DECISION

DEcompensated CIrrhoSIs: identification of new cOmbiNatorial therapies based on systems approaches

H2020 – 847949

D6.3 Public engagement strategy to design DECISION along with the need of patients

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Abbreviations

ACLF	Acute-on-chronic liver failure
AD	Acute decompensation
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
PCORI	Patient-Centered Outcomes Research Institute
PE	Public Engagement
PPI	Patient and public involvement
R&I	Research and Innovation
RRI	Responsible Research and Innovation

Executive Summary

The goal of this policy is to provide a framework of public engagement in research in DECISION to align this project with the Responsible Research and Innovation (RRI) framework. The first part develops public engagement as a tool to involve any of the possible stakeholders, whether they are patients, general public, policy makers or business and industry. It develops the RRI initiative in the context of Horizon2020 and provides practical tools and resources to help in its implementation.

The second part narrows down the public engagement strategy to include patients as the key stakeholder in the clinical trial. It covers benefits and challenges of patient inclusion in research and evidence of the areas that benefit from a patient approach, as well as references for resources and best practices. The third part is an analysis of the DECISION project regarding the role of patients, what is already being done and areas that can benefit from a deeper inclusion of patient voices. Finally, the fourth part sums up the recommendations provided in this document regarding each of the areas analysed.

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1 Public Engagement in the Responsible Research and Innovation framework

1.1 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, 2016b)[1]. It is *"the ongoing process of aligning research and innovation to societal values, needs and expectations"* (Gerber et al., 2020).

In this framework, scientific inquiry is a process not limited to the perspective of the researchers. Societal actors such as citizens, policymakers, business or third sector organizations can and should be involved during the whole research and innovation process. Implementing the RRI framework 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 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 consider 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.

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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

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.

RRI also has to be evaluated as part of the research process and there are resources and indicators for monitoring its development, that can be useful tools for all the stakeholders involved (Strand, Spaapen, Bauer, Hogan, & Revuelta, 2015).

In 2019, leading RRI researchers, practitioners, policymakers and stakeholder organisations, discussed the state-of-the-art and future perspectives for RRI, resulting into a joint declaration that urges the European Union to make RRI a key objective in the Horizon Europe programme. This joint declaration focused on how to implement RRI as a high-quality process and not a mere formality. To this end, they proposed that correct inclusion of RRI must be specific and wisely operationalized, interdisciplinary, treated as part of research, and without fragmenting the RRI agendas(Gerber et al., 2020).

1.2 The RRI agendas

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 through 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 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 are principles of research and innovation (RRI Tools, 2016a). To help applicants make sure that the proposals are ethically aligned with the European values, the European Commission offers guidance documents 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 considered.

Ethics in RRI is further divided into three main areas: Ethical research, research integrity, and societal acceptability (Casado González, Patrao Neves, de Lecuona, Carvalho, & Araújo, 2016). Ethical research conduct refers to 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 goals of the research, and this should correspond to actual social needs and reflect the basic values of society.

Gender Equality To integrate the gender dimension in research and innovation content means considering 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, 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. 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.

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.

1.3 Public Engagement

Public engagement is society's involvement, influence and initiative in research and innovation, 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, NGOs, etc.) in the Research and Innovation processes.

- **Anticipatory**: Researchers and innovators are asked to include new perspectives in R&I 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.

1.3.1 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, 2016a). 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 tackling 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 relevant for society and provides a breeding ground to foster a more scientifically literate society and empowered citizens.

Public Engagement (PE) is necessary to survey public opinion on a 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. In the Horizon2020 European Research Framework Programme, Engage2020 is an EU-funded project that looked into how members of society are involved in science and science policy, and how they can be further 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 Research and Innovation (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.

1.3.2 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, **consumers**, **employees**, **users**, etc.
- **Business and industry:** Engaging stakeholders in the implementation of responsibility measures in their products and industrial processes.
- **Civil Society Organisations:** 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.

1.4 Tools, references

1.4.1 RRI Tools

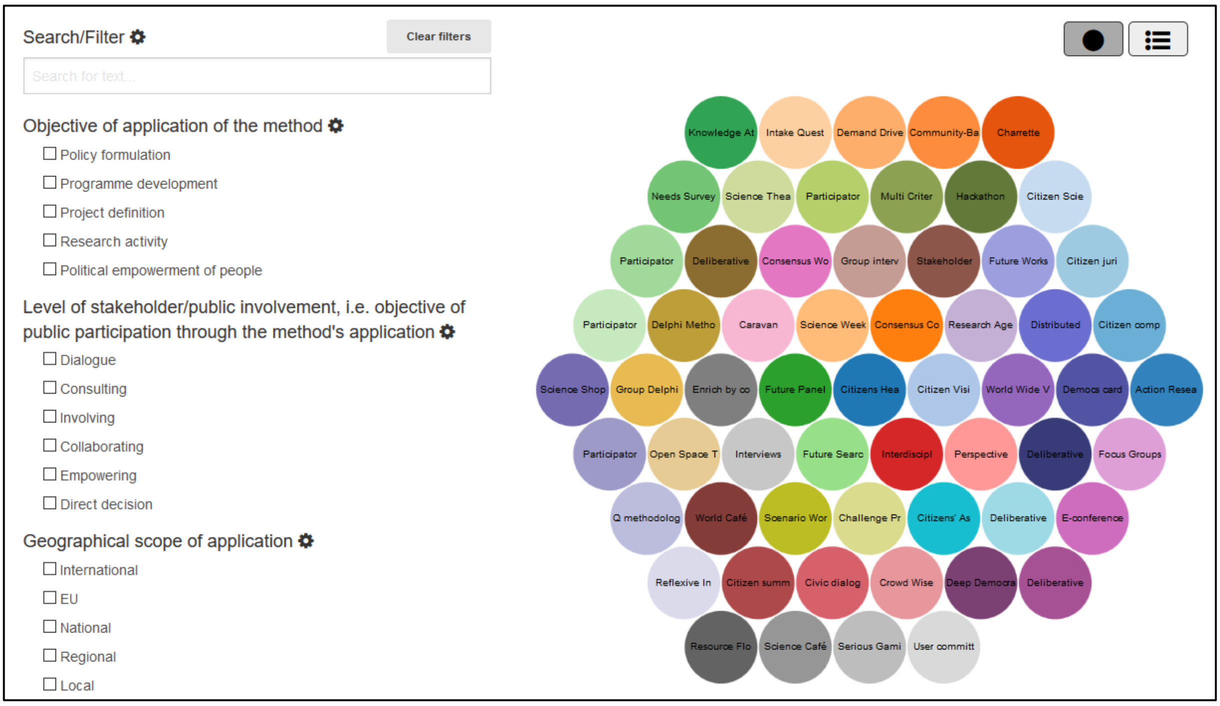
RRI Tools was a three-year long EU Research project to foster Responsible Research and Innovation (RRI) in Europe with a view to a harmonious and efficient relationship between science and European society. Coordinated by "La Caixa" Foundation in Barcelona, this project had a budget of 7 million Euros and counted on the collaboration of 26 institutions reaching 30 countries all over Europe. It developed an innovative and creative set of tools comprising practical digital resources and actions aimed at raising awareness, training, disseminating and implementing RRI.

Their website lists useful resources and materials available for all actors to put public engagement into practice (RRI Tools, 2016b); From practical guides and toolkits to materials for workshops and exhibitions, training modules to increase knowledge and expertise, prepared presentations and detailed explanations of how to implement all the agendas of RRI. It is an extremely valuable source for every stakeholder, from researchers to civil society.

1.4.2 Action Catalogue

One of the most prominent examples of resources available is the "Action Catalogue"(Engage2020, 2020) by the previously mentioned European project Engage2020. This resource is one of the most comprehensive, detail-oriented and practical tools to approach the challenge of promoting Public Engagement in a project. 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.

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



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 - Actiong Catalogue by Engage 2020 - http://actioncatalogue.eu/search

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.

The search option provided by Engage 2020 in the Action Catalogue selects the most appropriate public engagement methods depending on the objective of application of the method, the participants involved, the level of stakeholder/public involvement, and the degree of public involvement in the project.

The objective of application of the method can range between **policy formation, programme development**, **project definition**, **R&I activities**, or the **political empowerment of people**. P**articipants** involved can be any of the stakeholders of Public Engagements, such as CSO's, policymakers, researchers, citizens, consumers, employees, users, or the industry.

The degree of public engagement (PE) will depend on the degree of process control they possess over the project being developed and can range (from least to most public involvement) between **dialogue and discussion, consulting, involving**, **collaborating**, **empowering** and **direct decision**.

Figure 2 Public Engagement by level of interaction – Engage 2020

2 Patient involvement in research

2.1 Patient and public involvement

There is still a lack of clear consensus on both the terminology and the definition of patient engagement when it comes to design clinical research along the needs of patients (Duffett, 2017)(Carman, Dardess, Maurerm, & Sofaer, 2013). Patient engagement can also be referred to as patient participation, public engagement, client engagement, community engagement, public participation, patient participation or public involvement (Vat et al., 2020).

Some of the different terms are used in reference guidelines such as *Patient and/or Public Involvement(PPI)*, by the National Health Service in the UK (Staley, 2009), or *Patient-Centered research* used by the Patient-Centered Outcomes Research Institute (PCORI) in the US (Forsythe, Heckert, Margolis, Schrandt, & Frank, 2018).

For the PARADIGM group (Patients active in research and dialogues for an improved generation of medicines) patient engagement means “The effective and active collaboration of patients, patient advocates, patient representatives and/or carers in the processes and decisions within the medicines lifecycle, along with all other relevant stakeholders when appropriate.” (PARADIGM).

Patient Engagement and public involvement (PPI) are the most used in the literature and oftentimes, used interchangeably. PPI in research means a type of research that “is "co-produced" with patients, caregivers, or members of the public” (BMJ, 2019). This co-production is not limited to just participating in research or answering surveys about the involvement in a clinical trial, it also can mean helping to set research priorities, defining research questions and outcome measures. There are also roles in providing input into study design and conduct, dissemination, or results and evaluation.

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 at the co-production of knowledge by a diverse degree of commitment and engagement between the public and the researchers (Ec.europa.eu, 2020). To avoid confusing Public Engagement (the involvement of all stakeholders in research), with Patient Engagement (addressed to the inclusion of patients in the research process), we will be using Patient and public involvement.

There are many reasons put forward for the patient and public involvement in research. The NHS, in their initiative to support public involvement in health and research (Roberts, Turner, George', & Ward, 2012) mentions not only the benefits for research quality and relevance of research results, but also "*broader democratic principles of citizenship, accountability and transparency*". In the case of publicly funded research, the citizens who are affected by it have a right to have a say and be involved, for transparency and empowerment. There is also the underlying assumption that the unique perspectives of patients and other lay approaches can improve the quality of the projects and the results of clinical trials (Høeg et al., 2019).

PPI is getting more attention and becomes more important every day in the development of clinical research, medicines and technologies, and as a tool to evaluate research quality. For example, since 2018, the British Medical Journal makes it a requirement in all its journals to report how patients have been included in clinical research studies. An editorial of the BMJ outlined their strategy for public involvement (Wicks, Richards, Denegri, & Godlee, 2018), Partnering With Patients:

> "*The BMJ is extending its current requirement to report how patients and the public were included in the design, conduct, and reporting of clinical research studies across its portfolio of journals. In addition, from January 2019 onwards we will require authors of clinical research papers to provide details of how they intend to disseminate results to participants and relevant communities. We have also pledged to work with others to define and enshrine best methods for coproduction of research*."

This initiative was followed by a higher proportion of articles that described patient involvement in their development, and although the number of articles that include it is still low (Price et al., 2018), the role and relevance of patients in research is increasing rapidly.

Evaluation of PPI

Many analysis of the impact of PPI in research have come to the conclusion that it is hard to evaluate the role of patients in the improvements of the research projects (Høeg et al., 2019). There have been some criticisms around the impact of public involvement due to the limitation of empirical data, but some authors argue that quantitative methods are not the most appropriate tool to evaluate a process that is extremely context-dependent (Staley, 2015). The impact of patient involvement will always be unpredictable to a certain degree due to the qualitative aspect of patient inclusion. Nevertheless, recent analysis are improving the indicators used to evaluate the different contributions of PI (Vat et al., 2020) and the number of experiences is increasing, creating collective knowledge and expertise (Birch et al., 2020) that can be used to evaluate the impact of PPI.

Patient involvement in research is a qualitative process that must be tailored to the specific context of each initiative. It doesn’t exist a single framework that can be universally applied, nor it is possible to copy a successful experience from one project without a careful analysis of the transferability of it. A recent systematic review of the frameworks for supporting patient and public involvement found more than 65 different frameworks, with “*different provenances, intended purposes and their own strengths and limitations*” (Greenhalgh et al., 2019).

Vulnerable populations and best practices

There is a dilemma between the inherent inclusion aspect of public engagement, and the probable selection bias that projects are going to face. The patients who have a more active participation, can also be the ones with higher levels of education and knowledge about health and research. INVOLVE, the UK initiative for patient involvement in research, (INVOLVE, 2012b), calls for diversity and inclusion of the most vulnerable groups with the rationale of an equality framework. But precisely due to their vulnerabilities the people in these groups might not be able to bear the work required to be included (Høeg et al., 2019).

This must be considered by the people interested in increasing patient engagement in research. Knowing best practice activities developed in other projects can be a useful tool. For instance, the systematic review by Harrison et al. identified principles and best practice activities, creating a framework for supporting patient stakeholder engagement in research (figure 3) (Harrison et al., 2019).

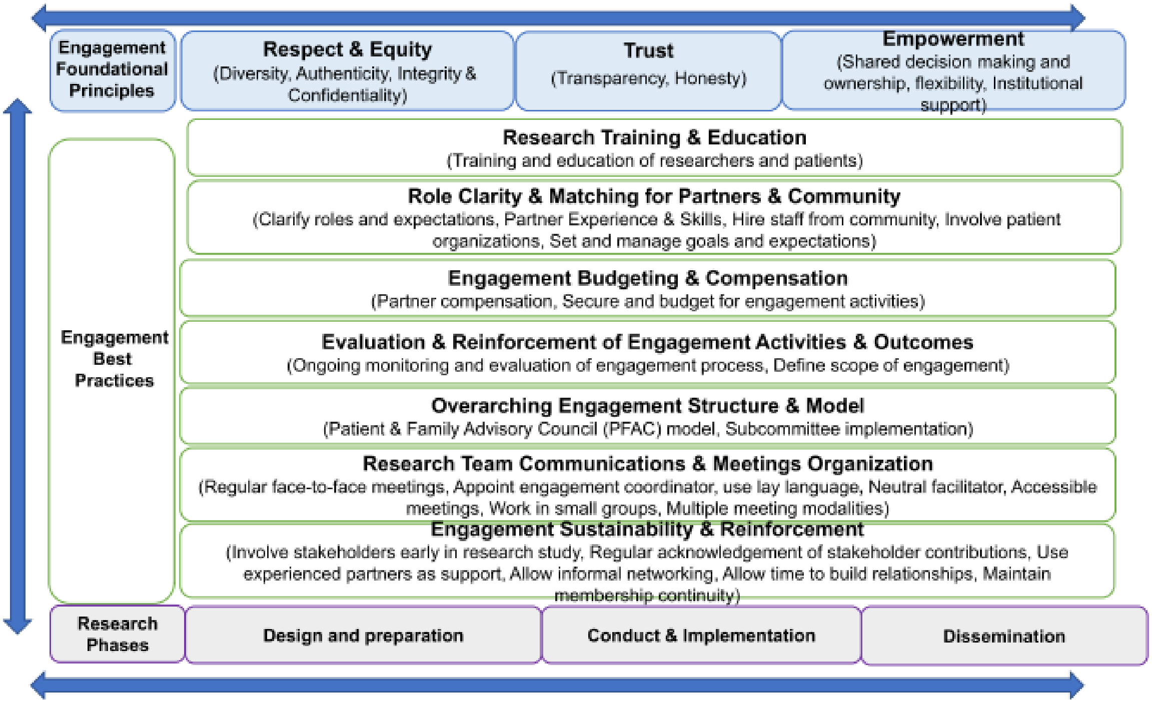


Figure 3 Foundational framework summarizing principles and best practice activities supporting patient stakeholder engagement in research (Harrison et al, 2019)

In their literature review of patient engagement projects, they found that the most common practices were the training and education of researchers and patients, bidirectional communication, the compensation and reimbursement of out-of-pocket expenses, the selection of patient partners based on their skills and interests and the clarification of the roles of stakeholders. Regarding foundational elements they found that respect, equitable power and trust were the most common ones.

2.2 Benefits and challenges of PPI

A literature review on how to evaluate the return on patient engagement initiatives funded by PARADIGM[2], found a total of 18 benefits and 5 costs of patient engagement, along with 28 indicators that can be used for their evaluation (Vat et al., 2020). The benefits were classified in three areas: research priority setting, design of clinical trials and regulatory processes, and health technology assessment (HTA).

Within the **research priority** setting, they identified benefits related to topic generation and prioritization process, such as more relevant research topics and priorities that were selected based on patients' needs, or more relevant research questions, hypothesis, interventions and medical technologies for patients; societal benefits such as more appropriate resource allocation, and funding benefits like improved fundability and credibility of research proposals.

Regarding the **design of clinical trials**, they reported ethical benefits such as more appropriate, inclusive and sensitive research designs. They also found methodological benefits such as more appropriate wording and timing of research instruments and interventions, increased readability and accessibility of research materials, and more relevant research outcomes and endpoints (Brett et al., 2010).

The inclusion of patients had also benefits regarding the **study quality**, amongst them an improved recruitment and retention of human subjects, increased diversity of study participants, improved trial experience/satisfaction by study participants, more adherence to the research protocol and faster study completion. Other studies tried to evaluate the impact of PPI on trial enrolment and retention rates and found that it varied widely between studies, with modest but significant increases in the odds of participant enrolment, but less clear evidence on retention rates (Crocker et al., 2018).

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[2] PARADIGM is a public-private partnership co-led by the European Patients' Forum and the European Federation of Pharmaceutical Industries and Associations (EFPIA) that receives "funding from the Innovative Medicines Initiative Joint Undertaking 2. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA"

Patient engagement in regulatory and Health Technology Assessments brought instrumental benefits such as higher accuracy in measuring needs and preferences of patients or improvement of time for approval and response of regulators and HTA bodies. In the development of HTA, there was evidence of an improvement in knowledge and public awareness of products, and democratic accountability and transparency effects.

From the patients' point of view, engagement initiatives have the potential of empowerment and enhanced well-being in the context of a trial. It can also be a learning opportunity not only about their own condition and treatment(Tran et al., 2019), but about the development of research and the skills needed to participate. Research participants have better access to information on all aspects of the disease and the treatment, and engaging in research can be a positive experience for them (Pushparajah, 2018).

Additionally, patient involvement has been specifically recommended by Vale et al., as it can improve the trial experience for other participants in cases where trials are assessing new therapies or processes (Vale et al., 2018).

Challenges and costs of patient engagement in research

Challenges from the researchers' point of view 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. The process of public engagement in research is perceived as time-consuming and requiring of extra resources (Hoffmann, Schou, Piil, & Jarden, 2019), which can put a strain in the usually limited research possibilities (Blackburn et al., 2018). Some recommendations include scheduling appropriate time for meetings and planning or logistics, as well as including extra costs from early stages of research planning for care and comfort (support, rest, food) and extra time and PPI expenditures.

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, there is limited guidance. Patient participation can involve methodological concerns (Blackburn et al., 2018), as well as power struggles when working with patients and advocacy groups(Brett et al., 2014). In addition, there is some fear of tokenism(Hahn et al., 2017), the effect of providing a false appearance of inclusiveness with the aim of complying with funding requisites, without genuine inclusion of patient inputs.

There are methodological limitations such as the patient skill level for engaging in the research process. In some studies,(Hoffmann et al., 2019) patients have been found it difficult to maintain focus on research purpose and understanding medical jargon. The recommendations to overcome these challenges revolve around building participant skills (both the patients and researchers). This can be achieved by formal training or ensuring support from researchers.

As another challenge there is also the possibility of underrepresentation of certain groups such as ethnic minorities, gender, age, socioeconomically disadvantaged groups, less involved patients or patients with advanced and aggressive illnesses. Some suggestions in this area are being aware of the possible underrepresentation of such groups, and to consider sampling to achieve diversity.

2.3 When to include PPI

There is some evidence 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, 2012a)(Sacristán et al., 2016). But patient engagement in research can be implemented in all stages of the research (Duffett, 2017) (Hoffmann et al., 2019) such as:

- **Development of research focus:** Research definition and prioritization, identifying research gaps, funding decisions according to the needs of stakeholders.
- **Development of research design:** Pragmatic inclusion criteria, participant access to trials, development of research tools, informed consent and trial information. Selection of interventions, comparators, and outcomes which are relevant for patients.

- **Study conduct:** recruitment, reducing barriers to participation, data collection, or monitoring study compliance.
- **Data generation and processing:** Participation in data generation, ensuring data integrity, participation in data analysis and meaningful subgroup analysis.
- **Research dissemination:** Knowledge translation to all end-users, development of dissemination strategies, dissemination of research as co-authors or presenters, implementation of result in clinical practice, peer-reviewing.

Patient engagement organisms such as INVOLVE[3] (INVOLVE, 2012a), SPOR[4] (Abelson, 2015) and PCORI[5] (Sheridan, Schrandt, Forsythe, Hilliard, & Paez, 2017) also recommend the inclusion of patient's voices in the early stages of research and it is considered to be best practice (Price et al., 2018). Qualitative analysis on the impact of PPI in research in clinical trials have found that the opportunity for PPI to make a difference in the development of clinical trials is influenced by the goals and plans for PPI made by the researchers and the quality of the relationship between the research team and the contributors, developed and planned at the early stages of the trial (Dudley et al., 2015).

3 DECISION strategy

3.1 Patient voices/Representatives

There are many different ways to select patients for involvement in research, from randomised selection, allowing the recruited sample to represent a bigger community, up to selected experienced patients that can share their opinions and insights on a personal level (Duffett, 2017). The selection process will depend on the tools and objectives identified; For instance, the "expert patient" approach has gained wide acceptance lately and is commonly

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[3] INVOLVE is a national advisory group that supports greater public involvement in NHS, public health and social care research.

[4] SPOR Strategy for Patient-Oriented Research by the Canada Institutes of Health Research

[5] The Patient-Centered Outcomes Research Institute is a United States-based non-profit institute created through the 2010 Patient Protection and Affordable Care Act.

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 encourage others to also become decision-makers in the treatment process (Tattersall, 2002).

Research ethics committees, interdisciplinary bodies to review the methodological, ethical, legal and societal issues of research with human 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.

Patient organisations can represent patients in trials and help to include their views in the development of the research. The DECISION 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 all European patient organizations for liver disease and it has 25 members from 22 countries and represents around 80,000 liver patients, their families and volunteers.

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.

The DECISION partners Erasmus University Medical Center (EMC) and the Institut National de la Santé et de la Recherche Médicale (INSERM) take also into account patient’s voices.

In 2003, INSERM created the *Think tank network with patient organizations (GRAM*), a unit to coordinate joint action programs between INSERM and over 500 support groups for patients, disabled people, and their families, to provide opportunities for dialogue and suggestions (INSERM, 2003).

The EMC implements patient involvement through the Patient Council. It represents the interests of patients and is one of the advisory bodies to the Executive Board, which is required to seek the Patient Council's opinion on certain subjects. The Patient Council also seeks to represent several common patient interests that involve quality aspects of care that have a direct bearing on patients' sense of well-being and the way in which they experience their stay. The objective of The Patient Council is to raise awareness of "how important it is to take account of patients' interests and encourages patient involvement in policy-making"(Erasmus MC, 2020).

3.2 Stakeholder Analysis

At the beginning of the project, ELPA and Concentris will perform a stakeholder analysis aiming to identify stakeholders and influencers and their connection to and potential interest in the project. Key messages of the project will be defined. For each stakeholder group, the appropriate means of communication will be selected in order to apply the most powerful strategies to convey the key messages. Key messages, stakeholders and communication channels will be laid down in a communication and dissemination plan. ELPA will evaluate on a 6-monthly basis the success of the chosen channels using the most appropriate measurements such as shares, likes, visits to and time spent on the website, etc. (all in conformity with the General Data Protection Rules). Based on the collected data, ELPA will propose strengthening or weakening certain communication channels.

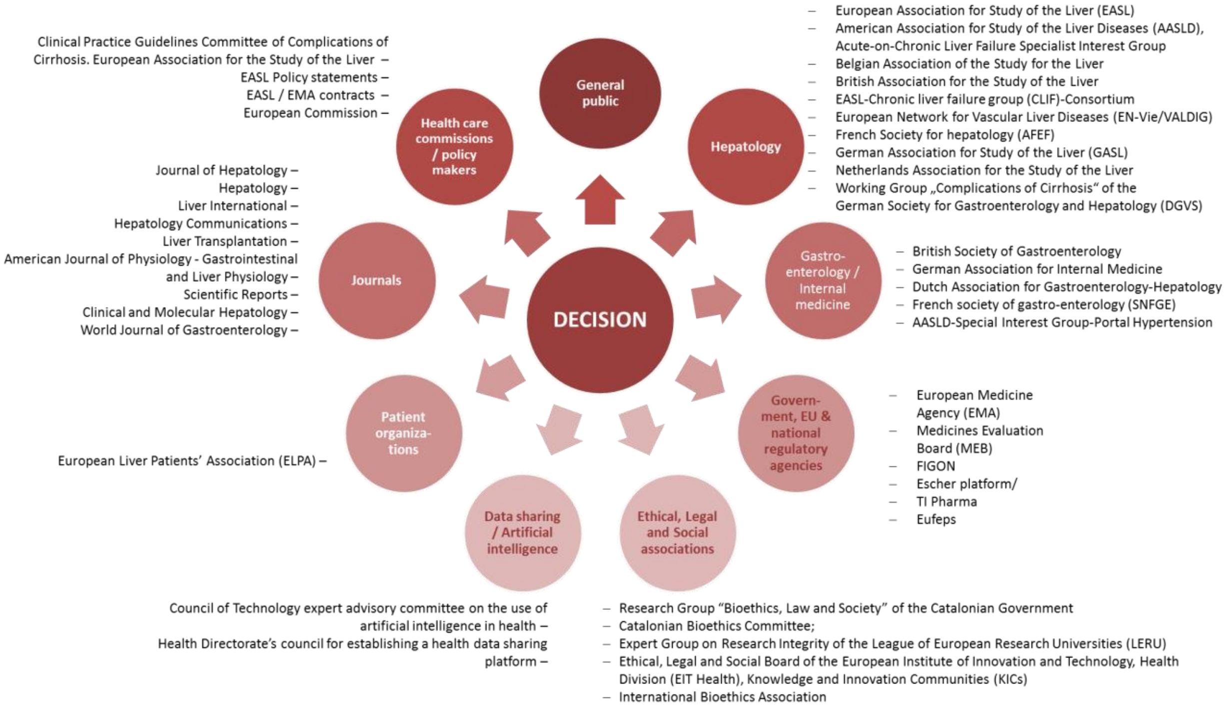

Figure 4 DECISION links into stakeholder groups.

3.3 Areas of DECISION that can benefit from PPI

Studies on the public and patient initiatives have identified numerous activities on how PPI can contribute to clinical trials (Brett et al., 2010)(Staley, 2015) (Bagley et al., 2016) such as:

- *Defining the most relevant research question to ask within a clinical trial;*
- *Identifying the outcomes of importance to be measured within a clinical trial;*
- *Developing a clinical trial protocol appropriate to the needs and lifestyles of the patient community it serves;*
- *Identifying appropriate and ethically acceptable research tools and methods;*
- *Developing clinical trial participant materials, including but not limited to the patient information sheet and consent form, patient diaries and questionnaires;*
- *Conducting the trial in a participant friendly and ethically acceptable way;*
- *Providing a public perspective on the interpretation of trial findings;*

- *Disseminating the results (to both trial participants, the general public and health professionals) to ensure awareness of study findings and adoption of the trial results in clinical practice*
- *Measuring the impact of a trial's findings and informing future trial design*

In the development of the clinical trial, the researchers and partners in charge of it should evaluate which of these potential areas can foster patient's voices and can have room for their input and point of view. There are plenty of resources available from other initiatives and organizations that are dedicated to including patient and public engagement in clinical trials. We are providing a thorough review of the available literature on patient and public engagement strategies in this report. This report aims to be taken by the DECISION partners as a transversal issue to study, to review and to apply during the life cycle of the project.

There are areas within DECISION that are already implementing PPI. For instance, ELPA will be responsible for dissemination and communication of the research results and any other information that can be beneficial for patients and patient communities (WP7). The process of dissemination and communication will involve all ELPA's communication channels and they will actively participate in events that will be organized by DECISION (WP8 Project Management and WP7 Dissemination).

Marko Korenjak is the president of Europen Liver Patients' Association (ELPA), a NGO and DECISION partner, with experience in the dissemination and communication of results of medical research studies in Horizon2020, e.g. in the projects Galaxy, Microb Predict and Liver Hope. He is responsible for organizing and managing dissemination activities of the different information of the project DECISION to patient communities. As such, he has already organized the first DECISION patient event for the 31st of August, 2020. Furthermore, he will be involved at the planning stage of the clinical trial.

Although dissemination tasks are extremely relevant, both Public Engagement in the RRI framework and Patient and Public involvement in research, require a higher degree of involvement and a bidirectional process with the members of the public, not just being seen as participants but as collaborators. Regarding this, it is very fitting to the purposes of PPI that ELPA is actively engaged in the translation of the project results and milestones to promote “patient-friendly” language and to incorporate the patient view during the dissemination process.

3.4 Critical implementation risks and mitigation actions

In the critical implementation risks and mitigation actions, the following foreseen risks (see DoA, Annex 1) can benefit from this patient engagement strategy:

Risk 19: Insufficient or delayed recruitment in WP5.

- Mitigation measures proposed: Competitive recruitment among the centers; and up-scaling recruitment through contracting EFCLIF-associated clinical sites (network of >100 large European liver centers).
- **Additionally, a patient engagement plan** could be used as a complementary risk-mitigation measure since evidence shows that increased enrolment and decreased drop-outs are common positive impacts from engaging patients in trial development.

Risk 22: Project results are not incorporated in clinical practice guidelines or accepted by insurance companies or policy makers. (WP9)

- **Mitigation measures proposed:** Continuous involvement of various stakeholders via workshops, scientific meetings and events.
- **Additional mitigation measure: 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 DECISION 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. From the inception of the research intervention, public engagement and patient involvement should be integrated, both the appropriate 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 DECISION project.

In the following sections, there is a set of recommendations based on the analysis and findings of the present report.

4.1 Public Engagement and Responsible Research and Innovation

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 problem or approach, involving the stakeholders in a more committed way, collaborating with different representatives, empowering the public, or making 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, where target groups and communication goals have been gathered and classified. As part of the dissemination work, ELPA and Concentris are performing a stakeholder analysis in WP7, aiming to identify stakeholders and influencers and their connection to and potential interest in the project. This allows them to select the appropriate means of communication to convey the key messages but it also can be part of a bigger strategy not just centred in the dissemination process. The rest of the partners should take this work into consideration when it comes to plan public engagement activities.

How might you engage them? Tools and resources

- 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 options depending on the details of each project[6]. If the different stakeholders do not have experience in public engagement activities, there are resources and training[7] 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.

- From the theoretical perspective we recommend two European research projects on the issue – Engage2020 and RRI tools - that have been the main basis of our research. They provide a corpus and give access to plenty of resources that could help the consortium to integrate the agendas of RRI. Likewise, by choosing these two EU research projects, DECISION contributes to cross-fertilization between projects.

- RRI requires an interdisciplinary approach to ensure 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.

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[6] See section “1.4. Tools and references” in this document

[7] See Bibliography

Therefore, to achieve this goal it is necessary to dedicate time and resources to understand what is RRI and its objectives.

Training in Responsible Research and Innovation

- All partners should be trained in the RRI framework and how to implement this transversal issue. Capacity building is needed for researchers, physicians, and all the different professionals involved. Teams with pre and postdoc positions should integrate this training that could follow the suggested resources by the RRI Tools project.

- This training is different from the one that could be offered to patients, relatives, caregivers, and other people who are part of the lives 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, not only the patients itself but individuals and groups in close relation to them. The healthcare system could benefit from having a more literate population who understand the state 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 and throughout this document. DECISION partners could also produce new materials following the examples provided and innovate in many ways. It is desirable to find methodologies to measure the impact of these training materials and know-how on RRI of DECISION.

Has it worked?

- The success of public engagement strategies 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 ways: replicating other experiences or developing a strategy of DECISION for public engagement. In this report, we highlight dissemination and communication strategies in areas that already implement patients' voices.

- A list of solid indicators[8] and process evaluators should be decided in advance to be able to evaluate the results of the activities chosen, and evaluation should be built into every stage of the process. Resources have been provided to help choosing the appropriate indicators to monitor the implementation process, and if needed, there can be guidance and help from experts in RRI and other European projects.

Gender equality and open access

- 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 the achievement of gender equality. It is applicable across all stages and actors: researchers and subjects of research, caregivers and relatives. DECISION should prioritize the gender perspective to ensure that public engagement strategy represents and integrates all views and all needs. In this sense, caregivers are key actors. Women are predominantly involved in the care of those who are ill or the elder of families. Likewise, the early career researchers and postdocs 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 daily and could provide reliable and accurate information on 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. DECISION partners advocate for open data in connection to open science.

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

- Putting the patient in research is central to promoting 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 ensured 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).

4.2 Patient engagement in clinical trials

- Patient's engagement in advising on the design of the clinical trial part of DECISION is useful. It is also relevant to promote mechanisms to integrate participants (human subjects in research) to be informed of all stages of the project once the clinical trial has started. This should be discussed with partners to find ways to achieve it and to measure the impact of this participation.

- 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 in 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's involvement that takes into consideration both qualitative and quantitative aspects of the process. It could be a good opportunity for the DECISION project to start integrating this approach in the information process and informed consent forms. In an indirect way, irrespective of the possible measurements that can be done to analyze the impact, it could help to sensitize the actors involved in the research process and contribute to create a culture of respect for RRI and public engagement.

- All the tools employed to communicate with patients can benefit from a patient-centered 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 DECISION project.

- 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 considered. DECISION has a privileged 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 center of the 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 analyzed from the ethical perspective to promote fairness in developing a public engagement strategy. But it must be considered 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 DECISION, all clinical partners and 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.

- 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.

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