Engaging participation of consulting and informing Patient organizations and patients in HARMONY and in HARMONY PLUS Research Projects

Standard Operating Procedure (SOP)

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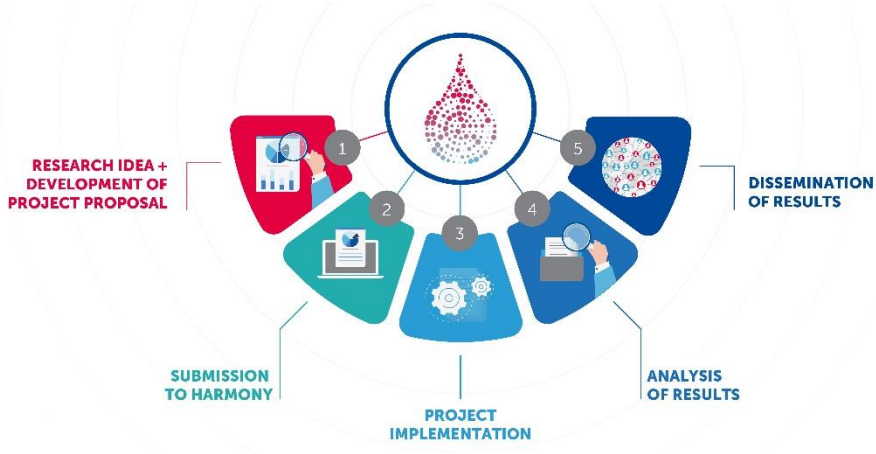

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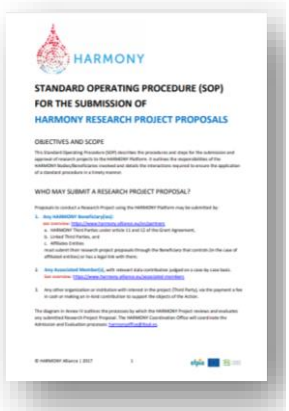
HARMONY

STANDARD OPERATING PROCEDURE (SOP)
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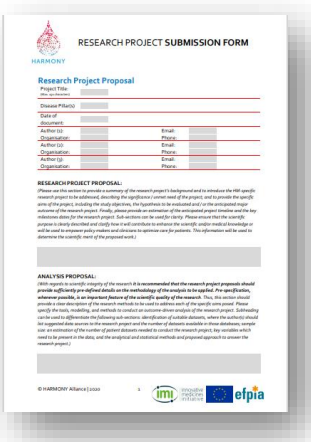

RESEARCH PROJECT SUBMISSION FORM

HARMONY

Research Project Proposal

RESEARCH PROJECT PROPOSAL:

ANALYSIS PROPOSAL:

Engaging participation of consulting and informing Patient organizations and patients in harmony AND HARMONY PLUS research projects

Standard Operating Procedure

1. Introduction

The importance and benefits of patient involvement across the entire health related research and development spectrum are well documented. HARMONY and HARMONY PLUS are based and built on a structure that involves patients consistently in both the project consortium and the work done by it.

It is therefore logical and essentially important that patients and their organisations participating in HARMONY and HARMONY PLUS through the Patient Cluster are granted the possibility to participate in the design, submission, evaluation, interpretation, and dissemination of research projects run on the HARMONY Big Data Platform.

The Standard Operating Procedures (SOP) and Recommendations on Patient Involvement in HARMONY PLUS is a short compendium of rules and procedures to be used in relation to research projects run on the HARMONY Big Data Platform to make sure that the patient perspective is adequately and consistently represented.

The HARMONY PLUS project will follow the same procedure than the one established for the submission of research project proposals in the HARMONY project (116026) regulated in the SOP for the Submission of HARMONY Research Project Proposals (see Annex I). This document concerns the inclusion of patients in the development and submission of research project proposals, and the dissemination of their results.

This Standard Operating Procedure and Recommendations contains a description of the benefits and recommended processes for engaging patients and patient organisations (PO) in biomedical R&D (research and development) projects and processes within the HARMONY and HARMONY PLUS projects.

2. Background

The overarching aim of HARMONY PLUS is to generate, operate and use a pan-European big data platform that integrates disease information and improves understanding on the most effective and efficient means to treat hematologic malignancies (HM). In addition, the project aims to enhance market access to innovative therapies. HARMONY and HARMONY PLUS aim to unite and align stakeholders from clinical, academic, patient, HTA, regulatory, payers, and pharmaceutical fields with regards to the use and relevance of clinical endpoints and standard core outcomes.

The rise of genotype-based therapies, increasing demand for earlier access to innovative therapies, as well as the focus on **outcome-based** research means that early trial designs need to address not only the regulatory hurdles of safety and efficacy but satisfy the demands of healthcare payers and patients' preferences. Hence, to increase market access to innovative treatments, a greater level of forward thinking that anticipates the criteria against which drugs will be evaluated by regulators/HTA/and payer organisations is needed. Links need to be established with HTA and reimbursement agencies at the earliest possible time points in the research and development programmes for these requirements to be met.

To mitigate this issue a common understanding from all stakeholders (clinical, pharmaceutical, academic, regulator, HTA, reimbursement, and patients) as to what is required to enhance the probability of meeting market access requirements in a timely manner is required. The objective of common metrics and core outcomes are to generate harmonised data that could enhance the acceptability of outcomes presented to regulators, HTAs, and payers.

Real world evidence (RWE) can be used to complement randomized controlled trial (RCT) evidence and to confirm the generalisability of RCTs to real life populations. It can also be used for designing more efficient clinical trials, understanding a drug's benefit/risk profile and aid market access by providing information for health economic models, indirect comparative effectiveness data and value demonstration. Whilst regulatory authorities often require the collection of RWD post-authorisation to monitor safety and effectiveness, payers and HTA across Europe have different views on the use of RWE.

The use of real-world data (RWD) faces a number of challenges including data accessibility, timely collection, the investment required to collect the data, dealing with missing data, and any bias within the data including the potential confounding[1] and firm causal conclusions. Generating RWE can be carried out throughout the entire process of clinical development and help to fill in any knowledge gaps for stakeholders. The ideal approach is to keep all the stakeholders in mind from the beginning in order to create evidence that can serve more than one purpose.

HARMONY is a big data project. RWD and clinical trial data, amongst others, forms a proportion of the information within a Big Data platform. To better utilise big data and establish the development of health-based outcomes-focused healthcare systems, the data type, source, and quality are critical to enable outcomes to be pooled effectively. This includes defining, prioritising, and selecting what outcomes and data (biological, clinical, demographic) should be considered and collected. The entire spectrum of research and subsequent care delivery should be considered, starting from the development of innovative medicines and treatments, to market access and adoption, diffusion, and use in healthcare systems by providers and patients.

As a general principle, HARMONY and HARMONY PLUS are implemented with the active and formal inclusion and involvement of patient constituencies through their representative organisations. Nine patient umbrella organisations for the different haematological malignancies participate through a contractual scheme.

Work Package 4 (WP4) of HARMONY PLUS

The work of WP4 of HARMONY PLUS focuses on the following core objectives:

1. To engage key stakeholders, and in particular the patient organizations, by collecting their inputs and supporting long-term implementation of the research projects.
2. To support the decision-making process for access (regulatory and reimbursement) of innovative medicines for HMs by identifying regulatory and HTA consultation mechanisms useful for HARMONY and HARMONY PLUS visibility and recognition and by developing a Proof of Principle project using one of these consultation mechanisms.

[1] A Confounder is an extraneous variable whose presence affects the variables being studied so that the results do not reflect the actual relationship between the variables under study.

WP4 aims to achieve the following specific objectives:

1. The Stakeholders and Patients' Organizations Forum (SPOF) will offer support to WPs, in particular to WP2 for developing a Core Outcomes Set for each new indication of HARMONY PLUS. The support takes the form of consultation of the stakeholders of the HARMONY PHSFF[2], and in particular of the patients' organizations.
2. Streamline the patient organizations (POs) involvement into the research projects developed in WP2 and keep the POs informed about their progress, as well as disseminate results of research projects to POs, in collaboration with WP2 research leads.
3. Development of guidance and decision tools to identify appropriate procedures and resources for regulatory, HTA, payer engagement in Europe with respect to the activities that are being undertaken by the individual projects and studies within HARMONY PLUS.
4. Proof of principle project: Subject to the identification of an appropriate topic in collaboration with WP2 and WP3, deliver an early regulatory/HTA scientific advice procedure on the appropriateness of evidence to be used in regulatory and/or reimbursement submission.

This SOP with Recommendations was created as part of Task 4.2 and aims at making sure that the interaction of patient organisations and other stakeholders involved in HARMONY PLUS is standardised, meaningful and easy to organise.

[2] The HARMONY PHSFF stands for the HARMONY Public Health Stakeholder Feedback Forum. The consultation mechanism is described in detail in the Annex to this SOP.

3. Patient involvement in biomedical research and development

General

Even though patient involvement in medicines research and development is a relatively new concept, a substantial body of evidence on its workings and benefits, and on the different methodologies of public and patient involvement has been generated from approximately 2010 onwards. The methodology described here and developed for HARMONY PLUS is based on these existing and documented experiences.

A key document in this regard is the 'EUPATI Guidance for Patient Involvement in Medicines Research and Development (R&D); Guidance for Pharmaceutical Industry-Led Medicines R&D published by the European Patients' Academy for Therapeutic Innovation[3]'. It contains general guidance and recommendations for the organisation and conduct of patient involvement in R&D projects conducted in commercial and other settings.

However, this document does not describe the general benefits, advantages, and potential drawbacks of patient involvement in R&D. Instead, it focuses on the processes and best practices that have proven to be effective when it comes to involving patients in R&D for meaningful results and an equitable distribution of priorities in the design and implementation of research projects under HARMONY and HARMONY PLUS.

Geissler, Ryll et al. give a detailed description (Figure 1) of the different tasks where patients can be involved easily and meaningfully[4]. As HARMONY and HARMONY PLUS focus primarily on early stage research, longitudinal studies and the exploration of novel diagnostic and treatment options, the recommendations contained in this document also focus on the earlier stages of research and development. However, patient involvement is (and should be) present across the entire lifecycle of medicines.

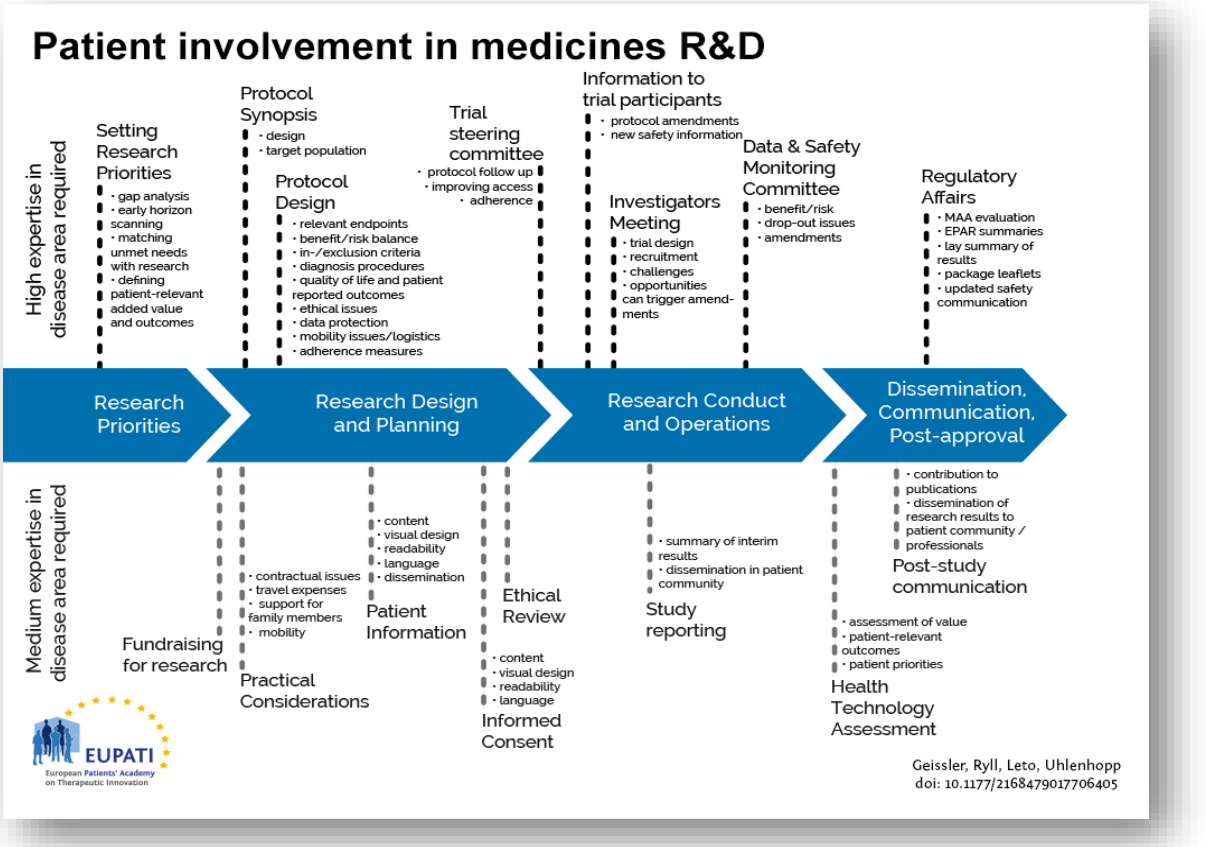
For the definition of the term "patient", the definition of EUPATI[1] is adopted:
"[...] we use the term "patient" which covers the following definitions:

- *"Individual Patients" are persons with personal experience of living with a disease. They may or may not have technical knowledge in R&D or regulatory processes, but their main role is to contribute with their subjective disease and treatment experience.*
- *"Carers" are persons supporting individual patients such as family members as well as paid or volunteer helpers.*
- *"Patient Advocates" are persons who have the insight and experience in supporting a larger population of patients living with a specific disease. They may or may not be affiliated with an organization.*
- *"Patient Organization Representatives" are persons who are mandated to represent and express the collective views of a patient organization on a specific issue or disease area.*
- *"Patient Experts", in addition to disease-specific expertise, have the technical knowledge in R&D and/or regulatory affairs through training or experience, for example EUPATI Fellows who have been trained by EUPATI on the full spectrum of medicines R&D."*

[3] Warner K, See W, Haerry D, Klingmann I, Hunter A and May M (2018) EUPATI Guidance for Patient Involvement in Medicines Research and Development (R&D); Guidance for Pharmaceutical Industry-Led Medicines R&D. Front. Med. 5:270. doi: 10.3389/fmed.2018.00270

[4] Geissler J, Ryll B, di Priolo SL, Uhlenhopp M. Improving Patient Involvement in Medicines Research and Development: A Practical Roadmap. Therapeutic Innovation & Regulatory Science. 2017;51(5):612-619. doi:10.1177/2168479017706405

Figure 1. *Patient involvement in medicines R&D*



In HARMONY and HARMONY PLUS, patients are represented through their respective disease-specific umbrella organisations with one of them acting as a hub for their work in the project.

The importance of patient involvement

In addition to the moral and ethical benefits of involving the end users and their representatives (e.g., in case of paediatric HM) in the R&D process, there are also substantial scientific and even financial benefits that can be gained from consistent and meaningful patient involvement.

The importance and merits of patient involvement in research and development are commonly acknowledged and offer benefits for all involved parties. Patient involvement also makes sure that clinical and medical research work more effectively together and deliver what patients really need. The discovery, development, and evaluation of new treatments is also improved if patients provide input throughout the design, conduct, and evaluation of studies and projects.

These improvements are based on the collaborative identification and understanding of patients' unmet needs, their research priorities, patient-centric clinical study design, and meaningful outcome measures and study endpoints. We encourage engagement with patients, caregivers, patient advocates, patient experts and patient organizations, and we also encourage and actively support the upskilling of patient organizations and patients to be able to be involved in such work. Contribution to and collaboration with "patient academies" and masterclasses for patients are linked to meetings organised under HARMONY Plus.

This engagement should be promoted throughout the entire funding framework, partnering concept, research and development process (including clinical trials), regulatory and market access processes, and the post-approval stages including pharmacovigilance. Involvement also extends to other work such as the sharing of evidence and outcomes with patients and patient groups. It is important for patients to be included in the review process, and during the conduct of clinical and other research and studies.

Involvement also enables increased credibility of knowledge and data, prevention of potential challenges that patients may face during the conduct of a study, and more effective dissemination (notification to other parties) and use of research outcomes in clinical practice. This SOP and recommendations focus on early involvement in the design and conduct of research on the HARMONY Big Data Platform.

Benefits of working with patients in R+D

The benefits of working with patients in R+D include:

- Better representation and understanding of the patients' unmet medical needs
- Better understanding and inclusion of RWE
- Improved buy-in from patient communities for relevant research projects
- Consistent and targeted dissemination of results
- Empowerment of the patient communities
- Flatter and more efficient research teams and organisations

4. Scope and responsibilities

This SOP and Recommendations apply to all research project proposals submitted to the HARMONY Alliance and HARMONY PLUS Big Data Platform for processing. They apply to research project proposals submitted by any stakeholder in the HARMONY Alliance, including patient organisations and/or the Patient Cluster.

The SOP and the Recommendations also apply to research projects submitted by patient organisations that participate in the HARMONY and HARMONY PLUS consortium through the Patient Cluster.

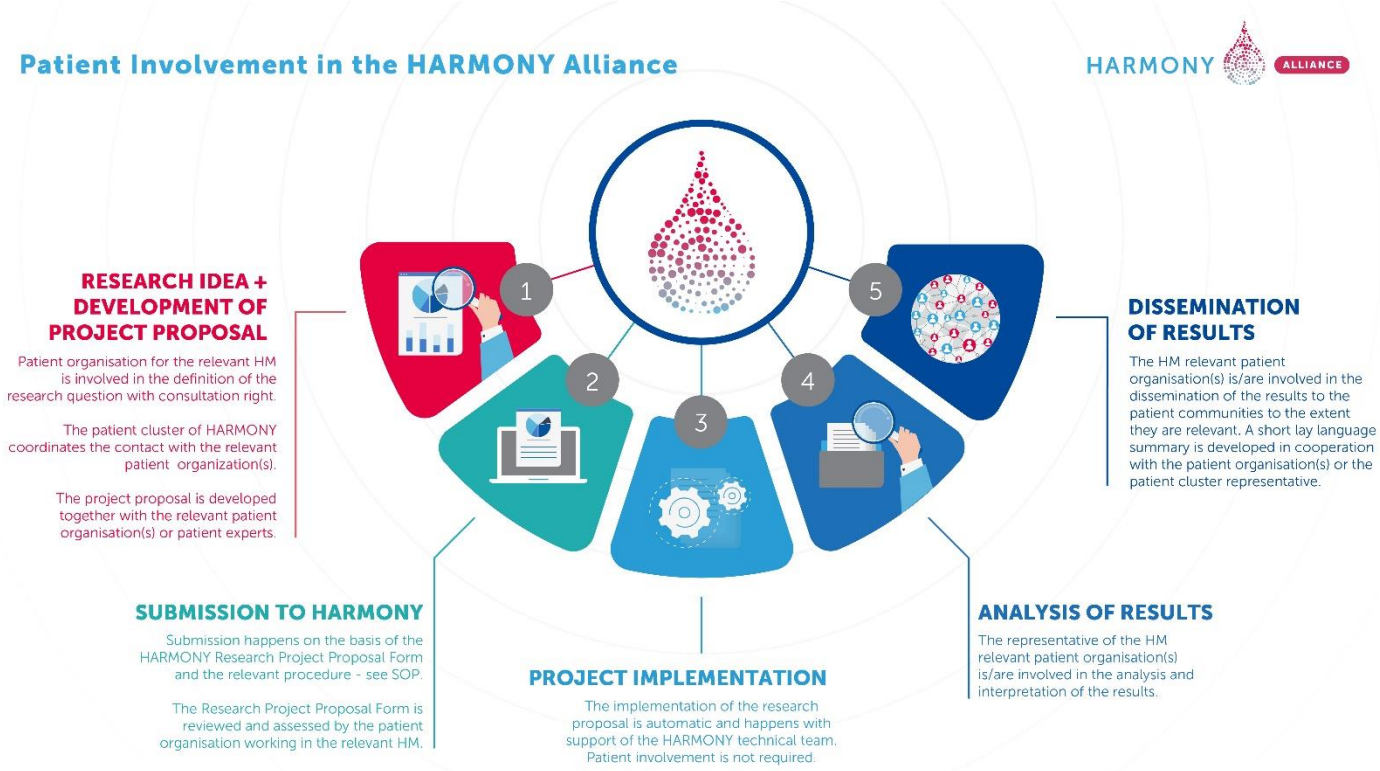
The Patient Cluster coordinates the work of the associated patient organisations that participate in the HARMONY Alliance. The Patient Cluster is led and coordinated by LeNET.

Role/job function	Responsibilities
Consortium partner	Participation in the general steering and conceptual development of the project, and contract signatory and beneficiary
WP Co-lead	Co-leading WP6 with CELGENE
Patient Cluster coordinator	Coordinating the work and contributions of patient organisations as members of the Patient Cluster

5. Specific procedure

The following procedure (figure 2) should be used to make sure patient involvement happens in research projects submitted and processed under HARMONY and HARMONY PLUS.

Figure 2. *Patient involvement procedure in HARMONY and HARMONY PLUS*



5.1. Research idea and the development of the research proposal

The patient cluster of HARMONY coordinates the contact with the relevant patient organisation(s). LeukaNET coordinates the Patient Cluster by way of emails and telephone conferences. Regular reports and assessments are developed and submitted to the HARMONY Office by LeukaNET upon consultation with the Associate Members.

These include:

- LeukaNET Leukemia Advocates Network, Consortium Member and Patient Cluster Coordinator
- ALAN Acute Leukemia Advocates Network, Associated Member
- CCI Childhood Cancer International Network, Associated Member
- CLLAN CLL Advocates Network, Associated Member
- CML Advocates Network, Associated Member
- Lymphoma Coalition, Associated Member
- The MDS Alliance, Associated Member
- MPE Myeloma Patients Network, Associated Member
- MPNAN MPN Advocates Network, Associated Member

The project proposal should be developed together with the relevant patient organisation(s) or patient experts to the extent possible. The patient organisation for the relevant HM should be involved in the definition of the research question with consultation right to the extent possible. For best results, the representative(s) of the patient organisation concerned or of the Patient Cluster should be part of the research team from its establishment, and its involvement should be consistent throughout the implementation of the research project.

Research ideas can originate from all stakeholder groups individually, but the proposal should be developed together.

Research project proposals submitted by the Patient Cluster or its members

1. The Patient Cluster makes sure that the research project team includes representatives of other stakeholder groups, especially clinicians and KOLs.
2. Submission of the project proposal to the HARMONY Office happens by using the standard procedure and the Research Project Proposal Form.
3. All other tasks like analysis and interpretation, and dissemination are to be implemented by the Patient Cluster or its member patient organisation with the involvement of the multi-stakeholder research team for the given project.

5.2. Submission of the project proposal to the HARMONY Platform

Submission happens based on the HARMONY Research Project Proposal Form and the relevant procedure – see SOP on Research Proposal Forms (Annex 1).

The Research Project Proposal Form is reviewed and assessed by the patient organisation working in the relevant HM.

The SOP for the Submission of HARMONY Research Project Proposals located (see Annex 1)

5.3. Project implementation

Research projects are implemented automatically and with support from the HARMONY PLUS technical team. Patients do not always have sufficient technical knowledge to influence all stages of this procedure, e.g., interventions of patients in the operation of the HARMONY Big Data Platform are unlikely. In each case, the possible contribution of patients should be considered and explored.

5.4. Analysis of results

As with all research projects, the analysis of results and findings is a process that requires consensus and can be contextual. Therefore, the participation of the representative(s) of the patient communities involved is recommended and necessary. The research team should include the representative of the patient organisation of the HM concerned or of the Patient Cluster. The patient representative should be involved in:

- the design of the implementation of the research project;
- the implementation of the project;
- the analysis and interpretation of the research results;
- the dissemination of the results and findings.

5.5. Dissemination of results

The visibility and understandability of the research results and their possible impact on the patient's health and quality of life are key requirements. Therefore, the representative of the patient organisation working in the relevant HM or of the Patient Cluster should be involved in the dissemination of results in the form of different communication vehicles such as communiques, scientific papers, conference contributions, etc. The official inclusion of a patient author is recommended, and the patient author should also be an active contributor to the implementation of the project as per good scientific practice. Patient organisations and the Patient Cluster have sufficient knowledge and skills to develop lay language summaries of the research findings for the dissemination of results, and several of them command sufficient scientific knowledge and preparedness to make meaningful contributions to research projects.

5.6 How to submit

Proposals to conduct a Research Project using the HARMONY Platform may be submitted by: [5]

1. **Any HARMONY Beneficiary(ies):**

see overview: *https://www.harmony-alliance.eu/en/partners*

a. HARMONY Third Parties under articles 11 and 12 of the Grant Agreement,

b. Linked Third Parties, and

c. Affiliate Entities

must submit their research project proposals through the Beneficiary that controls (in the case of affiliated entities) or has a legal link with them.

2. **Any Associated Member(s**), with relevant data contribution judged on a case-by-case basis. See overview: https://www.harmony-alliance.eu/associated-members.

3. **Any other organization or institution with interest in the project (Third Party),** via the payment of a fee in cash or making an in-kind contribution to support the objects of the Action.

The diagram in Annex IV of the SOP for the Submission of HARMONY Research Project Proposals outlines the processes by which the HARMONY Project reviews and evaluates any submitted Research Project Proposal. The HARMONY Coordination Office will coordinate the Admission and Evaluation processes: harmonyoffice@ibsal.es.

6. Forms, templates and procedures

The Standard Operating Procedure (SOP) for the submission of HARMONY Research Project Proposals can be found in Annex 1.

The Research Project Proposal Form can be found in Annex 2.

ANNEX 1: SOP for Submission of HARMONY Research Projects Proposals

ANNEX 2: Research Project Submission Form

[5] Standard Operating Procedure (SOP) for the submission of HARMONY Research Project Proposals