IMI2 821520 - ConcePTION

ConcePTION

WP4 – Establishment of a non-commercial, Europe-wide breast milk biobank and analytical centre

D4.1 Summary and review of collected SOPs from project partner and literature

Lead contributor	Andrea Wutte (4 – Biobanking and BioMolecular resources Research Infrastructure- European Research Infrastructure Consortium / BBMRI-ERIC) Daniela Krasser (4 – Biobanking and BioMolecular resources Research Infrastructure- European Research Infrastructure Consortium / BBMRI-ERIC)
	andrea.wutte@bbmri-eric.eu, daniela.krasser@bbmri-eric.eu
Other contributors	Alice Panchaud (24 – University of Geneva and University Hospital in Lausanne / ULAUS)
	Mikaela Magnusson (3 – Uppsala University / UPPS)
	Peggy Gandia (21- Toulouse University Hospital / CHUT)
	Hedvig Nordeng (14 – University of Oslo / UOSL)
	Matylda Czosnykowska-Lukacka (Third Party involved – Wroclaw Medical University)
	Ronny Baber (Third Party involved – University of Leipzig)

Document History

Version	Date	Description
V final	25 March 2020	Final version

Publishable Summary

As part of ConcePTION WP4, D4.1, standard operating procedures (SOPs) for sample handling of breast milk, serum and plasma were collected from the project partners and compared with specifications from the state-of-the-art literature.

Particular attention was paid to preliminary investigation processes, which have an influence on the sample quality and have a decisive influence on the subsequent laboratory analysis. Workflows like collection, specimen processing steps, processing times, storage temperature, freeze-thaw cycles. were assessed and a first version of a harmonised procedure for breastmilk collection was developed.

The open structure of the standardisation process (regular TC with the project partners, all documents and literature are online available at the members area for the ConcePTION consortium) enables transparency for all involved or interested partners. With regular meetings, an open discussion culture was cultivated with the project partners. All created documents and meeting minutes are available in the member area of ConcePTION.

Methods

In the first step, standard operating procedures (SOPs) for processing of blood and breastmilk samples were collected from the project partners. Subsequently relevant literature[1, 2, 3] and guidelines[4] was screened.

Following documents and literature was made available for the review and comparison analysis:

University of Geneva and the University Hospital in Lausanne / ULAUS:

1. Procedure Reception echantillons Lyon_130528
2. Récolte d'échantillons à domicile par la SFI
3. SamplingStorageProcedure_04042019 (excerpts from sample handling procedure, via E-Mail)

Literature recommendation:
Byrne J J, et. al. Is it safe? – The many unanswered questions about medications and breast-feeding. N Engl. J Med 380:1296. 2019 April.[1]

University of Uppsala / UPPS:

1. Blood Collection Uppsala (excerpts from blood collection from Uppsala Biobank, via E-mail)
2. Breast milk collection_Sweden (Excel table, description of breast milk collection from Umea Biobank and Lund Biobank)
3. Breast milk collection_Umea
4. Candida Lund (description of breast milk collection from Lund Biobank)

Wroclaw Medical University:

1. Collection of breast milk samples (from the Human Milk Bank (HMB) at Wroclaw University Hospital)
2. Study Protocol (for blood and breast milk collection, from the Neonatology Department at Wroclaw Medical University)

Literature recommendation:
Czosnykowska-Lukacka M, et. al. Breast Milk Macronutrient Components in Prolonged Lactation. December 2018.[2]

University of Leipzig:

1. 2018-12.17 Auszüge SOP Bearbeitung Muttermilch
2. SOP-LIFE-CHILD-PE01-Be-allgemein-V05

3. SOP-LIFE-CHILD-PE05-Milch_V03
4. Vorlage_Muttermilchprobengewinnung

Literature recommendation:
Poulain T, et. al. The LIFE Child study: a population-based perinatal and pediatric cohort in Germany. Springer Science+Business Media Dordrecht 2017.[3]

The above listed documents formed the basis for the summary and analysis of the pre-analytical processes (collection, processing, transport and storage). With the duration of the review process, the most relevant literature[5,7], guidelines[6,8,9,12] and best practices[10,11] for consideration was added on the recommendation of the project partners. No additional literature search has been carried out so far, but this is subject to constant review processes within the project partners.

The documents and the relevant literature is filed at the ConcePTION member area (https://members.imi-conception.eu/Member-Area/Work-Package-4?folderId=3321&view=gridview&pageSize=50) available for the ConcePTION consortium.

The individual documents (SOPs, protocols) were translated in English for further processing. Individual work steps of the SOPs were listed in an Excel table (Excel matrix) for better comparison. This step was carried out gradually with all SOPs. As a result, similarities and differences between the individual work steps of the different SOPs were made visible.

The summary of the comparison analysis (SOP Draft V2.0_16092019) was converted into a generic document for the collection and processing of human breast milk and plasma samples (Collecting and Processing Milk samples_Draft1.0_dkaw09182019).

Both documents (Excel matrix / SOP Draft and the generic document / Collecting and Processing milk samples) are filed at the ConcePTION member area (https://members.imi-conception.eu/Member-Area/Work-Package-4?folderId=3321&view=gridview&pageSize=50) available for the ConcePTION consortium.

As a Quality Management handbook for breast milk biobank management system according to ISO 20387:2018 “General requirements for biobanking” is currently under development, all drafted documents are going to be implemented in this handbook.

Discussion

The following key points emerged during the discussions with the partners due to the similarities and differences investigated in the SOPs of the project partners.

1) Time of breast milk collection and quantity determination

The time of the collecting and the quantity of the milk sampling were important points in the discussion. Within the comparison of the SOPs it was stated that the timing depends on what kind of milk is collected: foremilk, hind milk or a combination thereof. Additionally, the question arose, if the milk will be collected prior to feed (prefeed) and / or at the end of the same feed and how many days after birth.
The FDA guideline recommends that the milk should ideally be collected after the development of the mature milk (about 10 days postpartum)[4]. The time of the collection also depends on the half-life of the drug and needs to be taken into consideration when designing a demonstration study. The project partners were discussing the drug which will be investigated, and this will be taken up into the specific clinical trial protocol (Task 4.3: Demonstration studies).

The quantity of the milk sample is a key point as well which needs to be agreed upon. The specifications in the compared SOPs varied from 10 to 20 ml per sample. The literature doesn’t

specify the amount in ml but there is a recommendation for the collection of the entire volume from both breasts. The necessary amount (for the further processing) should be stored and the remainder of the milk could be refed to the baby.[4]

2) Material and equipment for breast milk collection

Breast milk sampling manually or with an electric pump is currently a matter of decision within the working group. In general, the recommendation of the literature clearly goes in the direction of using an electric pump, since it is more efficient in milk extraction. In addition, it does not necessarily have to be a "hospital pump", since modern electric pumps (simpler models) are based on the same or a similar technology[4,5].

3) Informed consent and data collection

The Guideline for good clinical practice E6(R2)[12] gives detailed information about the regulatory requirements of an informed consent and will adhere to the study protocol of the demonstration studies (Task4.3, Demonstration studies, M12-48) as well as in all breast milk / sample collection procedures for the breast milk biobank.

The demographic and medical questionnaire was also part of the discussion within the expert group. Although the questionnaire is not anchored in the SOPs as a work step, the inclusion and exclusion criteria for the participating women have an impact on both the demonstration studies and the project in general.

4) Collection at the clinical site and / or at home

The collection site of the breast milk and blood will have an influence on the standard operating procedure. Breast milk collection and blood sampling at mommy's home differs from the collection at the clinic site insofar as the individual process steps, i. e. the preparation of the sampling (e.g. disinfection, preparation of the sampling device), the sampling itself, the intermediate storage of milk or blood until transport (for further treatment in the clinic), needs to be standardized and controlled [6,7]

An important point for the discussion regarding the collection at the clinical site was the question of where the individual work steps are carried out, e.g. will the aliquoting be done at the laboratory or at the Biobank. For a harmonized SOP the details must be clarified.

It is similar with the description for the collection at home. Again, the detailed work steps have to be clarified and the period from sampling to intermediate storage (possible at room temperature, better in the refrigerator[6]), up to transportation to the laboratory or the biobank must be defined and validated to safeguard the integrity of the sample.

Ideally, the sample - regardless of whether it is breast milk or blood - should be filled in adequate containers (for milk, the recommendation is a food grade plastic container[6], for blood it should be the corresponding collection tube[8, 10, 11]) as fast as possible (times according to literature vary depending on the temperature of the intermediate storage[6, 7, 9]) and sent with a qualified shipping service provider (with the required documentation[8]).

The project partners are currently discussing the most suitable protocol for the demonstration studies. The decision will be converted into the protocols for the demonstration studies and for the Quality Management handbook for breast milk biobank management system.

Conclusion

The generic document for sampling and processing breast milk and plasma samples (collecting and processing milk samples_Draft1.0_dkaw09182019) covers the main processing at the clinical site (sampling at home was not taken into account for the time being). This document will be further adapted to the intended use (e.g. clinical study and/or breast milk collection for biobanking purposes), defined by the project partner experts.

The next step will be the further development of the generic document (Collecting and Processing Milk Samples_Draft1.0_dkaw09182019) with the summary and reviewing of the various SOPs of the project partners. According to the work plan a Technical committee will be established with the aim, to evaluate, to develop and to release standard documents with the focus on the harmonized pre-analytical and analytical management of breast milk.

Consequently, all drafted documents will be included in the Quality Management handbook for breast milk biobank management system according to ISO 20387:2018 “General requirements for biobanking” in Uppsala.

References

1 Byrne J J, et al. Is It Safe? – The Many Unanswered Questions about Medications and Breast Feeding. N Engl J Med 380. 2019 April; 14: 1296-1297.
2 Czosnykowska-Lukacka M, et al. Breast Milk Macronutrient Components in Prolonged Lactation. 2018 December 3.
3 Poulain T, et al. The LIFE Child study: a population-based perinatal and pediatric cohort in Germany”. Springer Science+Business Media Dordrecht 2017.
4 FDA, CDER, CBER. Clinical Lactation Studies: Considerations for Study Design”. Guidance for Industry. May 2019.
5 Wang J, et al. Evaluation of the Safety of Drugs and Biological Products used during lactation: Workshop Summary.Clin Pharmacol Ther. 2017 June; 101(6): 736-744.
6 Eglash A, et al. ABM Clinical Protocol #8: Human Milk Storage Information for Home Use for Full-Term Infants, Revised 2017. Breastfeeding Medicine, Volume 12. 12, number 7, 2017; 390-395.
7 Weaver G, et al. Recommendations for the Establishment and Operation of Human Milk Banks in Europe: A Consensus Statement From the European Milk Bank Association(EMBA). Front. Petidatr. 2019 March; 7:53.
8 ISO 20186:2019. Molecular in vitro diagnostic examinations – Specifications for pre-examination processes for venous whole blood – Part 1-3. 2019.
9 EDQM. Guide to the quality and safety of TISSUES AND CELLS for human application. 3rd Edition. 2017; 327-339.
10 Tuck M K , et al. Standard Operating Procedures for Serum and Plasma Collection: Early Detection Research Network Consensus Statement”, J Proteome Res. 2009 January; 8(1): 113-117.
11 The Early Detection Research Network (EDRN). Standard Operating Procedure (SOP) for Collection of Serum, and of EDTA Plasma. (https://edrn.nci.nih.gov/resources/standard-operating-procedures)
12 ICH: E6 (R2): Guideline for good clinical practice. EMA/CHMP/ICH/135/1995. December 2016.