FAMILY

"Running in the FAMILY – Understanding and predicting the intergenerational transmission of mental illness"

Grant Agreement number: 101057529

D1.2 2nd report about feedback from SEAB

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SUMMARY

This document introduces shortly the composition and tasks of our Scientific and Ethical Advisory Board (SEAB). Main part is the second feedback round we received from each member, related to three relevant questions we identified within our coordination team.

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1 INTRODUCTION

1.1 Purpose and Scope

Members of the SEAB:

- Prof. **Martien Kas,** University of Groningen, The Netherlands
- Associate Prof. **Ghislaine van Thiel**, University Medical Centre Utrecht, The Netherlands
- Dr. **Ali Jawaid,** EMBL-Nencki Center of Excellence for Neuronal Plasticity and Brain Disorders (Braincity), Warsaw, Poland

Role and tasks according to our DoA
Contributions to:

- D1.1 – 1st report about feedback from SEAB
- D1.2 – 2nd report about feedback from SEAB
- D1.3 – 3rd report about feedback from SEAB

In WP1, Task 1.4 mentions the SEAB: For key results, additional advice will be sought from the Scientific and Ethical Advisory Board.

And in part B:
Compliance with ethical principles and relevant legislations
All consortium members and researchers in FAMILY are committed to the highest research ethics and integrity standards and will conform to the applicable international and EU law, Horizon Europe standards, and to national law in the countries where the project will be carried out. Consortium members will constantly seek advice from ethics experts involved in the consortium, external ethics experts (in the Scientific and Ethical Advisory Board [SEAB]), specialised ethics departments at their institutions and national ethics bodies, compliance managers, research ethics committees and data protection officers (DPOs). WP8 will have the responsibility to coordinate handling previously identified, as well as any new ethical issues arising from the project.

Feedback report from SEAB
For the deliverable report, we identified three relevant questions that we shared with the SEABs:

- Do you have any suggestions or recommendations related to our scientific approach?
- Do you have any questions related to the project's progress?
- Do you have any concerns, questions or recommendations related to ethical issues (human and animal studies, AI – machine learning)?

1.2 References to other FAMILY Documents

- FAMILY DoA
- Data Management Plan (DMP), deliverable D2.1 1st version of data management, harmonisation, and open science plan

2 FEEDBACK FROM THE SEAB MEMBERS

2.1 Martien Kas

Do you have any suggestions or recommendations related to our scientific approach?

The answers to my questions provided by the researchers involved following their presentation at the meeting in Riga are sufficient to cover my initial concern with respect to implementation of control groups. Another aspect to keep in mind is that the currently presented effect sizes are relatively small which should be taken into account when interpreting the data obtained.

Do you have any questions related to the project's progress?

Animal work: The research progress for the Swiss team seems to be going well, and interesting findings have been obtained. The research progress for the Rotterdam team should be monitored carefully. Experiments have started now and first research results were presented. Please keep a close eye on the expected deliverables and the project timeline.

Do you have any concerns, questions or recommendations related to ethical issues (human and animal studies, AI – machine learning)?

No, the project is ongoing in full speed, and I assumed that the required national ethical approvals for the animal experiments for both the Swiss and Dutch research teams are in place.

RESPONSE:
We thank Dr. Kas for his input. We recognise the need to acknowledge the low effect sizes and will take this advice into account. Also, we will keep track of the timeline of deliverable in WP6. We can confirm that national ethical approvals for all animal experiments are in place at both sites.

2.2 Ghislaine van Thiel

Do you have any suggestions or recommendations related to our scientific approach?

Overall, clear efforts have been made to address ethical issues in the project. Especially worth mentioning is the contribution of EUFAMI about the risk of stigma and suitable approaches to mitigate this risk. In addition, there are plans for a communication strategy to address concerns about hype and over-promise related to the project's results.

Further steps are needed to implement the learnings from the project so far into the current conduct of the study.

1 The project is now at the point of starting analyses of data, which seems to be a good time to design and implement more fine-grained guidance for communication, including return of results to participants and dissemination of results to the wider public.

2 With regard to the EUFAMI recommendations, an update of the website has been realised, which yields the opportunity to incorporate risk-mitigation strategies for the potential harm of stigmatisation. This could be taken up in the planned communication strategy.

3 As I understand it, oral and written feedback on findings from clinical tests (psychiatric diagnosis and symptom assessments) is communicated to participants, which includes information on whether a referral for treatment or further tests are indicated. However, ethical issues are related to the question if so-called non-actionable results should be communicated to (all) participants. This concern is also highlighted in the results of the study on risks and benefits of risk information from WP8. My advice would be to devise a plan for returning research results to individual participants, based on available guidance about returning research results and taking the insights from WP8 and EUFAMI into account. Specific attention should be given to returning results about minors, the risk of bias and false-positives and the potential need for the provision of counselling about informing family members.

4 With regard to AI and ML, awareness and first steps towards responsible AI have been made. However, the ethical aspects of design of trustworthy AI are not explicitly addressed in the work of WP7. Especially for predictive modelling, it is advisable to apply an ethics-by-design approach from the start. Guidance on how to apply this approach can be found for example from the EU high level expert group for trustworthy AI (which includes an assessment list, known as ALTAI).

5 The work from WP8 is valuable, and not only underscores the potential risk of stigmatization, but also draws attention to the risk of harm. It is an ethical and legal duty to minimize the risk of harm to participants in the study. Furthermore, over-reliance on the study results could cause harm to individuals in the future, especially those who fall in the category of false positives. Moreover, seeing the conclusion of WP8 that benefits include early intervention is questionable if my understanding is correct that currently not many evidence-based strategies are available for early intervention to avoid or treat mental health issues (also in part because of underfinanced mental health care). Not having children to avoid risk to offspring is a major sacrifice for people who would have wanted to become a parent, and although more information would add to the autonomy of choosing such an 'intervention', potential bias in the information becomes an even more weighty issue.

Based on my current information on the project, in my opinion a comprehensive plan for careful assessment, analysis and planning on handling these issues is needed. Currently, awareness is raised and most issues are listed by WP8, but sufficient guidance on handling these ethical issues during the project and beyond seems to be missing. Priority setting could help to avoid the ethical advice to be too late.

Do you have any questions related to the project's progress?

Not for this period.

Do you have any concerns, questions or recommendations related to ethical issues (human and animal studies, AI – machine learning)?

WP2: I have a follow-up question about the assessment of proposals for the use of data from the FAMILY project. Which aspects will be included in the assessment by the steering committee? For example, is a check foreseen to determine if the planned project falls within the scope of the informed consent? How is this done when sensitive data (i.e. genetic data) are included in the analysis? My advice would be to describe this assessment in a charter or in the DMP.

RESPONSE: we thank Dr. van Thiel for her thoughtful advice. Here we provide a point-by-point response:

1. Within WP9 we will come up with further activities to promote the results from the project.
2. We will further develop strategies to reduce the potential harm of stigmatisation by planning a stakeholder event on this topic.
3. WP8 will develop ethical guidelines for professionals that will include guidance on communication of actionable and non-actionable results of risk prediction. Currently FAMILY project is aimed at development of predictive models and researchers do not deliver individual predictions. The guidelines will apply to future potential users of predictive models and will cover the ethical issues identified in WP8 and other work packages.
4. AI and ML: we are aiming at providing out-of-sample predictive models, not to retrospectively predict participants risk or future trajectory. We will communicate this strongly to all stakeholders so as to address possible concerns.
5. WP8 will develop ethical guidelines for professionals (physicians and genetic counsellors) for potential future use of prediction tools by the end of the project (D8.3., month 60) where all the aspects that were highlighted by the SEAB will be taken into account. WP8 will also communicate with other work packages on addressing the ethical issues during the lifetime of the FAMILY project to ensure implementation of ethics principles and joint reflection on ethical issues (e.g., with WP7 on including ethics by design elements for responsible and transparent use of AI). So far, discussions on ethics issues have been organized during internal PARADISE meetings and consortium meetings. Nevertheless, WP8 will organize one more PARADISE meeting specifically on implementation of ethics principles in FAMILY.

WP2: The clinical studies that are part of FAMILY are each performed following local ethical requirements that are in place at each site. The studies are longitudinally ongoing and as part of FAMILY a follow-up assessment has been made possible. Thus, ethics were already in place given the previous assessments. Before sharing data, all sites are responsible to check each individual's informed consent for approval. We will make these procedures clearer in a new version of the DMP, including who is responsible for what during the process of data sharing.

2.3 Ali Jawaid

Do you have any suggestions or recommendations related to our scientific approach?

It is evident that there is some effort to harmonize the platforms across WPs- with integration of the resilience perspective and sex-dimorphism in WP4. However, I believe there is still space for more: for example, DNAme and miRNA overlap analyses between WP4 and WP6 AND investigation for ERBB changes (identified in WP4) in samples collected in WP6.

Response: We agree that alignment of datasets in humans and mice is important and may reveal concordance or discordance. We will revisit our data analyses and try to integrate and harmonize molecular datasets from WP4 and WP6.

Do you have any questions related to the project's progress?

Unfortunately, I was unable to attend the GA in Riga. However, I am happy to schedule an online meeting to discuss the pathways that emerged from my research with the relevant WP leads (Prof. Cecil and Prof. Mansuy). Nevertheless, even based on the unbiased approach, some mechanistic leads do already emerge. A notable one is Tyrosine Kinase signalling (based on results from WP4).

Response: It would indeed be very useful to have a 3-party discussion about potential common pathways and can plan it accordingly.

Do you have any concerns, questions or recommendations related to ethical issues (human and animal studies, AI – machine learning)?

Again, comprehensively addressed by Prof. van Thiel and Prof. Kas. I do not have any specific questions or remarks on this. There was previously a discussion about including analysis of human sperm samples. I am very much interested in knowing the progress on that.

Response: We have no specific news about this aspect yet.

3 CONCLUSION

Several suggestions and recommendations regarding the scientific approach, the project's progress, and concerns, questions and recommendations related to ethical issues (human and animal studies, AI – machine learning) are made by the SEAB and have been adequately addressed by the consortium members, and confirmed by the SEAB members.

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