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

D8.3 Public engagement strategy to design MICROB-PREDICT along with the need of patients

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WP Leader:	University of Barcelona (13 Bioethics and Law Observatory-UNESCO Chair in Bioethics)
Authors:	Gemma Rabal (13 Bioethics and Law Observatory-UNESCO Chair in Bioethics, University of Barcelona) Itziar de Lecuona (13 Bioethics and Law Observatory-UNESCO Chair in Bioethics, University of Barcelona)
Contributors:	Marko Korenjak (8 ELPA), Minneke Coenraad (12 LUMC), Ameli Schwalber (19 concentris)
Approved by:	Jonel Trebicka (01 EFCLIF)
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Abbreviations

CSO	Civil Society Organizations
EFCLIF	European Foundation For The Study of Chronic Liver Failure
ELPA	European Liver Patients Association
EASL	European Association For The Study of the Liver
EU	European Union
FAIR	Findable, accessible, interoperable and reusable data
NGO	Non Governmental Organisation
OUH	Odense Universitets hospital
PE	Public Engagement
R&I	Research and Innovation
RRI	Responsible Research and Innovation

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1 Executive Summary

The goal of this policy document is to provide a framework of public engagement (PE) in research in MICROB-PREDICT, and to review the best approaches to patient involvement, as well as its benefits and costs. The first part summarizes the Responsible Research and Innovation (RRI) approach and goes in depth in the public engagement agenda. This involves defining what public engagement entails, identifying the reasons for this area to be included in the RRI strategy, the different actors, tools and methodologies for its implementation. The second part analyses the MICROB-PREDICT project to identify areas of its design that could potentially benefit from patient engagement and involvement, drawing evidence from the scientific literature and from publications by worldwide organisations that support patient engagement in research. The third part focuses on the tools that have been selected as a result of the previous analysis to help the MICROB PREDICT PE strategy and to come to recommendations.

2 Public Engagement Strategy in Responsible Research and Innovation

Responsible Research and Innovation (RRI) is a dynamic, iterative process in which all stakeholders become mutually responsive and share responsibility for both the process and its outcomes (RRI Tools[1]). In this framework, scientific inquiry is a process not limited to the perspective of the researchers. Societal actors such as citizens, policymakers, regulatory agencies, scientific societies, business or third sector organizations i.e. can and should be involved during the whole research and innovation process.

The objective of RRI is to create high-quality science aligned with the values, needs, and expectations of society. Implementing RRI leads to a more engaged public, responsible actors, and responsible institutions. It also has benefits for research and innovation, as RRI strives for making science and technology more ethical, sustainable and socially beneficial.

To achieve these outcomes, RRI entails four dimensions of the research and innovation process that try to reflect the social, ethical and political stakes associated with technological

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[1] RRI Tools is a three-year project (2014-2016) funded by the European Commission under the 7th Framework Program (FP7). The project has gathered online resources– the RRI Toolkit – to help stakeholders across Europe put Responsible Research and Innovation into practice. https://www.rri-tools.eu

and scientific advances. The four dimensions, based on the RRI Tools framework adapted from (Stilgoe, Owen, & Macnaghten, 2013) are:

1. **Diversity** and **inclusion**, to produce outcomes aligned with the values and expectations of society, since they take into account different perspectives and expertise.
2. **Openness** and **transparency** make the process of research and innovation more accessible to all actors, allowing people to discuss and scrutinize science and technology, which empowers them to make informed decisions.
3. **Anticipation** and **reflection**, to envision impacts and to reflect on the underlying assumptions, values, and purposes of the research, allowing responsible action.
4. **Responsiveness** and **adaptive change**, to respond to the views expressed by the stakeholders, changing circumstances or new knowledge.

The agendas of RRI

To embed RRI in the research and development process, the European Commission has set out key policy agendas for policymakers to consider governance, ethics, gender equality, public engagement, science education and open access (Horizon 2020).

Governance permeates all the other agendas of RRI. It deals with rules and processes that affect the way in which powers are exercised. In the European Union (EU) five requirements have been identified that underpin good governance: openness, participation, accountability, effectiveness and coherence (COM, 2001).

For all activities funded by the European Union, **ethics** is an integral part of research from beginning to end, and ethical compliance is seen as pivotal to achieve real research excellence (European Commission, 2020). Research, including its outcomes and the way it is conducted, should be ethically grounded and acceptable to society. Honesty, accountability, fairness and good stewardship should be core principles of research and innovation (RRI Tools, 2016). To help applicants on how to make sure that the proposals are ethically aligned with the European values, the European Commission has presented guidance on how to complete an ethics self-assessment for the Horizon 2020 Programme (European Commission, 2019) and an assessment on Ethics and Data protection (European

Commission, 2018). International and other relevant ethical and legal frameworks should be taken into account.

Ethics in RRI relates to three main areas, ethical research, research integrity, and societal acceptability (Casado González, Patrao Neves, de Lecuona, Carvalho, & Araújo, 2016). Ethical research conduct implies the application of fundamental ethical principles and legislation to scientific research in all possible domains of research. Research integrity means that research methods, activities, and processes are guided by standards, guidelines, and protocols; open to external scrutiny (for example, ethical bodies extended to societal stakeholders); and open to internal reflexivity (nurtured by a culture of open deliberative integrity). Social acceptability includes the consideration of the short-term and long-term implications of the research, and this should respond to actual social needs and reflect the basic values of society.

Gender Equality To integrate the gender dimension in research and innovation content means taking into account the biological characteristics of both females and males and the evolving social and cultural features of both women and men, girls and boys. The gender dimension invites researchers to conduct sex and gender analysis in the research process, when developing concepts and theories, formulating research questions, collecting and analysing data and using the analytical tools that are specific to each scientific area. "Integrating the gender dimension in the content of research and innovation is an added value in terms of excellence, creativity, and business opportunities. It helps researchers question gender norms and stereotypes, to rethink standards and reference models. It leads to an in-depth understanding of both genders' needs, behaviours and attitudes. It enhances the societal relevance of the knowledge, technologies and innovations produced. It also contributes to the production of goods and services better suited to potential market." (European Commission. 2020b).

Under Horizon 2020 (Ec.europa.eu. 2020), it is a priority to build capacities and develop innovative ways of connecting science to society, helping to make **science education** and careers more attractive to young people. And to prepare the next generation scientists to continue high level research. To achieve this, it is crucial to invest in the interactions between the relevant actors in the field, the different levels of the education system, universities and other higher education establishments, civil society organizations, professors, teachers, etc. The expected impacts of the science education approach for the Horizon 2020 programme are the development of a scientific citizenship, to attract more young people towards science and to develop RRI in higher education curricula.

Open Access has been a core strategy in the European Commission, improving knowledge information and innovation. Open access policies aim to provide readers with access to peer-reviewed scientific publications and research data free of charge as early as possible in the dissemination process, and enable the use and re-use of scientific research results. From the point of view of science efficiency, open access to scientific research data “enhances data quality, reduces the need for duplication of research, speeds up scientific progress and helps to combat scientific fraud” (EC - European Commission, 2012). This agenda also contributes to public engagement. There is the need for society to participate in science, but to achieve this goal it is necessary to make scientific research accessible to the whole of society.

Likewise, the FAIR principles are applicable here, regarding the data produced in research. Data should be findable, accessible, interoperable and reusable. The Open Acess policy of MICROB PREDICT has been described in D. 8.4. about codes on conduct and research integrity policies and is described properly in the Data Management Plan, a living document that is crucial for the success of the project.

Public Engagement is one of the key areas of the RRI approach, giving more weight to citizens and civil society organizations in the process of research and innovation, both in the definition of research needs and in its implementation. It is a tool to bring on board the widest possible diversity of actors, establishing iterative and inclusive participatory dialogues, to foster mutual understanding and wider acceptability of results.

2.1 What is Public Engagement?

Public engagement is about involvement, influence and initiative from society, and is not to be confused with communication of scientific results to the public, as it goes beyond a unidirectional dialogue to foster a two-way communication. “It is no longer about merely communicating scientific knowledge, but rather about what has been called “co-production of knowledge” and cooperative forms of governance involving a range of societal actors.” (Engage2020, 2015). At the core of the Responsible Research and Innovation approach, **public engagement** is:

- **Inclusive**: Involves diverse stakeholders (citizens, users, Non Governmental Organizations (NGOs), etc.) in the Research and Innovation processes.
- **Anticipatory**: Researchers and innovators are asked to include new perspectives in R&I in order to assess and manage risk.
- **Reflexive**: Researchers and innovators are asked to think about their own ethical assumptions, their role and responsibilities through public dialogue.
- **Responsive**: Flexibility and capacity to change R&I processes according to public needs and values.

2.2 Why the need for Public Engagement?

Society is facing many challenges today, such as health and demographic changes, environmental actions, agriculture and water tensions, digitization, etc. As the RRI Tools initiative explains, “Involving stakeholders and the public in the process of research and innovation helps to ensure that the results match the values, needs, and expectations of society” (RRI Tools, 2016). For the European Commission, in the context of *Science With and For Society* (Swafs) (Ec.europa.eu. 2020), the benefits of involving the broadest possible range of actors in research and innovation, includes the uptake of new and alternative forms of knowledge, as well as the consideration of a broader range of societal needs and perspectives, all of which are key towards helping tackle the complex and interconnected societal challenges that lie ahead. The approach of public engagement contributes to enhancing creativity in research and innovation, increases the likelihood that research and innovation are societally relevant and provides a breeding ground to foster a more scientifically literate society and empowered citizens.

Public Engagement can be needed to survey public opinion on a particular science project or a new technology, to assess a new technological application, to help researchers gather data for a given project or to get the public and experts to co-create knowledge or co-produce innovation. The Horizon2020 European Research Framework Programme, (Engage2020) is a EU funded project that looked into how members of society are involved in science and science policy, and how they can be involved in the future. Their core objective was to increase the use of PE, helping researchers to engage citizens, users or stakeholders in their work. To do so, they have developed tools for the application of PE, and analysed all aspects of the relationship between Research and Innovation and society.

The project identified three categories of motives and achievements of public engagement (Engage2020, 2014):

- **Functional motives** are directed towards better results and better research. They include R&I targeted towards societal needs, such as the approach of the European Union in funding the Horizon2020 programme, more effective R&I processes, and social acceptance of R&I outcomes.
- **Political motives** are related to the legitimation of R&I, the empowerment of civil society organisations (CSOs), and public accountability and responsiveness.
- **Cultural motives** are profoundly democratic and inclusive and are centered around a new view of the relationship between science and society. In this framing, people are not considered to be outside of science, but rather they are co-creators of science, which leads to a new mode of public understanding of science, more equitable than the usual top-down approach.

2.3 How to include Public Engagement?

The recommendations of the European Commission on how to implement public engagement in Horizon 2020 are centered around three key areas (European Commission, 2020c). The first one oriented towards **building participatory Research and Innovation (R&I) actions**. These actions should ideally be part of the design from the earliest stages of the research, and they should be an on-going process that contributes to a continuous revision of the goals and outcomes. Projects are also expected to provide inputs **to influence the EU R&I policy agenda** by planning initiatives that involve public engagement both virtual and face-to-face. Such initiatives have to include a high level of commitment and legitimized integration into the Horizon 2020 existing strategy. Finally, a major aim of R&I policy is to provide knowledge and evidence to **support the design and implementation** of thematic policies in relation to the societal challenges identified by the Horizon2020 framework such as demographic changes, food security, clean and efficient energy, health, climate action, etc. (European Commission. 2020d).

2.3.1 Self-assessment and development of Public Engagement activities

A few preliminary questions can be useful in the development of Public Engagement activities, as a self-reflecting tool. Answering these questions can help redefine and limit the scope of the PE project, as well as to consider some aspects that can be overlooked.

- **Why do you want to engage people with your research?**

The levels of interaction and influence of civil society can range between discussing topics, consulting for a particular problem or approach, involving them in a more committed way, collaborating with different stakeholders, empowering the public, or even make them part of a direct decision approach.

The purposes and objectives should be clear from the beginning and it is important to try to start as early as possible to include public engagement in the research process. The tools and methods must be appropriate to the objectives. There is a wide range of methodologies available, suitable for all the different criteria, but there must be a rationale behind choosing each one.

- **Whom do you want to engage? Who are the stakeholders that can be affected by the research or that can be interested in its outcomes?**

For this issue, it can be useful to look at the analysis undertaken in the dissemination and communication outline (WP9 D9.1) where target groups and communication goals have been gathered and classified. A stakeholder-mapping[2] tool can also be a valuable resource to apply to each context to start the reflection process. It is important to try to cover as many perspectives as possible from the different actors involved in the process, but the participants should be realistically informed of how much they will be able to influence outcomes.

- **How might you engage them?**

  From workshops to public forums, there are tools available depending on the degree of public engagement, the number of stakeholders involved or the online vs. face-to-face format. There are tools that can help navigate through the wide range of different

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[2] Stakeholder mapping is a tool for the visual representation of a stakeholder analysis, to organize the relevant actors according to the key criteria by which they are relevant to the project.

options depending on the details of each project[3]. If the different stakeholders do not have experience in public engagement activities, there are resources and training[4] that can help to build their capacity to enable effective participation.

As a framework, irrespective of the tools chosen, it is important to foster a culture of openness, transparency and participation. It is also relevant to dedicate enough resources in terms of time, skills and funding.

- **Has it worked?**

A list of solid indicators[5] and process evaluators should be decided beforehand to be able to evaluate the results of the activities chosen, and evaluation should be built into every stage of the process.

2.3.2 Key actors in Public engagement

Every initiative will have to consider the different stakeholders involved, but this is a brief non-exhaustive list of relevant actors and how PE can benefit them:

- **Policy makers:** Public engagement can increase the legitimacy of decisions on R&I policies, helping bring them closer to society.
- **Research community:** Through engaging citizens in research practices, the results and processes of R&I can be more suited to meet society expectations and needs.
- **Education community:** Empowering young students and lifelong learners to engage in R&I and R&I decision-making is key for RRI success.
- **Citizens:** There can be different types of citizen actors, depending on the degree of involvement with the issue, such as regular **citizens**, **affected** citizens such as patients and healthy volunteers participating in research, **consumers**, **employees**, **users**, etc.
- **Business and industry:** Engaging stakeholders in the implementation of responsibility measures in their products and industrial processes.

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[3] See section “2.3.3. Methods and tools” in this document

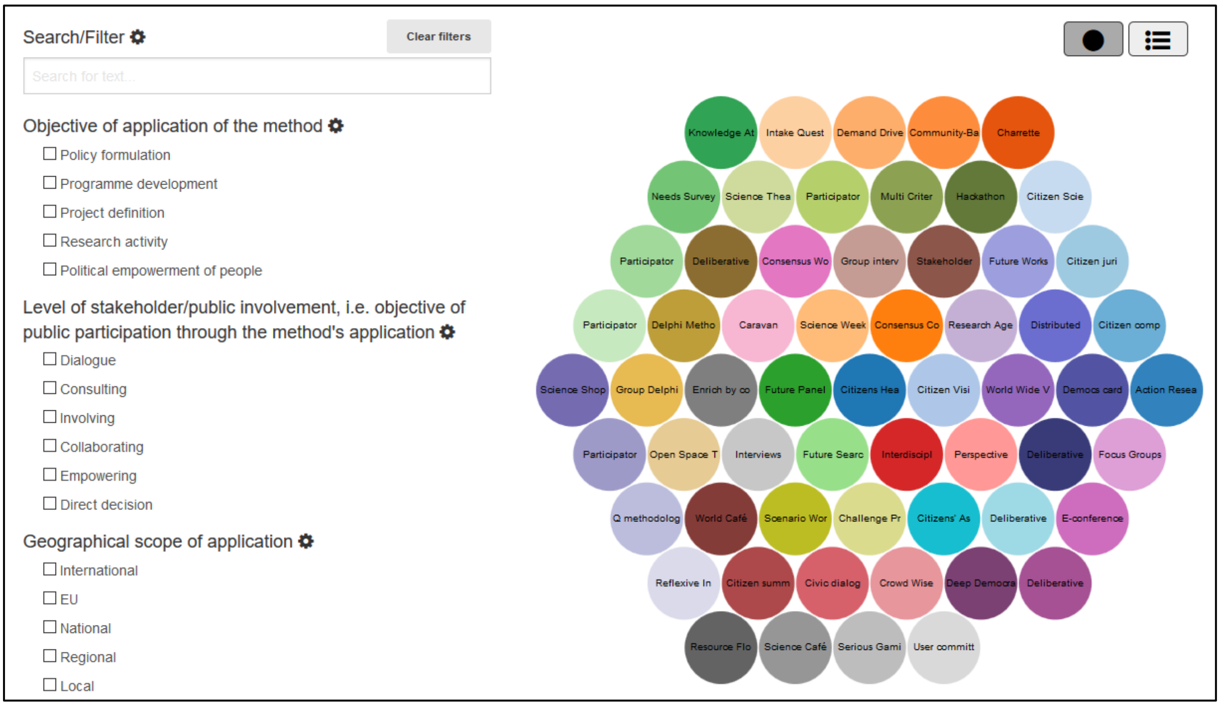
[4] See Bibliography, Public engagement manuals

[5] Good indicators are SMART: Specific, Measurable, Achievable, Relevant and Timely.

- **Civil Society Organisations** (CSOs)**:** It is necessary to engage CSOs to increase the democratic and public accountability aspects of R&I, and to introduce society’s voices in the research processes. Here patients associations could be represented.

2.3.3 Tools and Methods

The EU Research project RRI tools lists in its official website[6] useful resources and materials available for all actors to put public engagement into practice. Amongst them, one of the most prominent examples is the “Action Catalogue”[7] by Engage 2020. This resource is one of the most comprehensive, detail-oriented and practical tools to approach this challenge. Aligned with their main objectives to support the development of public engagement in Horizon2020, Engage2020 have mapped what is practiced in this key area of the RRI, spreading awareness of the opportunities of the different tools and methods. The result is “The Action Catalogue”, a decision support tool to find the method best suited to the specific needs of each project.


Search/Filter

Objective of application of the method
☐ Policy formulation
☐ Programme development
☐ Project definition
☐ Research activity
☐ Political empowerment of people

Level of stakeholder/public involvement, i.e. objective of public participation through the method's application
☐ Dialogue
☐ Consulting
☐ Involving
☐ Collaborating
☐ Empowering
☐ Direct decision

Geographical scope of application
☐ International
☐ EU
☐ National
☐ Regional
☐ Local

Figure 1 - Action Catalogue by Engage 2020 - http://actioncatalogue.eu/search

This catalogue consists of a searchable database of 57 different methods for public

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[6] Rri-tools.eu. 2020. Resources - RRI Tools. [online] Available at: <https://www.rri-tools.eu/training/resources> [Accessed 11 March 2020].

[7] Actioncatalogue.eu. 2020. [online] Available at: <http://actioncatalogue.eu> [Accessed 11 March 2020].

engagement. All the different tools and methods are classified by different criteria, with the possibility of weighing the relevance of each one according to the needs of the project. After selecting each of the appropriate filters, the Action Catalogue presents the different options available. Each activity or tool is then explained in detail, including the logistics involved, the requirements for its application, as well as concrete examples of its use. Selecting these filters and evaluating their importance also becomes a self-reflection process, extremely useful to consider the various aspects and implications of public engagement.

Some of the most relevant criteria used by Engage 2020 to classify the public engagement methods and tools are, the **objective of application** of the method or tool, the **participants** involved, and the level of **public involvement** of the societal group chosen:

A) The objective of application of the method can be **policy formation, programme development**, **project definition**, **R&I activities**, or the **political empowerment of people**.

B) The **participants** involved can be any of the key actors of PE mentioned previously, such as: CSO's, policymakers, researchers, citizens, affected, consumers, employees, users, or the industry.

C) When it comes to selecting the **level of PE**, the roles of the stakeholders or relevant actors, can be classified according to the degree of process control they possess:

Figure 2 Public Engagement by level of interaction – Engage 2020

- **Dialogue and discussion** aim to improve the “two-way” communication between scientists, policy makers and citizens to ensure a regular exchange of views.

- **Consulting** has the objective to obtain public feedback for decision-makers on analysis, alternatives and/or decisions.

- **Involving** aims to work directly with the public throughout the engagement process to ensure that public concerns and aspirations are consistently understood and considered in decision making processes.

- **Collaborating** implies partnering with the public in each aspect of the decision including development of alternatives and identification of the preferred solution.

- **Empowering** happens when the involved participants acquire certain skills/knowledge in the process of engagement.

- **Direct decision** takes place when final decision-making is in the hands of the public.

3 Design MICROB-PREDICT along the needs of patients

There is a lack of consensus on both the terminology and the definition of public engagement when it comes to design clinical research along the needs of patients (Duffett, 2017) (Carman, Dardess, Maurerm, & Sofaer, 2013). For instance, some of the terms used in different guidelines are Patient and/or Public Involvement, by the National Health Service in the UK(Staley, 2009), or Patient-Centered research used by the Patient-Centered Outcomes Research Institute in the US (Forsythe, Heckert, Margolis, Schrandt, & Frank, 2018). No matter which terminology is used, these terms have approximately the same meaning as per the definition of Public engagement in research by the European Commission: a two-way process that aims to the co-production of knowledge at a diverse degree of commitment and engagement between the public and the researchers (Ec.europa.eu, 2020).

3.1 When to involve patients in clinical research

There are some evidences that involving people at the early stages of a research process increases the sense of ownership of the research (Dudley et al., 2015), which can lead to, for example, higher response rates to questionnaires and thus better quality of the trial data (INVOLVE, 2012)(Sacristán et al., 2016). But patient engagement in research can be implemented in all stages of the research (Duffett, 2017) such as:

- **Pre-conception:** Identifying research gaps, priority setting and funding decisions according to the needs of certain stakeholder groups.
- **Study design:** Pragmatic inclusion criteria, participant access to trials, Informed consent and trial information, selection of interventions, comparators, and outcomes which are relevant for patients.
- **Study conduct:** Improved recruitment, reducing barriers to participation, data collection, or monitoring study compliance.
- **Analysis:** Ensuring data integrity and meaningful subgroup analysis.
- **Dissemination:** Knowledge translation to all end-users, implementation of result in clinical practice, peer-reviewing.

3.2 Who to involve

There are many different ways to select patients for involvement in research, from randomised selection so that the sample recruited can represent a bigger community, to selected experienced patients that can share their opinions and insights on an personal level (Duffett, 2017). The selection process will depend on the tools and objectives identified, but the "expert patient" approach is one that has gain acceptance lately and it is commonly used in clinical trials (Carman et al., 2013). This approach takes into account how patients can be an expert in managing their own disease and this can make others to also become decision-makers in the treatment process(Tattersall, 2002).

Patient organisations can also represent patients in trials and help to include their views in the development of the research. The MICROB-PREDICT partner European Liver Patients' Association (ELPA) facilitates dialogue with patients and their families and dissemination to policy makers (Asscat, 2020). ELPA is a representative organization of European patient organizations for liver disease and it has 34 members in 27 countries throughout Europe. ELPA's aim is to promote the interests of people with liver disease and in particular to highlight the size of the problem, to promote awareness and prevention, to address the low profile of liver disease as compared to other areas of medicine such as heart disease, to share the experience of successful initiatives and to work with professional bodies such as EASL and with the EU to ensure that treatment and care are harmonized across Europe to the highest standards. ELPA, an active partner of MICROB-PREDICT, will participate in meetings, act as a consultant and actively participate in WP9 (Dissemination).

Research ethics committees, interdisciplinary bodies to review the methodological, ethical, legal and societal issues of research with humans beings must include in their membership lay persons and patients. This is a legal requirement (European Parliament, 2014) that should be carefully analysed from the ethical perspective to promote fairness in public engagement. Having patients in research ethics committees could be very useful, they avoid the monopoly of the scientific language and prevent the rest to use technical approaches that could not help to see what really matters.

3.3 Impact of patient engagement

Patient involvement in research has shown to have different results, both positive and negative, and it is a process that involves some costs that have to be taken into account before deciding to engage in an activity. Positive results found include "improved relevance of research to patient priorities, significant contributions to trial design (deciding on comparators, outcomes, protocols), improved patient information material and/or informed consent documents, improved clinical trial enrolment and decreased attrition, improved dissemination and/or implementation of research findings, and increased public trust in research" (Duffett, 2017). Patient engagement strategies can also lead to better patient knowledge of their disease and management of it (Tran et al., 2019).

Challenges and negative impacts revolve around two main topics (Staley, 2009). On the one hand, there is an increase in time and resources needed for the development of these activities. On the other hand, there are challenges on how to resolve conflicts that may arise in the process, since it is a relatively new field and there is limited guidance. There is as well some fear of tokenism, which means providing a false appearance of inclusiveness with the aim of complying with funding requisites without including patient inputs.

An assessment of patient engagement in public health and social care research in the UK identified a few areas where this engagement had an impact: research agenda, research design and delivery, research ethics, on the public involved, on researchers, on research participants, on the wider community, on community organisations and on implementation(Staley, 2009). Areas of the development of MICROB-PREDICT where patient engagement and an analysis of patient needs can be an asset and provide valuable information for the different tasks and WP will be presented in the following sections.

3.3.1 Impact of patient engagement on research tools

There is some evidence from prior studies of the impact of involving patients in **developing research tools** such as: leaflets and patient information sheets, as well as for surveys, interviews and focus groups (Staley, 2009). These effects include improved wording on texts and questions to make them appropriate and accessible for people from different educational backgrounds; improved information provided to potential participants; adaptation of the materials to the different cultural backgrounds and local communities or ensuring that the length of a questionnaire is appropriate, and all its questions are relevant. Patient involvement has also helped identify important outcomes for patients that otherwise would have been overlooked (Brett et al., 2010).

Based on this, those areas of MICROB-PREDICT and work papers that involve materials being handed out to patients could benefit from a patient-centered approach, such as:

- D8.2 Information and Informed Consent template for participation
- D8.4 Codes of conduct and research integrity policy including publication in journal
- D8.7 Checklist for participants to assure informed consent / other mechanisms for those unable to give a written consent.
- D9.2 Project website content
- D9.4 and D9.7 First and second patient and layman event
- D9.6 Brochure to inform in brief about MICROB-PREDICT for participants involved in the clinical study
- D9.12 Updated clinical practice guideline on cirrhosis and translation for layman
- M45 Social media presence

3.3.2 Impact of patient engagement on recruitment

Positive impact in research of patient involvement can have the effect of increasing participation rates on research (Domecq et al., 2014)(Weisfeld, English, & Claiborne, 2012). This has been done through improving access to potential participants and the information provided to them, ensuring that the recruitment process is sensitive to the needs of the patients or increasing their confidence in the project and the credibility of the researchers.

The recruitment of participants is an area of MICROB-PREDICT that could benefit from including patients in the process. In this sense for example, the Odense University Hospital already considers on their research strategy: “Patients are the primary stakeholders in health care. The inclusion of patients, relatives, and patient organizations in the research process will encourage a wide collaboration between a range of parties who have an interest in solving a problem or promoting a cause – and can bring resources to the collaborative enterprise. If the research that is undertaken reflects patients’ needs and views on what needs to be researched, the results will be more readily implemented into clinical practice. It should also be easier to recruit citizens to participate in research projects.” (OUH, 2016). In the case of MICROB PREDICT the participation of ELPA in the planning and supervision of the project has been and will be crucial (Asscat, 2020).

In the critical implementation risks and mitigation actions, the next detected risks can benefit from this patient engagement strategy:

Risk 13: Slow recruitment of patients to the RCT will delay subsequent analyses (WP7)

- Mitigation measures: “1. competitive recruitment among the centers 10 months after start; 2. up-scaling recruitment through contracting EFCLIF-associated clinical sites (network of >100 large European liver centers).”
- Patient engagement: A patient engagement plan could be used as a complementary risk-mitigation measure since evidence shows that increased enrolment and decreased attrition are common positive impacts from engaging patients in trial development.

Risk 17: Project results are not incorporated in clinical practice guidelines or accepted by insurance companies or policy makers. (WP9)

- Mitigation measures: Continuous involvement of various stakeholders via workshops, scientific meetings and events.
- Patient engagement: patient engagement on research has the benefit of improving credibility of study results with stakeholders. Common tools for patient engagement such as focus groups, interviews and surveys can provide information on patient satisfaction with the project development and its results. This information can be a

strong selling point to incorporate the results of MICROB-PREDICT in the practice guidelines.

4 Recommendations

Public engagement in research is a process that requires expertise, flexibility and interdisciplinary approaches. It must involve all the different actors and stakeholders into the design of the intervention and include them in all decision-making processes. Following, there is a set of recommendations based on the analysis and findings of this report:

- From the inception of the research intervention, public engagement and patient involvement should be integrated, both the theoretical framework and the practical approach. In 2020 there is enough evidence, good practices and proposals that have been tested in order to illustrate how to integrate the RRI approach focused on public engagement and governance. This RRI approach should be part of the identity of the project.
- From the theoretical perspective we recommend two European research projects on the issue –Engage2020 and RRI tools- that have been mainly the basis of our research; They provide a corpus and give access to a plethora of resources that could help the consortium to integrate the agendas of RRI. Likewise, choosing this two EU research projects MICROB PREDICT contributes to cross-fertilization between projects.
- The references provided after a review of the literature helped to create this corpus that should be taken by partners as a transversal issue to study, to review and to contribute during the life cycle of the project. We encourage all kind of profiles in the project including those who are only treating data or in the laboratory, without any contact with patients to get used to the RRI approach promoted by the European Commission.
- Only a real interdisciplinary approach to RRI could assure a successful implementation in all stages and with the highest possible impact. To align societal interests and expectations of society needs the participation of all actors in the research and innovation process. But it is necessary tot dedicate time and resources to understand what is RRI and the goals to pursue.

- The first step of this process of integrating RRI and public engagement approach has been the publication of the policy on how MICROB-PREDICT implements responsible research and innovation. It contains measures to take into account regarding governance, ethics, gender equality, public engagement, open access and scientific education.
- MICROB-PREDICT is a research project longer than a regular project. It will last 6 years to combine data coming from different cohorts, a clinical trial and an innovation to be ready direct to consumer. Time and interventions that will allow partners to implement the proposals made here. All actors should put into practice the RRI agenda, and this report could help them to do so, but there are training needs that should be fostered by the different partners involved in different countries and with different backgrounds.
- All partners should be trained in the meaning of RRI and the way to implement this transversal issue that is about governance of the research and innovation process. Capacity building is needed for researchers, physicians, and all profiles involved. Teams with pre and postdoc positions should integrate this training that could follow the suggested resources by the RRI Tools project, available in different languages.
- This training is different from the one that could be offered to patients, relatives, caregivers, etc. that are part of the life of the patients affected. Scientific education agenda of RRI needs to develop specific contents to deliver scientific information to society in a clear and simple language grounded on scientific and technical knowledge. This will help to avoid misconceptions on the research process and its possible outcomes and have an impact on a wider population, no only the patients itself but individuals and groups in close relation to them. The health care system could be benefited of having more literate population on the issue to understand the estate of art of the illness.
- It is important to ensure adequate training and expertise in RRI areas for the professionals involved in this project. Materials and manuals have been provided in the reference section as well as throughout this document. MICROB PREDICT partners could produce new materials following the examples provided and innovate in many different ways. It is desirable to find methodologies to measure the impact of this training materials and know how on RRI of MICROB PREDICT.

- Public engagement of participants in the designing of the clinical trial part of MICROB PREDICT is crucial but is also relevant to promote mechanisms to integrate participants (human subjects in research) to assess and review all stages of the project once the clinical trial has started. This should be discussed with partners to find ways to achieve it and the produce results that could measure the impact of this participation.
- In addition, the participation of lay persons and patients in the development of the agendas in research is also suggested as part of the strategy. It could contribute to set the priorities of biomedical research at European level and at national level. In this sense, cultural and societal traditions shape this process and should be taken into account. MICROB PREDICT research project has a priviledged position because it has a sound scientific and technological knowledge due to the partners involved, including EASL, from bench to bedside; Likewise, it counts with what matters the most, the voice of the patients with ELPA. This combination of actors and stakeholders, is the perfect one to move forward in putting the need of the patients affected by cirrhosis and the population represented in the centre of the project.
- The success depends on the skills of all partners to be able to integrate RRI and public engagement strategy with the proper methodologies. It could be done in many different ways: replicating other experiences or developing a strategy of MICROB PREDICT for public engagement that is at this moment live. Until now there are different actions developing and ongoing to promote public engagement (see www.microbpredict.eu). In this report we highlight dissemination and communication strategies as one the strengths.
- To identify and organize relevant actors and stakeholders included or to be included in MICROB- PREDICT, it would be desirable to develop a stakeholder-mapping tool. As stated above, it is important to try to cover as many perspectives as possible from the different actors involved in the process, but the participants should be realistically informed of how much they will be able to influence outcomes.
- A MICROB-PREDICT self-reflecting tool about public engagement and the implementation of the rest of RRI agendas is recommended. This will need the collaboration of profiles from the project but also with the assessment of external

advisors experienced in the design, implementation and review of RRI self-reflecting tools. This tool can be helpful to future projects.

- All the tools employed to communicate with patients can benefit from a patient-centred approach, whether it's the more obvious choices, such as the information and informed consent policy or the information brochure, to any other guidelines that will result from the MICROB-PREDICT project.
- Research ethics committees are interdisciplinary bodies to review the methodological, ethical, legal and societal issues of research with human beings that must include in their membership lay persons and patients. This is a legal requirement (Regulation on Clinical Trials 2014) that should be carefully analysed from the ethical perspective to promote fairness in developing a public engagement strategy. But it must be taken into account that patient voices, mainly through patients' associations, should not represent the interest of the pharmaceutical or the biotechnology industry. There should be mechanisms to avoid biases, misconceptions and conflict of interests for the patient' representative in the decision-making process. In MICROB PREDICT all clinical partners, but especially ELPA, should assure that the interest of patients affected by the disease under study are truly represented. Spurious interest and conflict of interests should be avoided at any stage. Remember that conflicts of interest could be of different nature: economic, personal, hierarchical, etc. The way MICROB PREDICT public engagement strategy deals with conflicts of interest is closely related to assuring research integrity (see D. 8.4. Codes of conduct and research integrity policy including publications in journals).
- Connected to the previous recommendation, the principles of preserving autonomy of participants in research and the protection of the most vulnerable, transparency and accountability should guide the process of implementing a public engagement strategy. These principles could facilitate that the public engagement strategy developed for the research itself could influence future agendas of research in biomedicine. i.e. basic research, clinical research etc. Ensuring the application of this principles and the respect of research integrity will contribute also to enhance trust in the science and innovation ecosystem.
- Gender perspective is crucial in public engagement. Ensuring women representation is also part of the strategy that could help to rethink standards and models and to

break the rules that are not facilitating to achieve gender equality. It is applicable in all stages and to all actors: researchers and subjects of research, caregivers and relatives. MICROB-PREDICT should prioritize the gender perspective to assure that public engagement strategy represents and integrates all views and all need. In this sense, caregivers are key actors. Women are still focus on the care of those who are ill or the elder of families. Giving up works and other tasks to deliver the needed care should have a voice in the public engagement strategy. Likewise, the early careers researchers and postdoc as well as senior women participating in research and innovation processes should be represented. Thus, the scientific career and the needs of patients should have the gender perspective included. This is also the case of professional caregivers, mainly nurses and social workers, that should be trained and integrate RRI perspective. They are close to the patients and families and on a daily basis could provide reliable and accurate information of the situation of patients from a holistic perspective.

- Following the principle of transparency in research and according to the tendency to open science as opposed to publish or perish, all results from the research process should be available to the public in open access. There are different ways: through the traditional way of publishing via scientific journals and through public registries. In this sense, negative results should be available. There is a crisis of reproducibility that is not helping the scientific community to foster trust in their contributions. MICROB-PREDICT partners advocate for open data in connection to open science.
- Putting the patient in research in the centre to promote a public engagement strategy in the field of open access, also means to give access to the life cycle of research to society. This means giving open access to research data. Institutions should have the organizational and technical measures, facilities and human resources to store data and treat data properly (Data repositories, etc.). In the same line, it should be assured that it is possible for third parties to have access to data (following the FAIR data use principles), to treat data and to reproduce and disseminate it free of charge for any user (data and metadata).
- There should be a clear definition of a patient engagement plan. This engagement plan is a formal written strategy that outlines the guidelines for inclusion of patients in the research process. It should indicate the level of involvement of the patients on

the research, the level of contribution, aspects of the research that cannot be changed, the time commitments and the budget for these activities. It should also include a methodology to evaluate the impact of the patient involvement that takes into consideration both qualitative and quantitative aspects of the process. It could be a good opportunity for MICROB-PREDICT project to start integrating this RRI approach in the information process and informed consent forms. In an indirect way, irrespective of the possible measurements that can be done to analyse the impact, it could help to sensitize the actors involved in the research process and contribute to create a culture for the respect of RRI and public engagement.

- An interdisciplinary committee for the governance of MICROB PREDICT can be created to check, assess, and review all the implementation of the public engagement strategy as well as the RRI agendas across all interventions. The composition, functions and procedures of this Governance Committee shall be discussed and agreed by all partners, following the example of similar committees (see RRI Tools i.e). The Governance Committee could develop the guidelines for a research agenda for patients affected of cirrhosis and acute on chronic liver failure. The Committee will be in charge of developing deliberative methodologies to achieve the pursued goals and to promote workshops and actions to foster RRI and public engagement (See examples of Living Labs at RRI Tools i.e.). The MICROB PREDICT Governance Committee will participate in the review process of the clinical trial to be developed in MICROB PREDICT and to the research based on integration and exploitation of data from previous research protocols.

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