RESEARCH REPORT

Learning Health Systems

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

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Abstract

Introduction: While Learning Healthcare Systems (LHSs) have received increasing attention in health care and research, the amount of operational LHSs 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 toward building an LHS and are in the position to transition to an operational LHS.

Method: To articulate relevant ethical requirements, we analyze established ethics frameworks in the fields of LHSs, 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; and (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.

KEYWORDS
ethics, ethics framework, learning healthcare system, pregnancy and lactation

A contribution of the ConcePTION project.

1 | INTRODUCTION

In recent years, Learning Healthcare Systems (LHSs) have received increasing attention in health care and research.[1,2] LHSs are considered 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 and there is an increasing effort to learn from routine data in health care, not many healthcare organizations, networks, or projects are transitioning to an operational LHS.[1,5] With an operational LHS, we mean an LHS that can transform practice-related data into actionable knowledge and apply such knowledge in the clinical practice, while capturing the resulting outcomes as new data.[1,5,6] It seems that many organizations and projects aspire to embrace an operational LHS, including within our own academic hospital, yet the transition toward such a system appears formidable. However, given the substantial investment of both public and private resources in LHS projects and the substantial data collected in healthcare domains, there exists a moral responsibility to persist the efforts to transition toward an operational LHS to really impact health care. 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 accompanying ethical, methodological, and sustainability challenges.[2,7] Despite the growing literature addressing technical building blocks and challenges, there remains a notable absence of a robust ethics 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. In 2013, an ethics framework was published widely regarded as the most important framework for LHSs in general and continues to be cited as such.[8] However, this ethics framework focuses mostly on the (novel) challenge of integrating clinical research and clinical care within an LHS and lacks specific guidance for realizing an ethically responsible LHS. We would like to contribute to an ethical foundation for LHSs by focusing specifically on the transition phase of projects, organizations, and networks that have laid a considerable amount of groundwork for the development of an LHS. 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" becomes evident, continuous learning should be achieved to really impact health and care. This transition phase raises new questions regarding the capacities of the existing project or network to evolve into an LHS

and presents opportunities for establishing long-term arrangements to foster an ethically responsible LHS.

This paper aims to develop an ethics framework to guide projects that have taken steps toward building an LHS and need to transition to an operational LHS. We will use the Innovative Medicines Initiative (IMI) ConcePTION project as an example of a project that is in the phase of transitioning toward 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).[9] There is still much 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.[10-12] We will briefly go over the goal of the project and explain its main challenges regarding the transition toward an operational LHS.

Furthermore, to be able to identify relevant ethical requirements for this ethics framework, we will analyze various 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 an ethically responsible European LHS for pregnant and lactating people. While we apply the findings 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.

2 | INNOVATIVE MEDICINES INITIATIVE ConcePTION

IMI-ConcePTION aims to establish a sustainable and ethically responsible LHS, by creating an ecosystem that embodies a continuous loop of data collection, data analysis, knowledge generation, and knowledge dissemination (see Box 1 for a detailed description of the project).[8] The project envisions creating a public knowledge bank accessible to pregnant and lactating people including their HCPs. So far, 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.[13] Their approach shows similarities with what is also called a comprehensive data LHS in the literature.[14]

While efforts have focused on a sustainability roadmap (see Box 1, under point 7), the current gap lies in directing attention to the project's transition to an operational LHS. A key challenge involves establishing mechanisms to continuously implement knowledge into practice as rapidly and safely as possible.[1,5] This iterative cycle is essential for realizing improvements in care and for capturing resulting outcomes as new data. Such mechanisms also distinguish organizations and networks that support research activities from organizations and networks that have established an infrastructure for

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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.[13,15]

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 reuse of existing healthcare 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;
4. Training of healthcare 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.[16]

ConcePTION is in the last phase of the project and has completed most of the deliverables. It 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.[13] In the last years, this data infrastructure has been tested and improved and has been used to support COVID-19 studies. Furthermore, the project has mapped the existing knowledge on the impact of medications on milk and set up an infrastructure for the collection of milk for research and analysis. Training programs and the knowledge bank are still in development. While many elements, such as the data infrastructure, stakeholder interactions and training, a sustainability plan, and an overview of the current knowledge gap, contribute to facilitating an LHS, a vision for continuous learning appears to be lacking.

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continuous learning. Another challenge for the ConcePTION project is to integrate all of the results into a strategy that can achieve and sustain the system as well as embrace the shared value of learning from every pregnant and lactating person in an ethically manner. Considerable time and effort have been put into developing and testing the data infrastructure and collecting the views of relevant stakeholders, which has led to valuable insights into the performance of the network, the abilities to generate knowledge, and the needs, willingness to contribute, and priorities of stakeholders. These insights are needed to further define the direction of the LHS but also to consider ethical requirements that can improve the LHS. We aspire for this ethics framework to highlight essential steps toward evolving into a genuinely ethically responsible LHS for pregnant and lactating individuals.

2.1　｜　Exploring the landscape of ethics frameworks

We turned to the existing literature on ethics frameworks that focus on LHSs 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, namely, the transition phase toward an operational data-intensive LHS. This paper does not aim to encompass all ethics frameworks somewhat related to the topic and acknowledge that our search may not be entirely exhaustive. Instead, our objective is to learn from diverse ethics frameworks, each offering a unique perspective. Numerous articles explored ethical considerations for LHSs, public health issues, and data-intensive research. For instance, the National Academy of Medicine (NAM) published 10 core principles for shared commitments in learning health organizations,[17] and the FAIR Data principles provide guidance for enhancing data reusability.[18] While these publications

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

Learning health care system ethics framework by Faden et al[8]	Candidate considerations for health systems ethics by Krubiner & Hyder[19]	An ethics framework for big data in health and research by Xafis et al[20]	A public health ethics framework for health data research by Ballantyne[21]
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 healthcare systems 7. Contribute to the common purpose of improving the quality and value of clinical care and healthcare 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)

offer valuable principles, some lacked in-dept rationale or exhibited strong practical orientation, making it difficult to align them effectively with our specific scope. Furthermore, our focus on *ethics frameworks* led us to identify four distinct and well-defined ethics frameworks developed for purposes that aligned with the different characteristics outlined above, namely LHSs, transitioning health systems, big data research, and public health ethics. 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 (Table 2). 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.

2.2 | Description of the four frameworks

Faden and colleagues have developed the first ethics framework for a 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.[8]

Krubiner and Hyder 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. Instead of focusing on the individual interest, often translated in respect for autonomy, beneficence, non-maleficence, and justice from the perspective of individual patients or research participant, 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.[19]

Xafis and colleagues 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 toward researchers, policymakers, and 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.[20]

Lastly, Ballantyne 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 focuses 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.[21]

2.3 | Overlapping values and statements in light of transition

Upon closer analysis, the frameworks show overlapping values and statements, or commonalities (Table 2). In the process of formulating ethical requirements for projects transitioning toward 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. Additionally, we will

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 and favorable harm–benefit ratio	To provide optimal care to each patient, avoid imposing clinical risks and burdens on patients	Faden et al[8]
	Harm minimization, public benefit, proportionality	Xafis et al[20]
	Public benefit (scientific integrity and social value), proportionality (necessity and least infringement)	Ballantyne[21]
Equity and justice	Address health inequalities	Faden et al[8]
	Equity and empowerment, justice and fairness, responsiveness	Krubiner & Hyder[19]
	Justice	Xafis et al[20]
	Equity (solidarity and reciprocity)	Ballantyne[21]
Stakeholder engagement	Contribute to the common purpose of improving the quality and value of clinical care and healthcare systems	Faden et al[8]
	Public engagement and transparency	Krubiner & Hyder[19]
	Solidarity, engagement	Xafis et al[20]
	Trust (engagement)	Ballantyne[21]
Sustainability	Conduct continuous learning activities that improve the quality of clinical care and healthcare systems	Faden et al[8]
	Quality, efficiency, transparency, accountability, feedback	Krubiner & Hyder[19]
	Integrity, privacy, stewardship, consistency, transparency, trust	Xafis et al[20]
	Trust (engagement), accountability (public justification and transparency)	Ballantyne[21]

discuss how each ethical requirement is relevant to the transition phase by means of specification.[22] 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 to be done or avoided.*[22,23] 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.

2.4 | Public benefit and 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.[21] Faden and colleagues mainly refer to clinical harm,[8] and Ballantyne and Xafis refer to harms for both individuals and groups resulting from the (mis)use of big data for research purposes.[20,21] The three frameworks also refer to the importance of fair distribution of harms and benefits of (data) research and outcomes for patients, populations, and relevant stakeholders. All emphasize the importance of prioritizing the minimization of burdens or risks by exploring alternatives or employing minimal use of data[20,21] or disclosure of health information.[8,20,21] 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).[21]

Naturally, research projects aimed at developing an LHS might typically prioritize conducting research and establishing the data infrastructure and collaborations. However, it is important to realize that these efforts may not always yield immediate 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 (HCP). 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 is necessary.[6] 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.[24] 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

TABLE 3 Our ethics framework.

Ethical requirement	Short description of the ethical requirements in light of the transition toward 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 following: • 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.

potential benefit and that there are low risks of foreseeable harms for pregnant and lactating people, which involves installing a governance or review committee, such as a Data Access Committee (DAC).[25] 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.

2.5 | Equity and justice

All consulted frameworks share a commitment to health equity, and they include 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 and 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.[19] 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.[21] Both the frameworks presented by Faden and colleagues and Krubiner and Hyder also highlight the significance of addressing inequality that disproportionately affects marginalized populations.[8,19] 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.[8] Krubiner and Hyder further emphasize the necessity for health systems to be responsive and adaptive to the changing health needs of population.[19] 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.[20]

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.[26] 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.[27]

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, which brings us to the next ethical requirement.

2.6 | Stakeholder engagement

All frameworks place emphasis on stakeholder engagement. Krubiner and 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.[19] Ballantyne argues that stakeholder engagement is essential for the fair distribution of harms and benefits, as well as for fostering trust in health services.[21] 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.[8] 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.[21] Consequently, this approach suggests an obligation for patients to grant access to relevant health data in the collective interest.

First, for the transition toward 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.[28] 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.[28] Empowerment starts by creating awareness of the existing knowledge gap, understanding how scientific research can play a role in bridging it, and 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[29,30] 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*".[31] 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 communities 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, and the novel insights gained from studies conducted within the LHS. Krubiner and Hyder highlighted that giving feedback to communities is grounded in international guidelines such as the CIOMS guidelines (2016) and the Declaration of Helsinki.[19] 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.[21] 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.

2.7 | 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.[19-21] 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.[19-21] Krubiner and Hyder underscore the significance of sustainability and advocate for the development of long-term strategies to uphold and maintain improvements overtime.[19]

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.[32] It is therefore often directed toward 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.[5] 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.[5] Transitioning into an effective LHS requires attention to the systematic translation of evidence.[6] 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 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.[27]

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. Within 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.

3 | DISCUSSION

This paper proposed an ethics framework with a set of ethical requirements to guide the transition of research projects toward an ethically responsible operational LHS. This paper has taken the IMI-ConcePTION project as an illustrative case, exemplifying a project that is currently undergoing the transition phase toward 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. One of the main challenges of the ConcePTION project is to direct attention to transition into an operational LHS and to establish mechanisms for continuous learning. We hope our framework provides clear ethical considerations for the next steps toward establishing an ethically responsible LHS.

The requirements we propose deviate significantly from previous ethics 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 toward 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. While LHS receives much attention in research and in the literature, 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. Furthermore, we believe that the transition phase is a critical phase for projects, networks, and organizations to truly evolve into an LHS. This phase offers an opportunity to build on existing achievements and concentrate on making decisions that contribute to establishment of mechanisms for continuous learning that can impact health and care.

3.1 | Levels of learning healthcare systems

It is important to take into account the operational level at which the LHS functions. 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). The effectiveness of learning from data within these LHSs and the establishment of a robust feedback mechanism strongly depends on this operational 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 could pose greater challenges, given that they impact not just one health system but multiple systems with varying cultures. Our ethics framework focuses on an international LHS for a specific population, but we do not offer a step-by-step manual for the ideal feedback mechanism for a European comprehensive data LHS. To guide the development of appropriate feedback mechanisms for these large international LHSs, further research is needed. Nonetheless, we would

like to 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. Future 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 9 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.[18] 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 anticancer 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.

AUTHOR CONTRIBUTIONS

Marieke J. Hollestelle drafted the manuscript. Marieke J. Hollestelle, Rieke van der Graaf[1], and Johannes JM van Delden contributed to the development of the ethics framework. Miriam CJM Sturkenboom[2] contributed by clarifying how real-world data can be utilized to study the effects of medication during pregnancy. All authors read and approved the final manuscript. The research leading to these results was conducted as part of the ConcePTION consortium. This paper only reflects the personal views of the stated authors.

CONFLICT OF INTEREST STATEMENT

Miriam CJM Sturkenboom is leading a department that conducts regulatory required research for COVID-19 vaccine manufacturers based on the ENCePP code of conduct and is project coordinator of IMI-ConcePTION. The other co-authors declare no competing interests for this work.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

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