EJP RD

European Joint Programme on Rare Diseases

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Call documents for validation

Organisation name of lead beneficiary for this deliverable:

Partner 12 – FFRD

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European Joint Programme on Rare Diseases (EJP RD)

Rare Diseases Research (RDR) Challenges: Fostering partnerships to accelerate innovation

Call Text including guidelines for applicants

Submission deadline for full proposals: June 30th, 2020 2:00 PM (CET)

The application template with the link to the electronic proposal submission system and further information can be found at the EJP RD website: http://www.ejprarediseases.org/

Direct link to the electronic proposal submission: https://ffrd.evision.ca/eAwards_applicant/faces/jsp/login/login.xhtml?lang=EN

For questions, contact the Challenges Call Secretariat at the French Foundation for Rare Diseases, FFRD, France: CCS@fondation-maladiesrares.com

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1. RARE DISEASES CONTEXT

The Orphanet database contains information on 6172 unique rare diseases, the great majority being of genetic origin[1]. Although individually rare, taken together rare diseases affect at least 26-30 million people in Europe. Moreover, they represent a major issue in health care: a large number of these diseases have an early or very early onset and/or lead to a significant decrease of life expectancy. Moreover, most of them cause chronic illnesses with a large impact on quality of life and the health care system.

Therefore, research on rare diseases is needed to increase knowledge for prevention, diagnosis and better care of patients. Yet, research is hampered by a lack of resources at several levels: (1) Few scientists work on any given specific disease, (2) There are few patients per disease and they are scattered over large geographic areas, causing difficulties to assemble the necessary cohorts, (3) Existing databases and bio-material collections are usually local, small, and not accessible or standardized, (4) The complex clinical phenotypes of these diseases require interdisciplinary cooperation to improve research and treatment.

The specificities of rare diseases - limited number of patients per disease, scarcity of relevant knowledge and expertise, and fragmentation of research - single them out as a distinctive domain of very high European added-value. Rare diseases are therefore a prime example of a research area that requires collaboration/coordination at a transnational scale.

In this context, the European Joint Programme on Rare Diseases (EJP RD) is committed to create a comprehensive, sustainable ecosystem allowing a virtuous circle between research, care and medical innovation. The EJP RD brings over 130 institutions from 35 countries: 26 EU Member States (Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Croatia, Ireland, Italy, Netherlands, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Spain, Sweden, Slovakia, Slovenia), 7 associated (Armenia, Georgia, Israel, Norway, Serbia, Switzerland, Turkey), the United Kingdom[2] and Canada.

[1] Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database.

Nguengang Wakap S[1], Lambert DM[2], Olry A[3], Rodwell C[3], Gueydan C[3], Lanneau V[3], Murphy D[2], Le Cam Y[4], Rath A[3]. Eur J Hum Genet. 2019 Sep 16. doi: 10.1038/s41431-019-0508-0

[2] As of 1 February 2020, the United Kingdom became a third country. However, in conformity with the EU-UK Withdrawal Agreement, a transition period, which is currently planned to last until 31 December 2020, was established during which the EU treats the United Kingdom as if it were a Member State. This means that the UK and persons or entities established in the UK continue to be eligible to receive Union

The EJP RD is implementing a new funding scheme, focused on high added value in the field of therapeutic development, in order to promote and facilitate active collaboration between academia, Small and Medium-sized Enterprises (SMEs), Patients Advocacy Organisations (PAOs) and Industry: the Rare Diseases Research Challenges (RDR Challenges) scheme.

2. AIM AND CONTENT OF THE CALL

The main objectives of the RDR Challenges are to:

i. Solve specific research challenges in the field of therapeutic development for rare diseases;

ii. Facilitate and fund collaborative projects between industry, academia, SMEs and PAOs.

A call for expression of interest was sent before the first workshop to over 40 industries together with a briefing document explaining the principles and concept of the scheme. Industry representatives from 9 pharmaceutical companies participated in the first workshop to help identify potential RDR challenges. And 5 industry partners (Chiesi, CSL Behring, Cydan, Ipsen, Pfizer) eventually committed themselves as sponsors of the RDR Challenges.

Following two multi-stakeholder workshops organized in 2019, gathering experienced funders, experts in public-private partnerships, industries and patient representatives, 4 challenges were identified taking into consideration interests from industry partners & policy makers whilst addressing the needs of academic scientists and priorities for the rare disease patient community.

The ambition of the RDR Challenges relies on providing strong incentive for all participants:

- Facilitated pathway for academics to exploit their research,
- Access to scientific and technological innovations emerging from academic research for industry.

funds under actions carried out in direct, indirect or shared management, which implement Union programmes and activities committed under the MFF 2014-2020 until the closure of those Union programmes and activities.

Collaborative consortia of applicants (academics, SMEs, PAOs) and the involved industry partners will address the challenges and provide solutions.

Challenges must be solvable within a 30-month period with first milestones/deliverables at 18 months.

The RDR Challenges Call is the first innovative call in the rare diseases environment combining EC funding and co-funding from industry partners to develop proof of concept studies.

The total budget of 1,5 M€ will allow 4 projects to be funded (375,000€ per project). Once selection of projects is completed by an independent Challenges Evaluation Committee (CEC), the industry partners (referred to as "sponsors" below) who were involved in the challenges definition, will join and co-fund (in kind and in cash) the granted projects.

2.1 RDR Challenges

Detailed description is provided in Annex 1, below is an overview of the four RDR Challenges.

Challenge 1: Development of a non-invasive tool for measuring rare disease patient mobility in daily living

INDUSTRY SPONSOR. Chiesi Farmaceutici S.p.A. (Italy), CSL Behring (Australia)

AIM. To develop a set of coordinated non-invasive tools for measuring rare disease patient general movements distinguishing between voluntary and involuntary movements (e.g. by distributing movement-sensors in patients' home, on their body, on the wheelchair, etc.)

EXPECTED EXPERTISES. SME in the field of mobile health technologies is the perfect target, in particular in the selection and/or adaptation of existing technologies in the field of sensors and in the integration of data. People able to generate software for integration of data are also necessary.

Consortium members should be able to offer expertise and support for facilitating patient involvement in the project.

Challenge 2: Delivery system for intranasal administration of biological drugs to neonates

INDUSTRY SPONSOR. Chiesi Farmaceutici S.p.A. (Italy)

AIM. To develop a delivery system allowing administration of liquids or gels in nostrils of the neonates for intranasal (IN) administration of biological drugs.

EXPECTED EXPERTISES. Biomedical devices, biologics drug product formulation is preferred (especially if developed in neonatology therapeutic area). Optimal IN devices should not harm the nasal mucosal surface while ensuring reproducibility of drug administration and avoiding drug loss in the nasal mucus/cavity.

Challenge 3: Characterize Rare Bone Disorders (RBD) Mobility Challenges in Real World Setting

INDUSTRY SPONSOR. Ipsen

AIM. Develop full-body automated mobility assessment tool(s) to assess real-life mobility challenges in people living with RBD, to be compared vs available disease specific patient- and Health Care Professionals (HCP)-reported mobility assessments. Capturing these real-life data could help determine if patient characteristics or environmental conditions could be used to predict mobility outcomes and therefore open possibilities for preventive or corrective interventions, including home and assistive devices design.

EXPECTED EXPERTISES. Academic researchers working in the field of RBD. Involving PAO is mandatory. SME and academic researchers working in the field of mobile health technologies. Involvement of architects and designers (with or without expertise in assistive devices development).

Challenge 4: Pre-clinical assay to detect instability of microsatellite repeat expansions

INDUSTRY SPONSOR. Pfizer, Cydan

AIM. To develop and validate an assay for screening genes and/or compounds that modulate instability of microsatellite repeats. The rarity of repeat expansion/contraction events, estimated to be <1 per 10,000 DNA molecules, creates many challenges for assay development. The goal of this proposal is to devise, implement, and validate an assay that displays the robustness and sensitivity to detect repeat expansion/contraction events after ≤1 week of compound treatment. The assay should utilize a read-out that is suitable for a mid-scale screen of 100s to thousands of compounds in dose response. If such an assay is developed, it will be transferred to Pfizer for further characterization and validation.

EXPECTED EXPERTISES. Knowledge of the biology of repeat expansion diseases. Experimental methods used to study genomic instability and/or DNA repair at the cellular and/or molecular level. Access to reagents and instrumentation that is compatible with small molecule screening.

2.2 Networking event

In order to initiate exchanges and/or formation of collaborative consortia of applicants to the call, a Networking Event took place in Paris on March 3, 2020, where the challenges were presented. Pre-arranged bilateral/multilateral meetings were also organized in this occasion between potential applicants (academia, SMEs, PAOs) and the involved industry sponsors who identified the challenges.

If a potential applicant was not able to join the networking event it is mandatory to contact the industry sponsor in order to validate relevance and adequacy of the concept. See Annex 1 and contact details for each Challenge.

For matchmaking expertise, please register through the BtoB link:

https://rdr-networking-2020.b2match.io

3. APPLICATION

3.1 Eligibility

Partners belonging to one of the following categories may request funding under a joint proposal:

- **academia (research teams working in universities, other higher education institutions or research institutes)**
- **clinical/public health sector (research teams working in hospitals/public health and/or other health care settings and health organisations)**
- **small and medium-sized enterprises (SMEs)**
- **patient advocacy organisations**

Participating organisations have to be legal entities and established in one of the countries involved in the EJP RD mentioned in Annex 2A.

Annex 2A COUNTRIES PARTICIPATING IN THE EJP RD

Eligible small and medium-sized enterprises (SMEs), meeting the EC definition (see Annex 2B) must demonstrate positive financial results for the last 2 years and provide consolidate financial statements using International Financial Reporting Standards.

Also, Patient Advocacy Organisations (PAOs) are eligible when they are a legal entity established in the countries involved in the EJP RD. In general, an eligible participating patient advocacy group is defined as a not-for-profit organisation organised under private law, which is, according to their articles of association (also: articles of incorporation and their by-laws) patient focused, where patients and/or carers and/or family members of patients represent a majority of members in governing bodies and are financially independent, particularly from the pharmaceutical industry (max. 49 % of funding from several companies). More information on eligibility of Patient Advocacy Organisations is mentioned in Annex 2C.

The maximum duration of the project is 30 months, with first milestones/deliverables at 18 months.

Only transnational networks will be funded. The consortium submitting an application for a RDR Challenge budget must involve a minimum of **two eligible applicants** (researchers and/or health care professionals and/or SME(s) and/or patient advocacy organization(s)) from **at least two different countries** participating in the EJP RD at the time of the application (see Annex 2A). The Industry sponsors does not count in the total number of applicants.

The maximum number of eligible applicants in an applying consortium is six applicants.

It is mandatory to contact industry sponsors before submitting a proposal (see in Annex 1, contact details for each Challenges).

Consortia of applicants are strongly advised to include patient representatives and patient advocacy organizations (PAOs), which are **eligible to receive funding for their activities**. **If patient involvement is not deemed appropriate within a research project, this should be explained and justified.** Involving PAO is mandatory for Challenge 3 **'Characterize Rare Bone Disorders (RBD) Mobility Challenges in Real World Setting'.**

The consortia should clearly present the role and responsibilities of the PAO(s) involved, how they will operate, at what levels and stages of the research, and provide justifications for allocated resources. PAOs can be involved in all aspects of the proposed work, including in project design, by, for example advising on prioritization, members of advisory groups, being a member of the consortium steering group or the governance group of a registry. PAOs may be part of institutional scientific boards to discuss the proposal and subsequent study on issues.

There can be other collaborators that do not request funding if it is well justified within the proposal. These collaborators should state that they have secured funds to participate to the project. They do not count in the maximum number of partners within the consortium.

Each transnational proposal must nominate a project lead applicant among the project partner principal investigators, excluding the industry sponsor. The lead applicant will represent the consortium externally and will be responsible for its internal scientific management (such as controlling, reporting, and intellectual property rights issues). This workload should be taken into account in the estimation of the budget of the lead applicant. A single principal investigator will represent each project partner. Within a joint proposal, the principal investigator of each project partner will be the contact person.

Budget

The maximum budget that can be requested is:

575.000€ for Challenge 1: Development of a non-invasive tool for measuring rare disease patient mobility in daily living

487.500€ for Challenge 2: Delivery system for intranasal administration of biological drugs to neonates

487.500€ for Challenge 3: Characterize Rare Bone Disorders (RBD) Mobility Challenges in Real World Setting

487.500€ for Challenge 4: Pre-clinical assay to detect instability of microsatellite repeat expansions

Eligible costs:

- personnel costs
- travel and subsistence costs
- equipment costs [3] (depreciation costs of equipment used for the project)
- costs of other goods and services
- sub-contracting costs, limited to 15% of the total requested budget
- **funding for administrative costs and overheads are not allowed**
- **SMEs funding cannot exceed 80% of direct costs**

[3] See Chapter 3 page 83 and following: https://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/amga/h2020-amga_en.pdf

3.2 Submission of proposals

3.2.1 Registration

Consortia of applicants who intend to submit a transnational project proposal for a RDR Challenge should register at the eAwards application system (https://ffrd.evision.ca/eAwards_applicant/faces/jsp/login/login.xhtml?lang=EN).

Instructions for registration and application on this system are published on the EJP RD website (www.ejprarediseases.org).

3.2.2. Proposal submission

There will be a **one-stage electronic submission application procedure**. An application template (in English) has to be completed by the applicants of a proposal and must be submitted by the lead applicant using the electronic submission system.

Call Timeline

2nd April 2020	Opening of the call
30th June 2020	Full proposal submission deadline
30th September 2020	Deadline for rebuttals
December 2020	Notification of funding decision

Applications Content (30 pages max)

1- Scientific Excellence
- Objectives: clear, measurable, realistic and achievable within the duration of the project
- Relation to the challenge: how your proposal addresses the specific challenge
- Concept and approach, quality of the coordination and support measures: positioning of the project; national or international support activities linked with the project; overall approach and methodology
- Necessary expertise secured to achieve the objectives and to ensure engagement of all stakeholders and to complement the industry sponsors; preliminary/previous results obtained by consortium members

2- Impact

- Expected impacts: improving RD patients' health and wellbeing ; added value from the public-private partnership approach on R&D, regulatory, clinical and healthcare practice
- Measures to maximize impact: dissemination and exploitation of results; communication plan
- Description of participants (applicants) and if applicable, collaborators involved in the project (including collaborator resources)

3- Implementation

- Work packages, deliverables and milestones: work description, timing
- Management structure and procedures
- Contingency plan, risk management
- Data management plan (obligatory)
- Consortium as a whole: describe how it will match the project's objectives; how the members complement one another; how they will be able to work effectively together
- Resources to be committed: describe PM (person/month) involved and direct costs
- Budget requested and justification (per member)

4- Ethics

- Ethics self-assessment

Detailed workplan for the 30 months of the whole duration of the project, must be provided with first expected deliverables/milestones at month 18.

Lead applicants are expected, before submitting applications, to have discussed their proposals with their organization and technology transfer office (TTOs), or any other body whose co-operation will be required in the conduct of the project, including sub-contractors.

By submitting the application, applicants are confirming that the information given in the application is complete, that they are actively engaged in the project and responsible for its overall management and agree to administer the grant if made.

4. EVALUATION

4.1 Evaluation criteria

Proposals will be assessed according to specific evaluation criteria that are in line with Horizon 2020 rules (see below), using a common evaluation form. A scoring system from 0 to 5 will be used to evaluate the proposal's performance with respect to the different evaluation criteria.

Scoring system:

0: Failure: The proposal fails to address the criterion in question, or cannot be judged because of missing or incomplete information.

1: Poor: The proposal shows serious weaknesses in relation to the criterion in question.

2: Fair: The proposal generally addresses the criterion, but there are significant weaknesses that need corrections.

3: Good: The proposal addresses the criterion in question well but certain improvements are necessary.

4: Very good: The proposal addresses the criterion very well, but small improvements are possible.

5: Excellent: The proposal successfully addresses all aspects of the criterion in question.

Evaluation criteria:

- Excellence:
  - Clarity and pertinence of the proposal to meet all key objectives of the challenge;
  - Credibility of the proposed approach;
  - Soundness of the concept, including trans-disciplinary considerations, where relevant;
  - Ambition & innovation potential;
  - Mobilisation of the necessary expertise to achieve the objectives of the challenge, ensure engagement of all relevant key stakeholders.
- Impact
  - Added value from the public-private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant;
  - Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges;
  - Improving European citizens' health and wellbeing;
  - Effectiveness of the proposed measures to exploit and disseminate the project results (including management of IPR), to communicate the project, and to manage research data.
- Quality and efficiency of the implementation
  - Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget;
  - Complementarity and pertinence of the participants within the consortium, including PAO(s)
  - Appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.

Evaluation scores will be awarded for the 3 main criteria, and not singularly for the different aspects listed below the criteria. Each criterion will be scored on a 5-point scale. The threshold for individual criteria will be 3. The overall threshold, applying to the sum of the three individual scores, will be 12. The maximum score that can be reached from all three criteria together is 15 points.

4.2 Procedure for evaluation of proposals

4.2.1 Eligibility check

The Challenges Call Secretariat (CCS) will check all proposals to ensure that they meet the call's formal criteria (e.g. number of applicants, country of applicants, inclusion of all necessary information).

The evaluation of the eligible proposals will be carried out according to the following two-step procedure.

4.2.2 Peer review of proposals (first step of the evaluation procedure)

Proposals passing the eligibility check will be forwarded to the Challenges Evaluation Committee (CEC) for a remote evaluation (see evaluation criteria in section 4.1).

The Challenges Evaluation Committee (CEC) is composed of independent experts carefully selected to avoid any potential conflict of interest and chosen for their scientific, clinical, technical and/or disease-specific expertise. This include scientific experts, patient experts, methodological and statistical experts and also industrial experts (excluding experts from industries proposing the challenges). Special attention will be given that the expertise of the experts matches the addressed challenges. At least 3 experts from the CEC will be appointed to evaluate a submitted proposal. Biostatistics and Methodological reviewers will provide a score for the methodology presented in the proposals and will be there to assist in evaluating the feasibility of the projects with respect to bio-statistical methods.

CEC members will sign a confidentiality agreement and a statement to confirm that they do not have any conflicts of interest.

Applicants are invited to indicate any excluded reviewers in the application.

4.2.3 Rebuttal stage

Before the CEC meeting, each project lead applicant will be provided with the opportunity to read and provide a written response to the evaluations of the reviewers. The scores will not be given at this stage. This step allows applicants to correct factual

errors or misunderstandings in the review, and to reply to reviewers' questions. Issues which are not related with reviewers' comments cannot be addressed and the work plan cannot be modified at this stage.

The applicants will have up to two weeks (in September 2020) for this **optional** response to the reviewers' comments.

4.2.4 CEC meeting evaluation (second step of the evaluation procedure)

The CCS will send full proposals, reviews and rebuttals to the CEC members before the meeting. The CEC will meet to discuss each proposal, assign final scores, make a classification of the proposals and rank proposals recommended for funding with the support of the CCS. The final summary review report prepared by the CEC members will be sent to all applicants.

An independent observer will be invited during the selection process to ensure transparency accordingly to EC rules, and will provide a report on the whole process to the EC.

4.2.5 Ethical evaluation

After the CEC meeting, full proposals will also be remotely evaluated by independent experts in ethics. The expert in ethics will report on the feasibility of the RDR Challenge application to comply with the ethical requirements. If necessary, it will list those tasks that need to be done and documents that need to be submitted by the lead applicant of the evaluated application in order to receive the approval for funding from the ethical point of view. In case an ethical evaluation has taken place only those proposals approved by both, the scientific and ethical evaluations (complying with all central and regional/national ethical requirements), will be funded.

According to Horizon 2020 rules[4], an ethical evaluation is needed if personal data or large animal experiments are processed in the context of research. Therefore, the principal applicant is responsible for following these rules.

4.3 Funding decision and implementation

Based on the ranking list established by the CEC and on available funding, the CCS will communicate the final decision to the lead applicant.

A maximum of one consortium per challenge with a clear funding recommendation will be funded considering the available budget.

[4] https://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/ethics_en.htm

Funded projects shall start in March 2021; the first round of funding will be provided after grant agreement signature.

Second installment

At M18, the consortium lead applicant will submit a progress report, demonstrating the work undertaken and the milestones and deliverables achieved during the first phase study (see also section 6).

The CEC will examine the results and interview the consortium to evaluate how the deliverables were achieved in the specific timeline in order to validate second installment of funding.

The second installment will be release if the specific deliverables have been achieved.

5. FINANCIAL AND LEGAL ISSUES

5.1 Funding model

The administrative and financial management of the EC funding provided by the EJP RD to the successful applicants of the call will be handled by the French Foundation for Rare Diseases (FFRD) according to EU rules on a two-step basis.

The lead beneficiary institution of the lead applicant will receive the funds from FFRD and will distribute it within partners.

A Multibeneficiary grant agreement will be established between FFRD and the selected consortia to set out the rights and obligations and the terms and conditions applicable to the grant awarded to the beneficiaries for implementing the action.

The contractual obligations applied will be the ones of Horizon 2020 and will take the necessary regulations into account including the required ethical, legal and data protection approvals.

5.2 Research consortium agreement and ownership of intellectual property rights

The project consortium has to establish and sign a consortium agreement (CA) for cooperation **with industry sponsor**. For reference see the IMI Model Consortium

Agreement prepared by EFPIA (https://efpia.eu/media/25823/efpia-model-consortium-agreement-for-imi2-actions-2.docx). It is mandatory that the project consortium signs the CA early during the lifetime of the project. Consortium agreement will address all issues related to ethical considerations, communication, background and foreground IP and confidentiality, exploitation of results, contribution expected from all beneficiaries.

5.3 IRDiRC policies and guidelines

The project partners are expected to follow IRDiRC policies and guidelines. For more information see http://www.irdirc.org/

5.4 Respect of relevant European and international standards

The submitted proposals have to respect relevant European and international standards like:

- The General Data Protection Regulation, GDPR, EC Regulation (EC 2016/679) on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. This Regulation applies in all Member States from May 25, 2018 and thus also for the EJP RD RDR Challenges granted projects (https://publications.europa.eu/en/publication-detail/-/publication/3e485e15-11bd-11e6-ba9a-01aa75ed71a1/language-en).
- The EC Directive 2010/63/EU on the protection of animals used for scientific purposes(http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32010L0063)
- European Research Council Guidelines on Implementation of Open Access to Scientific Publications and Research Data (referred to in http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/open-access_en.htm)
- To make research data findable, accessible, interoperable and re-usable (FAIR), a data management strategy is mandatory in the full proposal. For an example of questions for a data management strategy, see Annex 1 in http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/oa_pilot/h2020-hi-oa-data-mgt_en.pdf .

A data management strategy/plan should include information on:

  - the handling of research data during & after the end of the project;
  - what data will be collected, processed and/or generated and/or reused;
  - which methodology & standards will be applied;
  - whether data will be shared/made open access;
  - how data will be curated & preserved (including after the end of the project).

- General ethical and legal requirements: Ethics is an integral part of research. Please be aware that regulations and ethical issues vary across different countries and should be considered from the outset. The EJP RD expects applications to fulfil ethical

and legal requirements. Among other things, special attention will be paid to potential ethical issues (e.g. research on humans or animals; privacy of data and biomaterials; informed consent; etc.). Only projects that fulfil the legal and ethical international/EU and national and institutional standards will be funded.

6. RESPONSIBILITIES, REPORTING REQUIREMENTS AND DISSEMINATION

The Challenges Call Secretariat (CCS), located at the French Foundation for Rare Diseases (FFRD), will be responsible for the administrative and financial management of the call. It will be the primary contact point between the research consortia, the industry sponsors involved and peer reviewers with regard to call procedures. **The project lead applicant is the point of contact for consortia during the application procedure and is responsible for forwarding relevant information from the CCS to their consortium members.**

The **lead applicants** will submit a **progress report** to demonstrate the work performed in the first stage of the project and describe milestones and deliverables achieved. If there is any deviation or delay, the lead applicant should inform the CCS as soon as possible and propose a revised timeline, which the CCS will have to validate in order for the project to continue.

The **lead applicants** of all funded projects must submit **a final scientific project report** (due within three months of the end of the project). This monitoring will be under the responsibility of CSO-MOH, Israel and FNRS, Belgium, which is responsible for the online monitoring system. All reports must be in English and must use the reporting templates provided. The research partners are jointly responsible for delivery of the reports. Only reports delivered on behalf of the consortium, via the project lead applicant, will be accepted.

The final reports, both scientific and financial have to be submitted in all cases before December 2023.

The public lay summary of the outcomes will be published on the EJP RD website.

All reports will be monitored and used for dissemination and communication purposes of the EJP RD.

Applicants must ensure that all outcomes (publications, etc.) of projects include a proper acknowledgement of EJP RD and the EC funding. This includes the display of the EJP RD logo when possible.

In addition, unless the EC requests or agrees otherwise or unless it is impossible, any dissemination of results (in any form, including electronic) must:

(a) display the EU emblem
(b) include the following text:

"This project has received funding from the European Union's Horizon 2020 research and innovation programme under the EJP RD COFUND-EJP N° 825575".

7. CONTACT AND FURTHER INFORMATION

The administrative management of the RDR Challenges Scheme will be ensured by the Challenges Call Secretariat (CCS) that is set up at FFRD, France. The CCS will be responsible for collection of the applications, supporting the Challenges Evaluation Committee (CEC) and communication with the lead applicants. The lead applicant will be the person contacted by the CCS during the application and selection procedure, so he/she must forward the information to the other applicants.

Further information on the EJP RD, the RDR Challenges Scheme and the follow-up is available at the EJP RD website (www.ejprarediseases.org).

8. ANNEXES

Annex 1 CHALLENGES

RDR Challenge 1

Development of a non-invasive tool for measuring rare disease patient mobility in daily living

INDUSTRY SPONSORS

- Chiesi Farmaceutici S.p.A. (Italy)

Contact: k.dallaglio@chiesi.com; d.ardigo@chiesi.com

- CSL Behring (Australia)

Contact: Thomas.Verish@cslbehring.com; Ruediger.Gatermann@cslbehring.com

AIM

To develop a set of coordinated non-invasive tools for measuring rare disease patient general movements distinguishing between voluntary and involuntary movements (e.g. by distributing movement-sensors in patients' home, on their body, on the wheelchair...)

BACKGROUND AND RATIONALE

- Rare disease patients-families-caregivers face important challenges every single day their life. Although enormous progress has been made by increasing international cooperation in the field of clinical and scientific research as well as by sharing of scientific knowledge about rare diseases, there is still a strong need to harvest disease-related information by monitoring patients' behavior and their symptoms.
- Mobile health technologies such as wearables, wireless medical sensors, apps are real-time registries that can help in determining rare disease patient best care and guaranteeing a tangible improvement of their quality of life.

Despite current technological level, there is a lack of integrated systems for collection of mobility information in free daily leaving distinguishing between spontaneous movements and assisted mobility that can generate data suitable for regulatory-accepted patient relevant outcomes

- Benefits for rare diseases

The availability of a such a tool has the potential to support the improvement of the quality of life of patients care and clinical outcomes by measuring physiological performance (e.g., movement and vital signs) as well as facilitating the assessment of new drugs benefits. In addition, remote assessment of movements offers a tangible

advantage as they can reduce travel to study sites for patients and families and increase patient access to research studies. Accurate daily mobility assessment can also help in interpreting overall patient quality of life especially when associated with additional information (e.g. use of pain killers) and can support the estimation of patient independency.

TIMELINES/MILESTONES AND DELIVERABLES <u>Stage 1 (M18):</u>

- Prototype finalized (6 months for the state of the art and user requirements analyses; 12 months for software programming and fine tuning in parallel with 12

months for preliminary testing and prototype finalization) **<u>Stage 2 (M30):</u>**

- Improved and validated set of tools + CE mark obtained

EXPECTED CONTRIBUTION AND EXPERTISE

SME in the field of mobile health technologies is the perfect target of the call, in particular in the selection and/or adaptation of existing technologies in the field of sensors and in the integration of data. People able to generate software for integration of data are also necessary.

Importantly, since patient involvement in the design and set up of these devices represents an added value to the project, the consortium members should be able to offer expertise and support for facilitating patient involvement in the project.

TOTAL BUDGET: 575.000 €

Contribution from the sponsors

In kind

- Chiesi

Support the involvement of patients in the project

Help in the definition of technical and regulatory requirements

- CSL Behring

Expertise in clinical data management

Expertise in e-clin operations

Financial

Project Name	Total budget (euros)	N° of industrial partners	Min % cash contribution from industrial partner	Cash contribution Industrial partners included in total budget
Mobility project	575.000	2	30%	100.000 (Chiesi) + 100.000 (CSL Behring) (53%)

RDR Challenge 2

Delivery system for intranasal administration of biological drugs to neonates

INDUSTRY SPONSOR

Chiesi Farmaceutici S.p.A. (Italy)

Contact: k.dallaglio@chiesi.com; d.ardigo@chiesi.com

AIM

To develop a delivery system allowing administration of liquids or gels in nostrils of the neonates for intranasal administration of biological drugs.

BACKGROUND AND RATIONALE

One of the biggest challenges in the rare disease field is the efficient delivery of therapeutic agents into the central nervous system (CNS) to target neurological symptoms. Currently, CNS drug delivery is achieved through invasive routes that bypass the blood brain barrier, such as intrathecal, intracerebroventricular or intraparenchymal injections that deliver directly to the cerebrospinal fluid (CSF) of the CNS. Although being currently employed in the clinical setting, the use of such techniques is limited as the risk of infections is very high. A promising strategy to bypass the blood-brain barrier is the delivery of drugs from the nose to the brain via Intranasal (IN) route. This is recognized as one of the most useful and reliable routes for brain drug absorption leading to quick drug action. In addition, intranasal administration bypasses gastrointestinal and hepatic metabolisms, thus enhancing drug bioavailability. Devices for IN delivery of liquid or lipid-based particulate formulations are already available in the market, however systems able to efficiently deliver biological drug formulations (e.g. viscous/semisolid cells suspensions, solutions of antibodies or large proteins) in the brain through nasal cavities are still lacking.

BENEFITS FOR RARE DISEASES

There are many rare conditions of the neonates (both term and preterm) that affect the CNS and require babies to be medically assisted with drugs delivered in the brain with the most efficient and delicate techniques. The development of a IN-delivery system for biological drugs specific for CNS targeting in the neonates would allow a safe and efficient administration of biological drugs minimizing product loss while increasing drug availability.

TIMELINES/MILESTONES AND DELIVERABLES Stage 1 (M18):

- Development of the prototype

•Intermediate step: engagement with EMA to validate the technical profile through ITF (early interactions on innovation) **Stage 2 (M30):**
•Demonstration of efficient delivery of different biological drug formulations in the brain in vivo in large animals (most probably non-human primates, NHP). This stage will include the treatment of at least 2 animals and tissue analysis (12 month-period).
•Obtain CE marking at the end of second stage is optional (preferred).

EXPECTED CONTRIBUTION AND EXPERTISE

Expertise in biomedical devices, biologics drug product formulation is preferred (especially if developed in neonatology therapeutic area). Optimal IN devices should not harm the nasal mucosal surface while ensuring reproducibility of drug administration and avoiding drug loss in the nasal mucus/cavity.

TOTAL BUDGET: 487.500 €

Contribution from the sponsor

In kind:

•Consolidated experience in Neonatology and biotech product formulation.
•Chiesi can also provide some biological material to be used for testing the device.

Financial:

Project Name	Total budget (euros)	N° of industrial partners	Min % cash contribution from industrial partner	Cash contribution from industrial partner included in total budget
IN Device project	**487 500**	**1**	**30%**	**112 500 (30%)**

RDR Challenge 3

Characterize Rare Bone Disorders (RBD) Mobility Challenges in Real World Setting

INDUSTRY SPONSOR

Ipsen

Contact: abdelali.majdi@ipsen.com

AIM

Develop full-body automated mobility assessment tool(s) to assess real-life mobility challenges in people living with RBD, to be compared vs available disease specific patient- and HCP-reported mobility assessments. Capturing these real-life data could help determine if patient characteristics or environmental conditions could be used to predict mobility outcomes and therefore open possibilities for preventive or corrective interventions, including home and assistive devices design.

BACKGROUND AND RATIONALE

RBD include a variety of disorders of bone formation, modelling, remodeling and removal, and defects of the regulatory pathways of these processes. The severity and progressive nature of some of these disorders such as fibrodysplasia ossificans progressiva (FOP), osteogenesis imperfecta (OI), or achondroplasia lead to mobility limitations. However, little is known about the mobility challenges individuals with these rare diseases are facing, potentially because their condition may limit their involvement in research studies that require frequent visits and/or travel over long distances. Several tools and scales are now available and used in clinical practice or in clinical trials setting to assess patient- and HCP-reported mobility and joint involvement. Although simple, and rapidlyadministered, these tools give only a snapshot of challenges patients are facing and do not reflect a 24/7 measurement in patients' home health care environment.

Digital technologies such as visual sensors and wearable devices have huge potential to measure mobility in the real-world setting. In parallel, the advances in home design and advanced robotics may offer new solutions to support these patients in daily living.

BENEFITS FOR RARE DISEASES

Better understanding of the daily mobility challenges will open possibilities to develop novel endpoints for clinical research to better understand the natural history of RBD and accelerate the development and approval of new therapeutic approaches aiming at preventing mobility decline, or at restoration of function and mobility in these

patients. In addition, a short to mid-term benefit could be in designing better home and assistive devices with an immediate impact on patient quality of life.

TIMELINES / MILESTONES AND DELIVERABLES

- **Stage 1 (M18)**

Development of a framework to inform larger real-world study of remote mobility monitoring

- Primary objective: Verification/validation of the tool(s) in real-life setting
- **Stage 2 (M30)**
- Exploratory objective: Development of adaptable home designs and assistive devices

EXPECTED CONTRIBUTION AND EXPERTISE

- Academic researchers working in the field of RBD
- Patient engagement is key in defining the research priorities and in every step of the project, therefore, involving Patient Organizations and CABs is mandatory
- SME and academic researchers working in the field of mobile health technologies is required
- Involvement of architects and designers (with or without expertise in assistive devices development)

TOTAL BUDGET: 487.500 €

Contribution from the sponsor *(provided all regulatory and legal requirements are met)*

In kind:

- Logistics and organizational support in planning and organizing workshop(s)
- Data sharing (including images, clinical data and Patient- Physician-Reported outcomes);
- Literature analysis (including systematic literature reviews)
- Expert (including Biostatisticians, Digital, Regulatory Affairs) and other technical support (translations, etc.)
- Support presentation of the results at relevant congresses and open access publications in peer reviewed scientific journals.

Financial :

Project Name	Total budget (euros)	N° of industrial partners	Min % cash contribution from industrial partner	Cash contribution Industrial partner included in total budget
Rare Bone Diseases Mobility Assessment	487.500	1	30%	112.500 (30%)

RDR Challenge 4

Pre-clinical assay to detect instability of microsatellite repeat expansions

INDUSTRY SPONSORS

- Pfizer

Contact person: Katherine.Beaverson@pfizer.com

- Cydan

Contact person: jmcarthur@cydanco.com

AIM

To develop and validate an assay for screening genes and/or compounds that modulate instability of microsatellite repeats. The rarity of repeat expansion/contraction events, estimated to be <1 per 10,000 DNA molecules, creates many challenges for assay development. The goal of this proposal is to devise, implement, and validate an assay that displays the robustness and sensitivity to detect repeat expansion/contraction events after ≤1 week of compound treatment. The assay should utilize a read-out that is suitable for a mid-scale screen of 100s to thousands of compounds in dose response. If such an assay is developed, it will be transferred to Pfizer for further characterization and validation.

BACKGROUND AND RATIONALE

There are >40 diseases caused by expansion of microsatellite repeats. These repeat expansions mediate pathology with a variety of mechanisms including loss of protein expression, toxic aggregation of the transcribed proteins, and toxic gain of function of RNA species that bind essential proteins among others.

There is increasing data supporting somatic expansion of repeats as a driver of disease. A working hypothesis is that in a fraction of cells, the repeats reach a threshold length and are destined to expand further throughout the lifetime of the patient. Because the pathology often correlates with repeat length, cells that have crossed the threshold are irreversibly degenerating.

Because of the stochastic nature of somatic expansion, it may be possible to protect the at-risk population with repeats that have not yet crossed the threshold length. While there are reliable animal models of somatic repeat instability, current cellular models (see Goold et al) require weeks to months of culture and the signal is not robust.

BENEFITS FOR RARE DISEASES

There are >40 diseases caused by expansion of microsatellite repeats. All are genetic (and therefore rare) and degenerative with no disease-modifying therapy. Examples include Huntingon's disease, spinocerebellar ataxias, myotonic dystrophy, Friedreich's

ataxia and Fuch's endothelial corneal dystrophy. More conditions are being linked to this mechanism as advances in DNA sequencing technology enable detection of repeat expansions in noncoding DNA. The unmet need is therefore high and increasing as new repeat expansion diseases are discovered. Somatic instability is a shared feature across different repeats and therefore, a therapy that prevents/slows repeat expansion may be able to treat multiple diseases. Drug discovery efforts are currently hindered by the lack of preclinical assays monitoring repeat size changes. The understanding of patients' unmet needs in diseases caused by repeat expansions will evolve as the ability to engage with patient communities to gain their perspectives and insights on meaningful benefit as applied to future investigational therapies increases. Consultation with patient representatives is certainly warranted and relevant when we have the ability to modify repeat instability.

TIMELINES/MILESTONES AND DELIVERABLES <u>Stage 1 (M18)</u>

- Assay development.

Identify a readout that can detect repeat expansions/contractions (rare events occurring in less than 1 in 10,000 DNA molecules). Build cellular/biochemical (eg, cell lysates, recombinant proteins, etc) assay that can monitor repeat size changes in ≤ 1 week. The ability to detect expansions in non-dividing cells or cell-free systems is highly desirable. The assay read-out should be based on a technology that is currently available and compatible with medium- to high-throughput screening and the manipulations should be compatible with automation.

<u>Stage 2 (M30)</u>

- Assay validation

Determine whether the performance of the assay is suitable to rank compounds and whether the assay is dependent on known modulators of expansion, eg, known genetic modifiers or tool compounds.

EXPECTED CONTRIBUTION AND EXPERTISE

Expertise would include knowledge of the biology of repeat expansion diseases and experimental methods used to study genomic instability and/or DNA repair at the cellular and/or molecular level.

Access to reagents and instrumentation that is compatible with small molecule screening is desirable.

TOTAL BUDGET: 487.500 €

Contribution from the sponsors

In kind

- Sponsors will provide technical input into assay design and requirements.
- Sponsors will be able to contribute with tool compound synthesis.
- If an assay meets the Phase 1 milestone criteria, sponsors will internalize it and evaluate performance, dependence on known modulators of repeat instability, and throughput during Phase 2. The intent is to make the assay, methods, and reagents available to the research community.

Financial

Project Name	Total budget (euros)	N° of industrial partners	Min % cash contribution from industrial partners	Cash contribution from industrial partners included in total budget
Microsatellite repeat expansions	**487.500**	**2**	**30%**	**112.500 (30%)**

Reference

Goold R et al. FAN1 modifies Huntington's disease progression by stabilizing the expanded HTT CAG repeat. Hum Mol Genet.2019 Feb 15:28(4):650-661.

Annex 2A ELIGIBLE COUNTRIES IN THIS CALL

Armenia
Austria
Belgium
Bulgaria
Croatia
Czech Republic
Denmark
Estonia
Finland
France
Georgia
Germany
Greece
Hungary
Ireland
Israel
Italy
Latvia
Lithuania
Luxembourg
Malta
Norway
Poland
Portugal
Romania
Serbia
Slovakia
Slovenia
Spain
Sweden
Switzerland
The Netherlands
Turkey
United Kingdom

Annex 2B What is a SME?

Small and medium-sized enterprises (SMEs) are defined in the EU recommendation 2003/361 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32003H0361

The main factors determining whether an enterprise is an SME are:

- staff headcount

- either turnover or balance sheet total

Company category	**Staff headcount**	**Turnover**	or	**Balance sheet total**
Medium-sized	< 250	≤ € 50 m		≤ € 43 m
Small	< 50	≤ € 10 m		≤ € 10 m
Micro	< 10	≤ € 2 m		≤ € 2 m

These ceilings apply to the figures for individual firms only. A firm that is part of a larger group may need to include staff headcount/turnover/balance sheet data from that group too.

SMEs must demonstrate positive financial results for the last 2 years and provide consolidate financial statements using International Financial Reporting Standards.

Annex 2C What is a PAO?

Patient organisations are defined as not-for-profit organisations which are patient focused, and where patients and/or carers and/or family members of patients represent a majority of members in governing bodies.

These are:

a. Umbrella organisations (e.g. representing either European organisations and/or national umbrella organisations for rare diseases);

b. European rare disease specific organisations (i.e. representing national organisations or individual patients on rare diseases) and

c. National rare disease specific organisations

The organisations shall fulfil the following criteria:

a. Legitimacy:

i. Represent rare diseases according to EU prevalence criteria (5/10 000) as defined in the: EU Regulation on Orphan Medicinal Products (1999), Commission Communication on Rare Diseases 2008), Council Recommendation on an Action on Rare Diseases (2009), and Directive on Patients' Rights in Cross-Border HealthCare (2011)

ii. the organisation should be formally established and registered as a not-for-profit organisation in one of the Member States of the EU/EEA/participating in the EJP for RD for more than 1 year

b. Mission/objectives: the organisation shall have its mission/objectives clearly defined and should agree to have it/them published on the EJP RD website.

c. Activities: the organisation shall have, as part of its activities, a specific interest in rare diseases which should be documented (e.g. through a report published on the organisation website).

d. Representation: the organisation shall be representative of rare disease patients within a member state or throughout the EU/EEA.

e. Structure:

i. the organisation should have governing bodies which includes a majority of rare disease patients or family members of rare disease patients.

ii. Includes in its governing structure a designated representative legally authorised to sign a contract with a public funder/Inserm

f. Accountability:

i. With proven activities such as rare disease patient support and/or advocacy activities and/or rare disease research

ii. statements and opinions of the organisation should reflect the views and opinions of its members and adequate consultation procedures with those members should be in place. In particular, the organisation should ensure that the appropriate flow of information is in place to allow dialogue both ways: from and towards its members.

iii. Can demonstrate that its account system is able to trace all costs related to the project and archive these costs for a duration of 5 years after the last payment received from the funder.

g. Transparency:

i. the organisation shall be financially independent, particularly from the pharmaceutical industry (max. 50% of funding from several companies) and disclose to the EJP RD its sources of funding both public and private by providing the name of the bodies and their individual financial contribution, both in absolute terms and in terms of overall percentage of the organisation budget. Any relationship with corporate sponsorship should be clear and transparent. This information shall be communicated to the EJP RD on an annual basis.

ii. The organisation shall publish on its website the registered statutes, sources of funding, and information on their activities.

iii. To facilitate communication, a contact person shall be identified for each organisation.