RESEARCH PROJECTS ON PERSONALISED MEDICINE – "MULTIDISCIPLINARY RESEARCH PROJECTS ON PERSONALISED MEDICINE – DEVELOPMENT OF CLINICAL SUPPORT TOOLS FOR PERSONALISED MEDICINE IMPLEMENTATION"

ERA PerMed

NATIONAL GUIDELINES FOR APPLICANTS FOR THE IMPLEMENTATION OF ERA-NET ACTION ON PERSONALISED MEDICINE (PM)

JOINT CALL 2021

The Ministry of Science and Education of the Republic of Croatia (here after, MSE) is the national funding and coordination body responsible for the implementation of the ERA PerMed programme in the Republic of Croatia.

As such, the MSE hereby prescribes the National guidelines for applicants for the implementation of ERA PerMed in the Republic of Croatia (2017 – 2022) which provides information regarding national participation criteria, including scientific criteria, funding, consortium and other requirements.

FUNDING BODY DETAILS

National funding body	Acronym	Address	Telephone	Fax
Ministry of Science and Education of the Republic of Croatia	MSE	Donje Svetice 38 10 000 Zagreb Republic of Croatia	+385 1 4569 000	+385 1 4594 301

NATIONAL CONTACT POINT DETAILS

NCP name and surname	E-mail	Telephone Number
Mateo Ante Bosnić	MateoAnte.Bosnic@mzo.hr	+38514594166

TOTAL BUDGET

Republic of Croatia has financially committed to contribute to *ERA PerMed programme* with a contribution of EUR 301.250,00. Hence, the Croatian applicants will have a budget for the Joint Call 2021 in the amount of EUR 120.000,00.

In particular, in 2021 Ministry of Science and Education is open to project proposals within all research areas (see "Scientific criteria"). The highest ranked project proposals evaluated on merit based criteria will be approved for funding, subject to available budget.

NATIONAL CRITERIA

Participation criteria: Terms and conditions of eligible entities

MSE funding is limited to a Croatian project partners only. Croatian project partner could be consortium (consisting of at least two national legal entities) or single legal entity.

Eligibility criteria for Croatian project partners are as follows:

- research organizations registered in the Register of Research Organizations at the Ministry of Science and Education of Republic of Croatia[1]:
    - public research institutes
    - public higher education institutions
    - other legal entities performing research activity

- other legal entities performing research activities
    - non-governmental and non-profit organizations (NGO's) or institutions whose main object is research activity or research and development activity registered by the Ministry of public administration
    - small and medium enterprises (SME's) registered by the Ministry of economy, entrepreneurship and craft.

- Only transnational projects shall be funded.

- Each consortium submitting a proposal must involve at least three partners eligible for funding from three different countries whose funders participate in the call (see list above). All three legal entities must be independent of each other.
  At least two partners out of the minimum three eligible project partners of the consortium must be from two different EU Member States or Associated Countries.

- The project coordinator must be eligible to be funded by his/her regional/national participating funding organisation.

- The maximum number of partners per project at the pre-proposal stage is six. At the full-proposal stage, the consortium may be expanded to up to seven partners in total only by inclusion of a partner from an underrepresented country. A list of underrepresented countries will be provided to the coordinators invited to submit full-proposals.

- Within one consortium, no more than two partners from the same country participating in the call will be accepted, including those partners with their own funding. For some funding agencies, the maximum number of eligible partners that can be funded in one project is limited to one (see also "Guidelines for Applicants" for individual funding rules)

[1] According to Article 22 of the Scientific Research and Higher Education Act (Official Gazette 123/03, 198/03, 105/04, 174/04, 02/07, 46/07, 45/09, 63/11, 94/13, 139/13, 101/14, 60/15, 131/17

- Partners not eligible for funding by one of the organisations participating in this JTC (e.g. from non-funding countries or not fundable according to the regional/national regulations of the participating funding organisations) may participate in projects provided that they demonstrate, with the full-proposal submission, that their economic and human resources have already been secured and will be available at the start of the project. No more than one partner with its own funding is allowed in consortia with at least three partners eligible for funding.

The eligibility criteria of the applicant will be verified based on the Excerpt from the Register of Scientific Organizations, which will be provided by the Ministry of Science and Education.

Consortia submitting applications to this call are strongly encouraged to include partners from different categories (A, B and C) in line with the crosscutting/multidisciplinary nature of the call, where the aim is to include partners at different levels in the value chain. The number of participants, the category of partner organisations and their research contribution should be appropriate for the aims of the research project and should be reasonably balanced in terms of international participation. Each collaborative project should represent the critical mass necessary to achieve ambitious scientific goals and should clearly demonstrate added value for the cooperation.

Research groups, SMEs and industry partners (non-SMEs) not eligible for funding by one of the organisations participating in this joint transnational call (e.g. from non-funding countries or not fundable according to regional/national regulations of the participating funding organisations) may participate if they are able to secure their own funding. Such partners must state in advance their source of funding for the project. They are treated as full partners and must be included in the pre- and full-proposal templates as such. Please be aware that **no more than one partner with its own funding** is allowed in consortia that comprise at least 3 partners eligible for funding (i.e. proposals with 4-6 partners in total, including the partner with its own funding, in the pre-proposal stage, and up to 7 for full-proposals). A letter of commitment must be included as an annex to the proposal in the full-proposal step summarizing the commitment of this partner to the project and demonstrating the source of funding. The budget of a non-funded partner shall not exceed 30% of the total transnational project budget requested.

To collect the necessary patient data and/or samples for the proposed study, a consortium may need to collaborate with other centers. If the only role of those centers is to provide patients' data and/or samples for the study, they will not be treated as partners of the consortium but can be included otherwise, e.g. via cooperation agreements or subcontracting.

Number of partners in the proposal*	**Pre-proposal**				**Full-proposal** (only by inclusion of one underrepresented country)
	3	**4**	**5**	**6**	**7**
Maximum number of partners with own funding	0	1	1	1	1
Maximum number of partners per country	1	2	2	2	2

*** minimum 3 partners eligible for funding from three different countries participating to the call**

Each project partner has to be represented by one principal investigator. Within a joint proposal, each project partner's principal investigator will be the contact person for the JCS and the relevant regional/national funding organisation. Each consortium must nominate one project coordinator from among the project's principal investigators. The nomination of a co-coordinator is not allowed. The coordinator must be eligible to be funded by his/her regional/national participating funding organisation. The project coordinator will represent the consortium externally and in his/her dealings with the JCS and the Call Steering Committee (CSC), and will be responsible for its internal scientific management such as project monitoring, reporting, intellectual property rights (IPR) management and contact with the JCS.

Although proposals will be submitted jointly by research groups from several regions/countries, research groups will be funded by the respective funding organisation of the region/country from which they have applied. Applicants are therefore subject to the eligibility criteria of the respective funding organisations (see also Annex II and "Guidelines for Applicants"). They should therefore read the funding rules and eligibility criteria of their funding organisations carefully. **Applicants are strongly advised to contact their relevant funding organisation (see also Annex I) prior to submission; please note that this step might be mandatory for some regions/countries.**

Please note that if a **partner** is found to be non-eligible by one of the funding organisations after the formal check, the entire proposal may be rejected without further review. For a definition of eligible partners see "Guidelines for applicants", the regional/national regulations, and contact your regional/national funding organisation (see also Annex I).

Nevertheless, the applicant will be informed that a redress procedure is available. The redress procedure pertains to the eligibility – checking process only; it is not an automatic re-evaluation, and the judgement of appropriately qualified experts is not called into question.

For regional/national eligibility reasons, applicants must indicate in the pre-proposal form if the study submitted is subject to other evaluation processes, such as other joint transnational calls and regional/national calls. Applicants shall avoid applying to different calls for same research activities. Double funding is not allowed.

Patient involvement

ERA PerMed strongly encourages the active involvement of members of the public in the proposed research projects. This includes patients, citizens/potential patients, healthcare providers, people who use health and social care services, as well as patient organisations. The goal is to raise awareness, share knowledge and improve dialogue between researchers, healthcare providers, policy-makers, industry and citizens.

Accordingly, consortia submitting proposals to this call are asked to describe the level of public involvement in the research throughout the various stages of research design, conduct, analysis and dissemination. The extent of citizen/patient involvement may vary according to the context of the study proposed and regional/national regulations of participating funding organisations. The involvement of patient representatives/organisations in research proposals submitted to this call is part of the evaluation: "*2. Impact*: *c. Involvement of pertinent patient organisations, patient representatives (if*

available/applicable)" and "*3. Quality and efficiency of the implementation:* e. *Coherent integration of all kind of project partners (e.g. academia, clinical/public health sector, industry partners/SME, Patient representative/organisation) needed to successfully accomplish the proposed work".*

REPORTING REQUIREMENTS

Each project coordinator, on behalf of all participating project partners, shall submit an annual and final scientific progress report the first year, second year and a final report of the transnational project in English to the JCS. A report template will be provided by the JCS stating the scientific progress, the goals that have been met, and corrective measures in the event that the annual project plan has not been fulfilled. It may also be necessary for project partners' principal investigators to submit reports individually to their national funding agency/body in accordance with the respective regional/national regulations. In addition, project coordinators may be asked to present the project results at ERA PerMed meetings and may be invited to attend at least one midterm seminar and one final symposium[2]. Accordingly, travel expenses to attend these mandatory meetings should be included in the proposal budget plans.

The coordinator must promptly inform the JCS in case of ANY significant changes in the work programme or the consortium's composition. The JCS will inform the relevant funding organisations, who will decide upon the proper action to be taken.

Additionally, Croatian project partner receiving the funding under this call will be monitored by MSE. Croatian project partners have the obligation to submit annual and final financial and narrative reports on the project progress, describing in clearly manner whether or not they achieved the set of key performing indicators. MSE will proscribe the form for the annual and final reports. Furthermore, Croatian project partners also have the obligation to submit the final financial and narrative reports.

The eligibility criteria for the applicant will be verified based on the Excerpt from the Register of Scientific Organizations, which will be provided by the Ministry of Science and Education. Legal entities receiving basic funding from the MSE can only be granted for funds covering extra expenditure, i.e. as an addition to their basic financing.

Maximum limit requested per partner / per country / per proposal

Only costs directly related to the proposed research activities are eligible for financing under this call. Activities supported by other sources are not eligible for financing. Applicant must ensure that there is no double financing during the whole project implementation.

Total available budget for Joint Call 2020 for **Croatian project** partners is 120.000,00 Euro.

Project duration

The maximum duration of the projects is three years in accordance with ERA PerMed funding organisation regulations. The studies performed should be finalised at the latest within the third year of the funding period. Eligible costs and funding provisions may vary according to the respective funding organisation's regulations. Project partners must refer and adhere to their own regional/national

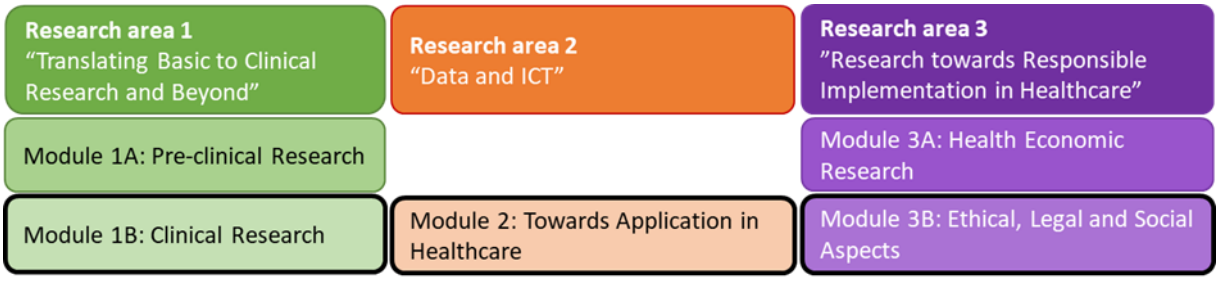
[2] If ERA PerMed funds are available.

regulations and scientific remits, as detailed in the relevant regional/national announcements (see Annex II).

SCIENTIFIC CRITERIA

Thematic areas and topics to be funded

The JTC2021 of ERA PerMed comprises three Research Areas:



ICT: Information and Communications Technology (or Technologies)

Each proposal **MUST address** the **modules 1B "Clinical Research", 2 "Towards Application in Healthcare" and 3B "Ethical, Legal and Social Aspects"**. Inclusion of modules 1A "Pre-clinical Research" and 3A "Health Economic Research" is optional. Their added value to the proposal and the mandatory modules has to be clearly described.

	Research Area 1	Research Area 2	Research Area 3
Mandatory	**Module 1B**	**Module 2**	**Module 3B**
Optional	Module 1A		Module 3A

Assessment of the coherent integration and combination of the different research areas and modules in the proposals is part of the evaluation process.

Research Area 1: *"Translating Basic to Clinical Research and Beyond".*

Research on the application and validation of known biomarkers in clinical practice and for the development of diagnostic and clinical decision support tools; on the therapeutic targets (including data e.g. obtained by omics approaches, dynamic simulations, imaging, biomarker monitoring, etc.) to predict, for example in advance of a specific therapy, the response of the patient in a dedicated stratification process or to adapt an ongoing therapy. The inclusion of a strategy to ensure the robustness and reproducibility of results is strongly encouraged. Research proposals should outline how implementation of the technology and research findings will be transformed into clinical practice and address regulatory questions conflicting with the implementation.

Optional additional topics for the JTC2021 (module 1A): Improving exchange between basic and clinical research to allow the transition from bench to bedside (e.g. by translational science, transferring pre-clinical technologies/other predictive tools to clinical application) but also vice versa by using, for example, existing clinical databases, repositories and cohorts, and by sharing experiences obtained in conventional and innovative clinical studies/trials. Appropriate validation strategies according to the translational gap to be bridged should be described.

Module 1A: Pre-clinical Research

Scope

- Development and implementation of high-throughput pre-clinical predictive models for (A) validation of data and hypotheses from human population, clinical, molecular and genomics studies and/or (B) prediction of clinical outcome. This may include in silico models, cell culture/co-culture, organoids and animal models, etc.
- Classification of of diseases at the molecular level, which can be instrumental for supporting successful clinical implementation of PM, including pre-clinical studies for the validation of biomarkers that can be used in diagnosis, prognosis and prediction of response to treatment.
- Validation and characterisation of the role of biomarkers in predictive medicine for future prevention, assessment and management of diseases (in preclinical models, in terms of reproducibility, safety and efficiency).

Mandatory Module 1B: Clinical Research

Scope

- Improvement, validation and combination of analytical tools and methods (e.g. imaging, physiological monitoring, omics or other biomarkers) for diagnostics and treatment using integrated analytical methods, allowing the discovery and validation of molecular and environmental factors (including co-morbidities, ethnic and sex-related differences) that can be used for patient stratification and treatment decisions.
- Pharmacokinetics and pharmacodynamics studies in preparation of clinical trials.
- Development and evaluation of concepts for innovative clinical trial methodologies, suitable for PM approaches, taking into account the fact that more flexible and innovative trial design is needed, considering both health benefits and health economics (see also Module 3A). Development of novel strategies that will enable clinical scientists to accelerate the transition from clinical observation to diagnostic development.
- Development of new concepts and stratification strategies in exploratory clinical studies (for further information, see also the blue box on pages 11/12).
- Clinical, omics and environmental data integration, use of machine learning to provide the basis for more personalised treatment for patients.
- Research on the implementation of PM approaches in the treatment of patients with comorbidities.
- Clinical support tool testing and validation in clinical practice.
- Innovative m/e-health or telemedicine applications testing and validation in a clinical setting.

Research Area 2: *"Big Data and ICT[3]".*

The PM approaches to be established should support the easy flow of experimental evidence and various types of data (such as omics data, data on biological samples, as well as patient outcomes) generated *in silico* or directly by patients, the robust analysis and interpretation of information and results such as clinical data (including imaging data and physiological monitoring data) among different institutions while ensuring data security and data protection.

The re-use and sharing of data through public databases are encouraged and the re-use or combination of existing tools is also welcome. Applicants have to describe both new and existing tools, methodologies, technologies and digital supports to be used in the project. This includes ICT solutions such as eHealth and mHealth solutions, and telehealth solutions for the timely and safe collection and transfer of health information; and to facilitate the use of already collected data, including electronic medical records (structured and unstructured sources), by respecting data security, protection and privacy on one hand, and ensuring interoperability, completeness, sufficient documentation and comparability of data on the other hand.

Outlining how the ICT solutions/decision support tools developed/used in the project will be maintained after the end of the project is also encouraged.

Applicants have to explain how data generated and used in the project will be stored and made available during and after the project.

Mandatory Module 2: Towards Application in Healthcare

Scope

- Use of large, multimodal datasets ("big data") to enable a new understanding of disease mechanisms. Application of artificial intelligence approaches to big data to find new subgroups of patients, to predict patient outcome to treatment and for biomarker validation. Research on health data integration and interpretation in order to advance PM by combining different kinds of datasets from various sources is necessary. These datasets can originate for example from large, multimodal and multi-centre public data repositories or clinical records from different sources. They can comprise data from multiple biological organisation levels or scales, for example, behavioural, physiologic, molecular and imaging data. In addition, different forms of mathematical, statistical and modelling frameworks can be used for exploring and validating data quality and information content. This might include, for example, the development of standardised strategies for cross-validating biomarkers across existing databases.

- Development of new and validation of existing innovative and easy-to-handle clinical decision support tools tailored to the needs of healthcare professionals. Such tools should provide reliable and accurate algorithmic interpretation of complex multifactorial and multimodal data (including e.g. clinically validated data and information on current diagnosis and treatment options) to be integrated in real time and accounting for expert feedback.

3 Information and Communications Technology (or Technologies)

- Development of good practices for sample and data management in compliance with FAIR principles and GDPR. Development of core standards and joint working practices for storage, accessibility, interoperability and reusability for samples and data.
- Development of approaches for innovative use and combination of already validated and novel eHealth and mHealth solutions, such as new physiological sensor and patient monitoring technologies combined with mHealth solutions for real-time personalised feedback.
- Research on the development of innovative telemedicine applications in different healthcare systems to complement the direct contact between healthcare personnel and patients. This can be beneficial for example if there is a high risk of infection or for patients with limited mobility living in rural areas. Telemedicine approaches could also be used to facilitate exchange between physicians in highly specialised centres and those in a more general healthcare setting.

Research Area 3: *" Research towards Responsible Implementation in Healthcare"*

Research on ethical, legal and social aspects (ELSA) of PM approaches, for example in the context of decision support tools or reflecting on questions of fair access to new and often expensive treatments. This could include research aiming to avoid biases due to machine learning techniques/tools and the use of artificial intelligence (AI) or research on suitable regulatory approaches for diagnostics, and drug development as well as fundamental societal challenges and patient representative involvement.

Optional topics for the JTC2021 (module 3A): Research on health economics aspects (e.g. through to market access, if applicable) is also welcome. Health economics research and payment models can assess the cost-effectiveness of PM approaches. New methods, models and tools to enable accurate assessment of PM approaches might be developed.

The studies conducted in research area 3 and the corresponding work package should relate directly to the research question(s) addressed in research areas 1 and 2.

Module 3A: Health Economic Research

Scope

- Research on health economic aspects of newly innovative PM approaches, e.g. on the cost-effectiveness of these approaches for treatments, taking into account patient outcomes, quality of life, patient preferences and socioeconomic contexts.
- Research investigating whether a patient-centred, new PM approach requires refinement of – or even new – health economic and pharma-economic models, not only for the treatment of diseases, but also for prevention.

Mandatory Module 3B: Ethical, Legal and Social Aspects

Scope

- Research on ethical, legal and social aspects, when using artificial intelligence techniques: availability and suitability of data for training (machine learning algorithms), requirements on transparent and explainable decision-making, questions of responsibility and liability, potential changes in the role and self-image of physicians, privacy and personal data issues, obligation of information towards patients.
- Research on benefits and harms of genetic engineering (gene transfer technology).

- Research on the role of genetic testing in clinical practice, the clinical interpretation of test results and on the potential clinical, ethical as well as legal consequences in the context of PM.
- Research on how to overcome potentially biased datasets lacking (sample) heterogeneity of information (e.g. gender, mixed and diverse populations, different cultural perspectives, social inequalities, etc.). This may also include the reflection on defining norms within decision support tools (definition on what is defining a "normal/healthy" status).
- Research on the personal/individual (objective vs. subjective) component during the creation of decision support tools (i.e. ethics applied to develop, program and train the decision support tool).
- Development of strategies for regulatory approval of clinical decision systems based on statistical learning, machine learning and artificial intelligence technologies.
- Research on the use of the decision support tools in the prevention and stratification of the healthy society/population and fair access to these tools for all citizens and populations.
- Right to know/not to know and sharing of research findings: how to use artificial intelligence predictive tools, finding a balance between patients' rights and research needs.
- Research on how to enable stakeholder exchange and collaboration (including all different key contributors – academic researchers from different disciplines, healthcare providers, industry/pharma and regulatory authorities, as well as citizens, patient representatives and communities, regardless of their social, environmental and economic conditions) including all essential key players in the development of PM approached from the very beginning of a study.
- ELSA research on the provision of equal access to PM approaches for all patients regardless of economic, educational or geographic status (including research on the effect of PM on social inequalities).

Consortia are asked to clearly demonstrate and describe how the selected research areas and modules are integrated in the proposal and addressed in the work plan. To address a module/research area adequately, there has to be a dedicated work package in the work plan with a topic fitting to the module. In addition, the partner responsible for the respective work package needs to have the appropriate expertise.

Croatian Principal Investigator

Principal investigator for Croatian project partner must hold a Ph.D. degree and should have at least 5 years of research experience after having obtained Ph.D. Research leader must be employed under employment contract at Croatian institution participating in transnational consortium. Croatian project partner will commit that minimum 30% of research leader's workload will be dedicated to the ERA PerMed project. Croatian project partner research leader will repost on project progress to national coordinating and funding body – MSE.

If coordinator of transnational consortium, Croatian project partner will appoint one research leader (principal investigator) who will monitor the implementation of transnational project activities, and report on it to ERA PerMed secretariat.

The funds will be allocated to the Croatian project partner when evaluated positively by ERA PerMed Secretariat and validated by MSE.

Only one principal investigator represents each project partner. Within a joint proposal, each project partner's principal investigator will be the contact person for the JCS and the relevant national/regional funding organisation. Each consortium must nominate only one project coordinator among the project's principal investigators. The coordinator must be an eligible project partner for the national/regional funding organisation participating in the call. The project coordinator will represent the consortium externally and towards the JCS and Call Steering Committee (CSC), and will be responsible for its internal scientific management such as project monitoring, reporting, intellectual property rights (IPR) management and the contact with the JCS.

FUNDING CRITERIA FOR CROATIA'S PROJECT PARTNER IN ERA-NET ACTION ON PERSONALISED MEDICINE (PM)

Eligible costs categories

For Croatian applicants, rules on eligible and ineligible costs can be found in the Annotated Model Grant Agreement (AGA) for H2020 Programme:
https://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/amga/h2020-amga_en.pdf.

All budget items must be justified and provided for eligibility. All costs must be made during the period of the project duration. Applicants are advised to contact the national contact point for the pre-eligibility check.

VAT eligibility

For Croatian applicants, the general H2020 rule applies regarding VAT eligibility within the ERA-Net Action on Personalised Medicine (PM) programme. VAT is an acceptable cost for all applicants that are non-profit legal entities if there is no right to tax deduction. VAT is in that case the ultimate expense for the applicant and as such is recorded in the accounting books. Regarding profit organizations (that are liable for paying and collecting VAT, and VAT for them is not the ultimate expense, the VAT expense is not eligible cost for the project cost within the ERA-Net Action on Personalised Medicine (PM).

Subcontracting rules

Subcontracting for the sake of performing and implementing certain tasks/activities that are part of the main project activities is allowed and considered eligible. For more information regarding subcontracting rules please consult:
https://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/amga/h2020-amga_en.pdf .

LINKS AND REFERENCES TO FIND SPECIFIC (NATIONAL) REQUIREMENTS

https://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/amga/h2020-amga_en.pdf
Applicants are advised to contact the national contact point for the pre-eligibility check.

The full version of ERA PerMed national guidelines for applicants for the implementation of ERA-Net Action on Personalised Medicine (PM) in the Republic of Croatia (2017 – 2022) will be published on the MSE website.