI ConcePTION project is used as an illustrative example to contextualize these building blocks. While this design is primarily directed towards a specific type of LHS, with a focus on pregnancy and lactation, the insights discussed in this paper hold relevance and applicability in other fields and disciplines.

Background

The impact of medications, both prescribed and available over-the-counter, on both maternal and fetal health is a major concern. Only a small fraction of available medications has been thoroughly monitored, tested, and labeled to ensure their safe and effective use in pregnant people.[3, 4] The limited availability of evidence-based information means that the majority of medications on the market lacks clear guidance on their potential risks and benefits in pregnancy. Even less clear information is available on the safety and efficacy of medications used during lactation.[5] Historically, pregnant and lactating people have been excluded from participating in clinical trials. This exclusion primarily arises from complex practical, ethical, and legal challenges, often rooted in concerns over potential harm to the developing fetus during research.[6-8]

Despite the limited availability of evidence-based information, numerous medications have been used during pregnancy and lactation, without systematically learning from these experiences. To change the way knowledge is currently generated, it has been proposed to transform the field into a Learning Healthcare System (LHS). In an LHS, care and research are aligned in such a way that it can accelerate improvements and innovation for patient outcomes, by studying real-world experiences and implementing new insights directly in the clinical practice.[9-11] A more detailed description of an LHS will be provided in the section "LHS building blocks" below.

It is important to emphasize that LHSs are not designed to replace clinical trials; however, they could serve as valuable complements to clinical trials. For instance, they can facilitate innovative study designs like Pragmatic Clinical Trials (PCTs) or trials within cohorts.[12] These study designs contribute significantly to the creation and application of new insights directly within the clinical practice. LHSs could also play a pivotal role in aiding patient recruitment and randomization in comparative effectiveness studies within clinical care settings.[12] Moreover, an LHS offers an opportunity for populations, such as pregnant and lactating people, who are often excluded from these types of clinical research. At the heart of an LHS is the utilization of health data, generated within healthcare organizations or elsewhere for research purposes.[13]

With the ongoing digital transformation of healthcare, vast amounts of health data, also called real-world data, are being stored and collected. In the past few decades, data generated in routine healthcare have been increasingly used and recognized as a valuable source for evidence generation.[14] The opportunities of utilizing real-world data from routine healthcare and continuously studying experiences in an LHS to generate evidence on the impact of medications used in pregnancy and lactation, led to the establishment of the Innovative Medicine Initiative (IMI) ConcePTION project (2019).[1] IMI ConcePTION aims to develop a safety ecosystem, which includes relevant European data sources, also called Data Access Providers (DAPs) to address questions about safety and effectiveness

of medications used during pregnancy and lactation (Box 1).[2] The IMI ConcePTION LHS aligns with what is referred to as a comprehensive data LHS in the existing literature.[12] A comprehensive data LHS uses real-world data, such as routinely collected health data (from for example electronic health records) to answer research question to improve health and care. Despite the substantial literature on LHSs, a universal blueprint for developing an LHS does not exist. Moreover, the interpretation of an LHS widely varies, and its design is often considered context dependent. Additionally, most LHSs are still primarily conceptual and strategic in nature.[11, 12]

To guide the progression towards a European comprehensive data LHS dedicated to studying the impact of medications used during pregnancy and lactation, this paper studies its necessary design elements. This paper will use the insights from the existing literature on LHS conceptualization and ethical challenges related to LHS development. Additionally, the IMI ConcePTION project will serve as an example to provide necessary context to the design elements. The design will encompass essential building blocks of the LHS, in addition to addressing relevant ethical considerations crucial to the development of an LHS. While this design is directed towards a comprehensive data LHS at the European level, focusing on pregnancy and lactation, the insights discussed in this paper are transferable to other fields and disciplines. These insights are, for example, valuable for projects aiming to establish an LHS that utilizes real-world data, whether operating at regional, national, or international levels. The overarching objective remains consistent across these endeavors: to advance research and improve the quality of health and care.

Box 1. Description of the IMI ConcePTION project

In April 2019, the Innovative Medicines Initiative (IMI) launched the ConcePTION project (Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now). ConcePTION is a European public-private partnership that aims to develop a Learning Healthcare System that can generate and disseminate reliable evidence-based information about medication safety and efficacy during pregnancy and lactation by learning from data from pharmacovigilance, modelling, routine healthcare, lactation samples and research data across Europe.[1] The partnership consists of experienced industry and academic organizations, already established networks such as the European system for the evaluation of safety of medication use in pregnancy in relation to risk of congenital anomalies (EUROmediCAT), European Network of Teratology Information Services (ENTIS), and Biobanking and BioMolecular resources Research Infrastructure Europe (BBMRI-ERIC), and patients, healthcare providers (HCPs) organizations, as well as (inter)national regulators and public health organizations.[2]

Once a technical infrastructure is in place, ConcePTION aims to operate a harmonized European information knowledge bank for uniform dissemination of evidence and provide e-learning facilities.[1]

LHS building blocks

Although step-by-step frameworks do not exist for building an LHS, there are some recurring distinctive features. For example, LHSs are often portrayed as loops and described as systems that continuously go through the stages of data collection, data analysis, knowledge generation, and knowledge dissemination to inform decision-making and drive improvement in care delivery and/ or inform new research questions.[11, 13, 15, 16] Furthermore, since an LHS affects and involves the effort of many different types of stakeholders, emphasis lies on co-creation, co-design, or stakeholder involvement for LHS development and knowledge implementation.[11, 13, 17-19]

Combining the characteristics of a comprehensive data LHS, described by Wouters and colleagues (2020)[12] with what we know about common characteristics of LHSs, we believe that there are at least three fundamental building blocks to discuss. These are: 1) the data (infrastructure), 2) the learning cycle, 3) stakeholder involvement.[11-13, 20, 21] We will briefly go over these elements and their corresponding ethical challenges, and subsequently translate them into the ConcePTION LHS, providing some concrete points for consideration for LHS development. Finally, we will illustrate our understanding of the ConcePTION ecosystem as an LHS through a visual representation (Figure 1).

The data (infrastructure)

Real-world data

In general, using real-world data poses a few challenges having to do with the nature and original purpose of these data.[22-24] First of all, real-world data in the medical and healthcare field encompass a diverse range of data sources that routinely capture patient health information and healthcare delivery, resulting in their inherent heterogeneity.[14] The most common sources from which real-world data can be gathered are electronic health records (EHRs), registries, claims data, and research. Second, real-world data are often incomplete and lack critical endpoints. HCPs often measure and document only what they deem relevant for providing care. Consequently, certain endpoints that are crucial in clinical research may be missing. Alternatively, data may be collected within a distinct research context, focusing on other characteristics. Third, as data are collected in different ways, it is challenging to exchange data or organize collaboration between different computer systems (limited semantic interoperability). The (re)use of real-world data requires a high-quality data infrastructure and robust methods for data structuring and analyses.[14, 19] There is growing attention on how to deal with real-world data, for which purposes it can be used, how to turn it into actionable data, and more importantly: to what extend it can replace traditional research methods such as randomized controlled trials.[25]

Besides methodological challenges, ethical challenges relating to the issues of privacy and confidentiality are also often mentioned in this regard.[14, 26-28] The processing of vast amounts of data warrants ensuring the confidentiality and privacy of pregnant and lactating people. This can be achieved through practices such as data encryption and removing (de-identification) or replacing identifiers (coding data), while also restricting unnecessary data sharing. Furthermore, the use of real-world data blurs the distinction between care and research, and with that, challenges the current ethical and regulatory frameworks. In a multi-country LHS, the databases of participating organizations can be used for multiple purposes, meaning that their activities may be designed to treat patients and to gather data (for research) at the same time.[16] Traditionally, the goal of clinical care is to preserve or advance the health of individual patients. Whilst the goal of clinical research is to advance general medical knowledge (which obviously in turn is needed to advance health), which requires the protection of the rights and interests of participants, often through comprehensive informed consent procedures and ethical oversight.[16, 29, 30] In the context of an LHS, when the precise purpose of data utilization becomes ambiguous, conventional informed consent procedures and ethical oversight may no longer suffice to ensure protection of patients' interests and rights, all while advancing general medical knowledge. Perhaps it could prove valuable to draw insights from intersecting ethical frameworks, such as data ethics and public health ethics. In the context of a comprehensive data LHS, data plays a pivotal role, and its use would greatly benefit from the guidance provided by a data ethics framework. For example, it could help address questions regarding the risks and benefits associated with utilizing health data in an LHS, and ensure the ethical development, deployment, and maintenance of the LHS.[27] Additionally, adopting a public health ethics perspective might be valuable, as the issue of the lack of knowledge regarding the impact of medications used by pregnant and lactating people extends into the realm of public health concerns. The lack of evidence does not only impact individual pregnant persons; it also affects whole communities, resulting in more people at risk and in potentially unsafe and less-controlled situations.[31] A public health perspective can shed light on questions relating to the justification of the use of health data within an LHS and striking a balance between the challenges associated with moral values such as autonomy, privacy, and confidentiality, and the benefits it brings to the broader population of pregnant and lactating people and their developing offspring.[32]

Data infrastructure

A data infrastructure can be interpreted as a support system for data capturing, storage, access, and presentation from different data sources.[11] The data infrastructure is one of the foundational elements of an LHS, and demands special focus and dedication, particularly in a multinational collaboration. In

such collaborations, the data infrastructure must harmonize various data types gathered within culturally diverse environments. A high-quality data infrastructure enhances the capacity to collect and (re)use data and evidence to study and generate new knowledge. A systematic review studying the implementations and evaluation of impact of LHSs on medical practices, described two common approaches for data infrastructures. The first approach is a centralized database architecture with deidentified data from several collaborators.[19] This enhances the matching capacities and thus the interoperability of data but increases the risks of re-identification of data subjects and limits the possibilities for data analyses as certain necessary endpoints/ variables are missing. Establishing a centralized database architecture can incur substantial costs and necessitates agreement among all contributing parties regarding the chosen architecture. Additionally, it places substantial demands on participating organizations, impacting their autonomy, operational integrity, and control over intellectual property rights. The second approach encompasses a network of local databases (elsewhere called a federated data approach[33-35]), each processing sensitive data and sharing the final results from data analyses.[19] In that way, the level of detail within the data sources can be maintained, data sources can continue to operate autonomously, and it could be a solution for data protection regulations that often form a barrier for data exchange in multinational networks.[2, 28] However, a federated approach requires local data sources to have large computational power and a well-equipped supporting team to handle the potentially extensive data analyses that need to be conducted locally.[28]

The IMI-ConcePTION project has a clear vision when it comes to the data infrastructure and adopts the federated approach, using a specific ConcePTION Common Data Model (CDM) to align 13 data sources.[2] These data sources include real-world data from healthcare, national or international pregnancy related registries, birth registries, health claims, epidemiological surveillance, teratology information service (TIS), pharmacovigilance centers and the pharmaceutical industry, and data collected for research purposes throughout Europe. Metadata was developed, enabling oversight, and providing information regarding the availability of data within these data sources (DAPs), while a unique standard vocabulary remains absent to guarantee fast and flexible CDM deployment.[2] This flexible approach empowers DAPs as local experts to contribute their expertise and guide the data processing and analyses, thereby facilitating a high level of detail in the information. Queries for data analyses are sent to the individual DAPs, ensuring both secure and efficient data analysis while upholding data privacy and ownership.[2] This approach not only ensures that sensitive data remains protected but also promotes collaboration between data sources, researchers, and HCPs. Nonetheless, individual DAPs ideally have a governance system to obtain authorization for the use and future use of the health data of pregnant

and lactating people. Research must not adversely affect the rights and welfare of pregnant and lactating people from whom data were collected.

The learning cycle

Learning is at the core of an LHS. By committing to the LHS model, it is important to decide beforehand what needs to be learned. A comprehensive data LHS aims to learn from routine healthcare to improve both health outcomes and clinical practices.[12] In this context, it focuses on generating knowledge from the current medication usage during pregnancy and lactation to assess their safety and effectiveness. Commitment to establishing a comprehensive data LHS inherently entails a commitment to ensuring that the knowledge generated is effectively integrated into the (clinical) practice. This commitment is essential to the learning cycle of an LHS.[16] Thus, the ultimate goal of an LHS is clear: to continuously improve health outcomes and care by facilitating research.[13] The Mobilizing Computable Biomedical Knowledge (MCBK), which is an international community led by the Department of Learning Health Sciences at the University of Michigan, proposes a few key aspects for the translation of knowledge into action. Their key aspects, together with insights from literature on LHS conceptualization led us to the formulation and interpretation of the following components that are relevant for the integration of knowledge to improve health and care: 1) standardization of knowledge representation to enable the application of knowledge across various care levels and countries, 2) establishment of a robust technical infrastructure to support the incorporation of knowledge into support systems, provide accessibility through websites or other accessible platforms, 3) ensuring transparency in the processing of health data and into the design of the LHS, and trustworthiness of the generated knowledge. Commitment to transparency means enabling people to understand how the system works and, if necessary, challenge those practices, as well as embodying transparency measures into the design of the LHS and the process of data interpretations.[36] Trustworthiness encompasses ethical data usage and adherence to the FAIR principles (Findable, Accessible, Interoperable and Reusable) throughout the LHS cycle. 4) Gaining trust of stakeholders in the LHS and the knowledge it produces. The level of trust of stakeholders is influenced by the way issues of privacy and confidentiality, transparency, engagement are managed and have significant implications for patients' perspectives on research and their willingness to engage.[37] Moreover, the routine involvement of pregnant and lactating people in an LHS through data collection requires a thorough examination of their voluntary participation and the establishment of trust.[12, 16] 5) Sustainability and inclusivity are key to ensuring the continuous contribution of the LHS to health and care improvements, while also guaranteeing that the LHS serves diverse populations and treats them fairly and equally.[13]

The IMI-ConcePTION project aims to develop a European knowledge bank and e-learnings particularly for HCPs. While the concept of a knowledge bank

may seem straightforward, the current landscape of information dissemination regarding the safety of medications used during pregnancy and lactation needs to be taken into account.

Currently, there is a multitude of information sources available to pregnant and lactating people seeking guidance. However, these sources are often contradictory, incomplete, or inadequate in addressing specific questions. In this landscape, the ConcePTION knowledge bank must distinguish itself, particularly in terms of usability and trustworthiness. It should aspire to become the primary go-to source for pregnant and lactating individuals, as well as their HCPs, as they make informed decisions about treatments. Whether a knowledge bank can attain this position largely depends on several factors. These factors encompass the capacity of the knowledge bank to cater to the specific information needs of pregnant and lactating people, as well as HCPs across all European countries. Equally crucial are the factors influencing the level of trust pregnant and lactating people place in the information provided. Furthermore, effective communication strategies, tailored to different European contexts, play a pivotal role in ensuring that pregnant and lactating people and their HCPs are informed about the knowledge bank's existence. At the same time, the position of the knowledge bank also depends on the effectiveness of the LHS to continuously incorporate new insights into the knowledge bank. An LHS, fundamentally, revolves around an ongoing cycle of data analysis that could potentially question the accuracy of information in the knowledge bank. Consequently, the knowledge bank, or any information system for that matter, must be able to promptly update its content in response to newly generated insights, especially concerning the safety and efficacy of medications.

Stakeholder involvement

As Friedman and colleagues wrote in 2015: "an LHS is not a digital infrastructure alone, it is also a network of people and institutions, and not only users of a technological infrastructure, but also parts of the information system itself".[15] This quote underlines the importance of taking the involvement of stakeholders seriously throughout the processes of development, transitioning, and sustainability of the LHS. The focus on stakeholder involvement is consistent with a broader trend towards the engagement and involvement of patients and participants in clinical care (patient and public involvement and engagement (PPIE) movement) and in research. In the LHS literature, stakeholder involvement and engagement is often mentioned as an important aspect for the success of an LHS as it helps to ensure that the system is effective, efficient, and meets the needs of all relevant stakeholders.[17] In the context of an LHS, the term "relevant stakeholder" refers to a broad spectrum of people and groups, extending beyond patients or the general public. For example, people who work for DAPs, researchers, HCPs,

ethicists, funding agencies, regulatory authorities, pharmaceutical companies, and, of course, pregnant and lactating people. Each of these stakeholders wields significant influence of the LHS functionality. Funders, regulators, and researchers hold the power to shape the research agenda and secure financial support for the LHS. Simultaneously, researchers DAPs, healthcare institutions, and pharma share the responsibility of constructing an effective data infrastructure. Nonetheless, the primary challenge lies in orchestrating meaningful engagement – or, more aptly collaboration – with these stakeholders to fully realize an operational LHS. Seid and colleagues (2021) have formulated a promising model for a collaborative LHS with the potential to enhance patient outcomes through the sharing of knowledge and active engagement.[17, 38] Their model represents a significant step towards a structured approach for integrating patient involvement into an LHS.

While stakeholder involvement offers potential practical benefits, such as promoting effectiveness and efficiency, it is also contended that when conducted effectively, it can foster respect among diverse stakeholders, including their norms, values, cultures, needs, and preferences.[16] Furthermore, stakeholder involvement can bolster the level of trust, while also enhancing stakeholders' willingness to contribute and sustain their contribution.[39] It also acts as a tool to establish transparency with stakeholders regarding ongoing LHS activities, including the methods of data collection, processing, and analysis in a multinational LHS.[40]

ConcePTION has dedicated a work package to stakeholder engagement, endorsement, and adoption.[41] The focus of this work package primarily centers on collecting stakeholder perspectives and on project outcomes rather than on stakeholder involvement throughout LHS building and implementation. Nevertheless, it does reflect the project's intent to generate outcomes that align with the needs of stakeholders. Delving further into the involvement of pregnant and lactating people in the ConcePTION LHS, it reveals a landscape that offers both challenges and opportunities. One often cited challenge is the temporary nature of pregnancy, which typically lasts up to nine months. However, when compared to patient engagement in the context of specific diseases, the duration of involvement during pregnancy may also be more manageable due to the presence of a defined endpoint. Nonetheless, their involvement is crucial and requires a clear vision and strategy. This approach should not only respect but should also have the potential to encourage the voluntary contribution of pregnant and lactating people to the LHS.

IMI ConcePTION as an LHS

Figure 1 illustrates IMI ConcePTION as an LHS, incorporating the building blocks and elements of the ConcePTION project as discussed above. Given that the project is still ongoing, it is important to emphasize that the figure represents our interpretation of how ConcePTION would operate as an LHS once fully operational.

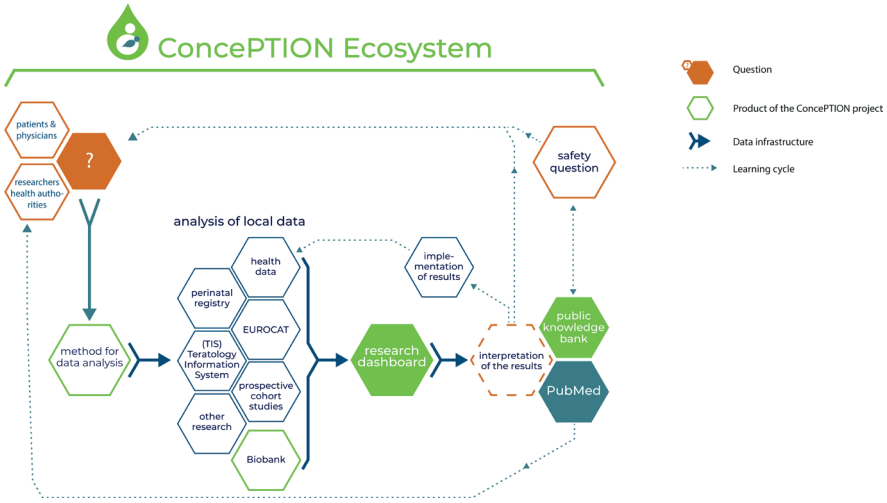

Figure 1. The ConcePTION learning healthcare system. Designed by Studio Terp 2021

This visualization of the ConcePTION LHS represents the current ConcePTION ecosystem and to some extent reflects the LHS building blocks discussed earlier. The diagram illustrates how various stakeholders, including patients (including "healthy" pregnant and lactating people), their doctors, researchers and health authorities may have safety questions regarding medical treatments. These safety questions can initiate a study, beginning with the development of a data analysis method, followed by local analyses performed by the DAPs. The results of these data analyses can be shared through a research dashboard, and strategies can be formulated to disseminate the findings to the point-of-care settings. As mentioned previously, ConcePTION aims to establish a public knowledgebank, which could present translated research results. Additionally, since many DAPs are affiliated with academic institutions, they may publish new insights in scientific journals accessible via databases like PubMed. To close the learning cycle: these new insights, accessible through various channels, should serve as the catalyst for new question, practice transformation, improved decision-making, and lay the groundwork for further data collection in clinical settings and registries.

Conclusion

In this paper, we have delineated the essential design elements required for developing a multinational comprehensive data LHS for pregnant and lactating people and some of the related ethical challenges. We described the importance of a high-quality data infrastructure and solid methods for working with real-world data, an operational learning cycle that ensures the implementation of new insights to improve health and care, and the diversity of benefits of arranging meaningful stakeholder involvement in an LHS. Furthermore, we discussed the IMI ConcePTION project as an example of a project that aims to develop a European comprehensive data LHS to study the impact of medications used during pregnancy and lactation. Although the discussion of these design elements has been tailored to the context of pregnancy and lactation, the insights from this paper can readily find applicability in diverse fields.

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CHAPTER 3

A Learning Healthcare System for pregnant and breastfeeding women: what do women during preconception, pregnancy, and nursing think? – A qualitative study

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Abstract

Background

Most medications lack evidence-based information about its safety and efficacy during pregnancy and breastfeeding, because pregnant women are often not included in clinical research. Another way to generate evidence is by using a Learning Healthcare System (LHS) approach. In an LHS, care and research are aligned in such a way that it can accelerate evidence generation and outcomes for patients, based on real-life medication use. For the development of an ethically responsible and sustainable LHS, it is of crucial importance to understand what women think of such an alternative approach to knowledge generation. Therefore, this paper explores their views on an LHS for pregnant and breastfeeding women.

Method

For this qualitative study, we interviewed 20 women during preconception, pregnancy, or nursing to explore their views on an ethically responsible LHS for pregnant and breastfeeding women. The pseudonymized transcripts were analyzed thematically.

Results

We identified four main themes describing women's views on LHSs. The first theme describes that respondents were positive about learning healthcare systems, and considered them to function as a central point for information about their medication, which they felt is currently lacking. The second theme shows that respondents want to contribute to and engage in generating new information because they want to help others and contribute to scientific research. Respondents also mentioned that, currently, not every woman is aware of the risks of the lack of evidence for medication used in pregnancy. The third theme shows that respondents regard their healthcare professional as essential for the translation and interpretation of information, regardless of a learning healthcare system. The last theme describes that respondents will trust a learning healthcare system more if the medical community supports it, and when data collection and processing is transparent.

Conclusion

Women during preconception, pregnancy, and nursing agree that an LHS could be a viable alternative to help close the knowledge gap on the safety of medication used during pregnancy and breastfeeding. The obtained insights from our interviews provide valuable stepping-stones for the development of an ethically responsible and sustainable LHS, as well as for the engagement of women in an LHS.

Background

Every year more than 5 million women* become pregnant in the European Union and the majority takes at least one medication during a pregnancy.[2, 3] Yet, most medications lack evidence-based information about safety and efficacy during pregnancy, because pregnant women are routinely excluded from most clinical research, due to a fear of harming the developing fetus.[4, 5] Even less information is available about the exposure of the newborn to the medication through breastfeeding. Only 5% of the available medications have been adequately monitored, tested, and labelled for use in pregnancy and breastfeeding and often long-term effects remain unknown.[6]

In real life, numerous medications have been used safely and effectively in pregnancy with minimal risk to the fetus and mother, but we are not systematically learning from these experiences.[1, 7] There are strong ethical reasons to change the way evidence is currently being generated and disseminated. In the literature, multiple solutions for conducting research with pregnant women have been suggested, such as, routine inclusion of pregnant women in clinical trials or using an adaptive trial design to support safe and efficient inclusion of pregnant women in different stages of medication development.[4, 8] However, pregnant women hesitate to participate in trials, and medicines manufacturers hesitate to have them included, because of potential liability issues. Given the vast availability of real-world data on medicines prescriptions and health outcomes, an alternative way to generate evidence is to learn from previous and current medication use, by transforming the field of pregnant and breastfeeding women into a Learning Healthcare System (LHS).[5] In an LHS, healthcare and research are aligned to accelerate research and outcomes for patients. LHSs have the potential to develop scientific knowledge based on health information and research data, and by directly implementing new insights from analyses to the clinical practice.[9]

Currently, information on the safety and efficacy of medications used during pregnancy and breastfeeding is fragmented and spread across different data sources, pregnancy or medicines cohorts, registries, and research groups with unique data regarding pregnancies, adverse drug reactions and the like. Examples are the European system for the evaluation of safety of medication use in pregnancy in relation to risk of congenital anomalies (EUROmediCAT) and the European Network of Teratology Information Services (ENTIS). Combining these unique data sources in a system of continuous learning could help clarify how medications impact pregnancy outcomes and breastfeeding exposures.[1, 5]

* This also includes transgender men, non-binary and gender fluid people who want to become pregnant or are pregnant.

Although an LHS approach may broaden the opportunities to strengthen the evidence base of medications used during pregnancies and breastfeeding, multiple ethical issues arise when establishing and sustaining an LHS.[10] These ethical issues are for a large part the result of the sharp distinction that is currently visible between research and practice. In general, there is the question of quality and usability of the results from the learning activities flowing from an LHS, and therefore, the classification of the learning activities as (scientific) research. Furthermore, LHSs might struggle with ethical oversight, especially when the boundary between research and care is becoming less clear. Other important issues involve notifying participants and asking informed consent, creating transparency regarding data analyses, commercial interests, and unintended negative consequences from implementation of new insights into practice.[11] Furthermore, transforming the field of pregnant and breastfeeding women into an LHS will, besides overcoming the ethical issues, also depend on the support of a broad range of key stakeholders within the health system.[12] For example, women need to trust there is significant value and quality in the alternative approach so that they can rely on this evidence, and they need to believe their concerns about this new approach are taken seriously.[12] However, there is not much knowledge of patients' perspectives, let alone women of childbearing age, on LHSs. Currently, we do not know what their concerns are and when they would trust and support an LHS. Understanding what women think of this alternative approach and what their concerns are, will be of crucial importance for the success of the implementation of new insights into care and the collection of new health-related data within the LHS. Therefore, this paper aims to explore the views of women on an ethically responsible and sustainable LHS for pregnant and breastfeeding women. To deepen our understanding of the views of women whose data may become part of such an LHS for pregnant and breastfeeding women, we conducted semi-structured in-depth interviews with women during preconception, pregnancy, and nursing. During our interviews, we used the Innovative Medicine Initiative (IMI) ConcePTION-project as a case study. ConcePTION aims to develop an LHS mechanism for pregnant and breastfeeding women. In this way, the questions and answers are less hypothetical and can already be placed in real life context.

Method

Design

We employed a qualitative study design to explore women's views on an ethically responsible LHS for pregnant and breastfeeding women. The study is reported in accordance with the consolidated criteria for reporting qualitative studies (COREQ).[13] This qualitative interview study is a sub study of the Innovative

Medicines Initiative (IMI) ConcePTION project. Our study focused solely on women, since we were interested in the primary target population of the LHS specifically, which accordingly could be aligned with the opinion of other relevant stakeholders within IMI ConcePTION. For example, other researchers within the ConcePTION-project conducted a survey study and focus groups with healthcare professionals (HCPs) to understand their needs regarding medication use during pregnancy.

We performed semi-structured interviews with a topic list (see Box 1), which came from two sources. We used some of the items from guideline 12 of the 2016 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Health-related Research Involving Humans.[14] The CIOMS guideline 12 covers essential elements for governing the collection, storage, and analysis of data in health-related research. A parallel can be drawn between data analysis within an LHS and health-related research in general, and therefore, the CIOMS guideline is very relevant for an LHS. We also used the results of a narrative review on patient and public views and attitudes towards the sharing of health data for research.[15] This review gave insight into key conditions for the use of health data in general, which were used as topics in the interviews.

Box 1. General topic list

1. Attitude towards the status quo and the goal of ConcePTION
2. Participatory engagement
3. Respect for autonomy
4. Perceived risks
5. Need for return of results
6. Inclusion and freeriding
7. Sustainability

Sample and setting

We aimed to include women whose data may become part of an LHS for pregnant and breastfeeding women. We therefore included women who wanted to become pregnant, were pregnant at the time of the interview, or were nursing** up to 6 months after giving birth. Furthermore, to obtain a broad range of perspectives on the topics, we aimed to include women with different medical backgrounds and diverse characteristics. Respondents were recruited by purposeful sampling with the help of our contact persons from the University Medical Center Utrecht, the Amsterdam University Medical Center, The Netherlands Pharmacovigilance Center Lareb, Eurocat Northern Netherlands, and by means of snowball sampling.

** We use the word “nursing” instead of “breastfeeding” to respect all different ways women can nurse their newborn, that is for example: breastfeeding, using a breast pump, or using formula milk.

Potential respondents were then approached and informed about the set-up of the study by e-mail or by phone.

Since an effective LHS for the treatment of pregnant and breastfeeding women is currently lacking, respondents were unfamiliar with the concept of an LHS. To collect valuable answers from the respondents, we decided to give them additional information at the start of the interview. With the additional information, we introduced IMI ConcePTION (see Box 2) as a case study to explain the lack of scientific knowledge and to explain the alternative way to help close the knowledge gap. We assumed all respondents were unfamiliar with the concept of an LHS, and therefore choose to explain the approach ConcePTION is taking and further explained the term LHS as an ecosystem of continuous learning from routinely collected health data. During the interviews, the term ecosystem was used to refer to an LHS, since an LHS is mostly an academic term. In this paper, we will use the term LHS, since it is a commonly used term for systems of continuous learning in healthcare settings in the medical literature. To further explain and to help visualize all the different components of the ConcePTION ecosystem, we used a diagram (see supplementary file 1). The diagram allowed us to emphasize the circular flow in an LHS and to show the important steps in an LHS: data collection, analysis and interpretation, and output. After this short introduction, we started with the first two topics. Once these topics were discussed, we made sure the respondents understood what was meant with health data and explained how currently in the Netherlands data is being collected, stored, and used. Then we continued with the rest of the interview.

Box 2. IMI-ConcePTION

In April 2019, the Innovative Medicines Initiative (IMI) launched the ConcePTION project (Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now). ConcePTION is a European public-private partnership that aims to develop a Learning Healthcare System (called "an ecosystem") that can generate and disseminate reliable evidence-based information about medication safety and efficacy during pregnancy and breastfeeding by learning from routinely collected data and research data across Europe.[1]

During the interviews we introduced ConcePTION, and made a distinction between ConcePTION as a five-year project, which aims to build a system of continuous learning, and ConcePTION as a sustainable ecosystem, which can eventually share new scientific knowledge. A way of sharing new knowledge is through a knowledge bank, which ConcePTION aims to build for both women and their HCPs.[1]

Data collection

The semi-structured interviews were conducted by MH (trained qualitative researcher, female, MA, PhD candidate) with a topic list. The topic list was refined after two pilot interviews. According to the technique of constant comparative

analysis, the interview topics evolved as the interviews progressed alongside the data analysis.[16] Data was collected from February 2020 to January 2021. In 19 out of 20 interviews, there had been no previous contact between the interviewer and the respondents beforehand. In 1 out of 20 interviews, the interviewer and the respondent had met each other prior to the interview in an informal setting. Five interviews were performed in person in rooms at the UMC Utrecht or at the respondent's home. Due to Covid-19 restrictions, 15 interviews took place via a secure online platform. The interviews took 41 to 94 minutes with a median duration of 64 minutes. During the interviews, the order of questions was adapted to the narrative flow and the openness of the individual respondent. During and after the interviews, MH made notes to enhance the data and to provide a clear context for data analysis. The interviews were audiotaped and transcribed verbatim, coded, and stored anonymously. Written consent was obtained from all respondents. Because no intervention was imposed on the participants, the Medical Research Ethics Committee (MREC) Utrecht determined that the study was exempt from ethics review under Dutch law.

Data analysis

After transcription, we analyzed the interviews according to the thematic analysis method and by going back and forth between data collection and analysis to develop codes.[16] MH coded the transcripts using software program NVivo 12. The interpretations and suitability of the codes were discussed and compared among the research team. During analysis, codes were adapted and combined, and new codes were added to the coding list where necessary. A meaning pattern was identified across the data set, leading to the formulation of higher order themes. To enhance the validity of our results, an intern, SDH (female medical student, BSc) read the full transcripts to check the consistency of the thematic framework and critically (re)read the coding list. The findings, including the coding list and formulated higher order themes, were discussed within the complete research team (MH, RG, MS, HD). Furthermore, a member check was executed in the last phase of data analysis to discuss the accuracy and interpretation of our preliminary results.[17] Thematic saturation was reached when the occurrence of new findings ended after 20 interviews.

Results

Out of the 30 people that were approached, 22 agreed to participate in the study, 2 were excluded, 6 were unable to participate and 2 did not respond. A total of 20 semi-structured interviews were conducted with women who varied in medical indication, stage of pregnancy and reproductive history. Table 1 shows all relevant characteristics of the respondents.

Table 1. Demographic characteristics of the respondents

Respondent	Age	Education	Medical indication	Gravida Para Mater (GPM)*	Stage pregnancy
1	31-35	Graduate degree	Chronic condition	G3P0M0	Third trimester
2	31-35	Graduate degree	Chronic condition	G1P1M1	Nursing
3	26-30	Lower vocational (MBO)	Chronic condition	G2P1M1	Second trimester
4	36-40	Graduate degree	Acute condition pregnancy related	G4P1M1	Third trimester
5	31-35	Lower vocational (MBO)	Chronic condition	G3P3M2	Nursing
6	31-35	College (HBO)	Acute condition pregnancy related	G1P1M1	Nursing
7	31-35	Graduate degree	Acute condition pregnancy related	G3P2M2	Nursing
8	26-30	Graduate degree	Healthy	G1P0M0	Second trimester
9	36-40	College (HBO)	Acute condition	G2P2M2	Nursing
10	21-25	Lower vocational (MBO)	Chronic condition	G1P1M1	Wish to become pregnant
11	31-35	College (HBO)	Healthy	G1P0M0	Second trimester
12	36-40	Graduate degree	Anomaly	G1P1M1	nursing
13	41-45	Graduate degree	Healthy	G3P2M0	Third trimester
14	31-35	Graduate degree	Acute condition	G3P2M2	Third trimester
15	31-35	Highschool	Chronic condition	G1G0M0	Second trimester
16	31-35	Graduate degree	Healthy	G3P1M1	Nursing
17	31-35	Graduate degree	Healthy	G2P2M2	Nursing
18	36-40	Lower vocational (MBO)	Chronic condition	G8P0M0	Second trimester
19	41-45	College (HBO)	Chronic condition	G3P1M1	Wish to become pregnant
20	36-40	Graduate degree	Healthy	G2P1M1	Nursing

*Gravida Para Mater (GPM) represents the reproductive history by indicating the number of pregnancies (G), births (P), and children (M) of the respondents

Based on the interviews we formulated four main themes characterizing women's views and moral intuitions regarding LHSs. The themes emerged consistently across all interviews. We provide representative quotations to illustrate the themes (see Table 2).

We started the interviews by asking the respondents about their experiences with the use of medication and with the search for information about their medication. Most respondents mentioned that they experienced difficulties in finding reliable and consistent information and that drug labels lack any useful information on the safety of the medication they wanted or needed to take. We also asked healthy women whether they had taken any medication during pregnancy or breastfeeding. Interestingly, most respondents replied they had not. Only after we asked whether they had looked for information online about medication and we discussed the return of results, did it become apparent that these women had in fact taken multiple medications for milder complications or conditions, during their pregnancy or during birth and/ or recovery.

Theme 1: Views on an LHS

In principle, all respondents expressed a positive attitude towards ConcePTION as a project and as an LHS (Q1). Most respondents considered an LHS to function as a central point for data analysis and/ or as a central point for information. Some respondents emphasized the need for such a central point to help overcome the problem of contradictory information available online or from their HCPs. Some respondents argued that the information that flows from an LHS could increase their confidence regarding the safety and efficacy of medications and would allow them to take control over their own medication intake. They mentioned that they often do not know whether a medication is safe, and therefore, they rather not take any medication at all (Q2).

Some respondents stressed the importance of organizations, experts, HCPs and patients working together within an LHS. They argued that working together oftentimes means learning from each other through knowledge sharing. Combining knowledge was seen by some of the respondents as an improvement for the generation of new knowledge about the safety and efficacy of medications for, for example, different types of patients, event congenital anomalies, and women in general.

Some respondents immediately addressed the potential risks and hurdles that are associated with large data projects. They argued that they were in favor of collecting health data and the use of their health data in an LHS, as long as their privacy can be protected.

Another initial response of some respondents was that an LHS is very complicated to understand. Some respondents said that they did not understand how an LHS would work in reality but argued that it was not up to them to fully grasp it. Furthermore, respondents thought that building an LHS must

be very challenging, labor-intensive, and above all highly ambitious, because it involves many stakeholders, and it concerns a lot of data (Q3). A few respondents compared an LHS with big data projects or information technology systems, which according to them, is complex and takes years to set up properly.

Theme 2: Willingness to contribute to an LHS

Motivations for contributing

The respondents considered helping other people or helping future generations to be one of the most important reasons to contribute to the development of new information. Respondents emphasized that they want to help with preventing people from experiencing the same struggles they experienced when searching for information on medication and the struggles with becoming pregnant while also dealing with a chronic condition (Q4). Another reason mentioned was to advance scientific research, even if there is no direct benefit for themselves. Respondents highly valued scientific research and argued that it would facilitate the progress in this little explored field.

Perceived barriers and facilitators

The respondents emphasized that contributing to the creation of new information within an LHS should be non-invasive and not too time consuming. Examples of invasive and time-consuming contributions mainly had to do with undertaking a complex action, such as having to arrange your own supplies to collect for example milk or urine. Many respondents suggested combining already planned hospital visits, or other pregnancy-related check-ups with research activities to make it more accessible to pregnant and breastfeeding women. Furthermore, most respondents emphasized that the aim of the project or an LHS should be relevant to their own situation, or should be in line with their own health needs and priorities, such as fighting an illness or condition and sharing experiences.

Respect for autonomy

Most respondents argued that it is important to at least notify people about collecting and using health data. A small group of respondents wanted to give informed consent for the use of their health data for a study within an LHS. They argued that consent would allow for some control regarding the use of their own data. According to these respondents, data are something personal that should be treated with caution (Q5). Other respondents argued that giving informed consent every time a new study is performed with their data is too invasive and could negatively influence a person's willingness to contribute. Being (re) contacted for research was sometimes experienced as annoying and was not considered a priority. Furthermore, respondents put forward that when data is anonymous, then there is no added personal value in knowing or giving consent. Furthermore, multiple respondents suggested that when an LHS has been

developed it would suffice to have a clear statement on the website explaining how and by whom data is collected, analyzed, and stored. Having information available online allows people to look for the information when they want to know more.

Responsibility
All respondents felt a level of responsibility to participate in or contribute to an LHS, if possible. Reasons included: to help prevent other women from experiencing the lack of information about a chronic condition, an adverse drug reaction, the pregnancy, the newborn, doing 'the right thing', and helping with research progressing (Q6). Most respondents with a chronic condition explained that they wanted to help other women by sharing their experiences and information, because they felt part of another group or felt connected to other women because of a shared chronic disease or other shared pregnancy or maternal features. Some healthy respondents argued that they did not feel more connected to other pregnant or nursing women and did not need another group to affiliate with and/ or did not want the opinion of other women on how to be pregnant. Some of the healthy respondents also mentioned that the feeling of being connected to other pregnant women was less present during their second pregnancy. A few respondents had the opinion that, unfortunately, some women were not always aware of the knowledge gap, and therefore, do not feel as responsible to participate in research activities (Q7). Further to this, they suggested that more awareness needs to be raised to also reach these women.

Theme 3: The role of the healthcare professional in an LHS
While the interviews did not specifically focus on the role of the HCPs in the creation of new knowledge, most respondents emphasized the importance of the HCP in both the search for and dissemination of information about medication and treatments while pregnant or breastfeeding.

Searching for information
Most respondents found interpreting medical information and research results to be extremely difficult and trying medication by yourself undesirable. Most respondents felt they should consult their HCP (Q8). Many respondents consulted drug labels, the internet, and their HCP for information on the medication they were considering taking. According to them, the internet can be used for personal research prior to a consult or after to read the information again at a slower pace.

Dissemination of information
When asked about the return of results in an LHS, most respondents expressed the wish for personalized information. Many respondents valued privacy as an important principle to protect, and therefore, it was acknowledged by a few

respondents that personalized information would be difficult to realize without sharing personal information. Respondents mentioned that to fully depend on the information in a knowledge bank, it needs to be able to give decisive advice. Some respondents emphasized the need for a "yes" or "no" answer. Other respondents argued that, if personalized information is not an option, it would still be useful to have information to guide a decision regarding medication intake. A small group of respondents argued that it is always one's own responsibility to make a good and informed decision (Q9).

Most respondents asked their HCP for advice about the safety and efficacy of medication. Respondents who visit their HCP regularly because of a chronic illness or condition, argued that they rely on their doctors to give them advice on what is desirable for their specific condition. Other respondents emphasized that "everybody is different" and could respond differently to treatment (Q10). Therefore, applying the little information available to one's own situation is difficult. In general, all respondents trusted their HCP to have the knowledge or to help with deciding what is best for them. Respondents also argued that the HCP probably knows how to interpret the latest news about medication safety, because of their expertise. Some respondents emphasized that in an LHS the benefits for the HCP are much higher in comparison to the direct benefits for themselves. Respondents argued that regardless of an LHS, they would still rather rely on the information from the HCP, because they know more about their specific condition and their context.

Theme 4: Trust in an LHS

Trust in research

Most respondents view research as objective, structured and believe there is no conflict of interest. Respondents explained that they trust researchers to handle data correctly and that they trust researchers to follow the rules and regulations regarding data protection. Furthermore, some respondents argued that because they trust researchers, they do not need to be informed about every detail of the research project (Q11).

Commercial use and purposes

Commercial use and purposes were also discussed by a group of respondents. Some respondents expressed a cautious or negative attitude towards public-private partnerships in an LHS. Respondents argued that such partnerships could jeopardize the neutrality of the information, since they feel that commercially interested parties' main objective is to make money (Q12). Some respondents explained that companies like Facebook, news articles on privacy breaches and the negative reputation of the pharma industry make them more cautious of data collection and analysis in general. Respondents emphasized that they would rather not share their personal information with private organizations that

make a profit from it. Respondents questioned the level of objectivity of those companies. Respondents expressed that the interference of commercial interests in any system, negatively influences their trust in that system, and therefore, in the information that flows from that system. A small group of respondents argued that although commercial parties have an additional goal, they also stimulate and realize important progress. These respondents expressed a more positive attitude towards collaboration with private organizations in an LHS.

Transparency

Most respondents argued that transparency is of great importance for the sustainability of an LHS and for earning their trust in such a system. Respondents explained that to be transparent includes honesty about data collection, data analyses, public-private partnerships, and the way privacy is protected. Transparency also makes the information that flows from it seem more reliable and solid, because it shows that there is "nothing to hide" and all relevant information on how the LHS works is available to anyone who is interested.

Broad support from the medical community and the government

Respondents emphasized the need for support of the LHS from the medical community and the government. Having broad support by different authoritative institutions shows that the LHS is well established, and that multiple authoritative people acknowledge and trust the value of the information developed by the LHS. The interviews demonstrated that the respondents considered the research and medical community to be the experts in the assessment of new information, and therefore, respondents rely on their opinion (Q13). Many respondents argued that they would not hesitate using ConcePTION as a source themselves when their HCP would recommend it. Respondents suggested that for ConcePTION to become a sustainable LHS, it should strive to become highly trusted by the medical community.

Table 2. Representative quotations

Views on an LHS	Q1	R13: It is making me happy, the fact that you can merge information from different places to create new knowledge. I get that it is complicated and that you need to think about the methods for analysis and interpretation of results. I think it is a good development, also for the users. In this way, HCPs and women can get unambiguous information.
	Q2	R18: I think [ConcePTION] is very good, because it is just great for future patients and others to easily find good information. [...] Because it can be very frustrating right now. [...] There is a lot of contradictory and unreliable information on the internet.
	Q3	R4: It is ambitious, because you need to gather a lot of data, you need the right data and the right method for data analysis. Then you also need to interpret results and translate the results into accessible information. Not only in jargon, so that nobody understands the information.
Willingness to contribute and engage in an LHS	Q4	R2: For others, yes. [The LHS] is of little use to me, but [contributing] is more to help others in the future.
	Q5	R4: I think it is important that [consent] is asked. And that everything is not just lying around all over the place. Especially when it concerns medical data, I don't think that's being careful. So, I think this should be handled with care. Certainly. [..] At least consent should be asked [before data is shared] and it should not be just assumed that people consent to sharing data.
	Q6	R15: I am doing pregnancy-yoga, there I am in a group with all big baby bellies. And I also find it useful that I hear various tips regarding the pregnancy. I like that.
	Q7	R20: I don't think a lot of people, or pregnant women know that they can contribute to scientific research. If they would know about it, I believe they will contribute. It would help to at least give women information about the possibilities [and about the burdens and benefits of contributing].
The role of the HCP in an LHS	Q8	R8: It is better to discuss the interpretation [of results] with a GP or gynecologist. Especially on how does this [medicine] influence me and my body?
	Q9	R3: [regarding medication intake during pregnancy] It depends on the choice you make. That goes for everything in life. You are the one to decide. And if your decision turns out wrong, that mistake is yours not someone else's.
	Q10	R18: Despite the fact that you can suffer from the same condition, everybody is different, every woman is different, and every pregnancy is different. So, what works for one person, does not necessarily work for the other.

Table 2. *Continued*

Trust in an LHS	Q11	R7: I actually trust that [research] will be conducted in a good and competent way and that my data is being used for scientific research and for improving clinical practice. That would be in line with my own goal, which is nice. So, I do not necessarily need to be informed about every detail of the research process. I don't think that is problematic.
	Q12	R13: Once there is this additional goal of making profit, you cannot be objective. Even as a researcher you cannot. The pharmaceutical industry can ask researchers for certain results in exchange for a trip to Haiti. In that situation, you are no longer transparent, honest, and objective. Commercial purposes clouds that.
	Q13	R19: It should be promoted by the right people. when I would go to my doctor, for example, my doctor would say to me this is a great website to go to. I go to the midwife and she would say to me this is a great website to go to, etc. I think that's important.

Discussion

Our study with 20 women during preconception, pregnancy, or nursing, showed that these women 1) are positive about an LHS for pregnant and breastfeeding women to help diminish the knowledge gap, 2) want to contribute to the development of new information and engage in an LHS, 3) view their HCPs essential in the translation and interpretation of information, regardless of the establishment of an LHS and 4) see trust and transparency as essential for the realization and sustainability of an LHS.

To our knowledge, this is the first study that conducted in-depth interviews with pregnant and nursing women to explore their views on LHSs. In addition to the literature on patients' and stakeholders' views on health data research or health information networks, these interviews provide for an extensive understanding of how women view medication intake during pregnancy and breastfeeding, from what perspective women argue for or against contributing to an LHS, and what women of childbearing age need and wish for regarding the return of results in an LHS.

Interestingly, although this is not a quantitative study, all our respondents had taken at least one medication during their pregnancy or during breastfeeding. This finding is in line with what is described in the literature about medication use among pregnant and breastfeeding women.[2] At first, most healthy respondents, who mainly used over-the-counter medication, seemed to think their medication was irrelevant to mention or not as serious compared to medication used for chronic or acute diseases. It seemed that these respondents did not entirely realize that they may be vulnerable when it comes to the risks of a lack of knowledge on medication. At the same time, all respondents experienced difficulties with finding reliable and straightforward information about their medication.

These experiences underline the current lack of knowledge and contradicting information, described in the literature.[18]

Solidarity

Earlier studies identified multiple motivators for pregnant women to contribute to clinical research. Similar to our interview study, main motivators are improving medical research, helping others, and having a personal connection to the research subject.[19-22] Interestingly, our respondents also mentioned they felt responsible to contribute and engage to help others with whom they share a specific experience, like having a chronic condition, being in the same stage of the pregnancy, and being a new and young or older mother. In the literature, acting upon this feeling of responsibility to assist others with whom one shares a specific experience, is described as solidarity.[23] Barbara Prainsack and Alena Buyx understand solidarity as a relational practice, where being able to identify with and care for another person in a similar context are of key importance in suggesting new practical solutions to existing problems.[23] Perhaps a solidarity approach in the field of pregnant and breastfeeding women is necessary to include women in the discussion and to allow them to be actively involved in closing the knowledge gap.

Another interesting observation from our study is that women with a chronic condition seemed to experience this personal connection with the research subject and with other women more intensively. A reason for this might be that they already belong to a group of patients with a specific chronic disease or condition. It might, therefore, have been easier for them to picture other women who are going through the same experience of managing their condition and their pregnancy, and they might already have a group of women with whom they share their experiences about having to deal with a chronic disease. Furthermore, their affinity with medical research can possibly be explained by the fact that their pregnancy is medicalized early on.[24, 25] Although, pregnancy and childbirth increasingly have become medically defined phenomena due to medical technology and surveillance focused on risks, women's experiences with pregnancy-related risks are determined by the interactions with a HCP.[25] Women who suffer from a chronic condition have interactions with their HCP at an early stage, often before their pregnancy. For healthy women, this is probably different, since there are fewer interactions with HCPs and their pregnancy is not fully depended on medical care.

Dissemination of information

In general, there is a cautious attitude towards medication use during pregnancy or breastfeeding.[26] Our interviews, as well as the literature, showed that women are concerned about the impact of medication on both fetal development and their own health.[22, 27] Our interviews showed that regardless of an LHS, respondents

want to know from their HCP whether a medication is safe to use in their situation. The anxiety towards medication use and the difficulty with interpreting medical information, results in a feeling of insecurity.[28] The question is whether an LHS can take away these insecurities. Not only are HCPs important in the dissemination of information among women, but they are also important in the interpretation and translation of new insights that are generated through an LHS. Therefore, the help of HCPs in validating research outcomes and deciding what type of knowledge would be useful to pregnant and breastfeeding women is necessary. Respondents explained they wish to have information that is applicable to their specific situation. It seems that an HCP is of crucial importance in making sure the results generated through an LHS flow back to the patient in understandable language.

Subsequently, pharmaceutical companies have the duty to monitor the safety and efficacy of their medication and to update drug labels once new information becomes available. Unfortunately, it has proven to be extremely difficult to stimulate the progress of updating labels. The European Medicine Agency (EMA) has set up post-authorization measures (PAM) to make sure drug agencies collect and provide data to enable further assessment on the safety or efficacy of medication in the post-approval setting.[29] Despite these regulations, it still takes too long before labels are updated, or the assessments are not completed because of a lack of data.[6, 30] However, providing readable and solid evidence on the safety and efficacy of medication is the task of drug manufacturers. Furthermore, labels are an important source for making an informed decision. Our interviews showed that almost all respondents read the labels before taking any medication during pregnancy or breastfeeding.

Public-private partnerships and LHSs

Even though we avoided using the term LHS, respondents associated the concept of an LHS mainly with big data, information technology systems, Facebook-like platforms, and medical research in general. Although their associations are not entirely surprising, it did influence their attitude towards ConcePTION as an LHS. The overall negative attitude regarding partnerships with private parties is also often described in the literature as a perceived barrier for sharing health data for research.[27, 31] Individuals seem to be opposed to data sharing if it is motivated by financial gain or profit, or if data is shared with private or commercial companies.[31] To earn the trust of women in an LHS, it seems important to be transparent about the collaboration with private organizations, and to explain why this is vital for the realization and sustainability of an LHS.

Engagement of pregnant and breastfeeding women

Because there are only a few effective LHSs in practice and because ConcePTION is still an ongoing project, it is not surprising that many respondents did not

fully grasp the concept of an LHS. However, for the sustainability and for the willingness of women to engage in an LHS for pregnant and breastfeeding women, it is of crucial importance that women understand what it is, how it works and how certain issues, like privacy, informed consent, and private partnerships are regulated. As Seid et al. (2014) explain, an LHS depends on collaboration and engagement to really improve health care and health outcomes. According to them, engagement can be understood as the extent to which an individual takes part in the generation of new information, knowledge, and know-how, and exists along a continuum ranging from awareness, to participation, to contribution and to ownership of the knowledge generating system.[32] They continue that awareness is the first building block that introduces the individuals with the system and could lead to them becoming participants (using the tools within the system) or eventually contributors (helping with improving the knowledge and resources).[32] The same could work for women of childbearing age. Meaning that clear information about the LHS, additional tools (sources for more information, research activities, survey studies), and ways for them to be involved (joining a pregnancy advocacy group) need to become available to them. The way to reach women might be, again, different for the group of chronically ill women in comparison to healthy women. As mentioned earlier, women who suffer from a chronic condition, might already be aware of their vulnerable position and might already be involved in patient advocacy groups, or already participate in research activities.

Limitations

Our study has a number of limitations. First, we have tried to purposefully include women of all different educational levels, however, we received more responses of highly educated women. Therefore, the possibility of selection bias exists, which challenges the generalizability of the findings. Furthermore, as the results show, we interviewed women who have a positive attitude towards scientific research. This general positive attitude might not be a good reflection of the total population. Second, due to Covid-19 restrictions most of our interviews were held via an online platform instead of face to face. Third, during some of the interviews the subject of privacy was brought up by one of the researchers to help the respondents reflect upon possible risks of an LHS. Bringing up privacy as a possible risk might have altered the answers of the respondents in such a way that privacy became a concern after hearing about it. Fourth, the graph used to visualize the ConcePTION ecosystem was designed with very bright colors. Using these colors might have triggered positive responses to the explanation of the ConcePTION ecosystem, and therefore, the concept of an LHS in general. Fifth, the interviews were conducted with Dutch women only who are in a heterosexual relationship. The Netherlands might reflect a different culture and attitude towards research and health data than other countries. Follow-up research could

explore the possible variety of views of women across Europe. In addition, a more inclusive approach is necessary to make sure the (health) interests of all pregnant and breastfeeding people with different sexual orientations and gender identities get equal weight. Despite the limitations of this study, we believe the insights from the study can be used in the development of a sustainable and ethically responsible LHS for pregnant and breastfeeding women.

Conclusion

To conclude, women during preconception, pregnancy and nursing agree that an LHS could be a viable alternative to generate evidence on medication safety in pregnancy and breastfeeding, which they feel is currently lacking. The obtained insights provide valuable stepping-stones for the development of a sustainable and ethically responsible LHS. Furthermore, the results from this interview study inform the implementation of real-time results flowing from an LHS, as well as encourage the engagement of women in the development of an LHS.

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Supplementary File

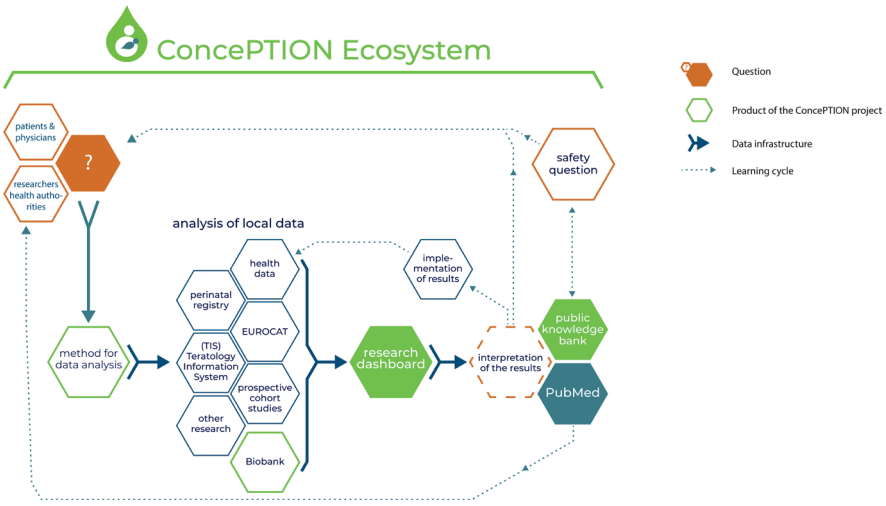

Figure 1. ConcePTION Ecosystem. *Designed by STUDIO TERP 2021*

This diagram is based on the graph used during the interviews. The diagram shows the different concepts in the ConcePTION Ecosystem and the different flows within the Ecosystem that emphasize the continuous process of collecting, analyzing, and interpreting data, the implementation of new results in care, and it shows how new results can pose new research questions for which the ConcePTION Ecosystem can be used. In this diagram, the green objects represent the results of the ConcePTION project, namely: a common data model to analyze local data, a Biobank (which will be developed in the future) that collects milk and urine samples for future research on medication exposure, a research dashboard that collects results from the analyses and can be used for the interpretation of results, and a public knowledgebank that will collect and present new insights to pregnant and breastfeeding women and their HCP.

CHAPTER 4

The perspectives of data access providers on building a sustainable learning healthcare system for pregnant and lactating people: a qualitative interview study

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Abstract

Background

In many areas of healthcare, Learning Healthcare Systems (LHSs) are seen as promising ways to accelerate research and outcomes for patients by reusing health and research data. For example, considering pregnant and lactating people, for whom there is still a poor evidence base for medication safety and efficacy, an LHS presents an interesting way forward. Combining unique data sources across Europe in an LHS could help clarify how medications impact pregnancy outcomes and lactation exposures. In general, a remaining challenge of data-intensive health research, which is at the core of an LHS, has been obtaining meaningful access to data. These unique data sources, also called Data Access Providers (DAPs), are both public and private organizations and are important stakeholders in the development of a sustainable and ethically responsible LHS. Sustainability is often discussed as a challenge in LHS development. Moreover, DAPs are increasingly expected to move beyond regulatory compliance, and are seen as moral agents tasked with upholding ethical principles, such as transparency, trustworthiness, responsibility, and community engagement.

Objective

The objective of this study is to explore the views of people working for DAPs who participate in a public-private partnership on building a sustainable and ethically responsible LHS.

Methods

Using a qualitative interview design, we interviewed 14 people involved in the Innovative Medicine Initiative (IMI) ConcePTION project, a public-private collaboration with the goal of building an LHS for pregnant and lactating people. The pseudonymized transcripts were analyzed thematically.

Results

A total of three main themes were identified: opportunities and responsibilities, conditions for participation and commitment, and challenges for a knowledge generating ecosystem. The respondents generally regarded the collaboration as an opportunity for various reasons beyond the primary goal of generating knowledge about medication safety during pregnancy and lactation. Respondents had different interpretations of responsibility in the context of data intensive research in a public-private network. Respondents explained that resources (financial and other), scientific output, motivation, agreements regarding the collaboration with the pharmaceutical industry, trust, and transparency are important conditions for participating and committing to the ConcePTION LHS. Respondents also discussed the challenges for an LHS, including the limitations to (real-world) data analyses and governance procedures.

Conclusions

Our respondents were motivated by diverse opportunities to contribute to an LHS for pregnant and lactating people, primarily centered on advancing knowledge on medication safety. While a shared responsibility for enabling real-world data analyses is acknowledged, their focus remains on their work and contribution to the project rather than on safeguarding ethical data handling. The results of our interviews underline the importance of a transparent governance structure, emphasizing trust between DAPs and the public for the success and sustainability of an LHS.

Background

In many areas of healthcare, Learning Healthcare Systems (LHS) are seen as a promising method for learning from real-world experiences.[1,2] In an LHS, healthcare and research are aligned to accelerate research and outcomes for patients and have the potential to develop scientific knowledge based on health information and research data, by directly implementing new insights from analyses to the clinical practice.[3]

For some patient populations, an LHS approach may be considered one of the most promising ways forward. For example, the group of pregnant and lactating people, who are often excluded from controlled clinical research studies and for whom there is still a poor evidence base for medication safety and efficacy. In real life, numerous medications, key to the health of the pregnant person, have been used safely and effectively in pregnancy with minimal risk to the fetus and pregnant person, but we do not systematically learn from these experiences.[4-8] Current information on medications used during pregnancy and lactation is fragmented and spread across different countries and data sources, including pregnancy or medicine cohorts, registries, research groups, and the pharmaceutical industry.[9] Examples of such data sources are the European system for the evaluation of safety of medication use in pregnancy in relation to risk of congenital anomalies (EUROmediCAT), the European Network of Teratology Information Services (ENTIS), and national population registries or regional cohorts. Accessing and analyzing these unique data sources in a system of continuous learning could help more effectively clarify how medications impact pregnancy outcomes.

In general, a remaining challenge of data-intensive health research, which is at the core of an LHS, has been obtaining meaningful access to data. A way to impact the field of pregnancy and lactation is through collaborations between various organizations (including public-public and public-private). These organizations, known as Data Access Providers (DAPs), often possess or have access to vast amounts of routine (healthcare) data, which reflect routine healthcare encounters and processes, and they have valuable expertise in managing large data sets. Collaborating with private organizations can also be beneficial as they also possess relevant data and resources. Additionally, private organizations, such as medicines marketing authorization holders, require evidence on the effects of medications during pregnancy to comply with regulatory requirements and to update product information. Public-private partnerships present their own set of challenges, such as ownership, benefits and effectiveness, impact on public interest, and achieving social license, all of which have been discussed in literature on public-private partnerships.[10, 11] Additionally, frequently discussed in the context of LHS development is the challenge of establishing a sustainable collaboration capable of consistently facilitating the processes of data collection, analyses, and dissemination of research results.[2, 12-14]

At the same time, more and more it is expected of these DAPs as data controllers and/ or processors to look beyond compliance with regulation to protect the privacy and use of data. The General Data Protection Regulation (GDPR) includes various rules and principles for data controllers to ensure transparency and adherence to principles such as fairness, purpose limitation, data minimization, accuracy, storage limitation, integrity and confidentiality, and accountability, while granting certain rights to data subjects (GDPR, Articles 5 & 6).[15] Ultimately, DAPs are viewed as moral agents who must respect ethical principles such as transparency, trustworthiness, responsibility, and community engagement.[16]

To realize a sustainable and ethically responsible LHS, it is important to know whether people working for these organizations acknowledge their role and responsibility in safeguarding responsible use of data and the dissemination of research outcomes to the public. Rising expectations with respect to DAPs' responsibility for ethical use of data and data ownership, does not necessarily mean that each of these organizations has a dedicated governance structure to safeguard these principles, or that people working for DAPs feel as if they are a moral actor in an LHS. Moreover, apart from the obvious differences in management and reward systems between DAPs,[17] these organizations may also have different motivations for collaborating in an LHS. Furthermore, their perspectives on the sustainability of an LHS and their roles once the project phase concludes may also diverge.

Objectives

In this study, we aimed to explore the views of people working for DAPs who participate in public-private partnerships on building a sustainable LHS. We were especially interested in the views of DAPs contributing to the Innovative Medicine Initiative (IMI) ConcePTION project, which aims to build an LHS for pregnant and lactating people.[18] By using a qualitative interview design, we hoped to identify, better understand, and juxtapose peoples' views and interests in collaborating in an ecosystem that utilizes routine health data to generate new knowledge for pregnant and lactating people and their doctors. By providing insight into the views and interests of people representing DAPs in this particular LHS, this study intends to inform a governance framework for LHSs, and in turn, to help facilitate the development of a sustainable LHS in which public and private organizations collaborate. Moreover, this study aims to contribute to the ongoing discourse on moral responsibilities associated with responsible data handling and dissemination of research findings, particularly by exploring whether DAPs themselves perceive and articulate this moral responsibility.

Method

Design

We conducted a qualitative study design to collect the views and interests of people who work for organizations and who act as a DAP in the ConcePTION project. This qualitative interview study is a sub-study of the IMI ConcePTION-project (textbox 1). IMI ConcePTION was used as the primary case study during the interviews and as the source for participation selection. The study is reported following the consolidated criteria for reporting qualitative studies (COREQ).[19] We performed semi-structured interviews with a topic list (see the general topic list in Table 1). The topic list was based on the topic list used for another qualitative interview study, in which we asked women during pre-conception, pregnancy, and nursing what they thought about an LHS for pregnant and lactating women.[20] The topic list was also based on an analysis of the challenges of public-private partnerships, LHSs, and responsible data sharing,[1, 10, 21] as well as discussions among the research team. In order to mitigate the potential for socially desirable responses from our respondents, it was determined that the topic of moral responsibility regarding the utilization of data and dissemination of research findings would not be included in the general topic list. Instead, the opportunity for spontaneous or organic discussion of the topic was provided during the course of the interview. Moreover, it was expected to be, for example, discussed under topic 2: "expertise and dual roles". This topic provided an opportunity for DAPs to elucidate their roles and responsibilities concerning their primary organization, their involvement in the ConcePTION consortium, and in certain instances, their clinical obligations.

Box 1. Description of the initiation, aim, and composition of the IMI ConcePTION project

In April 2019, the Innovative Medicines Initiative (IMI) ConcePTION project was launched, which aims to establish a trusted ecosystem that can efficiently, systematically, and in an ethically responsible manner, generate and disseminate reliable evidence-based information regarding the effects of medications used during pregnancy and breastfeeding to women and their healthcare providers (HCPs). The ConcePTION consortium consists of European public and private stakeholders, including national public health institutes, the European systems for the evaluation of safety of medication use in pregnancy in relation to risk of congenital anomalies (EUROmediCAT), the European Network of Teratology Information Services (ENTIS), research institutes, universities, and pharmaceutical companies. The ConcePTION consortium is currently a public-private partnership, however, the approach of ConcePTION to collect and learn from real-world data on the safety of medicines during pregnancy and breastfeeding is similar to what may also be called a learning healthcare system.[6]

IMI: Innovative Medicines Initiative. ConcePTION: Continuum of Evidence from Pregnancy Exposure, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now.

Table 1. General topic list used during the qualitative study to guide the interviews

Willingness to participate
Expertise and dual role
Future (after consortium agreement ends)
Conditions for working for the ConcePTION LHS
Added value

Sample and Setting

To capture a wide range of interests and perspectives (contrast maximization), a variety of people from different types of organizations and different countries were identified. We aimed to include people who are working as DAPs in partnering organizations and third parties in the ConcePTION project. To be able to invite people working for different DAPs, we distinguished between private (pharmaceutical companies and private centers) and public organizations (universities, teratology information centers, public health services, and hospitals), countries, regions, collaborative partnerships, and occupations. Respondents were recruited using purposeful sampling, with the help of colleagues from the ConcePTION consortium. Respondents were approached by e-mail. Most of the interviews started with an introductory question relating to the work of the respondent and the process of data collection, storage, and analysis within their organization. We then used the topic list to continue with the interview. Although the approach of ConcePTION is similar to an LHS, we used the term ecosystem and network interchangeably. The reason for this is that the term ecosystem is commonly used within the consortium and is more familiar to the respondents. The interviewer (MJH) created a safe space for respondents and invited them to share their views and experiences, by at least emphasizing 1) the privacy and confidentiality arrangements, 2) their autonomy during the interview (for example regarding answering questions, stopping the interview, asking for clarification), 3) the option to review the transcript before analysis. These points were emphasized by the interviewer before verbal consent was asked. The interview allowed respondents to introduce or emphasize particular new issues they considered relevant. Therefore, it is important to stress that the results reflect personal views and do not represent the view of the entire organization the respondents work for.

Data collection

The interviews were conducted by MJH (trained qualitative researcher, female, MA, Ph.D. candidate) using the topic list. The topic list was refined after two pilot interviews. Furthermore, according to the technique of constant comparative analysis, the interview topics evolved as the interviews progressed alongside data analysis.[22] Data were collected from November 2021 to February 2022. The

interviews were conducted in English and Dutch and took place via a secure online platform. The interviews took 33 to 60 minutes with an average duration of 44 minutes. In 12 out of 14 interviews, there had been no previous contact between the interviewer and the respondent beforehand. In 2 out of 14 interviews, the interviewer and the respondent had contacted each other before for project-relating work. During and after the interview, MJH made notes to enhance the data and to provide a clear context for data analysis. The interviews were audiotaped and transcribed verbatim, coded, and stored anonymously. Verbal consent was obtained from all respondents. One respondent requested to read the transcript before analysis.

Data analysis

After transcription, we analyzed the interviews according to the thematic analysis method and by using a backwards and forwards approach between data collection and analysis to develop codes.[22] An initial coding list was developed based on the topic list. Subsequently, we coded the transcripts. The coding list was evaluated and adapted, and all interviews were coded using NVivo 12 software. To enhance the validity of our results, an intern (medical student, BSc) also read and coded 8 randomly chosen interviews out of 14 pseudonymized interviews to check for consistency of the thematic framework and critically (re)read the coding list. In the course of the analysis, codes were adapted, and additional codes were added to the coding list where necessary. A meaning pattern was identified across the data set, leading to the formulation of interpretative higher-order themes. The themes capture the views and interests of DAPs regarding the ConcePTION ecosystem. The themes represent both topics that were often discussed by respondents and a variety of views that are of help in the development of a sustainable ecosystem of continuous learning. The findings, including the coding list and formulated higher-order themes, were discussed within the complete research team (MJH, RvG, MCJMS, JJMvD). Thematic saturation was reached when additional data did not lead to any new emergent themes after 14 interviews.[23] Furthermore, a member check was executed in the last phase of data analysis. A draft version of the manuscript was sent to all respondents to which they were invited to respond to discuss the accuracy and interpretation of our results.[24]

Ethical considerations

The research protocol including the procedure for informed consent was reviewed and approved by the institutional research support office at UMC Utrecht. As no intervention was imposed on the participants, this study was exempt from ethics review under Dutch law. All participants were provided with a letter of information and gave their verbal consent for participation and recording as required under the Dutch law that implements the GDPR (*uitvoeringswet algemene verordening gegevensbescherming*). Each participant was assigned a study ID number to

protect their privacy and confidentiality. Furthermore, their names, the names of their workplace and other names of consortium members mentioned in the interviews were redacted by the interviewer MJH. The participants were not compensated for participating in the study.

Results

Out of the 23 DAPs that were approached, 14 agreed to participate in the study, 4 declined and 5 did not respond. A total of 14 semi-structured interviews were conducted with 18 people involved in IMI ConcePTION. Two of the DAPs were represented by two employees of the same organization or research collaboration. Interview respondents worked in different organizations, including universities, public health centers, hospitals, teratology information centers, pharmaceutical companies, and private centers. Table 2 shows all the relevant characteristics of the respondents. We could not share all details, to ensure the privacy of the respondents.

As a result of constant comparative analysis during the qualitative study, we enhanced our interview guide. During the first couple of interviews the subject of (moral) responsibility was not (always) organically discussed. Therefore, we added to the second topic "expertise and dual roles" the possibility for asking DAPs directly about their sense of responsibility and to whom that responsibility was directed, if relevant. We still decided to leave the answers open and not steer too much in the direction of the sense of moral responsibility regarding the utilization of health data and dissemination of research findings, to avoid socially desirable answers.

Based on the interviews, we formulated three main themes characterizing the views and reflections of DAPs on the development of a knowledge-generating ecosystem for pregnant and lactating people. These themes emerged consistently across all interviews. We provide representative quotations to illustrate the themes (see Table 3).

Theme 1: Opportunity and responsibility

Most respondents wanted to contribute to the ConcePTION project because they view the project as an *opportunity* to 1) contribute to the goal of creating knowledge on the safety of medication used during pregnancy and lactation, 2) look at medication safety, birth defects in a bigger context (namely European wide), 3) collaborate and share experiences with other registries, databases and the like (Q1), 4) stimulate scientific research, 5) to learn from others and their registries, and 6) showcase their databases and share expertise (Q2).

Table 2. List of characteristics of the respondents

Respondent number	Type of organization	Public/ private organization	Location of the organization
R01	University	Public	Southern Europe
R02	Research Institute	Public	Southern Europe
R03	Pharmacoepidemiologic research institute	Public	Central Europe
R04	Research Institute	Public	Northwestern Europe
R05	Hospital	Public	Central Europe
R06	University	Public	Northern Europe
R07	University	Public	Western Europe
R08	Pharmaceutical company	Private	Central Europe
R09	Public Health Service	Public	Middle East
R10	Pharmaceutical company	Private	Western Europe
R11	University	Public	Northwestern Europe
R12	Hospital	Public	Northwestern Europe
R13	Centre of Health	Private	Middle East
R14	University	Public	Northwestern Europe

List of characteristics of the respondents, categorized based on the respondent number, type of organization, whether it is a public or private organization, and the general location of where the organization is based.

Respondents also emphasized the need to utilize real-world data. Some respondents mentioned that they feel it is their *responsibility*, or as one respondent expressed, *moral obligation* to contribute, because of the database or resources they have access to. They felt that they, with their organization, are in the position to contribute to something important, and therefore they must (Q3). Some have been working for a very long time on this specific topic and have already contributed greatly to solutions to close the knowledge gap on medication safety in pregnancy and lactation. Only a few mentioned they feel responsible for helping these groups of people, others saw the lack of knowledge more as a motivation to contribute to the ConcePTION ecosystem (Q4).

Besides articulating a responsibility towards pregnant and lactating people, their offspring and their doctors, the respondents of the private industry also explained that they need to generate knowledge because it is a requirement from the European Medicines Agency (EMA) and Food and Drug Administration (FDA). Because they are required to research medication safety among pregnant people, this was considered to be another type of obligation and with that, a different type of willingness to participate.

Table 3. Representative quotations

Theme 1: Opportunity and responsibility	Q1	R09: It was another opportunity for us to exchange data on a wider basis. […] Share with one another might be an interesting experience.
	Q2	R02: The first thing to remember, is that we want to be important. We want to continue being bold. Because at the end, it's big; ConcePTION. It has a lot of power. We want to be there. Not for, only for some type, scientific purposes. But the main one is, to include our data.
	Q3	R03: think it's two things. One is we feel the obligation, because we have a large database, so it's a moral obligation I think – or we think. And the other one is also because we like working in this team.
	Q4	R14: I'm excited to be in this field, because you can help people improve their health whether it's women or children, doing this study, or in other types of study we do. I'm not sure I'd use the word responsible in that context, but definitely it's a motivating factor.
	Q5	R03: then we would have some safeguards that we are the ones who say "Yes, this data can be used", or the results. We have obligations to the data providers; we need that these are full in. So the problem is if we have like one day to review the results and then something is published, we will kind of have problems with our obligations.
Theme 2: Conditions for participation and commitment	Q6	R07: To be sure that at least we have one [person] working on this. And that it is a very stable income. Because otherwise we are looking for the calls [tenders] and running for them. And yeah, it takes a lot of time, and when we spend time on this, we don't spend time on thinking about the research we're performing.
	Q7	R03: We are a research institute, and we get evaluated every seven years, and we are measured on publications mostly. So, research is a value for us and publications is important for us, and especially also first and last authorships. So we need to focus our resources on getting some publications.
	Q8	R13: There needs to be some rules, an agreement about our participation and how much pharma can affect the processes and how much pharma can receive from this and every package actually, so it should be in some agreement written down.
	Q9	R03: What I would want is to have more time to discuss things like double programming and also to decide like decisions implicitly made.

Table 3. *Continued*

Theme 3: Challenges for a knowledge-generating ecosystem	Q10	R02: [In] the end, you're going to need a person who understands the data and to analyze [the data] how is the meaning of the data? Because if you are, at the end, just a numbers situation. You are not thinking about this biological play. Classical or not. Or if it makes sense with your kind of population.
	Q11	R08: In many countries that are strict data privacy rules and when for a given observation, there are like less than four observations, the results are masked. […] that means that I cannot use the data when combining data from several studies. So one thing that I think would be beneficial is to see if there would be data privacy rules that would be lifted for pregnancy studies.
	Q12	R10: So, but it's a big assumption. Because academia is involved, you know, […], taking care of [the governance; the data privacy]. And […] they will handle the trust part. I trust them or [when academia] are taking the lead in this project, I'm like: "okay I think they will take care of everything". […] They (academic partners) are extra careful, and that extra carefulness is making collaborating complex and difficult.
	Q13	R08: But here one of the biggest questions is the sustainability. So how this platform will be, I'm saying platform and it's not the exact quote, but how this platform will be sustained after ConcePTION.

Representative quotations from the respondents used to illustrate the identified themes.

A few respondents also expressed feeling a responsibility for enabling research and the quality of the data analyses, and because of that, they want to be involved in the decision-making regarding the development and testing of analytical scripts within the research ecosystem.

Lastly, one respondent also mentioned their responsibility and obligations towards other *data providers*. Some organizations receive data from other organizations, such as health insurance providers. Because of these obligations, they wanted to remain in control over some of the review processes in terms of data programming and analyses (Q5). However, challenges in this regard were also discussed due time and financial constraints, and short research deadlines. None of the respondents talked about their role as data controllers, meaning their responsibility to determine the purpose for which and how personal data are processed.

Theme 2: Conditions for participation and commitment

Respondents explained that their willingness to collaborate within the ConcePTION LHS depends on certain conditions that need to be in place.

Resources and support

In all interviews, financial resources were discussed as an important condition. Interestingly, financial resources were mentioned as important for reasons beyond the immediate need to cover resource costs associated with participation in a project. Financial resources were discussed in the following ways: 1) as a stable flow of income, preferably contracted for an extended period and covering all the planned activities, and (2) as a source of funding. A stable flow of income is beneficial for attracting and training more employees in this area of work and will help with distributing tasks and becoming more specialized and efficient in the field of pharmacoepidemiology. Agreements on financial support are also necessary for planning and being less dependent on other sources to keep "the system running" (i.e. tendering), which is oftentimes time consuming (Q6). Regarding sources of funding, some respondents stated specifically that they cannot receive funding from the private industry. They believe that because they are independent (public) institutions, there would be a conflict of interest.

Other respondents mentioned that besides financial resources, they also need IT and computational resources for doing the actual analyses and for making sure they can keep up with the heavy computational work which is necessary for sustaining the data analyses.

Some respondents mentioned they are not used to writing certain types of protocols or experience challenges with receiving ethics approval for studies. Some respondents suggested that ConcePTION could have a permanent staff for support and to be able to ask questions regarding timelines, deadlines, funding, ethics, and events.

Scientific output and motivation

The importance of scientific output was stressed during the interviews. Some respondents work in academic institutions whose aim is also to produce scientific publications (Q7). Therefore, their willingness to participate in an ecosystem is also affected by whether they get to perform and design studies within the ConcePTION LHS and publish those results in scientific journals. With that, some respondents also emphasized the need for asking more scientific questions and implementing more scientific methods within the network. They mentioned that working within the ConcePTION ecosystem should be different from tendering for projects from pharmaceutical companies. Lastly, respondents also want to feel motivated to commit to the ConcePTION ecosystem. Motivation, according to them, is stimulated in different ways, but most importantly by scientific interest in the project, autonomy regarding work, respect for expertise, and good working relationships. A few respondents also expressed the importance of providing valuable and accessible knowledge to pregnant and lactating people and HCPs as

a condition for contributing to the ecosystem. They felt that generating valuable information for these stakeholders is the most important goal of an ecosystem such as ConcePTION.

Safeguards

Safeguards were also mentioned as a condition for working for the ConcePTION ecosystem. A few respondents were hesitant regarding the role of the pharmaceutical industry in the processes of formulating research questions, co-writing protocols, and analyzing results (Q8). According to them, industry involvement could conflict with the primary goal of the research, or they considered it challenging to align the goal of the private and public industries. Other respondents, who work for pharmaceutical companies, regretted this view and argued that collaboration is very much needed and possible because of independently determined regulations which govern both public and private organization research into the effects of medicines. With that, they stressed that trust and open-mindedness toward each other are important for good collaboration.

Another safeguard mentioned by some respondents had to do with transparency. They argued that in a large network and with a developing ecosystem, it is important to be able to track every step and decision made regarding techniques and methods. One respondent explained how in the process of data analyses, a lot of decisions are made, which can influence the quality and value of the results (Q9). A few respondents also mentioned that to safeguard the quality of data analyses, especially in the developmental phase of the ecosystem, decisions about technical aspects such as programming and writing scripts for analyses need to be transparent for all DAPs. In that way, DAPs can perform their own quality checks if desired and can provide valuable feedback.

Theme 3: Challenges for a knowledge-generating ecosystem

When asked about their perspective on the development of a knowledge-generating ecosystem, respondents talked about challenges they have experienced so far and which according to them, are relevant when building the ecosystem.

Data (is not information)

Some respondents explained that there are challenges in harmonizing the databases and executing studies because of the heterogeneity of the data across all databases. Some respondents also mentioned that it may be challenging to generate reliable information based on so heterogenic data, databases, and IT systems. And most importantly: data is not (yet) information/ knowledge. To overcome this challenge, respondents discussed three types of solutions. First, to

be able to interpret data and to develop valuable information, many respondents emphasized the need to involve experts who know the data and the real-life healthcare context of the subjects and data points represented in the different datasets (Q10). Second, respondents mentioned the need for security and quality assessments to make sure analytic scripts fit the data and are correctly run at every organization. Third, a few respondents would prefer to work in small teams so that they can exchange experiences with scripts, data analyses, and research questions. According to them, working in small teams creates a better overview of the possibilities and limitations of the data.

Governance

Some of the respondents experienced challenges due to governance procedures. On the one hand, it was mentioned that these procedures are challenging because countries have different data privacy rules, sometimes complicating the ability to perform observational studies (Q11). On the other hand, it was mentioned that these procedures are challenging because their own company or organization restricts certain (research) activities. Some respondents argued that in academia, people exert extreme caution regarding governance, which creates an additional barrier to collecting, sharing, and analyzing data. With that, one respondent assumed that the involvement of academic institutions in the consortium implied that matters such as data handling, privacy and confidentiality, and trust were adequately addressed. However, according to the respondent, this also led to an increase in bureaucratic steps, making collaboration more intricate and challenging (Q12). Furthermore, respondents agreed that having fragmented governance procedures lead to slow processes and unfulfilled opportunities. A clear overview of what can be done with the data could be of great help, according to these respondents.

Concerning governance, some respondents discussed the need for trust between all collaborators, especially regarding the aim of and methods used within the ecosystem. It was also mentioned that people need to trust the decisions made by people taking a more leading role in the ecosystem and that trust between the public and private participants is necessary for making sure robust knowledge is going to be generated transparently within the ecosystem. Lastly, many respondents emphasized the need for a good sustainability model for the ConcePTION LHS (Q13).

Discussion

The results of our analysis indicate that respondents feel responsible to participate in an LHS for pregnant and lactating people. Although respondents emphasized the professional opportunities that come with participating in a large public-

private partnership, many respondents collaborate because they want to help develop an ecosystem that can transform real-world data into new knowledge on medication safety and efficacy.

Moral responsibility

From our interviews, it seems that people mainly reflect upon their views and responsibilities from the perspective of their professional role as a data analyst or as a pharmacoepidemiologist. As a result, most answers were linked to the more technical side of realizing a system in which real-world data can be utilized, together with a sense of moral responsibility towards the quality of their data, databases, and data analyses (under theme 1 and as mentioned in Q5). On the one hand, technological responses are not surprising because of the expertise of our respondents. On the other hand, our respondents work at the core of data processing and analysis, which means that their role is also to handle the data ethically. Some of our respondents mentioned that they assume that compliance with rules and regulations is being taken care of by either other departments of their organization or other people within the LHS, and therefore, did not worry so much about the ethical handling of data. However, compliance with rules and regulation is a narrow understanding of handling data ethically, because it oftentimes solely refers to protecting the privacy and confidentiality of data subjects – an aspect extensively discussed in the interviews and sometimes perceived as a complicating factor for research. Although many respondents viewed contributing to ConcePTION as an opportunity to generate new information for pregnant and lactating people, there appears to be a lack of widespread moral responsibility towards data handling from the perspective of pregnant and lactating people. Some respondents also considered pregnant and lactating people themselves to be disconnected from the work they are responsible for. However, during the member check some respondents expressed that they did not feel accurately represented in the portrayal of their views on this topic. For them it was important to recognize that they feel responsible for contributing to the ConcePTION project.[25]

Trust and transparency

Interestingly, trust and transparency were discussed as important aspects of the relationship between the participating organizations. Respondents explained that trust and open-mindedness are important conditions for working towards a common data model and getting everyone to share the same vision for the LHS. In the literature on public-private partnerships, big data research, and data-intensive research in healthcare, trust is also often mentioned as a crucial principle for effective collaboration.[10, 26, 27] During the interviews, there was hesitancy among respondents about the prospects of public-private collaboration. . Some respondents mentioned that they believe they are officially constrained by their

institution to closely collaborate with the pharmaceutical industry or cannot share any data (pseudonymized or not) with the pharmaceutical industry. This constraint challenges the effectiveness of the collaboration and as a result, might complicate the development of a sustainable LHS as a public-private partnership. Interestingly, the ConcePTION project is currently a consortium operating with a consortium agreement, making reference to the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) code of conduct (2010).[28] The ENCePP code of conduct aims to maximize transparency and promote scientific independence. Furthermore, typically, a consortium agreement addresses the issues of a conflict of interest by making agreements on ownership and intellectual property, obligations and rights of the participating parties, and third-party agreements. It seems that although many of the concerns of our respondents are addressed in the consortium agreement, they are not aware of these arrangements or they still experience dilemmas regarding the collaboration and/ or their own interests, which can lead to a continued lack of trust between the public and private industry. It might be worthwhile closing this gap between the consortium agreements and the experiences of collaborators by making sure everyone understands the consortium structure. In the literature on large research consortia, it has been argued that transparency is important for realizing an appropriate governance framework for these types of complex collaborations. Here, transparency refers to the accessibility and visibility of the governance structures. Within a consortium, for example, good governance requires that those internal or external to the project know what governance structures and procedures are in place, what mechanisms for legitimate decision-making have been adopted, and where authority and responsibility for different types of actions are located in the consortium.[17] Our interviews underline the importance of transparency in the context of governance of an LHS with public and private organizations. One solution is the installation of a separate independent body, especially when the contractual agreement of the consortium has come to an end. Some scholars suggest a Data Access Committee (DAC) that can help protect data subjects from foreseeable harm, stimulate social value, and mandate clear lines of accountability, terms of reference, and membership.[29]

Public trust

The above-described perceptions of trust are of course important, however, both the literature and our previous interview study with women during pre-conception, pregnancy, and nursing show that public trust is also of crucial importance for the development of an LHS.[20] In the literature, it is emphasized that it is important to meet the public expectations for transparency when developing an LHS, which in turn will strengthen or maintain trust in not only the LHS but also the institutions working within the LHS.[26] People expect their voluntary contribution of their data to be used to improve the care for others, and that their good faith will not

be exploited. Much depends, therefore, on the extent to which uses of personal data are seen as serving the public interest and conducted by those with a public interest orientation. It is of great importance that in an LHS public interest is taken into account to realize transparency, increase responsibility and earn the trust of the public. Interestingly, some of our respondents seem to expect that others in their organization are taking care of these principles that are important for public trust, or are, again, not fully aware of the governance and arrangements within the organization or the collaboration.

Future of an LHS for pregnant and lactating people

Many respondents view the ability of conducting scientific research within a broader context as a crucial opportunity. Engaging with a diverse range of organizations can not only enhance the quality of data analyses, but also improve the integrity of individual databases. While research is essential in a knowledge-generating ecosystem, the implementation of research within the healthcare system is equally important. Respondents affiliated with academic institutions emphasized the significance of publishing new findings in scientific journals, as it is a key aspect of their professional responsibilities. In an LHS, it is imperative to move beyond the conventional practice of publishing primarily in scientific journals and instead prioritize the ethical integration of learning within the delivery of care.[30] This approach would allow for the continuous improvement of care through the application of new insights, while also ensuring the proper management of data. Pharmaceutical companies already apply this method to a certain extent by generating evidence and translating findings onto product labels and educational materials for healthcare providers. Perhaps the dissemination of new insights is an area in which these parties should work together and learn from each other. As LHSs mature, it is crucial that all stakeholders recognize and embrace the system's necessity and value, extending beyond the project phase to include patients, physicians, scientists, institutional boards, pharmaceutical companies, governments, and other relevant parties.

Limitations

Our study has several limitations. First, we have tried to purposefully include both public and private industry partners, however, we have received more responses from people working for public organizations. With that, we were not able to include people working in the eastern part of Europe, which challenges the generalizability of our findings as Eastern European organizations might reflect a different culture and attitude towards an LHS. Second, although we wanted to avoid socially desirable responses, the topic of moral responsibility regarding data handling was not always organically discussed during the interviews. To address the topic, the interviewer directly asked some of the respondents about their sense of responsibility for specific aspects of their work. Openly discussing

the topic could have influenced the initial position of the respondent. We would also like to stress that we spoke to individuals who represent their organization in the context of the consortium, however, they do not represent the views of their organizations. Therefore, their views were subjective and might be different from other people working for the same organization. It would be interesting to understand the views of DAPs outside the context of pregnancy. As mentioned in our introduction, in many areas of healthcare, LHSs are seen as a promising way to learn from real-world data. To establish a successful LHS, more research is needed on the perspectives of the stakeholders involved.

Conclusion

To conclude, people working for DAPs have different reasons for contributing to a project like IMI ConcePTION, which aims to build an LHS for pregnant and lactating people. The most common motivation was opportunity. The opportunities included creating knowledge on medication safety during pregnancy, examine medication safety in European context, collaborating with and learning from other experts, stimulating scientific research, presenting their database, and secure financial support. Although many respondents expressed a responsibility to enable real-world data analyses, their focus was primarily on their work and contribution to the project rather than safeguarding ethical data handling from the perspective of pregnant and lactating people. The results of our interviews underline the importance of a transparent governance structure that addresses decision-making processes, authority, responsibility, and accountability. Trust between DAPs and public trust are important for the success of a public-private LHS, and with that, the sustainability of such a collaboration. For an LHS, it is essential that all relevant stakeholders recognize and embrace the need for and added value of the system itself.

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CHAPTER 5

Stimulating solidarity to improve knowledge on medications used during pregnancy

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Abstract

Background

Pregnant people have been overlooked or excluded from clinical research, resulting in a lack of scientific knowledge on medication safety and efficacy during pregnancy. Thus far, both the opportunities to generate evidence-based knowledge beyond clinical trials and the role of pregnant people in changing their status quo have not been discussed. Some scholars have argued that for rare disease patients, for whom, just like pregnant people, a poor evidence base exists regarding treatments, solidarity has played an important role in addressing the evidence gap. This paper explores whether and how the enactment of solidarity among pregnant people can be stimulated to help address the poor evidence base on medications used during pregnancy.

Method

We use the concept of solidarity formulated by Prainsack and Buyx and enrich their concept by providing an account for stimulating the enactment of solidarity. Then we apply this account to the case of pregnant people who use medication.

Results

Solidarity means enacted commitment on the part of an individual to assisting others with whom the person recognizes a similarity in a relevant respect. Although solidarity cannot be imposed, we argue that the empowerment of people is a crucial concept in understanding how solidarity can be stimulated. Empowerment in the context of pregnant people means creating awareness about their status quo, explaining how scientific research can help close the knowledge gap, and how pregnant people can themselves contribute. In particular, how pregnant people can contribute to the collection of health data to strengthen the evidence base for medications used during pregnancy.

Conclusions

We conclude that acting in solidarity can help change the status quo for pregnant people. Furthermore, we argue that the empowerment of pregnant people and other relevant stakeholders is a way to stimulate the enactment of solidarity. The process of empowerment starts by raising awareness about the lack of evidence on medications used during pregnancy and by explaining to pregnant people how they can contribute to changing the way knowledge is being generated by, for example, sharing data on the health effects of medications.

Background

Although the inclusion of pregnant people in clinical research has been widely promoted over the last decade (see table 1), the evidence base for medication use during pregnancy remains poor. Drug manufacturers hesitate to conduct clinical trials with pregnant people, and pregnant people hesitate to participate in clinical trials, because of a fear of risks for the developing fetus.[1, 2, 3] Medications diethylstilbestrol (DES) and thalidomide are often mentioned as examples of tragedies that have strengthened the precautionary attitude towards the inclusion of pregnant people in clinical research. Between 1938 and 1971, DES was prescribed to an estimated 1.5 to 3 million pregnant people to prevent miscarriage. The drug was later found to be ineffective and linked to several harmful complications for the offspring.[4, 5] In the late 1950s, thalidomide was prescribed to pregnant people for nausea without prior testing, resulting in unforeseen teratogenic effects and severe birth defects in over 10,000 children.[6] Although neither tragedy involved clinical research, they had a significant impact on the research community's already protectionist approach towards pregnant people. Currently, 95% of medication labels (including vaccines, medication for obstetric and non-obstetric illnesses and conditions, and prescribed and over-the-counter medication) do not provide information on the safe use during pregnancy.[7, 8] Pregnant people and their healthcare professionals (HCPs) often face making treatment decisions based on limited evidence, which sometimes mistakenly leads to not taking medication or discontinuing treatments, which can have adverse effects on both the pregnant person and the developing fetus. Even less information is available about the exposure of the newborn to the medication through lactation. With that, the lack of knowledge on medication safety and efficacy does not only affect women but also transgender men and gender diverse people. Therefore, this paper will refer to pregnant people.[9]

There are strong ethical reasons to change the way evidence is currently being generated and disseminated. Given the vast availability of real-world data on medication prescriptions and health outcomes, generating evidence by learning from previous and current medication use through a Learning Healthcare System (LHS) could be an alternative strategy. In an LHS, clinical practice and research are integrated in such a way that they can support each other and accelerate research and outcomes for patients and their physicians and make the implementation of new insights in clinical practice easier.[10] Most pregnant people take at least one medication during pregnancy,[7] and numerous medications are routinely used safely and effectively in pregnancy; however, we do not yet systematically learn from these experiences. There are many databases across the world that collect or have access to unique and relevant data. None of these databases was designed to cover all aspects needed to evaluate (long-term) efficacy and safety of medications used during pregnancy or to function as a meta-registry.

Table 1. Overview of initiatives and guidelines on the inclusion of pregnant people in clinical research

Initiative or guideline	Description	Link to website
The Second Wave Initiative 2009	The Second Wave Initiative is a collaborative academic effort from the United States that aimed to identify, develop, and advance ethically and scientifically responsible solutions for increasing the knowledge base for the treatment of pregnant people who have medical conditions.	https://www.secondwaveinitiative.org
PHASES 2016	Pregnancy and HIV/AIDS: Seeking Equitable Study (PHASES) seeks ethical solutions to advance research at the intersection of people's reproduction and HIV prevention, treatment, and management. PHASES is an interdisciplinary, research-driven project funded through the U.S. National Institute of Allergy and Infectious Diseases of the National Institutes of Health and collaborates with international leaders in different fields across the world.	http://www.hivpregnancyethics.org
United States Task Force on research specific to pregnant and lactating women (PRGLAC) 2018	The 21st Century Cures Act established PRGLAC to advise the Secretary of Health and Human Services (HHS) on gaps in knowledge and research on safe and effective therapies for pregnant and lactating people.	https://www.nichd.nih.gov/about/advisory/PRGLAC
PREVENT 2018	Pregnancy Research Ethics for Vaccines, Epidemics and New Technologies (PREVENT) has developed concrete, actionable, consensus-driven ethics guidance on how to equitably include the interests of pregnant people and their offspring in vaccine research and development for priority pathogens and emerging epidemic threats. PREVENT is led by researchers from the United States, with external contributions from international experts.	https://bioethics.jhu.edu/research-and-outreach/projects/prevent/
CIOMS International Research Ethics Guidance (guideline 19) 2016	The Council of International Organizations and Medical Sciences (CIOMS) provides guidance to a number of pressing issues in research ethics, including research with pregnant people. CIOMS represents a substantial proportion of the international medical scientific community through its member organization across the world.	https://cioms.ch

Transforming the available evidence base for pregnant people by creating and operating within an LHS that utilizes real-world data to generate evidence reliably could be a solution. Such a system could stimulate informed decision-making regarding treatments for pregnant people.[11]

To be able to utilize real-world data in an LHS, pregnant people need to support this system change. Interestingly, instead of thinking about ways to change the system of knowledge generation altogether, the focus has been, until now, on the role of individual stakeholders, such as research ethics committees, researchers, funding agencies, manufacturers, pharmacologists, and guideline committees to safeguard the interests of pregnant people in clinical research.[12] As a result, the role of pregnant people in changing the status quo and the opportunities to generate evidence-based knowledge beyond clinical trials have not been explored. Moreover, there is little demand from within pregnant people acting as a community for a systemic change.[13]

From the literature, we know that solidarity plays an important role among rare disease patients, for whom, just like pregnant people, a poor evidence base regarding medications exists.[14, 15] It has been argued that solidarity among rare disease patients strengthened their role in shaping the research agenda and allowing them to share knowledge, experiences, and resources to achieve progress.[14, 16] Although the comparison between the group of rare disease patients and pregnant people is limited, the success from rare disease patients indicates that solidarity may be a key tool in engaging pregnant people in closing the knowledge gap. Moreover, in order to be successful, individuals might need to be encouraged to rely on solidarity to achieve progress.

In this paper, we investigate whether and how we can engage pregnant people in closing the knowledge gap by stimulating the enactment of solidarity on the part of pregnant people. This paper does not address whether solidarity is (always) morally desirable or if solidarity is even morally required because our focus is on understanding whether and how it is possible to stimulate the enactment of solidarity. Our aim is not to develop a new concept of solidarity but to apply the existing philosophical literature on solidarity to the situation of pregnant people using medications. In this paper, we first present a summary of the general discussion on solidarity. We will draw primarily on the concept of solidarity developed by Barbara Prainsack and Alena Buyx (2017), who have undertaken an extensive analysis of solidarity in the field of bioethics. We develop their concept of solidarity by providing a perspective on how to stimulate the enactment of solidarity among groups who are not yet unified or aware of their shared problem. Lastly, we apply solidarity in the context of pregnant people and address the need to provide information to pregnant people about the poor evidence base problem to stimulate their engagement on the basis of solidarity in, for example, an LHS. We want to emphasize that we do not place the responsibility of changing the

status quo regarding the evidence base on medication safety in pregnancy on pregnant people. The lack of scientific knowledge is not their fault, but we believe they could be part of the solution.

Solidarity in Bioethics

The concept of solidarity is receiving increasing attention in (bio)medical ethics. In addition to a special issue in the journal *Bioethics* in 2012, more researchers are exploring the role of solidarity in bioethical issues. For example, solidarity in the context of medical research involving humans,[17] big data, machine learning and artificial intelligence,[18] and organ donation.[19] A systematic analysis of the concept and definition of solidarity is beyond the scope of this paper and we therefore provide only a brief summary. When surveying the literature on solidarity in Bioethics, scholars are in agreement that it is a complex multi-faced concept that can be used in many different ways.[20, 21, 22] The term "solidarity" has been mostly theorized in political contexts, and there are only a few attempts at incorporating solidarity within mainstream ethical theory. According to some, this neglect results from the fact that modern ethical theory seeks universalizability and focuses on values related to individual freedom. Consequently, modern ethical theories focus on the individual and does not include references to collectivity, which leaves little space for the concept of solidarity.[20, 22, 23] According to some authors, solidarity is more suited to play a central role in contexts that necessitate collectivity, like public health ethics.[24, 25]

Solidarity is a challenging concept to define and theorize. There are different views on what solidarity as a phenomenon entails. Moreover, there are different conceptualizations of what solidarity is premised on; for example, concepts of empathy, altruism or collaboration, and/or more general pro-social behaviors.[26] Ter Meulen explains that although solidarity as a moral concept often implies a sense of non-instrumental support and cooperation based on the identification with a common cause, most conceptions base solidarity on self-interest. Solidarity is often explained as individuals being prepared to serve the collective interest because they expect the same behavior of others in return when needed or when the potential gains of participating outweigh the costs to them.[23]

There also is uncertainty about the role of solidarity in our normative discourse. There is genuine disagreement as to whether solidarity is a value worth pursuing or whether it can be the basis of obligations. Some authors who attempted to theorize solidarity within modern ethical theories argue that it does not have a freestanding normative power and it cannot be described as a universal principle, like justice or autonomy. Instead, solidarity is a concept that can help connect these universal or more general values with specific reasons and obligations to act.[20, 27, 28] More specifically, solidarity can help specify actions when a general (bioethical) value, i.e., justice or beneficence, does not tell us what to do or how to interpret that value in a specific situation.[27, 28] Some authors explicitly focus on

the relationship between solidarity and justice, arguing that justice and solidarity are equally important and complementary values that should be considered in healthcare practices and institutions.[29, 30]

Despite the ambiguity, many scholars agree that the concept of solidarity has both normative and descriptive aspects. The normative aspects refer to a disposition to act in solidarity. More specifically this relates to the moral obligation of members of a group to assist one another in various ways.[28] Actions of solidarity are described as how an individual sees what ought to be done, and how to behave towards others in a social group based on a particular identity or preference shaped by belonging to that group. This is what Dawson and Verweij call *constitutive* solidarity.[22] The descriptive aspects refer to the social practices and relationships within and among particular groups. Dawson and Verweij refer to the term *rational* solidarity, which they suggest arises when a collective threat, acknowledged by a group or society, requires "standing together" to avoid or minimize harm. As an example, the authors refer to social distancing as an act of solidarity during a pandemic.[22] This sense of solidarity fits more naturally with the self-interest-based notion of solidarity because of the direct benefit to the individual. Simultaneously, rational solidarity also underpins what seems to be one of the most central aspects of solidarity; that solidarity often refers to created relationships between individuals, between groups, or between individuals and groups.[31] These relationships are described as created because solidarity does not evolve naturally and is, in some instances, an artificial bond between individuals and groups. Solidarity does not have to arise between friends or people who know each other. There can be solidarity with strangers, e.g. solidarity based on some identity characteristic or common goal.[32] Jaeggi argues that the ability to form relationships of solidarity is related to the capacity to cooperate.[32] Cooperating or supporting others is seen as an important moral value. Intuitively, the relational aspect of solidarity is what draws us to the concept. A solution to the current knowledge gap on medication safety during pregnancy could be a common goal to invoke a bond of solidarity between pregnant people. However, establishing that solidarity may be of utility raises the question of what we can expect from individuals when we ask for solidarity.

In the next section, we outline solidarity as we see it having utility in addressing the problem outlined for pregnant people and turn to the work of Prainsack and Buyx (2017). Their description of solidarity attempts to bridge both the normative and the descriptive aspects of the concept to allow for a clearer concept that might have more real-world applications. Prainsack & Buyx's understanding of solidarity gives us a descriptive concept with normative implications. In addition, it tells us what kind of connectedness or relatedness provides the basis for solidarity.

The concept of solidarity by Prainsack and Buyx

Prainsack and Buyx understand solidarity as "enacted commitments to accept costs to assist others with whom a person or persons recognize a similarity in a relevant respect".[28] In their conceptualization, solidarity is understood as a practice. Important elements from this definition are three-fold. First, solidarity is enacted and is not a personal disposition, a general feeling, sentiment, or attitude towards another person (i.e. empathy and altruism). Second, solidarity involves a commitment and is not something an individual does once (i.e., solidarity involves more than marching in a protest on one occasion). Third, solidarity is based on the recognition of a similarity between individuals that matters in a certain context (i.e. solidarity is distinguished from donating to a charity which is oftentimes characterized by a top-down and asymmetric relationship).[28]

Solidarity relies on the *voluntariness* of individuals to help others with whom they recognize a similarity in a relevant respect. While bioethical values like justice, autonomy, and beneficence are articulated in a top-down manner, solidarity, especially at the interpersonal level, emerges *bottom-up*.[28] Solidarity, in that sense, is quite fragile. The essence of solidarity is what individuals are willing to do for people with whom they share a common goal. Therefore, solidarity cannot be demanded and sanctioned in the way duties of justice can be demanded.[27, 28]

According to Prainsack and Buyx, solidarity can take place on three different levels, also called the tiers of solidarity: 1) the individual level (between individuals), 2) the group level (between people who consider themselves bound together through at least one similarity, such as a shared medical condition), and 3) the institutionalized level (where solidarity is institutionalized in the shape of contracts, legal or administrative norms, such as societal welfare arrangements). Tiers 1 and 2 often exist without the solidaristic norms and provisions at tier 3, while tier 3 emerges out of solidified practices of solidarity at the interpersonal or group level.[28] Consequently, in this paper, we mainly focus on solidarity on the individual level since we aim to investigate whether there is a way for solidarity to take effect from the bottom up (for pregnant people using medications to act in solidarity with one another). Over time, the enactment of solidarity can become common among people and could transform into instances of group solidarity, where solidaristic practices are normal.[28]

Having explained how we conceptualize solidarity, we now should address the matter of what we expect from individuals when we ask for solidarity. Prainsack and Buyx's account suggests that in asking for solidarity we expect people to contribute to assisting people with whom one has something in common that matters in a specific situation, which in turn, contributes to the realization of a general bioethical value, such as justice. However, understanding this as the mechanism of change also poses a challenge: Prainsack and Buyx recognize that solidarity cannot be demanded and relies on the ability and willingness of individuals to recognize a similarity in a relevant respect and the voluntariness of

them to act. However, one can imagine that people might not often recognize that they share a similarity with another person or group in a relevant respect or that they need to act, and therefore, the enactment of solidarity may need encouragement. However, if soldiarity cannot be imposed, is there a way to stimulate the enactment of solidarity? Unfortunately, the work of Prainsack and Buyx does not immediately provide an answer to that question. In their work, Prainsack and Buyx use solidarity as an explanatory concept, mainly outlining solidarity as a social practice, rather than explaining whether there is a moral obligation to stimulate the enactment of solidarity among groups for whom cooperation would likely have meaningful consequences. In what follows, we contribute to the literature by providing a mechanism by which solidarity can be encouraged: the empowerment of individuals.

Empowerment

We argue that stimulating the empowerment of people is crucial in understanding how solidarity can be invoked. The literature on the concept of empowerment is rather large, and it is beyond the scope of this paper to provide a complete account. We understand empowerment as a process that enables people to gain (more) control over their own lives. It also involves enhanced decision-making and obtaining the ability to cooperate with others to bring about change.[33, 34, 35, 36] Empowerment is made possible by educating people and by providing information, opportunities, and resources for people to gain knowledge and experiences while also gaining (more) control over their lives.[33, 37] If people are simply unaware of their shared situation, the vulnerability resulting from it, and the ability to act, stimulating empowerment may mean providing information, opportunities, and resources for people so they can become aware that they share a specific struggle and can choose to act. Empowerment might then stimulate the enactment of solidarity because in awareness, people can understand that they can help overcome this struggle by assisting one another and standing up together. Jaeggi has made a similar observation regarding solidarity: “the ability to act [in solidarity] is related to becoming aware that one is in the same situation in such a way, that our positions are intertwined”.[32] Jaeggi does not elaborate further upon the role of empowerment in stimulating enactment of solidarity. Nonetheless, her statement underlines how empowerment could be necessary for solidarity to exist. Especially since solidarity, according to Prainsack and Buyx, emerges bottom-up and depends upon the voluntariness of individuals to act with other people with whom they share a common goal or problem.[28]

Empowerment of pregnant people

For pregnant people, to start the process of empowerment, we believe it is important to first raise awareness about the issue of the poor evidence base for medications used in pregnancy and the harms and risks resulting from this.

Raising awareness and increasing knowledge are often mentioned as the first steps for the process of empowerment in the Health Education and Patient Empowerment literature.[35, 36, 37, 38] Starting by raising awareness within, for example, the context of routine primary care and obstetric care could enable pregnant people to understand their shared situation, their vulnerability resulting from that situation, and the need for action to help realize justice through solidarity. Next, health literacy could be increased by explaining how scientific research can help close the knowledge gap and, accordingly, explain how pregnant people can engage and contribute to closing the knowledge gap. In this way, the enactment of solidarity could be stimulated, because it would allow pregnant people to gain experiences, skills, and knowledge which could enable them to recognize that they are in a relevant shared situation.

In this account, we need to examine what pregnant people can do to help improve their situation or the situation of future pregnant people. Establishing advocacy groups specifically for pregnancy can help increase engagement among pregnant people. Although such groups are commonly formed for specific diseases, they are not as prevalent for pregnancy. Apart from unifying and hopefully being more visible in demanding a change of their status quo (being a population where there is limited evidence on the impact of medications used during pregnancy), pregnant people can also contribute to already existing initiatives. The lack of knowledge is a multi-stakeholder problem, which means that the contribution of pregnant people could also potentially influence the work of many different stakeholders and their activities. For example, to be able to learn from routinely collected health data in an LHS, there needs to be enough relevant data to analyze. To make sure that there is enough relevant data to utilize, pregnant people must be aware of data collection and data analyses to improve care and generate knowledge. Although Prainsack and Buyx argue that sharing data would not necessarily count as a solidaristic action, as it does not involve active participation or some sort of personal deliberation or investment,[28] there are methods of data collection that do require a more active role of pregnant people. There are, for example, prospective cohort studies that collect data via surveys or other follow-up interventions. Another example of how pregnant people can act in solidarity is by reporting side effects of medications or treatments or other complications during all sorts of treatments for various things. In this way, medication uses and their effects can be registered, and trends can be followed, leading to further investigations on side effects. Subsequently, new insights from these studies need to benefit people within the group that made the insights possible, so that they can understand how their contribution impacts knowledge generation and informed decision-making regarding medication intake during pregnancy.

Discussion

Thus far, this paper has addressed three different points, namely: 1) there is a lack of evidence on the impact of medications used during pregnancy, 2) despite the efforts to guide the fair inclusion of pregnant people in clinical trials, a paradigm shift is needed regarding the way knowledge is being generated, by for example transforming the field into an LHS, and 3) that through empowerment, we can stimulate pregnant people to engage in the proposed paradigm shift on the basis of solidarity. However, we also need to acknowledge a few important challenges regarding the group of pregnant people that might be relevant when considering how to invoke solidarity. In general, there is a great fear of harming the developing fetus when taking medication during pregnancy. The question is whether this fear will interfere with the ability to act in solidarity with other pregnant people. Strengthening the evidence base for medication during pregnancy also depends on actual medication intake. As long as people fear taking any medication during pregnancy, it will continue to be challenging to study medication safety and efficacy. Therefore, raising awareness should cover a wide spectrum of topics, including the topic of maternal health. However, considering almost every pregnant person takes at least one medication during a pregnancy, there is a lot of knowledge to be gained from their experiences. It is of course important to prioritize the well-being of pregnant people and not ask them to try medications for the purpose of learning from their experiences. Instead, we should encourage them to share their experiences when they have decided to take a medication during their pregnancy.

To start the process of empowerment to stimulate solidarity among pregnant people, the support of many other important stakeholders is necessary. Besides pregnant people, HCPs, data scientists, funding agencies, registries, and other professionals must also act in solidarity with pregnant people. Their role is crucial for raising awareness on the lack of knowledge and on the importance of scientific research, and building the right infrastructure so that people can be more involved. Organizations that collect health data during pregnancies and study medication safety and teratogens, such as academic research groups and consortia, (regional and national) pregnancy and medicine registries, teratology information service (TIS) centers, pharmacovigilance and pharmacoepidemiology centers, and pharmaceutical companies, could take multiple actions to benefit pregnant people. For example, they can improve the level of transparency and earn the trust of pregnant people regarding data collection and data use by providing understandable information about the purpose and importance of data collection. A lack of trust concerning the way organizations handle people's data and protect their privacy might hinder actions of solidarity. Moreover, organizations could engage people in data-intensive health research, via for example social media and HCPs, to improve health data literacy, and with that, allow people to

take control over their situation by, for example, choosing to participate (or not) in a cohort study or to not opt out from birth and health registries.

An example of how stakeholders can contribute and work together is the Innovative Medicine Initiative (IMI) ConcePTION consortium (2019), which is a European initiative consisting of experienced public and private organizations that collect or have access to data related to pregnancy, childbirth, and lactation. IMI ConcePTION aims to reorganize the importance of and to ensure access to health data in such a way that it can be transformed to generate evidence and, in turn, improve the clinical practice with new insights. This initiative aims to build an ecosystem that can better monitor and communicate the safety of medications used during pregnancy and lactation, validating, and regulating workflows to hasten and optimize evidence generation across Europe. New insights will be shared in scientific publications and in a publicly available knowledge bank accessible in different languages.[39] The aims and methods of this initiative are quite similar to those on which an LHS is based. Especially an LHS that aims to generate evidence by routinely collecting and processing vast quantities of clinical and research data. This type of LHS can also be called a comprehensive data LHS, or a real-time LHS once new insights of data analyses are also directly provided at the point of care.[40] IMI ConcePTION serves as a potential concrete example of an LHS we imagine to which pregnant people could contribute by, for example, reporting adverse drug reactions to currently available local organizations that collaborate with the ConcePTION LHS. However, in order to realize and obtain the cooperation of pregnant people, stakeholders should engage in raising awareness among people and making the ecosystem accessible to pregnant people and their HCPs. It should be pointed out that this paper has not fully addressed all the ethical challenges that arise when transforming the field into an LHS. In general, an LHS challenges the current structures for evaluating care and research activities, which in turn complicates traditional safeguards such as additional protections for research participants or the responsibility of HCPs to prioritize the best interest of patients. Although it is not within the scope of this paper to respond to the ethical challenges of LHSs, future research should address these issues and provide concrete guidance for the development of an ethically responsible LHS in the field of pregnancy and lactation.

It might be challenging to encourage individual pregnant people to act in solidarity with all pregnant people, including future pregnant people. Therefore, raising awareness should also involve educating people early on in pregnancies. Particularly, on the challenge of not knowing whether a medication is safe during pregnancy and on ways to help strengthen the evidence base. As mentioned in the introduction, even less information is available on newborn exposure to the medication through lactation. Ideally, the empowerment of people should not only focus on pregnancy but also on lactation to stimulate the enactment of solidarity

through initiatives supporting research on lactation. These conversations can, for example, take place between primary care physicians and patients early in their pregnancy or as part of the obstetric consultations. Raising awareness among many people, including the potential partner of the pregnant person could help with normalizing actions of solidarity and even solidify into practices and norms at tiers 2 and 3.

In addition, it is important to think about how practices could be developed to educate people about the poor evidence base regarding medications used during pregnancy and to realize that 'the group of pregnant people' is not homogeneous in a number of ways. Furthermore, culture, religious beliefs, and perspectives considerably impact the decision-making processes of pregnant people.[41] For example, there is an ethical consensus in Western societies that treatment decisions are left solely to the pregnant person. A pregnant person's right to determine what happens to their body has great moral weight and overpowers many other ethical considerations.[41] For people with different cultural backgrounds, religious beliefs, and perspectives, understanding the collective problem might have different moral weight, or these decision-making processes might include other people, such as certain family members, close friends or HCPs, as well. This also means that a concept of solidarity could have a different place in their set of beliefs and values, influencing the role it could have during pregnancy.

There are also meaningful differences between pregnant people who are considered healthy and pregnant people who are also managing a chronic illness or condition during their pregnancy. These groups might have different perceptions and reasons for acting in solidarity. It has even been argued that the connection between people who share the same illness or condition is stronger, and therefore, invoking of solidarity is more easily imagined too.[28] With that, people with chronic illnesses or conditions may already be connected with other patients through patient advocacy groups and share similar experiences and struggles regarding pregnancy. Consequently, it could be valuable to draw attention to the evidence-base problem as well as ways for them to contribute to closing the knowledge gap within these groups. Another aspect to consider is the fact that pregnancies take up to nine months, which is not much time for being actively involved in all sorts of research activities or for participating in an advocacy group. Pregnancy is not a disease; we must not conceptualize it as such. While it may be something that affects people's identity in a very personal way because it is a temporary condition, it might not be something that lead people to identify with other pregnant people in the longer term as a chronic disease or condition could.[28] Perhaps we cannot expect pregnant people to commit to solidarity in the way Prainsack and Buyx argue and, instead, accept single contributions as an act of solidarity. At the same time, many pregnant people are active on social media platforms online, such as pregnancy and lactation forums.[42] On these online

platforms, they share experiences with and ask questions to other people who are either pregnant or just gave birth. So, in a way, there is already some sense of recognition and solidarity which could be reinforced.

Conclusion

This paper started from the position that so far, addressing stakeholders, such as research ethics committees, researchers, funding agencies, manufacturers, separately has not led to the much-needed change in the way evidence is being generated on the safety and efficacy of medications used during pregnancy. Therefore, we emphasize the need for a paradigm shift in which the involvement of pregnant people with the help of other stakeholders becomes more central. We believe that solidarity among pregnant people and other relevant stakeholders can help improve the situation for pregnant people regarding the evidence base problem. Furthermore, we argue that the empowerment of pregnant people is a crucial step to stimulate the enactment of solidarity on the part of pregnant people and other stakeholders. The process of empowerment starts by raising awareness on the lack of evidence on medications used in pregnancy and on how people can contribute to changing the way knowledge is currently being generated, by for example sharing their health data. Ideally, all stakeholders should feel responsible for not only raising awareness about the lack of evidence on medication safety and efficacy in pregnancy and helping pregnant people find their way in acting in solidarity, but also for helping with changing the system of developing evidence on medication safety in pregnancy.

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CHAPTER 6

An ethics framework for the transition to an operational learning healthcare system

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Abstract

Introduction

While many projects have been launched with the aim of establishing a learning healthcare system, the amount of operational learning healthcare systems remains limited. Given the investment of resources in these projects, a moral responsibility to pursue the transition toward an LHS falls on projects and their participating stakeholders. This paper provides an ethics framework for projects that have taken steps towards building an LHS and are in the position to transition to an operational learning healthcare system.

Method

To articulate relevant ethical requirements, we analyze established ethics frameworks in the fields of learning healthcare systems, data intensive health research, and transitioning or innovating health systems. The overlapping content and shared values are used to articulate overarching ethical requirements. To provide necessary context, we apply the insights from the analysis to the Innovative Medicines Initiative ConcePTION project. This project is specifically designed to generate knowledge on the safety of medications used during pregnancy and lactation through the establishment of an LHS.

Results

Upon analyzing the consulted frameworks, we identified four overlapping ethical requirements that are also of significant relevance within the scope of our ethics framework. These requirements are: 1) public benefit and favorable harm-benefit ratio, 2) equity and justice, 3) stakeholder engagement, 4) sustainability. Additionally, we apply these ethical requirements to the context of an LHS for pregnant and lactating people.

Conclusion

Although tailored to the context of pregnancy and lactation, our ethics framework can provide guidance for the transition to an operational LHS across diverse healthcare domains.

Introduction

In recent years, many projects have started on the premise of developing a Learning Healthcare System (LHS). LHSs are considered as a promising method for learning from real-world experiences, to provide better care and to quicker develop knowledge.[3] Furthermore, an LHS might also offer a solution to the gaps that are left by traditional research methods, such as Randomized Controlled Trials (RCTs), as these methods are often considered to suffer from slow evidence generation, and lack of alignment with the real world.[4] LHSs could hold significant promise for patient populations that are often underrepresented, excluded, or too small to study in clinical trials, such as minorities, rare disease patients and pregnant people.

While LHSs receive much attention, not many projects are successful in transitioning to an operational LHS. With an operational LHS we mean an LHS that can effectively extract and analyze data, generate evidence, and translate evidence to encourage learning and improve the clinical practice.[5, 6] Given the substantial investment of both public and private resources in LHS projects, there exists a moral responsibility to persist the efforts to transition towards an operational LHS. Literature on the implementation of LHSs is growing, however, these articles and reports are mostly focused on the operationalization of LHS design elements, such as the data infrastructure and research methods, and on various challenges.[8, 9] Despite the growing literature addressing challenges, including ethical challenges, there remains a notable absence of a robust framework for research projects that have dedicated considerable time to constructing the fundamental elements of an LHS but have not yet achieved the transition to an operational LHS. It is our understanding that ethical guidance should hold significant importance during the transition and implementation phase of an LHS. While ethicists, along with health lawyers and social scientists, ideally participate from the beginning of these research projects, establishing a framework at the initial stages can be complex. The engagement of various stakeholders and the potential fluidity of project details can pose challenges when attempting to define concrete ethical requirements, especially when certain aspects of the project remain subject to change.

This paper aims to develop an ethics framework to guide projects that have taken steps towards building an LHS and need to transition to an operational LHS. To be able to identify relevant ethical requirements for this ethics framework, we will first analyze various already existing ethics frameworks that have been developed for LHSs in general, for health systems that are transitioning or innovating, and for data intensive health research. Second, we will identify areas of common content and shared values before proceeding to articulate ethical requirements. Accordingly, to provide necessary context and specification, we will apply the

insights from the analysis of ethics frameworks to the Innovative Medicines Initiative (IMI) ConcePTION project as an example of a project that is in the phase of transitioning towards an operational LHS. IMI ConcePTION aims to build a European LHS that can generate reliable information on the impact of medications used during pregnancy and lactation through a large European network (Box 1).[10] There is still a lot of uncertainty about the effects of medications used during pregnancy, while at the same time most pregnant and lactating people take at least one medication during their pregnancy or lactation.[11-13] ConcePTION has built a network and a data infrastructure that can analyze routine care data and data from health research, from for example electronic health records and health registries across Europe.[2] Their approach shows similarities with what is also called a comprehensive data LHS.[14] While we apply the finding from our analysis of ethics frameworks to a European LHS for pregnancy and lactation, we aspire to formulate requirements that carry wider significance, effectively across health-related research projects that seek to establish a similar type LHS.

Box 1. Description of IMI ConcePTION project as an LHS

IMI ConcePTION was launched in April 2019 and is a European Public-Private Partnership (PPP), consisting of experienced industry and academic organizations, already established networks such as the European system for the evaluation of safety of medication use in pregnancy in relation to risk of congenital anomalies (EUROmediCAT), European Network of Teratology Information Services (ENTIS), and Biobanking and BioMolecular resources Research Infrastructure Europe (BBMRI-ERIC), and patients and healthcare providers (HCPs) organizations, as well as (inter)national regulators and public health organizations. IMI ConcePTION has been working on the development of an international safety evidence ecosystem to provide harmonized information to pregnant and lactating people, HCPs and researchers.[1, 2] To realize such an ecosystem, ConcePTION has worked on the development of a high-quality data infrastructure to integrate real-world data from different data sources across Europe and has worked on a method for data analyses, using a federated approach with a common data model, allowing for analyzing data without centralizing it in a single database. Instead, analysis scripts are sent to the individual data sources.[2]

Many results of the ConcePTION project are published in scientific journals and in reports to the European Commission (Open Access). Publications include for example results of specific studies on medication impact, description of the data infrastructure, overviews of status quos regarding post-marketing pregnancy research and online information discrepancies, and systematic reviews on availability of data. The deliverables are categorized and show the focal points of the consortium.

1. Studies to generate evidence on medicines safety during pregnancy from re-use of existing health care data sources;
2. Studies with data collected directly from pregnant women who take medicines during pregnancy development of models to predict transfer of medicines into milk;
3. Development of validated Europe-wide breastmilk collection for research and analysis center;

Box 1. *Continued*

4. Training of health care providers on medicines safety in pregnancy and knowledge transfer to pregnant women;
5. Outreach and organization of input from stakeholder to shape and grow the ConcePTION ecosystem;
6. Creation of the common data models, governance and information technology to analyze heterogeneous type of data and generate reliable and transparent evidence;
7. Project management and sustainability.[7]

ConcePTION wants to become a sustainable and ethically responsible LHS, by creating an ecosystem that embodies a continuous loop of data collection, data analysis, knowledge generation, and dissemination of knowledge.[10] Once new knowledge has been developed, the goal is to collect new insights and present them in a public knowledge bank, accessible to pregnant and lactating people including their HCPs. While initial efforts have been dedicated to developing a roadmap to sustainability (under point 7), which is undeniably relevant for an LHS, the current absence lies in directing attention towards the transition of the project to an operational LHS.

Results

Exploring the landscape of Ethics Frameworks

We turned to the existing literature on ethics frameworks that focus on LHS or have overlapping scopes, such as clinical research during pregnancy, transitioning health systems, data intensive health research, public-private partnerships, and research consortia. Furthermore, we searched the literature on public health ethics frameworks since the knowledge gap in the field of pregnancy and lactation is also very much a public health concern. We were specifically interested in ethics frameworks that could be applied to our specific scope. However, many ethics frameworks that we encountered during our search address highly specific (medical and/ or regional) situations, challenges, and questions. While these ethics frameworks could offer valuable insights, we often observed their strong practical orientation, making it challenging to align them effectively with the goal of our ethics framework. Nonetheless, we found a few ethics frameworks that were developed for distinct purposes and yet demonstrated useful adaptability, making them applicable to a more specific context. In table 1, we present these (four) ethics frameworks. In the following sections, we will first describe the four frameworks, followed by an analysis of these frameworks, identifying their shared values and areas of overlap. Subsequently, we will extrapolate overarching ethical requirements for projects transitioning to an operational comprehensive data LHS and apply these insights directly to an LHS for pregnant and lactating people.

Table 1. An overview of the content covered by the four consulted ethics frameworks

Learning Health Care System Ethics Framework by Faden et al (2013)	**Candidate considerations for health systems ethics by Krubiner & Hyder (2014)**	**An Ethics Framework for Big Data in Health and Research by Xafis et al (2019)**	**A Public Health Ethics Framework for Health Data Research by Ballantyne (2019)**
Obligation			
1. To respect the rights and dignity of patients 2. To respect the clinical judgement of clinicians 3. To provide optimal care to each patient 4. Avoid imposing nonclinical risks and burdens on patients 5. Address health inequalities 6. Conduct continuous learning activities that improve the quality of clinical care and health care systems 7. Contribute to the common purpose of improving the quality and value of clinical care and health care systems These obligations fall, to a greater or lesser extent on, researchers, clinicians, healthcare systems, administrators, payers, and purchasers. The seventh falls on patients.	1. Holism 2. Sustainability 3. Evidence and effectiveness 4. Efficiency 5. Public engagement and transparency 6. Accountability and feedback 7. Equity and empowerment 8. Justice and fairness 9. Responsiveness 10. Collaboration 11. Quality	1. Harm minimization 2. Integrity 3. Justice 4. Liberty/ autonomy 5. Privacy 6. Proportionality 7. Public benefit 8. Solidarity 9. Stewardship 10. Accountability 11. Consistency 12. Engagement 13. Reasonableness 14. Reflexivity 15. Transparency 16. Trustworthiness	1. Public benefit (scientific integrity and social value) 2. Proportionality (necessity and least infringement) 3. Equity (solidarity and reciprocity) 4. Trust (engagement) 5. Accountability (public justification and transparency)

Description of the four frameworks

Faden and colleagues (2013) have developed the first ethics framework for a Learning Healthcare System (LHS). This framework is frequently cited and serves as a guide for healthcare systems to adopt an LHS and reconcile the differences between clinical research ethics and clinical practice ethics when research and practice intersect.[15]

Krubiner & Hyder (2014) have constructed a comprehensive ethics framework for health systems, designed to address moral issues at the system level. Their research identifies morally relevant considerations that should guide policies and actions aimed at improving and innovating health systems. This framework provides valuable insights into the ethical implications of changes at higher, more complex levels of health systems, which we consider a European LHS to be. Additionally, it advocates for a holistic approach to ethics that encompasses broader impacts, such as wider societal implications.[16]

Xafis and colleagues (2019) have developed an ethics framework to help guide decision-making in health and research contexts where big data are used. Their framework is primarily directed towards researchers, policymakers, data controllers. They have identified 16 ethical values, both substantive and procedural. They also present a "step-by-step deliberative process" for discussing ethical issues in big data and for decision-making.[17]

Lastly, Ballantyne (2019) proposes a public health ethics framework to guide decisions about the secondary use of health data for research, which is also at the core of an LHS. The author claims that a public health ethics framework for the use of health data offers several advantages as it could facilitate attention to the social value of research and the collective interest. This framework mainly focusses on helping authorizing bodies such as research ethics committees or institutional review boards, data access committees, and similar governance bodies with assessing and evaluating data research.[18]

Overlapping values and statements in light of transition

Upon closer analysis, the frameworks show overlapping values and statements, or commonalities. In the process of formulating ethical requirements for projects transitioning towards operational LHSs, we have organized the values and statements of the analyzed ethics frameworks, and formulated overarching ethical requirements that reflect their overlapping content and hold relevance to the scope of our framework. Below we will describe the interpretations of the frameworks regarding these ethical requirements.

Public benefit & favorable harm-benefit ratio

Most frameworks refer to public benefit as an important value to make sure the health system or research proposal produces benefits for patients/ populations, and furthermore, that the anticipated public benefit can outweigh potential

harms to patients, stakeholders or other relevant communities.[18] Faden and colleagues mainly refer to clinical harm,[15] and Ballantyne and Xafis refer to harms for both individuals and groups resulting from the (mis)use of big data for research purposes.[17, 18] The three frameworks also refer to the importance of fair distribution of harms and benefits of (data) research and outcomes for patients, populations, relevant stakeholders. All emphasize the importance of prioritizing the minimization of burdens or risks by exploring alternatives or employing minimal use of data[17, 18] or disclosure of health information.[15, 17, 18] Ballantyne continues and offers a public health approach, saying that when harm is unavoidable, potential harm needs to be justified by "the relative potential benefits of data use" (proportionality).[18]

Equity & justice

All frameworks share a commitment to health equity and the inclusion of statements addressing various interpretations of health justice. These commitments are sometimes seen as obligations and are linked to the importance of stakeholder engagement and empowerment. Krubiner & Hyder conceptualize the commitment to equity as ensuring equal access to necessary health goods that requires taking positive actions to increase access to basic health needs while also holding negative duties to prevent the widening of disparity gaps.[16] Ballantyne explains that health equity requires fair distribution of health outcomes in societies and that it means the absence of avoidable or remediable differences among groups of people.[18] Both the frameworks presented by Faden and colleagues, and Krubiner & Hyder also highlight the significance of addressing inequality that disproportionately affects marginalized populations.[15, 16] Faden and colleagues elaborate on the notion that the learning activities within an LHS (the research activities and their outcomes) should aim to benefit marginalized groups or individuals and/ or should address specific disparities in clinical outcomes.[15] Krubiner & Hyder further emphasize the necessity for health systems to be responsive and adaptive to the changing health needs of population.[16] Xafis and colleagues conceptualize justice as a substantive value that should ensure that individuals and groups are treated fairly and with respect, and that there is a fair distribution of benefits and burdens of data activities.[17]

Stakeholder engagement

Furthermore, all frameworks place emphasis on stakeholder engagement. Krubiner & Hyder highlight the value of stakeholder engagement for the effective functioning of the health system, considering its multifaceted nature and the diverse array of stakeholders involved.[16] Ballantyne argues that stakeholder engagement is essential for the fair distribution of harms and benefits, as well as for fostering trust in health services.[18] Faden and colleagues have articulated an obligation for patients to contribute to the effectiveness, fairness, and high

quality of an LHS by providing access to information.[15] In a similar vein, albeit with different wording, Ballantyne's public health approach seeks to steer the conversation around the circumstances and justifiability of prioritizing public interest and benefit over individual liberties.[18] Consequently, this approach suggests an obligation for patients to grant access to relevant health data in the collective interest.

Sustainability

Lastly, all four frameworks incorporated guiding norms for health systems or research. These norms are also often used in the governance literature to, for example, define responsibilities and tasks to promote appropriate conduct, oversight, and cooperation. Values such as trust, transparency, accountability, feedback, and public engagement possess instrumental significance for the overall functioning of a health system or for conducting research in a responsible manner.[16-18] Closely intertwined with these values is the concept of sustainability. Sustainability is contingent upon a robust governance structure and relies on public and expert trust in the health system, in the research being conducted and in the outcomes generated.[16-18] Krubiner & Hyder underscore the significance of sustainability and advocate for the development of long-term strategies to uphold and maintain improvements overtime.[16]

Table 2. overview of the overarching ethical requirements and of the overlapping content of the consulted ethics frameworks

Overarching ethical requirements	Overlapping content	Authors
Public Benefit & favorable harm-benefit ratio	To provide optimal care to each patient, avoid imposing clinical risks and burdens on patients	Faden et al (2013)
	Harm minimization, public benefit, proportionality	Xafis et al (2019)
	Public benefit (scientific integrity and social value), proportionality (necessity and least infringement)	Ballantyne (2019)
Equity and justice	Address health inequalities	Faden et al (2013)
	Equity & empowerment, justice and fairness, responsiveness	Krubiner & Hyder (2014)
	Justice	Xafis et al (2019)
	Equity (solidarity and reciprocity)	Ballantyne (2019)
Stakeholder engagement	Contribute to the common purpose of improving the quality and value of clinical care and health care systems	Faden et al (2013)
	Public engagement and transparency	Krubiner & Hyder (2014)
	Solidarity, engagement	Xafis et al (2019)
	Trust (engagement)	Ballantyne (2019)
Sustainability	Conduct continuous learning activities that improve the quality of clinical care and health care systems	Faden et al (2013)
	Quality, efficiency, transparency, accountability, feedback	Krubiner & Hyder (2014)
	Integrity, privacy, stewardship, consistency, transparency, trust,	Xafis et al (2019)
	Trust (engagement), accountability (public justification and transparency)	Ballantyne (2019)

Our ethics framework

Having analyzed the frameworks and discussed the overlapping content, we now turn to our own ethics framework. Below we will discuss the relevance of the ethical requirement to the transition phase by means of specification.[19] Specification refers to the process of adding context and, as Henry Richardson explains, describing where, when why, how, by what means, to whom or by whom an action is be done or avoided.[19, 20] To provide additional context, we use the IMI ConcePTION project during the specification process. Table 3 presents our ethics framework and shows the ethical requirements and their descriptions translated to the transition phase.

Public benefit and favorable benefit-harm ratio

During the project phase, the primary focus is often on conducting research together with establishing the data infrastructure and collaborations, which might not result into tangible public benefits. Nonetheless, once the infrastructure is in place, the central objective of an LHS should also revolve around improving the clinical practice for, in our case: pregnant and lactating people, along with their healthcare provider (HCPs). To improve the clinical practice through an LHS, the development of effective designs that can streamline the implementation of new evidence into the clinical practice are necessary.[5] Commitment to the LHS approach, means accountability for developing mechanisms that ensure that pregnant and lactating people may benefit from the use of their health data.[21] Whether they will benefit depends for a large part on the likelihood that new findings can be translated into improvements for the clinical practice. It also rests upon the careful consideration of whether the potential benefits outweigh the potential harms not only to individuals, but also to communities and other stakeholders involved. Possible harms encompass a spectrum ranging from privacy and confidentiality breaches to discrimination and stigmatization resulting from, for example, data analysis methods.

Since an LHS does not fall solely under the purview of research or clinical practice, and thus outside their direct scope of evaluations, it is crucial to assess the net clinical benefit for pregnant and lactating people. One way to assure that the reuse of health data in an LHS has potential benefit and that there are low risk of foreseeable harms for pregnant and lactating people, involves installing a governance or review committee, such as a Data Access Committee (DAC).[22] A DAC or similar type of governance body would review both applications of organizations or groups wanting to make use of the LHS and could encourage secondary data uses that are in line with the interests of pregnant and lactating people, as well as the organizations contributing to the LHS.

Equity and justice

Commitment to equity and justice is vital during the development of the LHS infrastructure. These commitments could involve creating inclusive data registries and analysis methods, and refraining from practices that would further exacerbate existing harmful disparities among pregnant and lactating people. Once the infrastructure is in place, new goals that encompass equity and health justice commitments should be formulated for the entire LHS. These goals can include both short-term commitments (e.g., reviewing R-scripts for potential bias that could provide discriminatory results) and long-term commitments. For example, shifting from referring exclusively to pregnant "women" to using more inclusive language such as pregnant "people", acknowledging diversity and different experiences of those involved in pregnancy and lactation. The knowledge gap also affects transgender and gender diverse people, for whom even less knowledge exists, especially concerning hormone therapy during pregnancy and lactation combined with a chronic condition.[23] Challenges regarding quantitative representation may persist for these groups but converting this into a goal can drive efforts to determine data availability and necessities for data collection. Another example would be prioritizing equitable access to the benefits from the LHS. To ensure equitable benefits and access, requires recognizing differences among pregnant and lactating people, including differences in their health needs. The involvement of HCPs and representative groups or communities in translating and disseminating new insights could prove pivotal.[24]

Stakeholders with numerous responsibilities, such as designing research protocols, performing data analyses, interpreting outcomes, and translating new insights for the clinical practice, can actively prioritize inclusivity and responsiveness to the group of pregnant and lactating people. Responsiveness can be maintained when relevant stakeholders and communities are continuously engaged in the LHS design, transition, and evaluation processes.

Stakeholder engagement

First, for the transition towards an operational LHS, it is important that all relevant stakeholders involved acknowledge the value of an LHS and are willing to keep contributing. Especially for the field of pregnancy and lactation, a shift in changing the way knowledge is being generated is needed. Elsewhere, we have argued that in order to realize this paradigm shift requires solidarity among pregnant and lactating people.[25] We have formulated a framework for solidarity among pregnant people and argued that in order for solidarity to take effect, we need to empower them.[25] Empowerment starts by creating awareness of the existing knowledge gap, understanding how scientific research can play a role in bridging it, and by recognizing how pregnant people can actively participate in closing this gap.

Second, the notion of stakeholder engagement often functions as a means

to gather views of stakeholders rather than actively collaboratively shaping (co-creation) the research project[26, 27] and thus LHS design. In 2015, Friedman and colleagues wrote: "an LHS is not a digital infrastructure alone, it is also a network of people and institutions, and not only users of a technological infrastructure, but also parts of the information system itself".[28] This quote underlines the importance of taking the involvement of stakeholders seriously. To make sure the LHS is more centered around stakeholders who will use the knowledge generated through the LHS, it is crucial to engage stakeholders such as people of childbearing potential, HCPs, researchers, data scientists, and regulators. One way to shape engagement is by including pregnant and lactating people, and/or by involving community or patient representatives in steering and reviewing committees, such as the DAC. Moreover, meaningful engagement entails commitment to provide ongoing feedback to pregnant and lactating people and their HCPs regarding the transition to and operation of the LHS. Feedback includes information about the utilization of data, the novel insights gained from studies conducted within the LHS. Krubiner & Hyder highlighted that giving feedback to communities is grounded in international guidelines such as the CIOMS guidelines (2016) and the Declaration of Helsinki (2013).[16] Feedback empowers stakeholders to make informed decisions about their support to LHS and the use of new insights in treatment deliberations.

Third, as mentioned under 'equity and justice', stakeholder engagement is necessary to uphold the LHS's relevance and responsiveness to the (health) needs of all stakeholders. Moreover, it is important to recognize that these groups of stakeholders are not homogeneous entities unified by a single perspective.[18] Meaningful stakeholder engagement requires a structured approach that embraces these diverse stakeholder groups while simultaneously acknowledging and respecting the range of viewpoint they bring. Such viewpoints encompass the variety among pregnant and lactating people, stemming from cultural distinctions, as well as differences among specialists who prioritize distinct health concerns.

Sustainability

The moral consequences of (over)promising the development of an LHS to accelerate outcomes and improve the evidence base for patients, are deeply concerning. Without a successful transition and the long-term capability to maintain the LHS cycle and effectively disseminate new insights to patients and HCPs, the much-needed paradigm shift would lose much of its significance. Sustainability alone, is considered a challenging aspect for research projects, often operating under international consortia with fixed contracts.[29] It is therefore often directed towards developing a viable business model. While financial viability is a key sustainability feature, additional considerations should be noted.

First of all, the transition to an operational LHS mandates the integration

of the continuous "learning" element within the infrastructure. In the literature, LHSs are often displayed as closed loops and characterized as systems that continuously go through the stages of data collection, data analysis, evidence generation, and feedback and improvement.[6] New insights derived from data analyses inform decision-making, drive improvement, pose new research questions, which subsequently shape the content of data collection, once the LHS cycle is completed.[6] Transitioning into an effective LHS requires attention to the systematic translation of evidence.[5] An internationally operating LHS must encompass not just a singular clinical practice, but a multitude spanning diverse countries and cultures. Achieving sustainability in this context requires finding an answer to what the most optimal feedback mechanisms are in the long-term, given the established data infrastructure and collaborative partnerships. Cultural differences are important to integrate, and again, including patient and community representatives and HCPs in the design of feedback mechanisms and evidence translation is crucial.

Second, all (internal and external) stakeholders should be aware and convinced of the added value of the created infrastructure and of the LHS as an alternative or additional way to create knowledge. Pregnant and lactating people along with their HCPs need to be able to find their way to the knowledge created by the LHS and their trust in the LHS must be gained before they will use the knowledge to inform their treatment decisions. Getting recognition from the medical community, as well as esteemed regulatory entities such as the US Food and Drug Agency (FDA) and the European Medicines Agency (EMA) probably holds significant value. These entities are well-known and in a position to endorse the integrity of the data infrastructure and knowledge produced by the LHS. During our qualitative study, published elsewhere, our respondents (women during preconception, pregnancy, and nursing) also emphasized that obtaining recognition by these institutions is pivotal for acknowledging the ConcePTION LHS.[24]

Lastly, during the project phase, there may be experts involved to guide and give advice regarding ethical, legal, and social implications (ELSI). The prominence of ELSI necessitates continued attention, even after the LHS's establishment. Tackling ELSI issues underscores the imperative for a robust governance framework, delineating roles and responsibilities regarding ELSI matters. A DAC might serve as a suitable oversight entity for these concerns and could assign issues to pertinent experts if necessary. Furthermore, the establishment of a robust governance framework is essential for addressing stakeholder concerns comprehensively. This framework should facilitate ongoing evaluations of the LHS throughout and beyond the transition phase. Whitin this evaluation process, it is imperative to provide a seat at the table for pregnant and lactating people or their representatives. This inclusion should ensure that their concerns are not only heard but that decisions are collaboratively made with their input.

Table 3. Our ethics framework

Ethical requirement	Short description of the ethical requirements in light of the transition towards an LHS for pregnant and lactating people
Public benefit and favorable harm-benefit ratio	The primary objective should revolve around ensuring that pregnant and lactating people benefit from the utilization of their health data; Consider whether potential benefits of utilizing health data outweigh the potential harms to pregnant and lactating people, their community or other important stakeholders; Establishing a Data Access Committee to ensure that the secondary data uses align with the interests of pregnant and lactating people.
Equity and justice	Formulating new goals dedicated to advancing equity and justice, these might include: - The use of inclusive language - Inclusive data collection - Ensuring equitable benefits and access while acknowledging the unique needs and circumstances of pregnant and lactating people - The involvement of representatives for the translation and dissemination of new insights - Prioritizing responsiveness in LHS activities.
Stakeholder engagement	Empower pregnant and lactating people; Foster collaboration with a variety of stakeholders, including pregnant and lactating people, their communities and/or patient representatives, HCPs, researchers, data scientists, and regulators; Provide feedback regarding LHS activities to stakeholders; Recognize and respect cultural differences in stakeholder engagement.
Sustainability	Establish a sustainable long-term financial plan; Complete the LHS cycle by integrating new insights into practice to enhance it and gain knowledge from this integration; Secure recognition from pertinent communities and entities; Continue to address and prioritize Ethical, Legal, and Social Implications (ELSI) issues in an LHS.

Discussion

This paper proposed an ethics framework with a set of ethical requirements to guide the ethical transition of research projects towards an operational LHS. This paper has taken the IMI ConcePTION project as an illustrative case, exemplifying a project that is currently undergoing the transition phase towards establishing a European comprehensive data LHS. The project aims to change the way knowledge is generated regarding the effects of medications used during pregnancy and lactation by utilizing real-world data through a large European network.

The requirements we propose deviate significantly from previous frameworks for LHSs, transitioning health systems, health data intensive research, and public health ethics. We analyzed their frameworks and determined their overlapping content. We used the overlapping content to inform our own ethics framework. What sets our framework apart are the result of analyzing these frameworks from relevant fields as well as the specific focus on the transition phase of projects as they progress towards the establishment of operational LHSs. Contrary to the predominant emphasis on (ethical) challenges and facilitators in the existing literature on LHSs, these requirements offer a compass to steer decision-making throughout the phases of LHS implementation and sustainability. Numerous projects appear to promise an LHS structure, although the actual presence of fully operational LHSs remains limited. This observation underscores the significant challenge of transitioning to an operational LHS as well as the necessity of ethical guidance in this process. As research projects are naturally time-limited endeavors with fixed financial support, the topic of transitioning warrants reasonable attention while there is still enough time for discussions and actions. This critical phase allows for decisions to be made based on what has already been achieved and on what was promised. Meaning that as the data infrastructure matures and the potential scope of "learning" it offers becomes evident, the so-called LHS loop of continuous learning can be completed, by developing an appropriate feedback mechanism.

Important to emphasize is the level on which the LHS operates. LHSs can operate on many different levels, including local (e.g., within a hospital, clinics, or within departments), regional or national (e.g., between healthcare facilities and academic groups across a region or an entire country), multicountry or international (e.g., multiple healthcare facilities and academic groups across countries) levels. The extent to which one can learn from evidence from these LHSs and built a feedback mechanism strongly depends on that level. On the one hand, the potential outcomes from data analyses within an international LHS can have more weight as more data can be analyzed compared to more locally operating LHSs. On the other hand, implementing new insights generated through an international LHS might be more challenging, as they affect not just one health system, but multiple with differing cultures. Our framework focusses

on an international LHS, that needs to develop a feedback mechanism that can guarantee the translation of research insights into actual care improvements and really inform the decision-making processes of pregnant and lactating people and their HCPs. In this paper, we do not offer a step-by-step manual for the ideal feedback mechanism for a European comprehensive data LHS, and future research on appropriate feedback mechanisms is needed, we do emphasize the significance of co-creation in this context. A feedback mechanism designed to assist people can only be considered appropriate when it genuinely addresses the needs and preferences of the very people it intends to serve. Understanding these needs and preferences goes beyond merely collecting the views of those stakeholders; it necessitates their active engagement during the transition phase as the LHS takes form. Further research is needed to understand the best way to incorporate co-creation in LHS development, as current research focusses mainly on the potential benefits of co-creation, rather on the practical aspects of its implementation and organization in an LHS. However, we do have to acknowledge the limitations of engaging pregnant people, as a pregnancy takes up to nine months, which is not much time for being actively involved in all sorts of research activities or for participating in an advocacy group. The availability to participate might be different for other groups of patients or communities.

We acknowledge that our ethics framework may not be exhaustive and that not all relevant ethical challenges might have been addressed. This paper has made the assumption that research projects or consortia operate under certain predefined conditions, where critical elements have already been established or evaluated. For example, most projects work under a code of conduct, utilize only data for which the appropriate informed consent protocols have been adhered to, invite patient representation groups during the project time, and incorporate the FAIR (findability, accessibility, interoperability, and reusability) guiding principles for scientific data management. Nonetheless, this framework functions as ethical guidance mainly in the transition phase, necessitating the active involvement of various stakeholder to translate the ethical requirements into further actions. By means of specification and using the IMI ConcePTION project as an illustrative case, we were able to provide clear guidance for projects undergoing the critical transition phase. We are confident that our ethics framework holds considerable applicability to a broad spectrum of healthcare domains. This includes domains like oncology, aimed at enhancing and innovating anti-cancer treatments at national or international level by utilizing patient data to assess medication safety and efficacy earlier in the development process. While the field of oncology presents unique ethical challenges, constructing an operational LHS from a research project demands at least moral commitment to upholding the ethical requirements outlined in our ethics framework.

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CHAPTER 7

General discussion

This thesis started with highlighting a significant issue: there is still limited scientific evidence regarding the safety and efficacy of medications used during pregnancy and lactation.[1-3] Pregnant and lactating people have consistently been excluded from clinical research, a problem that became evident during the recent COVID-19 pandemic when they were initially excluded from COVID-19 vaccine studies.[4-7] The limited availability of scientific knowledge regarding medications used during pregnancy and lactation makes it difficult for pregnant and lactating people, as well as their healthcare professional (HCP), to make informed decisions about treatments. Despite the clarity of (inter)national ethical guidelines for clinical research with pregnant and lactating people, the calls for fair inclusion of pregnant people in clinical research, and suggestions for alternative trial designs,[8-12] the knowledge gap persists.

In this thesis, we reflected upon the ethics of an alternative approach to generating knowledge, known as a Learning Healthcare System (LHS). The idea of transforming the field of pregnancy and lactation into an LHS was already suggested by van der Graaf and colleagues (2017)[9] and initiated by the Innovative Medicines Initiative (IMI) ConcePTION project.[13] This transformation is grounded into two key factors: 1) the fact that 90% of people takes at least one medication during pregnancy and lactation,[14, 15] 2) the ongoing digital transformation of healthcare, which results in the accumulation of vast amounts of health data. Moreover, there are already several local initiatives in place that gather relevant pregnancy-related data for research purposes. With the establishment of the appropriate infrastructure, these data can be utilized to learn from the real-life experiences of pregnant and lactating people who are taking medications. Learning from real-world practice forms the fundamental premise of an LHS and presents an interesting path forward for the field of pregnancy and lactation.

The aim of this thesis was to offer insights into the development of an ethically responsible LHS for pregnant and lactating people. This was accomplished by addressing four open ethically relevant questions. In short, these questions were: 1) what constitutes as an LHS for pregnant and lactating people? 2) what do stakeholders think of an ethically responsible LHS? 3) what could be the role of pregnant people in addressing the knowledge gap? 4) what are important ethical requirements for transitioning into an operational and sustainable LHS? In this final chapter, we will summarize the main findings of this thesis. Accordingly, we will reflect upon these findings and identify remaining questions for future research. Lastly, we will provide some concluding remarks and some key recommendations to guide the development of an LHS.

Main findings

When reflecting on the chapters of this thesis, each chapter addresses one of the four open ethically relevant questions described in the introduction and above. In Chapter 2 we delve into the design of an LHS for pregnant and lactating people, Chapters 3 and 4 are dedicated to empirical research aimed at understanding stakeholders' perspectives regarding an LHS for pregnant and lactating people, in Chapter 5 we conduct a normative analysis of the concept of solidarity to explore its potential in stimulating pregnant and lactating people to help close the knowledge gap, and Chapter 6 presents an Ethics Framework designed to guide research projects towards transitioning to an operational LHS. While we could summarize these main findings following the flow of the chapters in this thesis, we believe it is more beneficial to organize these main findings according to the design elements for an LHS for pregnant and lactating people, as discussed in Chapter 2.

In Chapter 2, we identified at least three essential building blocks: 1) the data and its infrastructure, 2) the learning cycle and, 3) stakeholder involvement. Furthermore, we discussed some of the ethical challenges associated with these building blocks. The research conducted in this thesis provides additional insights into these challenges and offers potential approaches for addressing them. It also sheds light on how various stakeholders perceive the concept of an ethically responsible LHS. In what follows, we will revisit these building blocks, offering reflections and insights drawn from the research conducted throughout this thesis.

1. The data and its infrastructure

Data are an essential element of an LHS in general. Various approaches exist for utilizing vast amounts of available data within an LHS. Throughout this thesis, we have used the IMI ConcePTION projects as an example, as its aim is to build an LHS in the field of pregnancy and lactation. The IMI ConcePTION ecosystem aligns with what is being called a comprehensive data LHS in the literature.[16] A comprehensive data LHS is a system characterized by its extensive collection and processing of both real-world data and research data. The aim of such an LHS is to leverage these data to address research and clinical questions, and generate evidence, ultimately enhancing clinical practices by implementing new insights. In Chapter 2, we briefly discuss the field of pregnancy and lactation data, as brought together in the IMI ConcePTION project, and discussed the ethical and methodological challenges associated with the utilization of real-world data alongside research-specific data. This discussion underscores the imperative need for a robust infrastructure capable of managing the inherently heterogeneous and unstructured nature of real-world data. In a collaborative effort involving various (European) institutions, it becomes imperative to establish an infrastructure that can seamlessly integrate multiple established databases, either physically

or through a federated approach, all while safeguarding the rights and welfare of pregnant and lactating people. These ethical and methodological challenges surrounding the utilization of health data were also a focal point of our empirical research, where we interviewed important stakeholders.

Chapter 4 underscores an essential insight provided by Data Access Providers (DAPs): data do not equate to information. Transforming data into meaningful evidence requires the expertise of individuals, both healthcare professionals (HCPs), epidemiologists, and data scientists who are familiar with the context of data collection and extraction, and with robust methodologies that ensure data security and quality of evidence. According to DAPs, transparency plays a critical role in this process. It extends to the development and accessibility of analysis scripts and the interpretation of data analyses into knowledge. At the same time, in the literature, transparency is not just a technical necessity; it is also seen as a fundamental obligation to the people whose data are involved.[17, 18] Transparency emerged as a recurring theme in various contexts during our empirical research. Our interview study with Dutch women (Chapter 3) revealed a profound connection between transparency and the sustainability of an LHS. Transparency was considered important to earn and sustain trust in the LHS, ensuring the reliability of information derived from the LHS, and facilitating access to both the generated evidence and the mechanisms governing the LHS. These factors, among other considerations, were considered crucial in not only encouraging individuals to place their trust and reliance in the stewardship (responsibility to access and use data appropriately, but also protecting privacy and demonstrating trustworthiness) of institutions and the evidence generated by the LHS. Moreover, transparency influences their willingness to contribute to the LHS. A connection with the latter perspective can be drawn by referencing to our normative analysis in Chapter 5. In this chapter, we emphasized the significance of empowering pregnant people as a means to encourage their participation on the basis of solidarity. An important aspect of the process of empowerment is to offer information, often in collaboration with other stakeholders, facilitating access to knowledge about the LHS and about the avenues for data sharing and contributing to knowledge generation to improve the well-being of future pregnant people.

Simultaneously, our empirical research raised questions and concerns regarding the collaboration between public and private institutions. Collaboration with the private industry introduced a host of concerns, ranging from potential conflicts of interests and financial gain to questions of objectivity. Such collaboration was often perceived as a significant obstacle for women to place their trust in the LHS and the knowledge it aims to generate and disseminate. DAPs expressed concerns about the pharmaceutical industry's potential influence on shaping research questions, developing protocols, and interpreting results. The interviews with DAPs illuminated the intricate challenges of constructing a

robust infrastructure and the complexities of navigating negative assumptions regarding the pharmaceutical industry, also often addressed in empirical literature on public-private partnerships and data sharing initiatives.[19, 20] The public-private partnerships give rise to a delicate situation, necessitating a strong governance- and ethics framework. There may be various ways in which the interests of public and private parties diverge and these conflicts of interest within a public-private partnership will need to be carefully navigated,[21] ideally before the collaboration is officiated in contracts.

In Chapter 6, we mainly focused on how research projects should transition into an operational LHS. Within this context, we formulated essential ethical requirements. Regarding the data infrastructure, it remains important to consider the interests of data subjects, in our case: pregnant and lactating people. Therefore, constant consideration of whether the data infrastructure is going to demonstrate a reasonable likelihood of public benefit and that the potential benefits of utilizing the health data of pregnant and lactating people will outweigh the potential harms to them or their communities. While DAPs, as data stewards have the moral responsibility to ensure that the health data are processed and used appropriately, whilst also protecting privacy and demonstrating trustworthiness, an additional way to ensure better alignment with the interest of pregnant and lactating people, is the establishment of a Data Access Committee (DAC). The literature increasingly references a DAC as a potential alternative or complement to traditional research ethics committees.[22-24] DACs could have a central role in facilitating ethical data sharing and data reuse and the protection of data subjects, their communities, data producers and their institutions. A DAC should also be involved in offering guidance at the conclusion of a research project, particularly when collaborating parties need to operate within the framework of an LHS. These guidelines should encompass a range of considerations. This includes formalized agreements covering recognition requirements, benefit-sharing arrangements, and data protection agreements (also mentioned in Chapter 4). Moreover, they should extend to encompass agreements aimed at safeguarding the interests and rights of data subjects.

2. The learning cycle

The learning cycle stands out as perhaps the most pivotal element within an LHS. The learning cycle refers to the step in which new insights derived from data analyses will be effectively integrated into clinical practice. Without this continuous cyclical process, the research collaboration that invested substantial effort in constructing a data infrastructure cannot truly be called a *learning* healthcare system. In Chapter 2, we outlined five key aspects crucial to integrating knowledge to improve health and care. These were: 1) standardization of knowledge representation, 2) robust technical infrastructure to ensure accessibility, 3) transparency and trustworthiness, 4) trust, and 5) sustainability

and inclusivity. While these aspects offer a solid foundation for constructing strategies to achieve this integration, our empirical research (Chapters 3 and 4) uncovered additional complexities and challenges that demand consideration.

Through our interviews with Dutch women who wish to become pregnant, are pregnant, or nursing (Chapter 3), it became evident that, concerning the integration of knowledge, their primary reliance is on the information provided by their healthcare professionals (HCPs). Moreover, the majority emphasized the significance of receiving information that is clear and specifically tailored to their personal situation. In their eyes, HCPs were considered best equipped to interpret novel insights and apply them to their unique circumstances. However, the utilization of real-world data introduces challenges to these formulated needs of pregnant and lactating people. In a comprehensive data LHS, the capacity for individualized interpretation of results may be limited, and the generated evidence may serve as a valuable source for informed decision-making rather than directly dictating decisions. At the same time, our empirical research provides valuable insights into the expectations and needs of pregnant and lactating people. The interviews underline the importance of involving trusted professionals, such as HCPs, in the interpretation, translation, and overall integration of knowledge within the clinical practice. They are a key stakeholder in striking a balance between addressing the safety concerns and needs of pregnant and lactating people on the one hand, and upholding the validity of the evidence generated, on the other. A similar argument was made by the DAPs in Chapter 4, as also described under building block 1 "the data and its infrastructure". The transformation of data, or more precisely, the outcomes derived from data analyses into meaningful insights capable of improving the clinical practice and the health of pregnant and lactating people, requires engaging individuals experienced in the context of pregnancy and lactation. These findings underline the pivotal role that HCPs play in closing the learning cycle, particularly in bridging the gap between research and patient care.

Another aspect that could complicate the integration of knowledge to improve clinical practice, worthy of discussion, also pertains to the interviews from Chapter 4. Our interviews with DAPs revealed a notable discrepancy in their motivations to continue contributing to the LHS. DAPs highlighted that a driving force behind their contribution to the LHS is the opportunity to publish their research in scientific journals. Many of these DAPs are affiliated with academic institutions, where publication holds substantial importance. However, it is essential to note that merely publishing results does not suffice in completing the learning cycle as it does not guarantee their direct application in the clinical practice. It has been argued that within the health care sector, while a substantial amount of innovative research is conducted, regrettably, a significant portion of the valuable knowledge generated from this research often remains underutilized in clinical decision-making.[25] Adopting the LHS approach

suggests this better alignment between research and care. However, there is not enough attention for the infrastructure necessary to enable this alignment in such a way, that it increases the likelihood that findings will be translated into real-time health care improvements.[26] In our ethics framework (Chapter 6), we mentioned this crucial step under the ethical requirement of sustainability. The moral consequences of (over)promising the development of an LHS to accelerate outcomes and improve the evidence base for patients, are deeply concerning. Without a successful transition and the long-term capability to maintain the LHS cycle and effectively disseminate new insights to patients and HCPs, the much-needed paradigm shift would lose much of its significance. For research projects that started on the premise of developing an LHS, the learning cycle should receive significant attention during the transition phase and requires a sense of moral responsibility among DAPs and other relevant stakeholders for ethical data handling and dissemination of results. While it is important to identify the *learning* objectives before commencing on a research project, we are aware of the complexities involved in creating an infrastructure capable of translating findings into immediate healthcare improvements at the beginning of a research project. Especially when considering that an internationally operating LHS must encompass not just a single clinical practice, but a multitude spanning diverse countries and cultures. Establishing a sustainable learning cycle in this context requires the identification of optimal long-term feedback mechanisms, considering the established data infrastructure and collaborative partnerships. Cultural differences play a crucial role in this integration process. Therefore, involving pregnant and lactating people and community representatives along with HCPs in the design of feedback mechanisms and evidence translation is imperative. Which brings us to the third building block, as discussed in Chapter 2.

3. Stakeholder involvement

The involvement of stakeholders in all processes from LHS development to LHS implementation to the sustainability of an LHS seems crucial. Not only does stakeholder involvement receive increasing attention in the literature on LHSs,[27-33] the involvement of relevant stakeholders has also been discussed throughout this thesis. In Chapter 2, stakeholder involvement has been discussed as an important element in the design of an LHS as it could help ensure that the system is effective, efficient, and meets the needs of all relevant stakeholders, including pregnant and lactating people. Besides the group of pregnant and lactating people, the word 'stakeholder' refers to a very broad range of people and groups, for example: DAPs, researchers, HCPs, ethicists, funding agencies, regulatory authorities, and pharmaceutical companies. Moreover, when stakeholder involvement is organized effectively, it can have positive outcomes regarding stakeholders' willingness to contribute to the LHS, the level of trust in the system as more features of the LHS become transparent to them, and a sense of participation in

decision-making processes related to the LHS.

In Chapter 3, we empirically examined these insights from the literature and asked our respondents whether they wanted to be involved in an LHS for pregnant and lactating people. In general, most of our respondents wanted to contribute, because they want to help other people. Especially if it would mean that they could help prevent people from experiencing the same struggles they experienced when searching for information on medications and the struggles of having to deal with both pregnancy and a chronic condition. In the literature, acting upon this feeling of responsibility to help others with whom one shares a specific experience, is described as solidarity. In Chapter 5, we explored the role of solidarity in the field of pregnancy. We wanted to understand whether and how we can engage pregnant people in closing the knowledge gap by stimulating the enactment of solidarity on the part of pregnant people. We used the concept of solidarity as described by Barbara Prainsack and Alena Buyx (2017).[34] They understand solidarity as "enacted commitments to accept costs to assist others with whom a person or persons recognize a similarity in a relevant respect".[34] We found that through empowerment, pregnant people can be stimulated to engage in closing the knowledge gap on the basis of solidarity. Empowerment, understood as a process that enhances peoples' decision-making and ability to cooperate with others, is a key element in stimulating pregnant people to recognize they are in a similar situation and can help improve the situation for pregnant and nursing people by, for example, contributing to an LHS. The process of empowerment starts by raising awareness on the lack of evidence on medications used in pregnancy and on how people can contribute to changing the way knowledge is currently being generated, by for example sharing their health data. To start the process of empowerment to stimulate solidarity among pregnant people, the support of many other important stakeholders is necessary. Besides pregnant people, HCPs, data scientists, funding agencies, registries, and other professionals must also act in solidarity with pregnant people. Their role is crucial for raising awareness on the lack of knowledge and on the importance of scientific research, and building the right infrastructure so that people can be more involved.

In the introduction of this thesis, Chapter 1, the need for a co-creationistic approach for LHSs was mentioned. However, throughout this thesis, the emphasis has predominantly been on stakeholder involvement and engagement. We are aware that even the research presented in this thesis leans more towards an attempt at stakeholder engagement rather than co-creation. In Chapter 6, we once more refer to the need for co-creation as opposed to the notion that stakeholder engagement often functions as a means to gather views of stakeholders rather than actively collaboratively shaping (co-creation) the research project[35, 36] and thus LHS design. To make sure the LHS is more centered around stakeholders who will use the knowledge generated through the LHS, it is crucial to engage

stakeholders such as people of childbearing potential, HCPs, researchers, data scientists, and regulators. One way to shape engagement is by including pregnant and lactating people, and/or by involving community or patient representatives in steering and reviewing committees, such as the DAC. Moreover, meaningful engagement entails commitment to provide ongoing feedback to pregnant and lactating people and their HCPs regarding the transition to and operation of the LHS. Lastly, meaningful stakeholder engagement also requires a structured approach that embraces these diverse stakeholder groups while simultaneously acknowledging and respecting the range of viewpoint they bring. Such viewpoints encompass the variety among pregnant and lactating people, stemming from cultural distinctions, as well as differences among specialists who prioritize distinct health concerns.

Reflecting upon the main findings and future directions

Learning healthcare systems

Overall, the development of an LHS in the field of pregnancy and lactation appears promising and, some might argue, long overdue. Despite calls for the fair inclusion of pregnant and lactating people in clinical trials, a substantial shift in their inclusion and thus to evidence generation for medications used during pregnancy and lactation has not been achieved so far. There is a moral imperative to change the current situation for pregnant and lactating people, including their HCPs, by improving their decision-making regarding medical treatments. Learning from current real-life experiences of pregnant and lactating people who use medications may be seen as low hanging fruit – an almost readily available opportunity. Given that pregnant and lactating people routinely use medications within the current health care context, there is an opportunity to systematically learn from these exposures. Across various healthcare and research domains, LHSs are considered promising systems for bridging the knowledge gaps present in the clinical practice.[25] Consequently, numerous research initiatives are in progress with the goal of establishing LHSs.[33]

LHSs have also received substantial attention in the literature, with a particular focus on their potential and design. In a sense, LHSs have gained popularity, potentially even becoming a popular approach symbolizing the desire for alternative systems that align research and care. Historically, research and care were viewed as similar and as intertwined. However, the Belmont Report disentangled research and care, defining clear boundaries between the two.[37, 38] Now, the sharp distinction between research and care is becoming increasingly blurred, because of (among other arguments) the digital transformation of health care providing access to patient data in more comprehensive and less labor-intensive ways, cultural shifts in evidence-based medicine, and the perceived social

value in the integration.[37] Unsurprisingly, the exploration of an LHS emerges as a promising avenue for generating new evidence regarding the safety and efficacy of medications used during pregnancy and lactation. Moreover, utilizing data collected in real-life settings for research purposes is by no means a novel concept. The field of epidemiology, for instance, draws its conclusions predominantly from these data, also called observational data.[39]

As may be evident by now, the utilization of real-world data comes with both strengths and limitations that researchers and research advisors must thoroughly understand to ensure that no unwarranted claims are based on the analyses conducted with such data. Inappropriate analyses run the risk of yielding inaccurate results, potentially leading to misguided policy and practice decisions.[40] Illustrating the complexities involved, the case of the medication diethylstilbestrol (DES) serves as an example of flawed observational research, where a clinical trial in 1953 already reported no evidence of effectiveness, yet its findings were largely ignored.[39, 41] It is important to acknowledge that the results derived from real-world data fundamentally differ from evidence generated through traditional clinical research methods, such as Randomized Controlled Trials (RCTs). Moreover, there are situations where the conduct of RCTs proves challenging, such as with vulnerable populations. However, certain questions demand the controlled setting afforded by clinical trials, especially those related to questions of efficacy. However, for medicines safety assessment, the use of real-world data is currently state of the art for regulators.[42, 43]

Nonetheless, critics of clinical trials, including RCTs, argue that they are slow and that their reported results deviate from real-world experiences, making translation into health care improvements challenging. Herein lies the appeal of LHSs, as they enable faster knowledge generation and provide a better reflection of the real-world context of patients. In turn, facilitating improvements for patient outcomes. In the field of pregnancy and lactation, adopting an LHS that utilizes real-world data is probably the most promising step forward in bridging the knowledge gap. An LHS may even emerge as a better alternative to clinical trials, especially in addressing safety questions regarding medications used during pregnancy and lactation, given the necessity of extensive data to address such questions.

IMI-ConcePTION

In the last four years, the IMI-ConcePTION consortium has dedicated efforts to establish an LHS in the field of pregnancy and lactation. The ConcePTION ecosystem and the achievements of the consortium have been briefly outlined in Chapters 2 and 6 of this thesis. The consortium shows progress in the ability to transform real-world data into actionable data particularly for studying safety questions regarding medications used during pregnancy and lactation.[44] Moreover, the ConcePTION infrastructure has been successfully used for studying

the impact of COVID-19 and medications, including vaccines, on maternal, pregnancy, and neonatal outcomes.[45] This success is attributed to the utilization of real-world data extracted from electronic health records and health registries across Europe.[46] Furthermore, IMI ConcePTION is developing educational materials for HCPs on teratology and long-term consequences of medication exposure during pregnancy, and on effective evidence generation methods, along with communication strategies for people on medication use during pregnancy and lactation.[47] Lastly, a centralized digital knowledge bank is being developed to provide up to date evidence-based information to both HCPs and members of the general public regarding the use of medications during pregnancy and lactation. This knowledge bank will contain information on the use of specific medications in pregnancy and lactation.[48]

To transition into an operational LHS, the consortium must address some remaining steps, primarily focusing on stakeholder engagement, commitment to equity and justice, the sustainability of the ecosystem, and on closing the learning cycle (as discussed in Chapter 6). Throughout this thesis, closing the learning cycle has been underscored as a crucial aspect of LHS development. While this step is inherently connected to the broader challenge of establishing a sustainable ecosystem for ongoing research into the safety of medications used during pregnancy and lactation, it is important for the ConcePTION ecosystem to evolve into a true LHS by establishing a sustainable infrastructure capable of implementing new insights to improve care and health outcomes for pregnant and lactating people. Establishing a knowledge bank is an important step towards providing new evidence to stakeholders. However, to significantly impact clinical practice and to close the LHS cycle, attention must be directed to several aspects. For example, on other ways to directly influence clinical practice, such as clinical guidelines, but also on establishing the knowledge bank as a reliable source of information for both pregnant and lactating people, and for HCPs. This position largely depends on its ability to address the specific information needs of pregnant and lactating people, as well as HCPs across Europe. Moreover, becoming a reliable and influential source of information demands attention to transparency regarding the utilization of health data, earning the trust and recognition from all relevant stakeholders in the LHS and the knowledge it generates, and fostering meaningful stakeholder interaction.

Ethical oversight

As mentioned before, in an LHS, the distinction between treating patients and conducting research becomes less distinctive. This so-called alignment between these domains raises questions about the delicate balance between the goal of research to generate knowledge and foster continuous improvement on the one hand, and the ethical treatment, the protection of patients' wellbeing and interests, and safeguarding their privacy and confidentiality on the other. More

specifically, this alignment gives rise to questions regarding ethical oversight and regulation, aspects that have not been explicitly addressed in this thesis. In what follows, we will introduce two relevant questions that warrant further research.

First, should we address an LHS as one system or is it a constituent of different elements? For example, the IMI-ConcePTION LHS exists of multiple participating organizations across many countries, not capturing one single healthcare system. Defining rules and regulations, and ethical guidance is challenging, as it cannot do justice to all different systems in as much detail. Furthermore, these types of LHSs are also in a way quite detached from the actual clinical practice, lacking a tangible connection (apart from the data they are using, that are produced in healthcare practices). Meaning that greater efforts are needed to actively involve and engage healthcare facilities, medical professionals, nurses, insurance providers, and researchers. It is possible that these stakeholders may not even be aware, at first, of the existence of the LHS, which complicates efforts to communicate and implement new insights into their clinical practice. Perhaps, an alternative interpretation or framework for a multicountry LHS is essential to better align with the distributed approach employed for the data infrastructure. Such an LHS could be called a federated data LHS, requiring local or national health systems to undertake specific tasks for operationalization, regulation, and oversight.

Second, what normative framework would be most appropriate to guide ethical oversight? While a definitive answer to this question remains elusive in the literature, the fact that many scholars are actively exploring it underscores it significance. Some scholars propose the creation of a new category of activities within an LHS, aligning with public health studies. Examples of such activities are observational studies, which are at the core of a comprehensive data LHS and are similar to epidemiological and public health studies. Other scholars argue that a strict conceptual distinction between research and care is unwarranted and unhelpful because it misdirects our focus to whether data analyses within an LHS should be considered research, and therefore, whether consent is necessary and practical. Rather, we should focus on whether the data analyses will generate socially valuable knowledge and whether the harms are proportional to the benefits. This brings us back to a public health ethics approach that could guide the development of a framework for ethical oversight. Traditional ethical review and informed consent procedures may seriously impede multicountry LHS studies.[22, 49] Perhaps ethical review that aligns with public health ethics would be a better fit as the main focus of an LHS and public health is not an individual pregnant person, but promotion of public health. Furthermore, in an LHS it is very difficult to distinguish research from routine clinical care. As mentioned earlier and as underlined by the literature, the establishment of a DAC could be a first step towards a direction, in which a public health approach can be adopted. A DAC, as opposed to a research ethics committee, should not be guided by

research ethics principles, but DAC reviews should be guided by the principles of public health ethics instead.[22]

Data ecosystem

Whether we should address an LHS as one system or as a constituent of its elements is also an interesting question for the future of projects that aim to develop an LHS. Developing a reliable, robust, and sustainable data ecosystem requires a lot of work and effort of many different stakeholders. IMI ConcePTION is an example of a project that has not only brought together different stakeholders but has also dedicated substantial efforts to developing methods for analyzing vast amounts of heterogeneous health and research data. Many other (future) projects can learn from ConcePTION and probably use many elements of the ConcePTION approach as their foundation for a similar data ecosystem. Moreover, the ConcePTION data transformation 'pipeline' has been used for other purposes, such as COVID-19 observational studies. This example emphasizes the idea that an LHS should be perceived as an ecosystem comprising of numerous reusable and interchangeable elements, adaptable based on the specific topic and area of interest. IMI ConcePTION is a European collaboration, primarily utilizing data from people on the European continent. Expanding the ConcePTION ecosystem into a global LHS or the establishment of multiple LHSs on different continents based on the ConcePTION ecosystem could further strengthen the evidence base and increase the relevance of information for people beyond the European context. Considering sustainability and the efficient use of resources, it would be meaningful to focus on investing in a singular strong foundation capable of supporting data analyses with heterogeneous real-world data, applicable to various questions. The establishment of such a data ecosystem is contingent upon the commitment of DAPs, and other relevant institutes and companies to commit to designated data transformation methods and analysis procedures, as well as strong ethical guidance and rules and regulations. As mentioned before, in many areas of healthcare and research, LHSs and the utilization of real-world data are seen as promising ways for accelerating research and outcomes for patients. Therefore, further research into data ecosystem(s) and LHSs could contribute to a more sustainable approach and efficient use of resources.

Strengths and limitations

As described in Chapter 1, the research approach of this thesis was based upon the wide reflective equilibrium. This approach allowed us to combine empirical research with ethical analysis and reflection. We have collected morally relevant facts about LHSs and the utilization of real-world pregnancy and lactation data. We have studied morally relevant perspectives of Dutch women during preconception, pregnancy, and nursing, and people working for DAPs from the IMI ConcePTION project on an LHS. Lastly, we combined these facts and

perspectives with relevant moral concepts, principles, and background theories to work towards achieving a reflective equilibrium. Moreover, adopting this specific empirical-ethical approach enabled us to explore the many distinct aspects of an LHS. LHSs are intricate and dynamic approaches, influencing not only various areas of healthcare and research but also engaging diverse stakeholders. While there exists a robust technical and methodological dimension to building an LHS, this thesis, through its empirical research and ethical reflection, underscores that the success of an LHS – both methodological and ethically – depends on the involvement of individuals and groups of individuals, for which, ideally, a co-creationistic approach is adopted.

As mentioned in the general introduction of this thesis, we have used various ethical theories as background theories for the research in this thesis. In this thesis, there is a notable alignment with the principles of public health ethics. First and foremost, because the lack of evidence about medical treatments affects the whole population of people who want to become pregnant, are pregnant, or who are nursing, putting them at risk and in unsafe situations.[50] Improving scientific knowledge to assess therapeutic safety, dosing, and effectiveness of medications during pregnancy and lactation are necessary in order to improve the overall public health and to develop evidence about public health needs for pregnant and lactating people.[3, 51] Secondly, it has been consistently mentioned across several chapters of this thesis that considering a public health ethics approach for LHS development in the field of pregnancy and lactation might be a valuable proposition. This perspective aligns more effectively with the ethical prerequisites for establishing a responsible comprehensive data LHS. Traditional public health values include public benefit, proportionality, equity, trust, and accountability.[52] In Chapter 6, we use the public health ethics approach from Angela Ballantyne, who proposes a framework for data research based on these traditional values.[49] In her paper, she shows how these values can better guide decisions about the secondary use of health data for research, compared to a research ethics approach. While there is much overlap between the two paradigms, there is difference in how to weigh the interests of the public against the interests of individuals.[49] The balance between the health of the community with the respect owed to individuals is a key ethical challenge within the domain of health data research, a context within which an LHS operates. The learning process in an LHS is driven by data that are produced in healthcare practice and then collected and analyzed in a search for generalizable knowledge. Efficiency of LHSs requires a different ethical approach. Here, protection of an individual is not necessarily a priority, since an individual pregnant or lactating person is not exposed to risks other than those inherently associated with healthcare practice.[22] Instead, as advocated in this thesis, the emphasis during the transition towards an operational LHS should be on closing the learning cycle. The primary objective should be to generate public benefit for pregnant and lactating people, with careful consideration of whether the

secondary use of their health data aligns with their interests.

This thesis has only been able to touch upon some of the most important questions regarding the development of an ethically responsible LHS for pregnant and lactating people. By focusing on a comprehensive data LHS, we have not been able to reflect upon other models of LHSs that might also (if not better) suit the field of pregnancy and lactation. There are ideas for LHSs that have a stronger interaction with research and care, such as a 'real-time' or 'full' LHS.[16] Especially in a full LHS, clinical trials become embedded into routine care delivery, allowing for, for example, prospective data collection in a more controlled setting. However, given the persistent underrepresentation of pregnant people in clinical research, despite the calls for fair inclusion, diminishes the attractiveness and potentially the effectiveness of this LHS model. Furthermore, in this thesis, we have used IMI ConcePTION as an example for an LHS in the field of pregnancy and lactation. IMI ConcePTION provides an opportunity to study the safety and efficacy of medical treatments retrospectively based on health- and research data collected throughout Europe. A European collaboration provides the opportunity to learn from more data and thus more pregnant and lactating people. Results from data analyses might have more weight and potential to impact (clinical) decisions, than if the effects had been studied in one specific department within one health institution. However, a collaboration with many different countries also requires to be sensitive towards regional and cultural differences regarding data utilization and LHSs in general. For example, people in Nordic countries might have a different attitude towards the utilization of health data to study the impact of medical treatments during pregnancy, compared to Dutch people. Nordic countries are regarded as having excellent data infrastructures and the features of the Danish data landscape are even considered to be embedded in its culture and history.[53]

There may also be different views and interpretations regarding maternal care, which can influence discussions about the conditions of the LHS, the type of research questions, and interpretation of results. Furthermore, 'the group of pregnant people' is not homogeneous in several ways. Culture, religious beliefs, and perspectives considerably impact the decision-making processes of pregnant and lactating people.[54] Throughout this thesis, we have acknowledged the importance of sensitivity to regional and cultural differences among stakeholders. However, we have not extensively examined or incorporated these differences into our ethical reflection. We believe that future research is needed to explore and compare differences in perspectives and attitudes of, for example, people of childbearing potential. Understanding these differences would help in making sure the LHS is more centered around stakeholders who will use the knowledge generated through the LHS. Moreover, it would have been valuable to include the perspectives of HCPs in the context of an LHS for pregnant and lactating

individuals. HCPs play a central role in the LHS by contributing to the collection of health data, particularly through electronic health records of pregnant individuals. Furthermore, our empirical research has highlighted the reliance of pregnant and lactating individuals on the information provided by their HCPs. General practitioners, gynecologists, obstetricians, and other physicians involved in the care of people during preconception, pregnancy, and lactation stand to benefit from the insights generated through the LHS. Unfortunately, we were unable to gather empirical data on their views and needs regarding an LHS, thereby limiting our ability to provide insights into their perspectives.

Lastly, we would like to shortly reflect on our involvement and collaboration with the IMI ConcePTION project. The collaboration with the IMI ConcePTION project proved invaluable for the organization of the empirical studies and for establishing a coherent context for reference throughout both our empirical and normative research. In our role as ethicists, we were integrated into the consortium as a member of a workpackage named: "*information and data governance, ethics, technology, data catalogue and quality support*". This allowed us to conduct (again) empirical research in collaboration with other consortium members and participate in annual consortium meetings, provide firsthand insights into the perspectives, developments, challenges, and opportunities involved in building a data infrastructure, stakeholder engagement, and the journey toward establishing an LHS in the field of pregnancy and lactation. This interaction also provided opportunities to share newly acquired insights with the consortium.

Despite this close collaboration, we tried to maintain a clear separation between our involvement in the consortium and the research conducted for this thesis. Although we certainly did not work as embedded ethicists, some aspects of the project may have been somewhat comparable. In the consortium, our responsibilities included delivering two specific outcomes framed to meet the needs of ConcePTION, wherein the consortium played a central role in shaping how our research findings were documented. In contrast, the research presented in this thesis utilizes ConcePTION as an illustrative case of a research project aiming to develop an LHS for the field of pregnancy and lactation. These two distinct approaches occasionally introduced a degree of tension, stemming from the unique circumstances ConcePTION presents. The distinct goals of ConcePTION in developing an LHS to study the impact of medications in pregnancy and lactation make it highly unlikely that a similar large research consortium will emerge any time soon. In a sense, the LHS discussed in this thesis can be viewed as the ConcePTION LHS. However, as an ethicist, maintaining a critical distance from the project is crucial to reflect on ethical questions, such as determining what constitutes an ethically responsible LHS in the context of pregnancy and lactation. Maintaining this critical distance occasionally posed challenges, requiring reminders from time to time that our research was not

solely aimed at improving the directives of the IMI ConcePTION project. At the same time, finding the right balance in presenting ConcePTION as an illustrative example in this thesis also presented a challenge. We aimed to avoid appearing as advocates for the IMI ConcePTION project to prevent any perception of a potential conflict of interest.

Concluding remarks and recommendations

The limited availability of scientific knowledge on medications used during pregnancy and lactation poses challenges for pregnant and lactating people and their HCPs, in making informed decisions about medical treatments. Considering the widespread use of medications by pregnant and lactating people and the lack of a systematic approach to understand the impact of current medication exposure, transitioning the field into an LHS seems a promising way forward. The main objective of this thesis was to reflect on the development of an ethically responsible LHS for pregnant and lactating people. Developing and implementing an LHS is a complex endeavor, both ethically and methodologically, with no universal blueprint. While this thesis has provided fresh perspectives on an LHS for pregnant and lactation people, there remains a considerable journey ahead.

A central theme of this thesis, and important recommendations for an LHS in the field of pregnancy and lactation, are the importance of closing the learning cycle and making sure pregnant and lactating people, including their HCPs, benefit from the insights generated through the LHS. Once the LHS cycle is complete, new insights derived from data analyses can inform decision-making, drive improvement, pose new research questions, which subsequently shape the content of new data collection. This process requires investments in an infrastructure for systematic translation of evidence, accessible to *all* pregnant and lactating people. Furthermore, commitment to equity and justice is necessary to avoid practices that could worsen existing disparities among pregnant and lactating people. It is also crucial to ensure that the LHS is inclusive and responsive to the health needs of all pregnant and lactating people. Achieving such an inclusive and responsive LHS, which also benefits pregnant and lactating people, requires certain stakeholders, including data access providers, to recognize a sense of moral responsibility for ethical data handling and the dissemination of results from the LHS. This thesis also underlines the significance of trust and transparency as both essential ethical requirements for an LHS and as mechanisms to increase the willingness to contribute to an LHS. Moreover, the sustainability of an LHS also depends on whether stakeholders, including pregnant and lactating people and HCPs, are aware and convinced of the added value of the LHS as an alternative or additional method for generating knowledge on the safety of medications used during pregnancy and lactation.

Another central theme and recommendation underlined in this thesis is the

imperative to involve stakeholders throughout the processes of LHS development and the transition towards an operational LHS. Ideally, stakeholder involvement should transcend mere opinion gathering, fostering active collaborating (co-creation). Recognizing the profound benefits of stakeholder involvement, it has also been deemed crucial for the success of an ethically responsible LHS. This thesis has formulated a framework for solidarity, among pregnant people to stimulate their willingness to contribute to an LHS. For solidarity to take effect, it is essential to empower pregnant and lactating people, fostering their awareness of the existing knowledge gap, clarifying the role of scientific research in bridging it, and outlining how they can actively participate. This process of empowerment requires the active contribution of many other stakeholders involved, including HCPs, DAPs, researchers, regulators, and pharmaceutical companies.

Finally, the transition towards an operational LHS in the field of pregnancy and lactation as well in other domains of healthcare, requires continuous ethical reflection. The growing attention to LHSs, including the utilization of real-world data, requires adjustments in how ethical guidance and regulatory frameworks are established. Moreover, for the success of new projects focused on LHS development and to ensure efficient use of resources, it would be valuable to encourage the reuse of many elements from already established data ecosystems, but at least share lessons learned and insights regarding LHS development. Learning is at the heart of an LHS, it involves not only learning from real-world data to drive care improvements, but it also involves the commitment to continuous learning regarding strategies for building the most appropriate and ethically responsible LHS.

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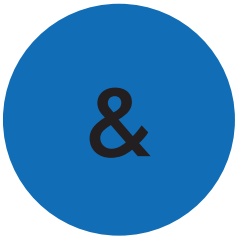

Summary

Throughout history, there has been a consistent hesitancy to include pregnant people* in clinical research, primarily due to the fear of potential harm to the fetus. As a result, little information is available about the safety and efficacy of medications taken during pregnancy. In the absence of evidence-based knowledge, clinicians are sometimes compelled to prescribe medications without sufficient supporting evidence or based on conflicting information. These challenges also extend to medication use during nursing, as there is even less information available concerning the impact of medication exposure on newborns through lactation. Although (inter)national ethical guidelines for clinical research increasingly provide clarity on the conditions under which pregnant and lactating people can be included, pregnant and lactating people are still being excluded regularly. In many areas of healthcare and research, a different approach to knowledge generation is being suggested, namely the adoption of a Learning Healthcare System (LHS). An LHS is a system in which the clinical practice is more aligned with research in such a way that it can accelerate research and outcomes for patients, by studying real-world experiences and implementing new insights directly in the clinical practice. LHSs can take various structures, but at their core, each follows a comparable cycle involving data collection, analysis, and interpretation, followed by feeding new insights back into the clinical practice to stimulate change and improvements. Given the widespread medication usage by pregnant and lactating people and the lack of a systematic approach to understand the impact of current medication exposure, transitioning to an LHS seems a promising way forward. In April 2019, the Innovative Medicines Initiative (IMI) ConcePTION project was launched to investigate the potential of utilizing various real-world data sources, including electronic health records, registries, and claims data, to generate new knowledge on the impact of medications during pregnancy and lactation. IMI ConcePTION aims to build a European LHS that can generate reliable information through a large European network, consisting of already established networks.

The development of an LHS is a complex endeavor, as there is no blueprint for LHS development and implementation. Moreover, the interpretation of LHSs widely varies. Additionally, the implementation of an LHS introduces ethical challenges that require careful reflection. The main aim of this thesis is to critically reflect upon the development of an ethically responsible LHS for pregnant and lactating people and specifically address five open ethically relevant questions:

* In this thesis, we aim to use more inclusive language, considering various groups of people, such as trans men or gender diverse people who also face disadvantages due to the lack of scientific knowledge about medications used during pregnancy and lactation. At the same time, we want to emphasize that the discussion about the correct wording remains subject of ongoing debate, with little (international) consensus.

1. What constitutes an LHS that aims to study the safety and efficacy of medications used during pregnancy and lactation?
2. What are the views of pregnant people on an LHS for pregnant and lactating people?
3. What are the views of data access providers within an LHS?
4. Can the enactment of solidarity among pregnant people be stimulated to help address the poor evidence base on medications used during pregnancy?
5. What are the necessary ethical requirements for guiding the transition of research projects to an operational LHS?

Each chapter of this thesis answers one of the research questions presented above.

In **Chapter 2** we answer the first research question and offer an overview of essential building blocks for a European comprehensive data LHS that aims to study the impact of medications used during pregnancy and lactation. By drawing insights from existing literature on LHS conceptualization and ethical challenges related to LHS development, this chapter discusses three essential LHS building blocks, namely: 1) the data (infrastructure), 2) the learning cycle, and 3) stakeholder involvement. Additionally, the IMI ConcePTION project is used as an illustrative example to contextualize these building blocks. We described the importance of having access to meaningful data, the existence of a high-quality data infrastructure and solid methods for working with real-world data. Furthermore, an LHS requires an operational learning cycle that ensures the implementation of new insights to improve health and care. Lastly, we describe the diverse benefits of arranging meaningful stakeholder involvement for an LHS.

In **Chapter 3**, we discuss the results of an interview study to address the second research question. The goal of this study is to understand what Dutch women during preconception, pregnancy, and nursing think about an LHS for pregnant and lactating people. We identified four main themes: 1) views on an LHS, 2) willingness to contribute to an LHS, 3) the role of the healthcare professional in an LHS, 4) trust in an LHS. We conclude that women are positive about an LHS: they want to contribute to the development of new information about medication safety, and think trust and transparency are important for the realization and sustainability of an LHS. Furthermore, these women view their healthcare professional essential in the translation and interpretation of information, regardless of the establishment of an LHS. While an LHS could help close the knowledge gap, the anxiety towards medication use and the challenges regarding the interpretation of medical information should be taken into account for the development of an LHS. Moreover, it underlines the crucial role healthcare professionals have in the last steps of the LHS cycle, namely: the interpretation, translation, and implementation of knowledge.

In **Chapter 4**, we collect the views of people who work as data access providers in the IMI ConcePTION project on an LHS for pregnant and lactating people to address research question three. Additionally, we want to know whether they perceive and articulate a moral responsibility directed to themselves regarding ethical data handling and dissemination of research findings. By means of a qualitative interview study, we established three relevant themes: 1) opportunity and responsibility, 2) conditions for participation and commitment, 3) challenges for a knowledge-generating ecosystem. We concluded that data access providers are motivated by diverse opportunities to contribute to an LHS. While a shared responsibility for enabling real-world data analyses is acknowledged, they focus mainly on their work and contribution to the project itself, rather than safeguarding ethical data handling. Furthermore, the results underline the importance of a transparent governance structure and emphasize the need for trust among data access providers, as well as trust from the public in the way their data is being collected and stored. These elements are important for the success and sustainability of an LHS.

In **Chapter 5**, we challenge the concept of solidarity to formulate an answer to research question four. We aim to understand whether and how enactment of solidarity among pregnant people can be stimulated to help shift the way knowledge on medication safety during pregnancy is being generated. We use the concept of solidarity formulated by Prainsack and Buyx. We propose to enhance their existing concept by emphasizing that for solidarity to take effect, the empowerment of pregnant people is necessary. The process of empowerment starts by raising awareness about the lack of evidence on medications used during pregnancy, and by explaining to pregnant people how they can contribute to changing the way knowledge is being generated. We believe that acting in solidarity can help change the status quo for pregnant people, however this requires the help of other relevant stakeholders. Within the context of an LHS, pregnant people could actively contribute by, for instance, reporting adverse drug reactions to local organizations collaborating with IMI ConcePTION. Here, we emphasize that the LHS, or more specifically, IMI ConcePTION should ensure the accessibility of the ecosystem to pregnant people and their healthcare professionals.

Chapter 6 presents an ethics framework for the transition to an operational LHS to address research question five. We emphasize the necessity of an ethics framework for projects and networks that have taken steps towards building an LHS and need to transition towards an operational and ethically responsible LHS. The framework is based on existing frameworks in the areas of LHSs, transforming health systems, big data research, and public health. We analyzed these frameworks, identify their overlapping content, and apply the insights from

the analysis to the context of a European LHS for pregnant and lactating people. We propose four ethical requirements: 1) public benefit and favorable harm-benefit ratio, 2) equity and justice, 3) stakeholder engagement, 4) sustainability. With these four ethical requirements we hope to stimulate projects, networks, and organizations to make decisions that contribute to establishment of mechanisms for continuous learning that can impact health and care in an ethical way.

In **Chapter 7** we present and reflect upon the main findings of this thesis and identify areas for future research. The main findings are organized according to the essential building blocks as discussed in chapter 2. Regarding the data and its infrastructure, we show that transparency emerged as a recurring theme in both qualitative interview studies. Transparency is considered important in the process of transforming data into meaningful evidence and it seems to play a crucial role in both earning trust of stakeholders and for the sustainability of an LHS. Regarding the learning cycle, the results of this thesis highlight the importance of closing the cycle, meaning the ability to transform practice-related data into actionable knowledge and apply such knowledge in the clinical practice, while capturing the resulting outcomes as new data. It also shows the challenges associated with this process and emphasizes the need for more research into appropriate feedback mechanisms. Furthermore, this thesis emphasizes the moral responsibility to ensure that pregnant and lactating people, including their HCPs, benefit from the insights generated through the LHS. Regarding stakeholder involvement, this thesis discusses the importance of organizing meaningful stakeholder engagement throughout the entire development phase and transition to an operational LHS. It also suggests stimulating the enactment of solidarity on the part of pregnant people to allow them to become actively engaged in closing the knowledge gap. In this chapter we reflect upon the approach of an LHS and conclude that while an LHS that utilizes real-world data poses challenges, it is probably the most promising step forward in bridging the knowledge gap. Addressing safety questions regarding medications used during pregnancy and lactation requires access to extensive data, which can be organized through an LHS. We also reflect upon the question of ethical oversight and regulation, and wonder whether an LHS should be seen as an ecosystem comprising of numerous reusable and interchangeable elements, adaptable to specific topics and areas of interest. Understanding an LHS as a data ecosystem could help with the establishment of more uniform data transformation methods and analysis procedures, as well as to the formulation of strong ethical guidance, rules, and regulations. Considering sustainability and the efficient use of resources, instead of reinventing the so-called LHS wheel, projects, networks, and organizations could add to existing data ecosystems. Furthermore, we also argue that a public health ethics approach for the development of a framework for ethical oversight might be most appropriate, as an LHS challenges the traditional distinction between

research and routine clinical care, making it equally challenging to differentiate between the individual patient and the public. Lastly, we argue that learning is at the heart of an LHS, which also involves the commitment to continuous learning regarding the development of appropriate and ethically responsible LHSs. Hence the title of this thesis: Keep learning.

Nederlandse samenvatting

Door de geschiedenis heen worden zwangere en lacterende mensen* doorgaans uitgesloten van deelname aan gerandomiseerde klinische studies, met name vanwege risico's voor de foetus. Door hen stelselmatig uit te sluiten is echter schaarste ontstaan aan wetenschappelijke kennis over de veiligheid en werkzaamheid van medicijnen die desalniettemin worden gebruikt tijdens de zwangerschap of lactatie. Het gebrek aan wetenschappelijk onderbouwde informatie leidt soms ten onrechte tot het niet nemen van medicijnen of het staken van behandelingen. Hoewel (inter)nationale ethische richtlijnen voor onderzoek met mensen in toenemende mate duidelijkheid bieden over de voorwaarden waaronder zwangere en lacterende mensen kunnen worden geïncludeerd, blijkt de praktijk nog weerbarstig.

In verscheidene domeinen binnen de gezondheidszorg en onderzoek wordt een nieuwe, innovatieve benadering voor kennisontwikkeling voorgesteld, namelijk die van een lerend zorgsysteem, ook wel: *Learning Healthcare System (LHS)*. In een lerend zorgsysteem zijn onderzoek en zorg dusdanig met elkaar verbonden dat er (1) kennis wordt verkregen middels patiëntgegevens direct uit de klinische praktijk en (2) de vergaarde kennis terugvloeien naar de klinische praktijk om de zorg te verbeteren, waarna (3) deze cyclus weer opnieuw begint. Deze dynamiek vormt een zogenaamde *leercyclus*.

Gezien het wijdverbreide medicijngebruik onder zwangere en lacterende mensen, samen met het ontbreken van een systematische aanpak om de impact van medicijnen bij deze groepen te bestuderen, biedt een lerend zorgsysteem een veelbelovende strategie.

In april 2019 is het Europees *Innovative Medicine Initiative (IMI)* ConcePTION project gestart. ConcePTION is een publiek-private samenwerking waarin verschillende bestaande netwerken en organisaties meedoen die verschillende gegevens verzamelen en bewaren die relevant zijn voor studies naar medicijnveiligheid tijdens de zwangerschap en lactatie. ConcePTION heeft als doel te onderzoeken hoe deze verschillende relevante gegevens vanuit de klinische praktijk (ook wel *real-world* data genoemd) kunnen worden gebruikt om nieuwe kennis te genereren over de veiligheid van medicijnen die tijdens de zwangerschap en lactatie worden gebruikt. ConcePTION streeft ernaar een Europees lerend zorgsysteem te bouwen dat betrouwbare informatie kan genereren en verspreiden voor zwangere en lacterende mensen, en hun zorgverleners.

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* In dit proefschrift streven we ernaar om inclusievere taal te gebruiken, waarbij we rekening houden met groepen mensen, zoals transmannen of gender diverse mensen die ook nadelen ondervinden van het gebrek aan wetenschappelijke onderbouwde kennis over medicijnen die gebruikt worden tijdens de zwangerschap en lactatie. Tegelijkertijd willen we ook benadrukken dat de discussie over correcte terminologie voortdurend aan verandering onderhevig is en dat er weinig (internationale) consensus bestaat.

Het opzetten van een lerend zorgsysteem is echter een complexe onderneming. Daarbij bestaat er geen blauwdruk voor de ontwikkeling en implementatie ervan. Bovendien varieert de interpretatie van een lerend zorgsysteem sterk. Daarnaast brengt het opzetten van een lerend zorgsysteem ethische uitdagingen met zich mee die zorgvuldige reflectie vereisen. In dit proefschrift beogen we kritisch te reflecteren op de ontwikkeling van een ethisch verantwoord lerend zorgsysteem voor zwangere en lacterende mensen en behandelen daarbij vijf ethisch relevante vragen:

1. Hoe ziet een lerend zorgsysteem eruit dat als doel heeft de impact van medicijnen tijdens de zwangerschap en lactatie te bestuderen?
2. Hoe denken zwangere mensen over een lerend zorgsysteem voor zwangere en lacterende mensen?
3. Hoe denken gegevensbewaarders over een lerend zorgsysteem?
4. Kan solidariteit onder zwangere mensen worden gestimuleerd om de beperkte wetenschappelijke basis met betrekking tot medicijngebruik tijdens de zwangerschap aan te pakken?
5. Wat zijn de noodzakelijke ethische vereisten voor het begeleiden van onderzoeksprojecten in de transitie naar een operationeel en ethisch verantwoord lerend zorgsysteem?

Elk hoofdstuk van dit proefschrift heeft als doel een van de bovengenoemde onderzoeksvragen te beantwoorden.

In **hoofdstuk 2** bieden we als antwoord op vraag 1 een overzicht van essentiële bouwstenen voor een Europees, data gedreven lerend zorgsysteem dat als doel heeft de impact van medicijngebruik tijdens de zwangerschap en lactatie te bestuderen. Door inzichten te gebruiken uit de bestaande literatuur over lerende zorgsystemen en bijbehorende ethische uitdagingen, worden er drie essentiële bouwstenen voor een lerend zorgsysteem besproken, namelijk: 1) de data (infrastructuur), 2) de leercyclus, en 3) de betrokkenheid van belanghebbende. Bovendien wordt het IMI ConcePTION project als voorbeeld gebruikt om deze bouwstenen verder in context te brengen. We beschrijven het belang van toegang tot betekenisvolle gegevens, het bestaan van een hoogwaardige gegevensinfrastructuur en solide onderzoeksmethoden voor het werken met gegevens uit de praktijk. Verder vereist een lerend zorgsysteem een werkende leercyclus, die ervoor zorgt dat nieuwe kennis daadwerkelijk wordt gebruikt om de gezondheid van patiënten en de zorg te verbeteren. Tot slot beschrijven wij in dit hoofdstuk de diverse voordelen van het organiseren van betekenisvolle betrokkenheid van verschillende belanghebbende voor een lerend zorgsysteem.

In **hoofdstuk 3** beschrijven we als antwoord op vraag 2 een interviewstudie met Nederlandse vrouwen met een kinderwens, die zwanger zijn of onlangs bevallen zijn met als doel te begrijpen wat zij van een lerend zorgsysteem voor zwangere en lacterende mensen vinden. We stellen vier thema's in de antwoorden vast: 1) visies op een lerend zorgsysteem, 2) bereidheid om bij te dragen aan een lerend zorgsysteem, 3) de rol van de zorgverlener in een lerend zorgsysteem, 4) vertrouwen in een lerend zorgsysteem. We concluderen dat deze vrouwen positief tegenover een lerend zorgsysteem staan, dat ze willen bijdragen aan de ontwikkeling van nieuwe informatie over medicijnveiligheid. Waarden die zij belangrijk vinden zijn: vertrouwen en transparantie. Deze waarden zijn onder andere essentieel voor de realisatie en duurzaamheid van een lerend zorgsysteem. Bovendien beschouwen deze vrouwen hun zorgverlener als spil bij de vertaling en interpretatie van informatie, ongeacht de oprichting van een lerend zorgsysteem. Hoewel een lerend zorgsysteem dus mogelijk kan helpen om de huidige kennisklоof te dichten, zullen de zorgen over medicijngebruik tijdens de zwangerschap en de uitdagingen met betrekking tot het begrijpen van medische informatie moeten worden meegenomen in de realisatie van een lerend zorgsysteem. Daarbij zien we dus een cruciale rol voor de zorgverlener bij de interpretatie, vertaling en implementatie van nieuwe kennis uit het lerende zorgsysteem.

In **hoofdstuk 4** beschrijven we als antwoord op vraag 3 een interviewstudie met mensen die werken voor organisaties die gegevens verzamelen en bewaren (ook wel gegevensbewaarders genoemd) binnen het IMI ConcePTION project. We willen zo begrijpen wat zij van een lerend zorgsysteem voor zwangere en lacterende mensen vinden. Daarbij willen we weten of zijzelf een morele verantwoordelijkheid ervaren om op een ethisch verantwoorde wijze gegevens te verwerken en onderzoeksresultaten te verspreiden. Wij stellen drie relevante thema's in de antwoorden vast: 1) kansen en verantwoordelijkheid, 2) voorwaarden voor deelname en betrokkenheid, 3) uitdagingen voor een lerend zorgsysteem. We concluderen dat gegevensbewaarders worden gemotiveerd door diverse kansen om bij te dragen aan een project zoals IMI ConcePTION. Hoewel erkend wordt dat er een gedeelde verantwoordelijkheid is om analyses met gegevens uit de praktijk mogelijk te maken, concentreren de respondenten zich hoofdzakelijk op hun eigen werk en bijdrage aan het project en in mindere mate op het waarborgen van een ethisch verantwoorde verwerking van gegevens. Bovendien benadrukken de resultaten het belang van een transparante bestuurlijke (governance) structuur en de noodzaak van vertrouwen tussen gegevensbewaarders onderling, maar ook de aanwezigheid van vertrouwen bij mensen in de wijze waarop hun gegevens worden verzameld en bewaard door gegevensbewaarders. Deze elementen moeten bijdragen aan het succes en de duurzaamheid van een lerend zorgsysteem.

In **hoofdstuk 5** bestuderen we het concept solidariteit om antwoord te geven op de vierde onderzoeksvraag. We proberen te beargumenteren of én op welke manier solidariteit onder zwangere mensen bevorderd kan worden om een verandering teweeg te brengen in de manier waarop kennis over medicijnveiligheid tijdens de zwangerschap wordt gegenereerd. We gebruiken het concept van solidariteit geformuleerd door Barbara Prainsack en Alena Buyx en voegen hieraan toe dat solidariteit effectief kan zijn, maar hiervoor de bekrachtiging, ook wel *empowerment*, van zwangere mensen noodzakelijk is. Het proces van *empowerment* begint met het vergroten van bewustzijn over de beperkte wetenschappelijke kennis over medicijnen die tijdens de zwangerschap worden gebruikt. Daarbij zal het duidelijk moeten worden voor mensen hoe zij kunnen bijdragen aan het veranderen van de manier waarop kennis wordt gegenereerd. Om *empowerment* te realiseren en solidariteit onder zwangere te bevorderen, is de hulp van verscheidene relevante belanghebbenden noodzakelijk. Binnen de context van een lerend zorgsysteem kunnen zwangere mensen actief bijdragen aan het verzamelen van relevante gegevens, bijvoorbeeld door het melden van medicijnbijwerkingen aan lokale netwerken (zoals bijwerkingencentrum *Lareb* in Nederland), die op hun beurt samenwerken binnen IMI ConcePTION. Tenslotte benadrukken we dat het belangrijk is dat het lerend zorgsysteem toegankelijk is voor zwangere mensen en hun zorgverleners.

In **hoofdstuk 6** presenteren we een ethisch raamwerk voor de transitie naar een operationeel lerend zorgsysteem. Dat is ons antwoord op vraag 6. We onderstrepen het belang van een ethisch raamwerk voor projecten en netwerken die reeds stappen hebben gezet in de richting van een lerend zorgsysteem, maar nog verdere actie moeten ondernemen om te voldoen aan de criteria van een operationeel en ethisch verantwoord lerend zorgsysteem. Het raamwerk is gebaseerd op bestaande ethische raamwerken op het gebied van lerende zorgsystemen, innovatieve gezondheidssystemen, *Big Data*-onderzoek en de publieke gezondheidsethiek. We hebben deze raamwerken geanalyseerd, hun overlappende content geïdentificeerd en de inzichten toegepast binnen de context van een Europees lerend zorgsysteem voor zwangere en lacterende mensen. We stellen in ons raamwerk vier ethische vereisten voor: 1) maatschappelijke waarde en een gunstige verdeling van voordelen en lasten, 2) gelijkheid en rechtvaardigheid, 3) betrokkenheid van belanghebbenden en 4) duurzaamheid. Met deze vier ethische vereisten hopen we projecten, netwerken en organisaties aan te moedigen ethisch verantwoorde beslissingen te nemen die bijdragen aan het voltooien van de leercyclus om de zorg te verbeteren.

In **hoofdstuk 7** presenteren en reflecteren we op de belangrijkste bevindingen van dit proefschrift en bespreken we onderwerpen voor toekomstig onderzoek. De belangrijkste bevindingen bespreken we aan de hand van de noodzakelijke

bouwstenen voor een lerend zorgsysteem, zoals we die in hoofdstuk 2 hebben beschreven. Met betrekking tot de data en de data-infrastructuur, laten we in dit proefschrift zien dat transparantie een terugkerend thema is, onder meer in de interviewstudies. Transparantie wordt belangrijk geacht, zowel voor het verzamelen en transformeren van gegevens in bruikbare kennis als voor het opbouwen van vertrouwen in het lerend zorgsysteem en de duurzaamheid ervan. Wat betreft de leercyclus, onderstrepen we in dit proefschrift het belang van het sluiten van deze cirkel. Dit betekent dat het lerend zorgsysteem in staat is om gegevens uit de dagelijkse praktijk om te zetten in bruikbare kennis en deze kennis toe te passen in de praktijk met als doel de zorg te verbeteren, waarna de cyclus opnieuw begint. In dit proefschrift identificeren we ook de uitdagingen die bij het voltooien van deze cyclus gepaard gaan en benadrukken we de noodzaak van meer onderzoek naar geschikte mechanismen om dit te realiseren. Verder benadrukken we het morele belang dat zwangere en lacterende mensen, samen met hun zorgverleners, profiteren van de kennis die wordt gegenereerd door het lerende zorgsysteem. Wat betreft de betrokkenheid van belanghebbende partijen en individuen, bespreekt dit proefschrift het belang van hun betrokkenheid gedurende de gehele ontwikkelingsfase en transitie naar een operationeel lerend zorgsysteem. We beargumenteren het voordeel van solidariteit en het stimuleren van solidariteit onder zwangere mensen om hen actief te betrekken bij het dichten van de huidige kenniskloof. Verder reflecteren we in dit hoofdstuk op de benadering van een lerend zorgsysteem en concluderen we dat, ondanks de uitdagingen die gepaard gaan met het gebruik van gegevens uit de praktijk, dit waarschijnlijk een veelbelovende stap vooruit betekent voor de groep zwangere en lacterende mensen wat betreft kennis over medicijnveiligheid. Vragen over veiligheid vereisen toegang tot een grote hoeveelheid gegevens, iets wat een lerend zorgsysteem goed zou kunnen structureren. We reflecteren ook op de ethische toezicht en regulering van een lerend zorgsysteem. We vragen ons hierbij af of een lerend zorgsysteem niet beter kan worden gezien als een data ecosysteem, bestaande uit verschillende herbruikbare en uitwisselbare elementen, aanpasbaar aan specifieke onderwerpen en interessegebieden. De idee van een data ecosysteem zou kunnen helpen bij de realisatie en toewijding aan meer uniforme data transformatie methoden en analyseprocedures, evenals bij de formulering van meer uniforme ethische richtlijnen. Om te bewegen richting een duurzaam systeem en efficiënt gebruik van middelen, kunnen projecten, netwerken en organisaties zich aansluiten bij bestaande data ecosystemen, in plaats van steeds opnieuw het wiel van het lerend zorgsysteem uitvinden. Verder betogen we dat voor de ontwikkeling van een kader voor ethische toetsing, de benadering van de publieke gezondheidsethiek geschikt zou kunnen zijn. Een lerend zorgsysteem laat namelijk de traditionele scheiding tussen onderzoek en zorg los en focust minder op de individuele patiënt, maar meer op groepen. Tenslotte willen we benadrukken dat in een lerend zorgsysteem leren centraal

staat. Hierbij bedoelen we ook de toewijding aan voortdurend leren met betrekking tot de ontwikkeling van een ethisch verantwoord lerend zorgsysteem. Vandaar de titel van dit proefschrift: Blijven leren.

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About the author

Marieke Johanna Hollestelle (1994) grew up in Middelburg, Zeeland. After graduating from high school (Christelijke Scholengemeenschap Walcheren), she moved to Leiden to study Political Science at Leiden University and obtained her bachelor's degree International Relations in 2017. After a premaster philosophy, she commenced her master's degree Applied Ethics at Utrecht University in 2019. During a research internship under the supervision of Inez de Beaufort at the Erasmus Medical Center, she became particularly interested in bioethics research.
In 2019, she started her work as PhD student at the department of Bioethics and Health Humanities at the Julius Center for Health Sciences and Primary Care of the University Medical Center Utrecht (UMCU) under the supervision of prof. dr. Hans van Delden, prof. dr. Miriam Sturkenboom, and dr. Rieke van der Graaf. Next to her research, Marieke taught many different classes related to medical humanities, ethics of data science, moral case deliberation, and research ethics. In 2023, she obtained her Basic Teaching Qualification (BKO) and became the coordinator of the Medical Humanities course of the premasters program *Klinische Gezondheidswetenschappen* (clinical health sciences). Furthermore, she is a member of the reproductive ethics committee (Beraadsgroep voortplantingsgeneeskunde) and a substitute member of the Biobank reviewing committee, both at the UMCU. Marieke will continue working as an assistant professor at the department of Bioethics and Health Humanities.

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