EJP RD
European Joint Programme on Rare Diseases

H2020-SC1-2018-Single-Stage-RTD
SC1-BHC-04-2018
Rare Disease European Joint Programme Cofund

Grant agreement number 825575

Del 2.1
Final List of Prioritization Criteria

Organisation name of lead beneficiary for this deliverable:
Partner 27 – CVBF

Due date of deliverable: month 05

Dissemination level: Public

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1. Introduction and Objectives

Prioritization is necessary everywhere, as resources are never unlimited. It is aimed to select among different options in order to address first the most important needs and to facilitate decisions about further development of activities on the basis of the outcome reached or to be reached.

This deliverable D2.1 is a result of the activity developed in Task 2.1 of the Work Package 2 (WP2), within the transversal Pillar 0 of the European Joint Programme on Rare Diseases (EJP RD). WP2 is specifically aimed at the development of EJP RD research and innovation strategy in connection to all related stakeholders. Within WP2, Task 2.1 focuses specifically on the "Prioritization scheme for EJP RD actions". The main outputs of Task 2.1 are:

- **Deliverable 2.1 (D2.1): Final list of prioritization criteria**. According to the EJP RD approved proposal, such prioritization criteria should serve to order mapped needs and actions that contribute to the EJP RD objectives or that stand in need of further exploration. The identified criteria will encompass scientific evidence aspects, demands of the RD community, regulatory and societal concerns, and take into account financial and technical feasibility. This D2.1 includes an enumeration and description of the main principles which could be applied for the assessment of any EJP RD activity that should be subject to prioritization. Therefore, this document (D2.1) has to be read and applied in conjunction with the content of deliverable D2.2.
- **Deliverable 2.2 (D2.2): Prioritization scheme including decision-making process.** Such scheme provides detail on the different steps for the process of prioritization. Such process includes the application of the prioritization criteria (expressed in this D2.1) whenever needed, and its successive validations to progress on the decision-making.

In short, the EJP RD Prioritization scheme will be used:

- to support and assess the decision-making process by which to prioritize mapped needs and actions that contribute to the EJP RD objectives
- to facilitate the planning of future actions within the annual work plan of the programme
- when some deviation from the EJP RD's plan happened or were envisioned (in such case, the involved WPs should notify the Coordination Team, so the most adequate measures can be adopted)
- to further ameliorate the criteria, indicators and methodology used for the process itself, after assessing the impact of the decisions taken.

Due to the complexity and the early stage of the EJP RD activities when this document was prepared, it is difficult to fully predict all future pathways and requirements, implying that this document should be general enough to cover most eventuality, and at the same time the procedure should be flexible enough to make it applicable along the whole life of the project and to any item of the EJP RD.

2. Prioritization criteria

A set of wide scope criteria are defined in this document. Such criteria may be applied to all EJP RD activities. In fact, four general criteria were identified in the Proposal of the EJP RD:

(i) scientific evidence aspects,

(ii) demands of the RD community,

(iii) regulatory and societal concerns,

(iv) financial and technical feasibility.

According to the Proposal, the criteria should be defined based on the input collected, through a survey, from RD stakeholders representing research community, European Reference Networks (ERNs), patients and policy makers, which would constitute the National Mirror Groups (NMG). The constitution of the NMG is being a complex process and it has not finished yet when this deliverable was written. Therefore, Deliverable 2.1 has been prepared taking into account relevant documents previously available and, in particular, the survey about priorities for research on RD, performed within E-Rare [Posada et al.], as it continues to be applicable.

A number of different aspects for each criterion may be used depending on the Pillar and specific activity to which it needs to be applied. A list of such possible aspects applicable to each pillar is detailed in the Annex. Nevertheless, for each specific prioritization process, the criteria to be applied should be selected and determined. These are the four broad categories of criteria:

(i) Scientific evidence aspects

This criterion refers to either the scientific data on which any proposed action could be based, as well as the likely knowledge impact of the action (i.e. the potential for the proposed action to positively affect rare disease research). It also includes the applicability to a variety of RD and the technological innovation. In this particular area all aspects related to the following points might be included for each of the Pillars:

- an experimental approach (P1)
- access to relevant data of consistent quality (P2)
- increase of the capacity of the consortium to perform or to contribute to high impact scientific research (P3)
- access to data of consistent quality which can support a development plan and participation of industry (P4)

Social and economic impact aspects related to the scientific evidence are included in the criteria iii and iv. It also should keep open the possibility of high risk/high impact science, i.e. the so-called blue-sky research approach.

(ii) Demands of the RD community

It refers to the level of interest of the RD community on any element of the EJP RD. It includes both patients, researchers, health care providers, industry, and other stakeholders which are involved in the RD wider ecosystem. In this sense, the National Mirror Groups (NMG) will play a key role to this respect. Patients, their relatives and caregivers should be specifically consulted regularly either directly through wide ranging questionnaires or through the consultation with patient organizations on the relevance of the actions planned for their quality of life and future. It is important to include also the opinion of physicians and nurses specialised on the treatment and follow-up of rare disease patients, to put the applicability in the health care system in the overall picture.

(iii) Regulatory and societal concerns

It refers to the society's values and vision about the rare diseases, and regulatory prescriptions and policies applicable to medical practice and products. Differences between EU and national rules can affect clinical trials, reimbursement and coverage including the freedom to choose the location for a patient's treatment, among others. On the societal side, for instance, the possible reluctance to particular therapeutic approaches should be addressed.

(iv) Financial and technical feasibility

The need to cover all the known rare diseases with a personalised approach is a worthy target but, due to the limited resources, each action should be evaluated as cost against potential benefit. The feasibility of the translation of a specific research or activity depends on the financial cost and capacity of the EJP RD, possible self-sustainability, or the availability of further sources of funding.
Technically, the capability/ability to execute the action/activity, should be also taken into account.

3. Regular update of this list of prioritization criteria

Before each Annual Work Plan can be prepared, this list will be reviewed and updated if necessary, to better approach real needs.

4. References cited

- Posada M, Ramírez A, Carroquino MJ, Messlich H, Schuster R, van Weely S, Lievens J, Koutouzov S, De Andrés R , on behalf of E-Rare Consortium Survey and Strategic Analysis on "Future Themes and Needs for Rare Diseases Research Funding". Available at: http://www.erare.eu/sites/default/files/E-Rare%20Survey%20and%20strategic%20analysis(1).pdf

5. Annex

Here, some examples of the aspects that are applicable to each Pillar for each of the four general prioritization criteria, is presented,

These aspects are ordered by pillars and, within each pillar, by the four main general criteria for prioritization. For the explanation of each criterion, see above. For details on how to apply the criteria to the prioritization process, see the deliverable D2.2.

(P1): Funding of research.

(i) Scientific evidence aspects

For each element, it should be assessed:

1. Potential for scientific and technological innovation. Discovery of novel targets or creation of large common resources should be both considered as resources for future translation to care.
2. Potential for strengthening top-level research through the creation or validation of relevant services.
3. Clinical utility and applicability should be measured in terms of the end-point strength and impact on providing a cure.
4. Bottom-up approach/Scientific excellence should be favoured, opening to alternative approaches and innovative solutions.

(ii) Demands of the RD community

Each element should be assessed thinking if:

1. It responds to an obvious gap and need in healthcare, diagnosis and treatment.
2. It focuses on a group of diseases with common mechanism of action.
3. It approaches a very rare disease for which little is known.
4. It provides a definitive cure more than a maintenance treatment.
5. Responds to quality of life's relevant issues.
6. Receivability in the health care system

(iii) Regulatory and societal concerns

These aspects can include, among others:

1. Unmet medical need and the application of the regulatory facilitation for the development of products responding to it.
2. Disease prevalence and incidence, including reliable data for the rare disease population in Europe, patient distribution and traceability.
3. Compliance with regulatory checkpoints for the clinical trials authorization and the marketing authorization.
4. Intellectual property protection and exploitation or licensing approaches.
5. Ethical assessment and acceptance of the specific therapeutic approach by country, including adequate communication strategies.

(iv) Financial and technical feasibility

1. High Social Burden is usually defined on the basis of the cost per year of life or for the expected lifespan of the patient.
2. Availability of sufficient resources to perform the specific action in a manner which would give a significant impact, either societal, economic or technical. In-kind contribution and availability of technical and administrative structures to perform pre-clinical or clinical research.
3. Economic burden based on the cost of the current therapies or palliative care per patient per year.
4. Economic efficiency measuring the rate of return from investment. The metrics used to measure the return on investment are defined either in terms of quality of life or extension of lifespan.
5. Likelihood of translation to the market by industry including the willingness to reimburse the final cost, should be addressed.

(P2): Coordinated access to data and services:

(i) Scientific evidence aspects

1. Potential for scientific and technological innovation. Discovery of novel targets or creation of large common resources should be both considered as resources for future translation to care.
2. Potential for strengthening top-level research through the creation or validation of relevant services.
3. Clinical utility and applicability should be measured in terms of shared end-point and harmonised data storage and curation.
4. Top-down approach should be favoured paving the way to harmonised databases allowing access to the largest dataset achievable.

(ii) Demands of the RD community

1. Access to data responding to an obvious gap and need in healthcare, diagnosis and treatment
2. Focus on a group of diseases with common characteristics allowing pooling of dataset.
3. It provides access to relevant data provided by patients directly, their caregivers or the relevant health structure under a common harmonised informed consent
4. Allows the collection of samples and access to data regarding quality of life relevant issues
5. Compatible with multiple dataset format and remote access to data in the health care system

(iii) Regulatory and societal concerns

1. Compliance with the GDPR and the national, local rules on privacy protection.
2. Access to data to calculate disease prevalence and incidence, including reliable data for the rare disease population in Europe, patient distribution and traceability.
3. Compliance with regulatory checkpoints on personal and clinical data management for the trials and marketing authorization.

4. Intellectual property protection and exploitation or licensing approaches.
5. Ethical assessment and acceptance of the specific privacy requirement by patient individuals and organization.

(iv) Financial and technical feasibility

1. Quantification of the cost for access, curation and managing of dataset.
2. Quantification of the cost of long-term maintenance of data especially for patients' registries.
3. Availability of sufficient resources to perform the specific action in a manner which would give a significant impact either societal, economic or technical. Financial and technical resources indicate both funding available, in-kind contribution and availability of technical and administrative structures to perform the required actions.
4. Economic efficiency measuring the rate of return for investment. Quantification of the cost of creating storage, curation and operating algorithms against the return in term of avoided duplication of efforts.
5. Possibility of economical return in terms of use by commercial partners.

(P3) Capacity building:

(i) Scientific evidence aspects

1. Increase of the capacity to perform high impact science as the addition of novel technologies to the resources developed by the consortium.
2. Increase of the capacity to grant access to relevant research on rare disease by creaiting shared resources and validated analytical tools.
3. Increase of the capacity to fund by creating novel funding opportunities

(ii) Demands of the RD community

1. Increase the capacity of supplying relevant data and to participate to the definition of quality of life endpoint
2. Increase of the capacity to perform high impact science by participating actively in population and epidemiological studies.
3. Increase of the capacity to grant access to relevant research by participation to the studies definition.
4. Increase of the capacity to fund by creating novel funding opportunities

(iii) Regulatory and societal concerns

1. Increase the capacity of supplying relevant data by better communication with regulatory and societal stakeholder
2. Increase of the capacity to perform high impact science by making available regulatory guidance and societal concerns to the researcher and users of the EJP RD services.
3. Increase of the capacity to grant access to relevant research by creating regulatory liaisons at the early stage of research.

(iv) Financial and technical feasibility

1. Increase the capacity of the users to reach the clinical application by creation of supporting activities.

2. Increase of the capacity to translate basic research into novel therapies by liaisons with commercial and non-profit funders

(P4): Accelerated translation of research projects and improved outcomes of clinical studies.

(i) Scientific evidence aspects

1. Increase the regulatory compliant data on rare disease
2. Increase of number of validated tools for the evaluation of surrogate endpoints in studies involving rare disease small population
3. Increase of validated platform for the application of similar target to multiple rare diseases

(ii) Demands of the RD community

1. Increase the communication and understanding between the RD community and regulatory agencies.
2. Increase the communication and understanding between the RD community and social media and communication agencies.
3. Inform the RD community of the concern and methodologies of the regulatory agencies and in particular of the reimbursement policies.

(iii) Regulatory and societal concerns

1. Increase the communication and understanding between the RD community and regulatory agencies.
2. Increase the communication and understanding between the RD community and social media and communication agencies.
3. Inform the RD community of the concern and methodologies of the regulatory agencies and in particular of the reimbursement policies.

(iv) Financial and technical feasibility

1. Actively search for non-standard channels for the translation of novel therapies to the clinical use.
2. Develop alternative model for non-profit drug development.
3. Increase the users and RD Community understanding of the cost defining mechanism of innovative therapies.
4. Discuss and develop novel model for cost reducing and payment.

The above list of aspects for each criterion is only a partial example and will be revised regularly.