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**Project title:**

*Understanding, predicting, and treating depression in pregnancy to improve mothers and offspring mental health outcomes*.

# *D1.5 Risk Registry and Management Plan*

***Research and Innovation Action***

*HORIZON-HLTH-2021-STAYHLTH-01-02*

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## Disclaimer

## Executive Summary

This document provides the framework to make *HappyMums* achieve its objectives, respecting its time, budget, and quality constraints, by setting up procedures for risk management and ensuring that adverse situations are properly managed along the evolution of the project.

This deliverable is produced by WP1 (*Management and Coordination*) which aims at ensuring a smooth coordination of the project for a high quality of results and implementation.

This plan documents the processes, tools and processes that will be used to ensure that risks are identified in advance, assessed and responses integrated into the work plan.

Moreover, this plan will address the roles and responsibilities of the different partners in risk management, identification, analysis, monitoring and control.

Some of the major perceived risks related to the project work plan have been already identified, including a classification of their probability and a description of contingency measures envisaged by the consortium. All this information has been reported in the *Happymums* Risk Registry, which includes all the risks that need to be monitored throughout the project or as long as they remain relevant.

However, risk assessment will be updated throughout the project lifecycle as unexpected sources of risk can be identified at any time. Indeed, new risks have been added to the Registry, besides those identified at the proposal stage.

The final objective of the continuous mapping and monitoring of possible risks is to decrease the probability and impact of events adverse to the project. In contrast, any event that could have a positive impact should be exploited.

## Acronyms

| Abbreviation | Full term |
|---|---|
| BHRCS | Brazilian High-Risk Cohort Study |
| CA | Consortium Agreement |
| EU | European Union |
| ECNP | European College of Neuropsychopharmacology |
| EMC | Erasmus Medical Center |
| GA | General Assembly |
| GenR | Generation R Study |
| KCL | King's College London |
| OSR | Ospedale San Raffaele (San Raffaele Hospital) |
| PC | Project Coordinator |
| PM | Project Manager |
| PO | Project Officer |
| RIA | Research and Innovation Action |
| SESAB | Scientific, Ethical and Social Advisory Board |
| SC | Steering Committee |
| TC | Teleconference |
| UB | University of Barcelona |
| UZH | University of Zürich |
| WP | Work Package |
| WPL | Work package Leader |

# 1. Introduction

The purpose of this deliverable is to guarantee the early identification of potential problems to ensure that adverse situations will be properly managed throughout the evolution of the *HappyMums* project. The plan explained below defines the processes, tools and procedures that will be used to manage and control those events that could have a negative impact on the project implementation. In case the problems cannot be completely eliminated, a scenario of reduction of potential damage needs to be anticipated.

The goal of this document is to allow the different members of the project, according to their role and responsibilities, to accurately and timely try to avoid unwanted risks and, as necessary, take action in mitigating or applying corrective measures to control potential negative effects to the project.

The risk management actions will be carried out throughout the project life cycle; the Project Coordinator (PC) will be primarily responsible for monitoring the potential risks and will have regular communication with the Work Package Leaders (WPLs) in order to provide an updated mapping, elaborate appropriate solutions and timely adjustments.

The PC must ensure that potential risks are properly assessed, evaluated, and managed in terms of communication and contingency management. The WPLs themselves are responsible for the communication of any problem faced during the implementation of the tasks assigned.

## 2. The *HappyMums* risk management strategy

The *HappyMums* consortium holds very ambitious goals. Therefore, it is important to understand any potential risks and have a good process for managing them. As described in *D1.2 Project Handbook*, the Steering Committee (SC) is the supervisory body for the execution of the Project, which includes risk identification and mitigation as an important task. The SC consists of the WPLs, the Project Coordinator (PC) and the Project manager (PM).

The general Risk Management Strategy of *HappyMums* is to:

- Identify potential risks at the earliest possible stage through constant monitoring;
- Estimate the potential probability of the identified risk;
- Assess the potential impact of the risk on the project implementation;
- Identify a set of actions that may be necessary to offset the risk;
- In case the risk cannot be completely countered, define strategy and actions to minimize its impact.

The PC, together with the PM, is responsible for the set up and the update of the project Risk Register (See below), which is the document used to track each identified risk and all related information about it (likelihood and impact, plan to avoid the risk or contingency measures to minimise its impact).

The process for risk management will be iterative. During each iteration the Risk Register will be updated:

1. Each partner in the project is responsible for reporting potential risks (and proposing remedial actions) to their WPLs and, if necessary, to the SC and the PC and PM.
2. The WPLs and the PC have the responsibility, together with that partner, to assess the risk impact, probability of occurrence and remedial actions. All risks that can be managed at this level should be addressed as soon as possible.
3. For risks of more severe grade, the project coordinator should inform the General Assembly (GA), which comprises the whole consortium, and the Scientific, Ethical and Social Advisory Board (SESAB) which is an external advisory board composed of international experts who can provide feedback and advise. Together, they can discuss on how the problem should be addressed and take actions and decisions,

where needed. All risks reaching this level shall be reported and discussed also with the Project Officer (PO).

4. With the risk register in place, monitoring and management of the identified risks will be performed in direct contact with the technical work. The risk register will be reviewed and updated at least twice a year within the Consortium meetings.

# 3. The *HappyMums* risk management process

The Risk Management process implemented in *HappyMums* includes continuous improvement cycles by which plans, analysis, and mitigation can be updated to remain both current and effective.

The risk management process contains the following steps:

- Identification
- Assessment
- Risk closing or Response Planning
- Implementation and Monitoring

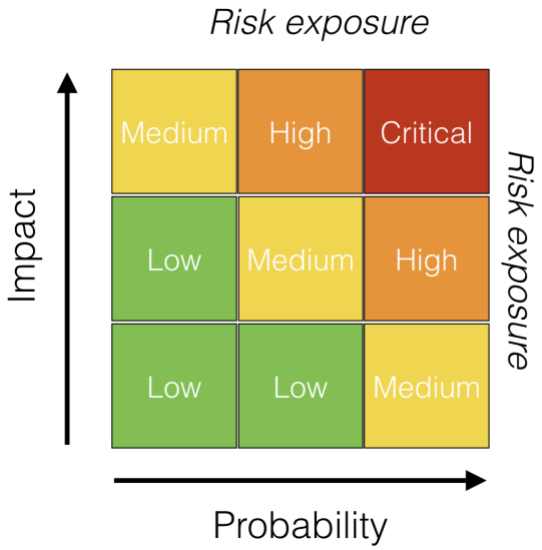
## 3.1 Risk Identification

Risk identification is the first step of the risk assessment process. Risks cannot be managed until they are identified and described in an understandable way. Each partner is in charge of identifying and reporting new risks throughout the course of the project supported by the pertinent WPLs. In this way, mitigation actions will be established in advance, ensuring the correct evolution and coordination of all the activities. If any new risk is identified by a partner, it will be analysed alongside those on the original risk list and then added to the Risk Registry. In order to do so, the pertinent WPL needs to provide to the PC and PM detailed information about the identified risk, together with countermeasures.

## 3.2 Risk Assessment

Once possible risks are identified, a preliminary quantification provides some prioritisation for further evaluation. The partner who identified the risk also determines the level of risk, taking into account the following facts: the likelihood of occurrence of the event (Probability), the severity of consequence if the event should occur (Impact), which requires the identification of consequences and the degree of impact.

The exposure to a given risk is estimated using the following risk matrix:




## 3.3 Risk response planning

After the risk identification and assessment, the first choice will always be to avoid risk materialisation, but this action will rarely be achievable.

If a risk cannot be eliminated, then it will have to be handled properly. Therefore, mitigation actions will need to be put in place.

The WPLs are primarily responsible for developing an appropriate response for risks associated with their WP. If a mitigation action cannot be effectively carried out or does not solve the problem, the WPL must contact the PC in order to find the right measure to mitigate the risk.

The PC is responsible for developing an appropriate management for risks associated with the whole project. The current status of risks is a permanent agenda item on each Consortium meeting, on which the risks and the management responses are discussed and agreed upon.

## 3.4 Risk response implementation and monitoring

All the risk responses must be monitored and their effectiveness assessed. Corrective actions need to be taken, if the responses are found ineffective. The partner who identified the risk is also responsible for the implementation of the mitigation measures.

When mitigation measures are successfully implemented or the likelihood or the impact of a risk decrease sensibly the risk can be considered “closed”.

# 4. Risk Registry

*Happymums* risks are registered within the Risk Register reported in the table below, reviewed and updated at each Consortium meeting by all partners. The table contains 2 different sections.

Sections 4.1 is dedicated to the foreseen risks, i.e., those risks, which have been identified at the proposal stage. Some of them have been slightly updated.

Section 4.2 lists the unforeseen risks, which have been identified since the beginning of the project.

## 4.1 Foreseen Risks

| Description of risk | Probability | Impact | WP | Risk-mitigation measures |
|---|---|---|---|---|
| Difficulty for a partner to perform a task | Low | Medium | 1 | The issue will be addressed within the affected WP and the General Assembly.<br>UPDATE: The procedure has been refined:<br>The partner experiencing problems in performing their task/tasks is responsible for informing the pertinent WPL and, if necessary, the SC and the PC and PM.<br>The WPLs and the PC assess the situation together with that partner, defining remedial actions.<br>If problems still persist, the PC inform the GA and the SESAB for advice and corrective actions to take. In needed, also the PO will be involved. |
| A consortium member leaves the consortium | Low | Medium | 1 | Most of the partners of *HappyMums* Consortium have been working together for years and are collaborating in several projects, including other H2020 EU projects. Therefore, it is unlikely that a partner will leave the project, unless serious and unpredictable events occur. In this case, given the extensive networks of the consortium members, a new partner with similar expertise will be invited to join or we could decide to split the work among the *HappyMums* consortium partners. |

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| | | | | Considering that the consortium is made up of 3 associated partners, among which 2 are WP leaders (UZH-WP7 leader; KCL-WP8 leader), specific attention will be devoted to closely monitor the situation trying to act proactively in case that one of these partners starts having problems. However, we deem this situation very unlikely, considering their status and financial capacity and their experience in other projects as associated partners. Nonetheless, we have already obtained specific reassurance about both their financial and scientific commitment to the project. In the remote event this situation occurs, we will achieve the tasks by exploiting the high number of partners of the project, redistributing tasks among the *HappyMums* partners. |
| Lack of communication between some partners | Low | Medium | All | Most of the partners of *HappyMums* Consortium have been working together for years and are collaborating in other EU projects, therefore are used to communicate frequently and periodically. Moreover, dedicated working groups/task forces to promote contact and collaboration and periodic meetings will be organized. If we realize that a lack of or a low communication occurs, we will promptly act by organizing dedicated online meetings.<br>UPDATE: to avoid this risk or minimize its impact, new collaborative and communication tools have been implemented (ad-hoc mailing |

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| | | | | lists, collaboration platform and document repository in the private area of the project website). Moreover, monitoring TCs (with WPLs and PC, PM) are regularly held. |
| Ethical/legal issues in releasing existing cohort data into the research platform | Medium | Low | 2 | Data will remain in local servers for federated data analytics. |
| Available studies include heterogeneous measures and variables | Medium | Medium | 2 | Key variables are harmonized based on previous experience and standardized protocols.<br>Several partners (e.g. EMC, OSR, UB) have long lasting experience in harmonizing heterogeneous measures and variables and have done/are doing so also for other projects (e.g. EarlyCause and LifeCycle) with similar data to those in *HappyMums*. Therefore, there is no reason why they cannot do the same successfully also in *HappyMums*.<br>UPDATE: Data Harmonization Procedures and Protocols are being set up and shared. The final versions will be included in D2.3 *Data Harmonization Procedures and Protocols* which will be delivered at M10. |
| Computational complexity due the high dimensionality | Low | Low | 3 ,4 | Use of Topological Data Analysis, a powerful unsupervised machine learning approach already successfully implemented |

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| Insufficient statistical power to detect genetic and molecular signatures | Low | Medium | 3,4 | Additional data will be obtained from relevant consortia such as EarlyCause. |
| Delay in communication between human studies and animal studies | Low | Medium | 3-7 | Task forces and dedicated physical/virtual meetings at different partner sites. |
| New digital biomarkers do not provide any predictive value | Low | Medium | 3-8 | Focus on the integration of established clinical markers of risks. |
| Some App Modules are not ready by the start of the clinical study | Low | Medium | 5 | We will start the clinical study with a first version of the App, that will be then updated |
| Delays in the recruitment for the multicenter clinical study | Low | Medium | 5 | Involve other centres or other associations |
| Clinical decision support tool does not meet clinical acceptability | Low | Medium | 8,9 | Gather requirements from clinicians from day one and integrate key aspects such as explainability and data visualization. |
| Disagreement over IP or intentions of partners for exploitation diverge | Low | Medium | 9 | A dedicated exploitation meeting will be set up to clarify issues. |
| Insufficient statistical power | Low | High | 3,4,6,7 | Data in *HappyMums* will come from:<br>-Clinical cohorts that will be used to generate new biological data or to analyze already generated data (e.g. *PRAMD, PREDO, ITU*): some data, as mentioned, have been already obtained and the samples size was large enough to detect statistical significant differences and |

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| | | | | association. They are among the largest perinatal samples available to date.<br>-The longitudinal clinical cohorts where MRI scans, blood samples and clinical data have been collected longitudinally (*GenR and BHRSC)*: these are the two largest longitudinal neuroimaging epigenetic resources in the world, creating unprecedented opportunities for characterizing epigenetic and brain-related changes across development.<br>- Animal studies: we have planned to have at least N=10 animals per group and per phenotype, that based on consortium preliminary data and publications is powered enough to detect significant differences in biological and behavioural variables. |
| Limited knowledge on mechanisms from the clinical cohorts (with pharmacological and non-pharmacological intervention) | Medium | Medium | 7 | IMPRINt and PReSENT are ongoing studies where pregnant women at risk for or with a depressive symptomatology will receive non-pharmacological or pharmacological interventions. Clinical assessment and biological samples collection will be performed at different time points during treatment to allow the detection of longitudinal changes in peripheral biomarkers that can be associated with an improvement (or not) of the symptomatology. As in humans only associations can be tested, in the same WP (WP7) data from |

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| | | | | these clinical cohorts will be integrated with data obtained from animal models where biological analyses will be performed both in blood samples, as in humans, but also in the brain. These animal models will also allow to target specific biological systems to go inside the mechanisms underlying the effects of non-pharmacological or pharmacological interventions.<br>The integration of preclinical and clinical data and the use of cross species and cross tissue approach has been already successfully used by us to identify mechanisms underlying the presence of depressive symptoms and to assess the efficacy of interventions. It also provides peripheral biomarkers that can be useful in the clinical setting for the monitoring of the symptomatology. |

## 4.2 Unforeseen Risks

Considering what happened in the first months of the project, new risks have been included in the Risk Registry. These risks are reported here with a brief description of how the risk manifested (to be kept as lessons learned) and with mitigation measures, should the risk materialize again.

| Description of risk | Probability | Impact | WP | Risk-mitigation measures |
|---|---|---|---|---|
| At the beginning of 2023 the new Illumina Infinium HumanMethylation EPIC version 2.0 microarray was released, impacting the cost of analyses planned in the GenR and BHRCS Cohorts. | Low | Medium | 4 | Plans have been defined to centralize all the analyses at EMC (Erasmus Medical Center) to counteract the prize increase and minimize technical differences.<br>If the problems cannot be solved, the discussion will be escalated to the Steering Committee (SC) and, if needed, the General Assembly (GA). Advice will be also asked from the SESAB and the PO. |
| Difficulties in finding tests and resources to be implemented in the APP in all the language of the different centers.<br>For example, initially we planned to include an Emotional Stroop Test in the App. However, some clinical partners proposed to add another test related to emotional recognition in the faces of adults and children, and, on the other hand, we encountered difficulties in | Medium | Low | 5 | New proposals from partners for new features to add into the App or difficulties in finding resources in the different languages will be discussed with the partners involved to find ad-hoc solutions, exploiting the clinical expertise within the consortium.<br>If needed, advise will be also asked from the SESAB. |

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| finding adequate resources in all the different languages.<br>After few meetings, we are considering replacing the Stroop test with another test more focused on emotional recognition which seems to be more suitable, taking also into account the gamification aspect of the App. | | | | |
| Due to drastic changes in the regulations for animal experimentation in Switzerland and Europe and the restrict temporal frame of the juvenile and adolescence period, it will be difficult to perform the entire battery of behavioral tests planned in Task 6.4 without exceeding such time frame and exposing the animals to excessive manipulations that are not allowed by the regulatory entities. | Medium | Medium | 6 | Mitigating actions are being discussed with WP6 partners. An alternative could be the decision to perform a restricted number of behavioral evaluations in such restricted temporal frames. |

# 5. Conclusions

This deliverable provides a complete description of the *HappyMums* Risk management strategy and the related Risk Registry. This document will be updated constantly under the supervision of the PC and the PM.

Modifications and improvements to this document will be discussed at every consortium meeting to address any needs/risks not identified at this stage of the project.