MICROBiome-based biomarkers to PREDICT decompensation of liver cirrhosis and treatment response

Informed consent policy for human subjects, human biological samples and personal data in MICROB-PREDICT (MS41)

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1. Project objective

Decompensation of liver cirrhosis and progression towards acute-on-chronic liver failure (ACLF) causes 1.2 million deaths/year. Microbiome is causally involved in cirrhosis progression and is for drugs the first interaction point with the patients. Drugs can alter the microbiome leading to unwanted effects or even facilitating their effects, but the microbiome metabolizes the drugs, shapes their effects and possibly determines the host response to drugs. As each person carries an individual microbiome, insight in these processes should help stratify or even personalize patient health care and treatment.

The aims of MICROB-PREDICT are 1) to better understand the role of microbiome and the gut-liver-axis interactome with respect to microbiome functionalities, 2) to identify and validate microbiome-based biomarkers and signatures for personalized prediction of decompensation and ACLF, and response to treatment, 3) to design three new tests as easy-to-use tools and point-of-care, smartphone-connected nanobiosensors, and 4) to validate them in a randomized controlled trial. MICROB-PREDICT will assemble existing data and samples from major microbiome initiatives in hepatology (12 international studies, >10,000 patients), and enrich them with holistic and in-depth analysis using cutting-edge multi-omics technologies of host and microbiome from different body sites in samples of >1,000 patients collected in a longitudinal manner with sequential visits and controlling for confounders.

MICROB-PREDICT results will foster more accurate, personalized risk stratification and significant steps towards personalized treatment of decompensated cirrhosis and ACLF. World-leading microbiome specialists, technology leaders and clinical experts make this a programme of scientific excellence; patient organisations (ELPA) and the European Association for the study of the Liver (EASL) will channel our results into a powerful dissemination, communication and exploitation programme.

2. Introduction

The MICROB-PREDICT research project deploys different interventions in research: clinical trials with patients and healthy volunteers, biomedical research with human biological samples from diverse origins (blood, stool, mucosa, etc.) and collection, transfer and processing of personal data. These different types of research require designing specific research protocols, information and informed consent procedures and templates to assure the protection of rights of participants, while promoting freedom of research at any stage. This policy describes the ethical and legal framework for the planned research interventions, the implications for research participants (patients and healthy volunteers) and obligations for those conducting research: First, we will elaborate on the information that potential study participants should have received in order to be able to decide whether or not to participate ('informed consent'), and the implications this decision may have for their own personal situation. Second, in line with the requirements introduced by the General Data Protection Regulation (GDPR), we will define and summarize the information that should be included in the information process and informed consent procedure when informing participants, collecting and using human biological samples and personal data for research purposes. Our information and informed consent policy respects also the main ethical and legal guidelines on ethics in research at international and European level and the research integrity that the Consortium should take into account for achieving the goals of the project, while respecting research subjects.

3. Information for potential human subjects in research and informed consent procedures

To promote autonomy of potential participants in research and according to international and European requirements for information and informed consent procedures information about MICROB-PREDICT research interventions should include the following **general information**: title of the study; clear information, comprehensive for the general population, about the purpose and content of research, the investigators in charge of the research and findings, adding official references of the project. This information should be followed by a brief description informing potential participants about the proposed research intervention for them to decide whether or not to participate. Participants should be aware that the research has been approved and reviewed by the entitled research ethics committee of the center or research institution involved.

Specific information should be provided about the ethical and legal framework applicable integrating international, European, national and local regulations, depending on the type of research (i.e. clinical trial) in a clear and simple way, avoiding excessive legal references. The final goal is to provide potential participants with all necessary tools to make a rational, free, and voluntary decision that is confirmed by the requisite of informed consent. It is neccesary to check that the participant decides to be part of the research process based on voluntary grounds.

The **patient information sheet and the informed consent form** are part of a process that includes verbal communication and written information that obliges the investigators to provide any information that participants could need at any time of the research cycle:

It is necessary to provide them with **full information about the principal investigator**: name, surname, phones and contact address to them to contact him/her at any time and to state clearly that they can ask any question.

It must be explained that **study participants are free to participate** in any research activity and that they may revoke consent at any time without any explanation or justification. It should furthermore be stated that there will be **no negative consequences** for them and their care (i.e. receiving treatments, if there is the case, etc.) should they change their mind at any time. In this sense the information provided should be adequate for the general population and should tend to avoid therapeutic misconceptions of potential participants.

If participants are not able to consent, representatives should be informed, and their consent be collected following the established procedures. The information should be provided in a language and way that potential participants or their representatives can fully understand. Those who cannot read and/or write can consent through other specific formats (video, audio recordings etc.). In general terms, the information should be adapted to the level of understanding of the potential participant and translated into the different languages of the Consortium. Local and cultural issues related to the patient information sheet and informed consent issues should be integrated and respected.

The principle of respect for human vulnerability and personal integrity should underlie the whole research process meaning that individuals and groups of special vulnerability should be protected, and the personal integrity of such individuals be respected. In light of the Convention on the Rights of Persons with Disabilities, United Nations (2016), persons with disabilities should be included in the research process, and the research process should include in the research project following the universal design approach[1]. The principle of non- discrimination for any reason including genetic conditions and disabilities shall be respected.

[1] "Universal design" means the design of products, environments, programmes and services to be usable by all people, to the greatest extent possible, without the need for adaptation or specialized design. "Universal

The process of information continues with a **general description** that should be very brief, with relevant information expressed in clear and understandable terms according to the level of understanding of potential participants. The main content of this patient information sheet and informed consent templates should include what the research is about (indicating and defining the type of research: clinical trial, biomedical research, etc.); the main goal; the methodology and techniques; the study duration; possible benefits, and known and possible **risks of the participation** in the study. Information on the number of visits should be included, and if there will be complementary tests. Furthermore, inclusion and exclusion criteria and what happens during visits (if any) etc. could be described.

The main goal is to make potential participants aware of any **tests and interventions that will be done outside of routine clinical care**, and only because of their participation in the study. The principle investigator in charge of the research intervention should provide clear information on the impact expected on participants as individuals, but also to the groups that they could represent. Potential participants must be informed about their **responsibilities** within the proposed research, e.g., about the **procedures and the obligation to inform** about any adverse event that could happen to them.

It is important to make potential participants understand that their participation in the study does not necessarily imply a direct benefit to their health or specific condition. In this sense, they should be aware that their contribution could also be for the general advancement of scientific knowledge. Potential participants should be informed about **alternative treatments and interventions** to the ones proposed, if there are any, that are effective for their situation. In case of doubt, the principle investigator will be available to provide the necessary information. Furthermore, research participants should know that in specific research arms or activities, being a participant does not modify the standard treatment or intervention (i.e. observational studies). Insurance policies, when applicable, should be explained according to regulations in place.

If it is the case, potential participants should be informed about the possibility and consequences of **compassionate use** in research meaning that under strict conditions, products in development can be made available to groups of patients who have a disease with no satisfactory authorised therapies and who cannot enter clinical trials (source: European Medicines Agency). Partners of the Consortium in charge of the research with compassionate use should consult the rules and procedures of each Member State.

Monetary or in-kind compensations, if any, should be carefully analyzed by the investigators and the research ethics committees in order to ensure that potential participants are not tempted, pressured or induced by them. Equally it should be clearly stated, if no compensation of any kind is offered. Participants should be aware about the conditions for reimbursement of travel, dietary or other expenses occurring due to their participation in the study. Any kind of compensation offered should not affect or modify the free will or influence the participants unduly in their decision about their study participation.

MICROB-PREDICT research must avoid any kind of conflict of interest and, if any, investigators must declare it and investigators and institutions should avoid research misconduct or any questionable behaviour. Participants should understand that there are different types of conflict of interests, e.g. economic, of a personal or hierarchical nature, etc. At any time, researchers should check and avoid misconceptions of participants regarding the specific intervention proposed.

design" shall not exclude assistive devices for particular groups of persons with disabilities where this is needed. (Article 2 Convention on the Rights of Persons with Disabilities, United Nations ,2016)

Finally, MICROB-PREDICT patient information sheets and informed consent processes need to specify in **any type of research intervention** any other information considered necessary to be explained to potential participants. **Any new information** regarding the treatment or interventions used in the study that may affect the willingness to participate, or that could be discovered during participation, will be communicated to those affected by the entitled persons (principal investigators) as soon as possible. If participants decide to **withdraw their consent** to participate in a study, no new data will be added to the database and participants may require the destruction of all identifiable samples previously held to prevent further analysis.

Participants should also know that they can be excluded from the study if the principal investigator and entitled researchers of the study consider it appropriate. Reasons may include, e.g., safety reasons, any adverse event that occurs and is considered related to their participation, or because participants consider that the study is not complying with established procedures. In any case, if the withdrawal of a study participant was decided by any study staff, participants should receive an adequate explanation of the reason for their withdrawal from the study.

To assure and check that potential participants have properly understood the implications of their participation and their rights, the legal and ethics team of MICROB-PREDICT developed **templates and checklists**, which include questions and answers to provide information in the easiest way and to check the free will of the subject. In this sense, an "experimental bill of rights" has been developed, a catalogue composed by ten issues to include but not to limit the participants' rights in the research process has been elaborated.

Finally the verbal and written process of information is accompanied by an **informed consent template** covering all these aspects to be signed by participants, where they agree or not to participate in the proposed research intervention. The specific template should include again general information about the project (title, reference, funding, principal investigator, etc.) and the name and surnames of the potential participant. The informed consent template should clearly state that participants: 1) have read the information template given to them about the research study after being informed of the above mentioned issues; 2) are able to ask questions about the study; 3) received enough information about the study; 4) have spoken with (name of the principle investigator); 5) understood that their participation is voluntary and that they can withdraw from the study at any time and without giving any explanation and with no negative impact on their situation (medical care, etc.)

4. Information about personal data protection: privacy and confidentiality of potential participants in research

A core issue for the MICROB-PREDICT Consortium is protecting privacy, confidentiality, integrity and dignity of patients and healthy volunteers. Protection of personal data linked to human biological samples is of particular relevance considering the multi-omics use of samples.

Each institution as part of MICROB-PREDICT, where research is carried out, is responsible for assuring privacy and personal data protection of participants and for that the data controllers are clearly identified (indicating who is in charge, including address and contact information). The principles of data protection according to Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data (GDPR) should be followed during all biomedical research: lawfulness, fairness, non-discrimination, transparency, accuracy, necessity, data minimisation, purpose limitation, privacy by design and by default and of course, explicit and legitimate purpose relying on informed consent of the research participants. These principles allow researchers to respect human rights of potential

participants in research. In addition, the new figure of Data Protection Officers established by the GDPR, as independent advisors on the issue of data protection in each research institution, is crucial. Likewise, the Data Protection impact assessment introduced by the mentioned regulation to evaluate the impact of the research specifically in the potential subjects to be involved. These are institutional and practical requirements that help to prevent, to protect and to promote the rights and freedom of involved study subjects, including the freedom of research of the research team.

In general terms, as it has been described before in the context of informed consent, participants should be informed in a simple, adequate and clear way about their rights and the procedures established to make their rights effective according to GDPR and other regulations applicable (i.e. National Laws on Data Protection). To protect privacy and personal information of participants, including special categories of data such as health, genetic data, etc. participants should be informed about the applicable techniques: codification, pseudonymisation[2] or anonymisation and the impact of these techniques on their privacy and lives. Participants should be informed that their identity will be protected and no one will have access to this information, unless there is a justification. The aim is to prevent participants from being identified, understanding that investigators and those with a specific permission and access could, if it is justified, connect personal data of participants with i.e. medical records. Only entitled authorities (i.e. medical healthcare), and Research Ethics Committees involved and staff authorized by the study leader, will have access. Any staff in contact with personal data will apply the highest standards of protection of privacy and respecting secrecy and confidentiality as stated in deontological, ethical and legal regulations.

The study protocol should explain if there will be encrypted data transfers to third parties and/or to other countries. This means that there will be no information that can identify the participant directly (such as name and surnames, initials, address, social security number, etc.). If a transfer of encrypted data is made outside the European Union, either to entities related to a research center where the study is conducted, or to service providers or to researchers who collaborate with the principle investigator, participant data will be protected by safeguards such as contracts or other mechanisms established by the data protection authorities (i.e. Privacy Shield).

In addition to the rights already covered by the legislation (access, rectification, cancellation and opposition), participants should be informed that according to GDPR, they can also limit the processing of incorrect data, request a copy or transfer data that they have provided for the study to a third party (data portability). To exercise these rights, or if participants want to know more about confidentiality, they should contact the principal investigator of the study or the Data Protection Officer of the center. Participants also have the right to contact the National Data Protection Agency (National, local authority entitled) if they are not satisfied with the handling of their data.

Participants should be informed that if they decide to leave the study, no new data will be collected, but data generated for research purposes until that point in time cannot be destroyed. Participants should be informed about the obligations of researchers and promoters to keep the data collected for the study and for how long after its completion. Personal information will only be kept by the entitled research center/institution and by the main investigator for other scientific research purposes if the participant has given his/her consent to do so, according to the ethical and legal framework applicable.

[2] "'Pseudonymised' means to divide the data from its direct identifiers so that linkage to a person is only possible with additional information that is held separately. The additional information must be kept separately and securely from processed data to ensure non-attribution." Source: ethics self-assessment European Union (version 4th February 2019)

http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/ethics/h2020_hi_ethics-self-assess_en.pdf

Participants should declare in writing (or adapted to specific format to give consent) that in accordance with the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data (GDPR) and the national regulation applicable (if applicable), they have been informed of the existence of a file or treatments of personal data, of the purpose of the collection of their data and the recipients of the information. According to GDPR, participants could consent to the handling of their personal data after the information process to use personal data in the framework of the specific research and to provide a broad consent in order to be used in further research projects that will be part of the same line of research initiated. Then, they can proceed to consent or not (by ticking the box yes or no) and include their signature and the signature of the principle investigator indicating the date. Specific consent should be added about the right of participants to receive information derived from the research that could be relevant for their health.

5. Information to donors of human samples from biological origin and personal data associated

MICROB-PREDICT research interventions obtain, use, store and share biological samples of human origin and personal data associated (Peripheral serum, EDTA-buffy coat, EDTA-plasma, Li Hep-plasma, urine, stool, saliva and gastro intestinal biopsies). For this reason, international, European and local policies on human data samples and associated personal data are applicable.

The principle investigator should explain to potential participants the purpose of the study and the scientific and possible therapeutic value of the uses of their human biological samples for research purposes. This information could be useful for having more science-based knowledge on the progression of the disease, related to cirrhosis. Altruism and solidarity are the principles that form the basis of our health care system, based on sound research and promoting translational medicine, personalized treatments and interventions. Potential participants in research should consent to donate, to store and use their biological samples in the entitled biobanks: as part of the biobank or collection regime, they should be informed about possible access of third parties and the time for how long the samples will be stored. Full contact of biobanks (including contact person in charge and address) should be provided. The principles of quality, security, safety and traceability should be respected, and proper confidentiality measures to protect involved human beings should be taken. The participants should be informed about the use of leftover materials, and that their samples are going to be codified, pseudonymized or completely anonymized depending on the purpose of the research. In the case of codified samples, participants should be informed that the samples will be frozen and stored with a number assigned to them instead of their names. Since the samples are codified, the owners of the material can revoke consent for the use of them at any time, but they should be aware as well that the information, the data generated for scientific purposes, will remain.

The information process and informed consent procedures for conducting research with human biological samples should include the information that the research itself could result in new products, tests or discoveries which may have commercial value. Donors should be informed and clearly understand that they do not retain any property rights to the materials nor any financial benefits from these products, tests or discoveries.

In case of incidental findings or any new information discovered during the research process that could affect the entitled person this should be properly managed: From the beginning, participants should be informed about the possibility of being contacted if there is relevant health-related information that affects them and/or their relatives. Main researchers should follow national and local regulations on the issue.

Participants should be informed that any research based on their samples is reviewed by the entitled research ethics committees, and that biobanks that store these human biological samples have scientific and ethical committees evaluating and monitoring the whole process, including data transfers if any, to assure the protection of their rights, specifically privacy and confidentiality.

6. Information about publication of MICROB-PREDICT results

The study participants should be informed that data and research results of the MICROB-PREDICT project may be published. No personal information revealing the identity of participants will be published. Privacy and confidentiality will always be assured and research integrity is a priority. All Consortium members are obliged to follow the European Code of Conduct for Research Integrity, Allea, 2017 in order to assure research integrity and avoid research misconduct and other questionable practices from the inception and during the whole process of research.

7. Information about Doctoral Thesis in the framework of MICROB-PREDICT

In the case of doctoral theses to be developed in the frame of the MICROB-PREDICT project, participants should be informed about this situation and PhD candidates and supervisors should be clearly identified. Both are bound to follow the above described requirements, and participants have the right to know what kind of activities and interventions in the field of research are going to be developed by the PhD candidate. Doctoral thesis projects should as well be reviewed by the entitled Research Ethics Committee.

8. Main international and European ethical and legal guidelines and regulations for conducting research in human beings

From the legal perspective:

- The Universal Declaration on Bioethics and Human Rights, UNESCO, 2005. http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/bioethics-and-human-rights/

- The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (ETS No 164) was opened for signature on 4 April 1997 in Oviedo (Spain). (The Oviedo Convention on Biomedicine and Human Rights, Council of Europe, 1997) https://www.coe.int/en/web/bioethics/oviedo-convention

- The European Charter of Fundamental Rights, European Union, 2000 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:12012P/TXT

- Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0536

- Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation-GDPR) https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A32016R0679

From the ethical perspective:

- The Helsinki Declaration, World Medical Association, 2013 https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

- European Code of Conduct for Research Integrity, Allea, 2017 https://www.allea.org/allea-publishes-revised-edition-european-code-conduct-research-integrity/

- Ethics and Data Protection**.** See the lastest guide on the issue published in november 2018 after the application of the General Data Protection Regulation http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/ethics/h2020_hi_ethics-data-protection_en.pdf

Moreover, MICROB-PREDICT is respecting all national and local guidelines and regulations applicable to all research settings.

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