IMI2 821520 - ConcePTION

ConcePTION

WP7 – Information and data governance, ethics, technology, data catalogue and quality support

D7.13 Interim Report on Ethical Issues – task 7.3

Lead contributor	Marieke Hollestelle (1– UMCU)
	m.j.hollestelle-2@umcutrecht.nl
Other contributors	Rieke van der Graaf (1 – UMCU) Miriam Sturkenboom (1 – UMCU) Hans van Delden (1 – UMCU)

Document History

Version	Date	Description	Non-contributor reviewers (if applicable)
V2.0	11 March 2020	First Draft	
V2.1	18 March 2020	First Draft	
V2.2	24 March 2020	First Draft	
V2.5	31 March 2020	Draft	
V3.0	01 April 2020	Final Draft	Managing Board
V3.1	07 April 2020	Reviewed Draft	
V4.0	21 April 2020	Final version	

Summary

This deliverable is describing the activities performed in the first year for task 7.3: Ethical Issues. Task 7.3 is aimed to address important ethical issues that arise in ecosystems like ConcePTION. The focus of the first year has been to describe ConcePTION as a Learning Healthcare System (LHS) and to deepen the ethical issues that we identified for this project. Our approach has been both conceptual and empirical. Conceptually, we studied literature on LHSs and explored descriptions of LHSs in order to be able to compare these descriptions with the ConcePTION ecosystem. As for the empirical approach, we set up a qualitative interview-study with women in the Netherlands and planned for interviews in Norway collecting their opinion on the ethics of ConcePTION as a knowledge generating and disseminating ecosystem.

Purpose and scope of this document

The purpose of this document, deliverable 7.13, is to show the progress made on the activities regarding task 7.3, the “Ethical Issues”. Deliverable 7.13 calls for an interim report on the ethical issues. Therefore, this document will go over the steps undertaken in the first year, which includes: designing a method for addressing the identified objectives of task 7.3 and the interim results. Note that no final conclusions can be drawn from this interim report.

Introduction and Rationale

More than 5 million women get pregnant in the EU every year and the majority take at least one medication during pregnancy [1,2]. Yet there is almost no evidence-based information available on most medications to guide a woman’s fully informed decision. Even less information is available regarding medication exposure through breastfeeding.

As few as 5% of available medications have been adequately monitored, tested and labelled for safety in pregnant and breastfeeding women. On average, it takes an estimated 27 years to determine the teratogen status of a novel medication [3]. The field, while inherently difficult to study, has suffered from a lack of systematically gathered insights that could lead to more effective data generation methodologies. Fragmentation and misinformation abound, resulting in confusing and contradictory communication and perception of risks by both health professionals and women and their families.

In real life, pregnant women become ill and ill women become pregnant. Medication use is not uncommon in pregnancy and physicians are advised to select the safest drugs, but often data are not robust or lacking altogether. Moreover, the trend of later age pregnancies and the associated higher prevalence of some chronic conditions, such as obesity, chronic hypertension, diabetes, multiple sclerosis, and systemic lupus erythematosus, results in a rapidly increasing proportion of pregnant women who need medications to treat their chronic or acute disease during pregnancy. The World Health Organization recommends exclusive breast feeding for infants to six months of age to achieve optimal growth, development and health. Women living with severe and chronic illness may need to take medications before, during and after pregnancy, but little to no adequate and well-controlled studies have been conducted to characterize the levels of maternal medications in human breast milk.

Uncontrolled disease in pregnancy can lead to suffering and irreversible damage to the mother and for some conditions may also be harmful to the foetus. With the dearth of scientifically based information on medication transfer through breastfeeding, women may be counselled not to breastfeed if they are on a prescription medication, or a mother may decide to forgo postpartum treatment of her illness in favour of breastfeeding her baby. Given the lack of solid evidence, neither pregnant or breastfeeding women, nor their doctors, can adequately assess the risks, which challenges informed choice and decision making. Numerous medications have been used safely and effectively in pregnancy with minimal risk to the foetus and mother, although the decision to use them is not without apprehension. The availability of more detailed and reliable information related

to the safety and effectiveness of medications in pregnancy and breastfeeding may assist healthcare professionals and patients in making more evidence-based decisions leading to improvement in care that will benefit women, their babies, and their families.

At the time of first marketing, product labels almost invariably state there is lack of evidence regarding use during pregnancy and breastfeeding [4], and any new evidence that might be generated is incorporated into labels only after many years. To begin to improve this untenable situation, regulators are beginning to request that drug manufacturers improve the quality of the information provided in product labels and governments are beginning to consider legislative changes in policy.

Since April 2019 the Innovative Medicines Initiative (IMI) ConcePTION project has started to study the way we generate and disseminate evidence on the effects of medication in pregnancy. ConcePTION aims to establish a trusted ecosystem that can efficiently, systematically, and in an ethically responsible manner, generate and disseminate reliable evidence-based information regarding effects of medications used during pregnancy and breastfeeding to women and their healthcare providers. This will be achieved by generating, cataloguing, linking, collecting and analysing data from pharmacovigilance, modelling, routine healthcare, pregnant women and their children through a large network.

ConcePTION as a Learning Healthcare System
The approach of ConcePTION to collect data on safety of medicines during pregnancy and breastfeeding is similar to what is increasingly being called a Learning Healthcare System (LHS). In an LHS, care and research are aligned to accelerate research and outcomes for patients and to overcome current problems, such as low inclusion rates and study specific informed consent procedures in order to improve health care. Taking an LHS approach to knowledge generation in the field of pregnancy and breastfeeding may broaden the opportunities to strengthen the evidence base, among others by learning from routinely collected data. However, if care and research become integrated in drug use in pregnancy and breastfeeding, we postulate that it will be virtually impossible to escape from this learning environment. Therefore, it is important to know **1)** how we should weigh the risks of the current status quo (where women hardly participate in research and we do not learn) versus the benefits and risks of participating in a system where routinely collected data of pregnant and breastfeeding women will continuously be studied to improve the evidence base, **2)** whether there is a moral duty around continuous learning in healthcare for pregnant and breastfeeding women and the healthcare professionals involved in their care? If so, how could such a moral duty be implemented in practice? and **3)** what are the considered features are of an ethically responsible and sustainable ecosystem according to pregnant and breastfeeding women.

Activities

For task 7.3 we aim to describe ConcePTION as an LHS and to identify important ethical learnings for ConcePTION as an LHSs. Three open ethical issues were already identified, namely:
1. How should we weigh the risks of the current status quo (where women hardly participate in research and we do not learn) versus the benefits and risks of participating in a system in which pregnant and breastfeeding women will continuously be studied to improve the evidence base?
Currently, pregnant and breastfeeding women are typically excluded from research for reasons of risks to the fetus/child and potential liability. At the same time, the practice of prescription of off-label medication exposes pregnant and breastfeeding women and their children to risks without learning for future patients;
2. Is there a moral duty around continuous learning in healthcare for pregnant and breastfeeding women and the healthcare professionals involved in their care? If so, how could such a moral duty be implemented in practice? If care and research become integrated regarding drug use in pregnancies and breastfeeding, it will be virtually impossible to escape from this learning environment. Ethical evaluation of a moral duty to participate in such a system is essential when regular care becomes inherently intertwined with learning components; and

3. What are the features of a responsible and sustainable LHS for pregnant and breastfeeding women? A radical turn to continuous learning from routinely collected data in the field of pregnancy and breastfeeding also requires as set of ethical criteria to render this learning environment responsible and sustainable. At least ethical criteria of review, informed consent, fair inclusion and benefit-sharing need rethinking in light of an LHS in this field.

In order to deepen the ethical issues, we take both a conceptual and empirical approach. For bringing these two approaches together, the method of Reflective Equilibrium is most suitable. Originally, the Reflective Equilibrium has its roots in the ideas of the political philosopher John Rawls. We will use a version of this method that has been developed by members of the project team and the Department of Medical Humanities of the Julius Centre (Van Delden and Van Thiel): the normative empirical reflective equilibrium [6,7]. It has proven to be successful in giving guidance to ethical thinking in practical contexts [8]. The aim of the Reflective Equilibrium is to produce coherence between empirical, conceptual and normative data. The empirical and conceptual elements will be brought into Reflective Equilibrium in order to be able to develop a framework for fair inclusion of pregnant women in a learning healthcare system.

1. Conceptual approach

The conceptual approach consists of a literature study on Learning Healthcare Systems. We have studied potential ways in which ConcePTION can be interpreted as a Learning Healthcare System and what the relevant ethical implications are for such an interpretation. In the second year we will finish this conceptual analysis. In the first year we have identified the literature relevant for our analysis. In the second year we will analyze the literature by a three step approach. First, we will try to find similarities between components of the ConcePTION ecosystem and Learning Healthcare Systems. Important questions for describing ConcePTION as an LHS are: What is the potential outcome of the ConcePTION consortium long term? And what is a sustainable ecosystem or learning health care system based on? [9]

A second step is to identify relevant analogies with other LHSs. This approach allows us for application of insights to ConcePTION as an LHS.

As a third step we will try to understand the relevant ethical questions that arise in such LHSs. As a theoretical framework, we will utilize conventional ethical principles for care and research as well as for LHSs. As mentioned earlier, in an LHS, care and research are integrated. This integrated structure may raise questions about, for example: the way informed consent is obtained, the degree of patient participation once a learning element is being added to care. Furthermore, adopting a learning activity raises questions about transparency and unintended (negative) consequences, such as group discrimination or exposing patients to avoidable nonclinical risks, i.e. inappropriate disclosure of health information [8,9,10,11]. We are exploring these ethical issues in relation to the ConcePTION ecosystem.

2. Empirical approach

As part of the empirical approach, we set up a qualitative interview study (semi-structured interviews) with women in the Netherlands, who are chronically/ acute ill, or healthy and who are at the pre-conception, pregnant, breastfeeding or post-partum stage. The aim is to also conduct this study in Norway, to include the views of women from a different European country.

We decided to only focus on the view of women (chronically/ acute ill/ healthy and who are at the pre-conception, pregnant, breastfeeding or post-partum stage). Ethics board members will no longer be interviewed, since it appears that they do not review the activities within a Learning Healthcare System.

Study design of the qualitative interview study

A qualitative interview study is most suitable to generate a rich understanding of the broad range of attitudes, opinions and experiences of individuals in a specific context or practice [12]. For this study, we perform semi-structured interviews with a predefined topic list which for a large part is based on the guideline 12 of the *2016 CIOMS International Ethical Guidelines for Health-related Research Involving Humans* [13] and on the 2008 *Ethical Framework for Biomedical Research* in the Oxford Textbook of Clinical Research Ethics [14]. The CIOMS guideline covers the collection, storage and use of data in health-related research and contains certain items that must be regulated in order to create a good governance structure for institutions where data is collected and (/or) stored. Multiple items are considered to be of great importance for ConcePTION as a trusted ecosystem. ConcePTION might not aim to store all available data within the consortium, but it does regulate large amounts of (personal) data. The items from the CIOMS guideline that correspond with the objectives of this study are aggregated into the topic list of our qualitative study.
Data collection is aimed at thematic saturation on a group level, i.e. ending when no new issues can be identified in the subsequent interviews (coding saturation) and all formulated themes are sufficiently understood (meaning saturation) [15]. Our normative analysis of the interviews aimed to provide insight into the views of women regarding ConcePTION showing various perspectives, without engaging in an argument of any kind. Therefore, we will provide a transparent description of respondents' reasoning and normative conclusions [16].

Sample

To obtain a broad range of perspectives on the topics, we conduct the study among women whose data might in principle become part of ConcePTION, but have different characteristics: women who are taking medication for a chronic/ acute disease and women who are healthy. Both type of women may be either at the preconception, pregnant, breastfeeding/ post-partum stage.
In total, we will conduct 40 interviews with 20 respondents in the Netherlands and 20 respondents in Norway. We chose to include Norwegian women in stead of British women (as mentioned in an earlier stage of the task description), since Scandinavian countries not only have a different policy regarding the collection of health data, but also because they have a tradition of having a more open attitude towards sharing personal data. It is useful to see whether this open attitude also applies to the view of Scandinavian women on ConcePTION.
From the 20 women in the Netherlands, all women are or will be registered in the Dutch national perinatal registry, for the collection of data on pregnancies, births and neonatal outcomes of births. Within this group of women, six other types of sources of health related data were identified in the Netherlands that will likely also become part of the ConcePTION ecosystem, but will consist of smaller groups of women. These are:

1. Women whose data are stored in routinely collected health data, registered in electronic healthcare records of gynaecologists, midwifes and pharmacists
2. Women whose data are collected via the European network of population-based registries for the epidemiological surveillance of congenital anomalies (Eurocat);
3. Women whose data have been spontaneously reported by themselves or by their health care professionals to the Netherlands Pharmacovigilance Centre Lareb;
4. Women who participate in lactation studies;
5. Prospective cohort studies, such as pREGnant
6. Women who participate in other types of research

All women are part of their national perinatal registry, therefore, in order to reach as much diversity within this study as possible; we include women whose health related data can represent at least one of the different data sources (1 to 6), as described above.
We recruit women by means of purposeful sampling . This is a technique used in qualitative research to identify and select information-rich cases for the most effective use of limited resources [17]. This means, that the researchers makes a selection of women in such a way that women with different characteristics are represented in the study in order to reach saturation and avoid bias.

Women are approached for the ConcePTION-ETHICS study by our contact persons from the different data sources. Women who indicate that they are interested receive a participant information letter and an informed consent letter from the ConcePTION-ETHICS researcher. Subsequently, the researcher contacts them within a week to clarify the research and ask if they want to participate in the study and subsequently schedule an appointment for the interview. If, at this point, women want to receive more information about ConcePTION or the interview, they can contact the researcher by phone or e-mail. There will be sufficient time between the first contact and the interview itself. On the day of the interview the researcher explains the research again and emphasize the voluntary nature of participation. If the women still indicate to be willing to participate, the informed consent letter is signed before conducting the interview.

Data collection
We aim to perform 40 semi-structured in-depth interviews in total, in both the Netherlands and Norway using a predefined topic list (Table 1). According to the technique of constant comparative analysis, the interview topics will evolve as the interviews progressed alongside the data analysis [18]. Data collection is taking place from March 2020 to December 2020. The interviews are audiotaped and transcribed verbatim, coded and stored anonymously. Written consent is obtained from all patient respondents. Because no intervention will be imposed on the participants, The Research Ethics Committee (REC) of the University Medical Center Utrecht assessed the study exempt from formal ethics review. Ethical review for the study in Norway will be done separately by a Norwegian formal institution.

Table 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

Data analysis
The collected data is thematically analyzed by going back and forth between data collection and analysis to develop codes and concepts and, subsequently, more interpretative themes, identifying a meaning patterned across the dataset [19]. When analysing the data, we filter the morally relevant considerations of respondents using the *Ethical Framework for Biomedical Research* of The Oxford Textbook of Clinical Research Ethics (2008). NVivo 12 software is used to organize the data and to develop a coding structure. By constant comparison and (re)labelling of codes, higher order themes can be formulated. To enhance the validity of our findings, we will organize an expert meeting in the last phase of data collection to discuss whether our findings are an accurate representation of the view of women regarding ConcePTION as an ethically responsible, knowledge generating ecosystem.

Interim Results

The first results that can be shared regarding our conceptual and empirical approach are interim and therefore, no large and final conclusions can be drawn from it.

Conceptual approach

In the first year, we have identified relevant literature for our conceptual analysis. The subjects of these articles vary, for example, from literature on the description of LHSs to the ethical implications of an LHS and the added value of LHSs. For example, in an article written by Wouters et al. (2019), a first attempt is made in organizing the different types of existing LHSs that are described in the literature. They present four models with distinct organizational and ethical implications. The four models are: 1) optimization LHS, 2) comprehensive data LHS, 3) real-time LHS, and 4) full LHS. Each model has different ethical implications for ethical principles such as informed consent, privacy and ethical oversight [20]. In a first attempt to classify ConcePTION as an ecosystem that fits the description of one of these four models, we may conclude that ConcePTION is an LHS model 2. ConcePTION, like model 2, wants to generate evidence by routinely collecting and processing vast quantities of health data. In the future, ConcePTION might have the effect of changing care, and therefore, directly affecting the care received by individual patients.

Currently, this hypothesis is being explored by searching for similar cases like the ConcePTION project and by creating a thorough understanding of ConcePTION as an ecosystem. The latter will be done by taking a closer look at the ecosystem.

Another example, is the article by Faden et al (2013). In this article an attempt is made in developing an ethics framework for LHSs. The ethical principles and issues mentioned in this paper, are based on conventional research and clinical ethics principles. It is interesting to investigate whether the context of these ethical issues, or moral obligations as they call it, is similar to ConcePTION. If so, we can take these ethical principles and issues into account for the ethical learnings for ConcePTION as an LHS. This will be done in the second year of the project.

Empirical approach

An ethical waiver for conducting the interview-study in the Netherlands has been given by the Research Ethics Committee of the UMCU. Organizing the recruitment and finding the women who fit the described study-population is a time-consuming matter. So far, five interviews have been conducted with women recruited through the obstetric department at the UMCU and Amsterdam Medical Centre, and Pharmacovigilance Centre Lareb. What is already interesting, is the difference in attitude between these 5 women. Three of these women have a chronic disease. It seems that their experience with their disease and medication use influences the way they want to receive knowledge about the safety of medication during their pregnancy, but also possibly influences their attitude towards collecting and analyses of their health data. They have a somewhat clear view of what they would want to receive in terms of knowledge and understand that their data is of great importance. What they all seem to have in common, is the desire to help other (pregnant) women. This desire can also be seen as one of the main motivations for participating or sharing health data. The analysis of these interviews is currently taking place (the method used for this analysis is described earlier in this report).

Meanwhile, the interview-study is being set up in Norway. This study will take place from September 2020 till December 2020. Ethical review for the study in Norway will be done separately by a Norwegian formal institution. Organizing this study will be done with the help of our Norwegian contact persons.

References

1. Lupattelli, A., et al. "Medication use in pregnancy: a cross-sectional, multinational web-based study." *BMJ open* 4.2 (2014): e004365.
2. Mitchell, A. A., et al. "Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008." *American journal of obstetrics and gynaecology* 205.1 (2011): 51-e1;
3. Adam, M.P., Polifka, J.E. & Friedman, J.M. "Evolving knowledge of the teratogenicity of

medications in human pregnancy." *American Journal of Medical Genetics Part C: Seminars in Medical Genetics.* 157, (2011): 175–182;
4. Ramoz, L.L. & Patel-Shori, N.M. "Recent changes in pregnancy and lactation labeling: retirement of risk categories." *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy.* 34, (2014): 389–395;
5. van Delden, J.M., and van Thiel, J.M.W. "Reflective equilibrium as a normative-empirical model in bioethics." *Reflective equilibrium*. Springer, Dordrecht, 1998. 251-259.
6. van Thiel, J.M.W., and van Delden, J.M. "Reflective equilibrium as a normative empirical model." (2010).
7. Van der Zande, ISE, et al. "Vulnerability of pregnant women in clinical research." Journal of Medical Ethics 43.10 (2017): 657-663.
8. Hemingway, H, et al. "Big data from electronic health records for early and late translational cardiovascular research: challenges and potential." *European heart journal* 39.16 (2018): 1481-1495.
9. Faden, R., et al. "An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics." *Hastings Center Report* 43.s1 (2013): S16-S27.
10. Botkin, R. "Transparency and choice in learning healthcare systems." *Learning Health Systems* 2.1 (2018): e10049.
11. Piasecki, J., and Dranseika, V. "Learning to Regulate Learning Healthcare Systems." *Cambridge Quarterly of Healthcare Ethics* 28.2 (2019): 369-377.
12. McLennan, S., et al. "The spectrum of ethical issues in a Learning Health Care System: a systematic qualitative review*." International Journal for Quality in Health Care* 30.3 (2018): 161-168.
13. Boeije H. “A purposeful approach to the constant comparative method in the analysis of qualitative interviews.” *Qual Quant* (2002);36:391–409.
14. Council for International Organizations of Medical Sciences. "International ethical guidelines for health-related research involving humans." *International ethical guidelines for health-related research involving humans* (2017);
15. Kalkman S., et al. "Patients’ and public views and attitudes towards the sharing of health data for research: a narrative review of the empirical evidence." *Journal of medical ethics* (2019); Published Online First: 12 November 2019;
16. Hennink. M.M, Kaiser B.N, Marconi V.C. “Code saturation versus meaning saturation.” *Qual Health Res* (2017);27:591–608.
17. Ives. J., et al. “Standards of practice in empirical bioethics research: towards a consensus.” *BMC Med Eth* (2018);19:1–20.
18. Patton, M.Q. “Qualitative research and evaluation methods”. *Thousand Oakes*. (2002).
19. Charmaz, K. “Constructing Grounded Theory: A Practical Guide Through Qualitative Analysis.” London, UK*: Sage Publications*, 2006.
20. Braun, V., Clarke, V. “Using thematic analysis in psychology.” *Qual Res Psychol* (2006);3:77–101.
21. Wouters, H.P., et al. "Learning health care systems: Highly needed but challenging." *Learning Health Systems* (2020): e10211.