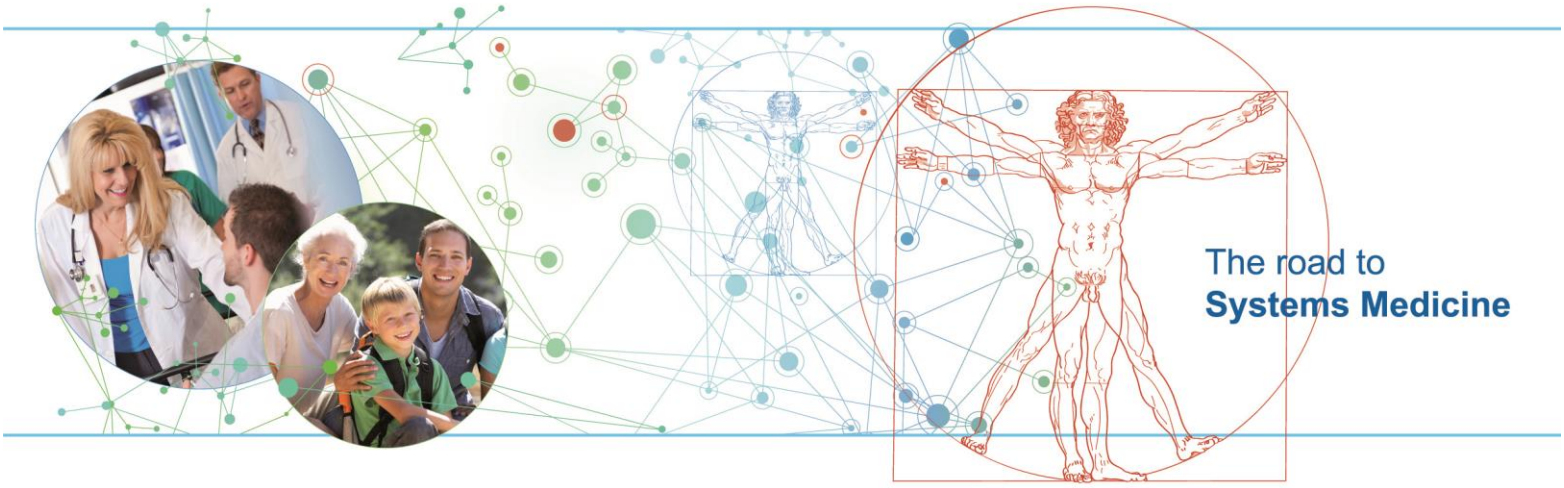
Coordinating Action Systems Medicine
Implementation of Systems Medicine across Europe



Common funding initiatives

CASyM strategy paper

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COMMON FUNDING INITAITIVES

Executive summary

Systems Medicine is a cross-disciplinary approach fusing classical biological and medical disciplines with informatics and computer science to integrate all relevant classes of data sets. It holds great promise for the establishment of new preventive and therapeutic approaches to tackle current and future medical challenges. Due to its complexity, a common approach of actors from different disciplines is needed to realise Systems Medicine at its full potential. For an efficient implementation of Systems Medicine in the European Research Area both national and private funding bodies play a decisive role. As it has been demonstrated before in Systems Biology, incentivising truly interdisciplinary consortia by issuing specific calls for project funding plays a pivotal role in supporting successful development of promising new research areas in a top-down fashion.

This strategy paper is supposed to serve as a basis for further discussion in the Member States on a realisation of joint measures for the implementation of Systems Medicine in Europe. It is based on intensive consultations with European funding stakeholders in which several fields of actions have been identified. These include (i) establishment of funding measures for proof of concept (PoC) studies to demonstrate feasibility and to allow demonstrating the added value of Systems Medicine approaches, (ii) improving data access –sharing and –standardization through dedicated eligibility funding criteria for full leverage on existing and future data from Systems Medicine projects, and (iii) integrating interdisciplinarity as a central requirement for project consortia and in training measures.

Background

This strategy paper deals with the needs for an implementation of Systems Medicine in Europe from the perspective of research funding stakeholders. It is built on the efforts of work package 5 within the Coordinating Action for the implementation of Systems Medicine in Europe (CASyM) initiative, which deals with possible modes of alignment of national efforts to achieve common European funding initiatives in the field of Systems Medicine.

The strategy paper is based on dedicated, intensive discussions with stakeholders from both public and private entities active in the funding of public research activities. Different modes were employed to perform these discussions in the most efficient way: they ranged from written questionnaires to one-to-one telephone interviews and dedicated annual funding stakeholder meetings. The results of these diverse interactions have been collected, consolidated, and put into the condensed form of this strategy paper, which is supposed to both summarize decisive matters in this field and point to potential solutions for currently open issues in European funding initiatives. This paper should serve as a basis for further discussion in the member states to agree on a realisation of joint measures. It is aimed at supporting national and European funding stakeholders in the process of identifying the best mode and practice in collaborating across borders and in gaining true added value by employing common funding initiatives for the implementation of Systems Medicine.

Introduction

A systems approach to medicine

Systems Medicine is a cross-disciplinary approach fusing classical biomedical disciplines with informatics and computer science to integrate all relevant classes of data sets. This approach holds promise for a more comprehensive understanding of human health and disease through the development of computational

models, which enable researchers to map the (mal)functioning of the human body, its processes and interactions across multiple levels of structural and functional organization. Systems Medicine is currently laying the foundation for a new medical practice having the potential to lead to beneficial economic and social impacts through the targeted and personalized application of therapeutics and preventative measures.

Europe is currently facing a plethora of societal challenges, many of which are related to healthcare due to an ageing society, ineffective drugs, empty drug pipelines, and missing approaches for disease prevention and prediction. The "low-hanging fruits" have been picked with classical medical approaches, but the complexity of the human body and its diseases require new approaches to get to a real understanding of these and consequently to novel applications in prediction, prevention and therapy. It has become apparent in recent years that personalized medicine is supposed to be one of the central answers to these challenges. The expression of a "4P" (Hood and Gallas, 2008[1]) as medicine of the future has been coined: Predictive, personalized, preventive, and participatory. However, the way to reaching this goal remains largely elusive.

As complexity of the human system has been identified as the major problem to reach an understanding of medically relevant processes, a systemic view on the human body, its diseases and the disease-causing mechanisms is needed. Systems Medicine leverages on the technological and economical advances in biomedical sciences (specifically the –omics technologies such as Genomics, Transcriptomics, Metabolomics etc.) by integrating the complex molecular with clinical data into computational models. Such models allow a comprehensive analysis beyond the limited data processing capability of the human brain. Systems Medicine computational models can be used to translate such complex data into understandable results and to generate hypothesis about the biological system in question, which can be challenged again by obtaining and feeding-in new biomedical information. Predictive models based on a mechanistic understanding can lead to preventive and new therapeutic approaches. Based on individual profiles, personal models for each patient can be derived. Hence, Systems Medicine provides the conceptual framework through which 4P medicine can be established.

Need for a community effort

Complexity of Systems Medicine

Taking the next step in medicine towards interdisciplinary collaboration and leveraging on the high-dimensional data both from disease models as well as from patients is now overdue. True Systems Medicine research does afford the interaction of many different scientific and computational areas. Already on the computational side, these include: (i) Biostatistics for clinical trial and cohort study data, (ii) Health informatics for patient data, (iii) Bioinformatics for biomedical (e.g. –omics) data, and (iv) Systems Biology for building in silico models. On the biomedical side, clinicians, biologist, biochemists, epidemiologists, and, dependent on the field of interest, even ecologists can be of central importance to build and drive a successful project.

Learning from systems biology success

The advancement of novel technologies in the field of biological sciences has led to a dramatic progress in the field of biological sciences in the past decades in classical biomedical research approaches, only single biomolecules could be analysed and their restricted set of interactions with e.g. binding partners could be unravelled. Gaining knowledge about the full spectrum of biomolecules made it possible to look at a much bigger part of the picture than before. However, the development of the so-called systems biology was not

[1] Hood L, Galas D. P4 Medicine: Personalized, Predictive, Preventive, Participatory: A Change of View that Changes Everything. Computing Community Consortium; 2008 (Article, PDF)

straightforward: the amount and complexity of generated data exceeded the capability of most biologists and only the inclusion of bioinformaticians, mathematicians, and computer scientists into collaborative projects allowed interpreting the data and making use of their full potential. The shift towards the multi-disciplinary consortia was achieved in a "top down" approach by issuing calls for research projects explicitly requiring interdisciplinary teams working on cutting edge systems biology questions. This was most successful in trans-national initiatives and the collaboration across European borders. Hence, if Europe wants gain leadership in defining, building, and employing future medical approaches based on systems medicine, funding of multidisciplinary research projects on a European level will be a necessity.

Gaining critical mass in funding

The high level of complexity that successful Systems Medicine projects bring about reveals a need for collaboration amongst scientists and clinicians from all over Europe. Next to building multidisciplinary consortia across borders, the needed scientific services provided by infrastructure functionalities, such as cohorts and databases, might often require transnational coordination. Even within the larger countries in Europe, there is not always the critical mass in all relevant fields to build such research consortia that are successful and internationally competitive. Therefore collaboration between funders is needed to realise the full potential of competences for Systems Medicine in Europe.

Fields of action from the Systems Medicine perspective

The following fields of action for European funders have been identified as crucial for the implementation of Systems Medicine in Europe. In this process, the CASyM roadmap, V1.0 has been a valuable tool.

Proof of Concept projects to demonstrate feasibility

Proof-of-concept projects are an important tool to support the spreading of new approaches. Due to the emerging status of Systems Medicine, PoC projects, which are able to demonstrate the potential of Systems Medicine for developing a better and more personalised medicine, are still scarce. Therefore an emphasis in Systems Medicine programmes is to launch successful PoC projects that will provide evidence for the feasibility of Systems Medicine projects both on the methodological as well as on the technological level. A tangible clinical benefit should be one of the main drivers for creating the project and should be a central outcome. The aim of such PoC projects is to raise interest in the medical and scientific communities, the pharmaceutical industry and the political decision makers. This effect will be a key for a broad and efficient implementation of Systems Medicine in the European Research Area.

Improved data access, -sharing and –standardization

The production of high or even massive amounts of data in most research projects that deal with –omics technologies, clinical data, and/or cohorts poses an ever-increasing challenge to the biomedical scientific community in general and research project consortia in particular. Among the most pressing threats for successful and comprehensive utilisation of existing and newly generated data are their fragmentation and lack of standardization. Moreover, standardised data need to be sustainably stored and, if possible and applicable, openly shared amongst consortium members and with the research community. These prerequisites are being widely acknowledged as crucial for successful Systems Medicine projects with sustainable impact.

Hence, project funding should include strict eligibility criteria concerning data management: the use of international data formats, the sustained integration of newly generated data into existing repositories and data bases, as well as the integration of existing data into the project to be funded need to be essential aspects in a data management concept. This element should be demanded in all calls for proposals.

Next to these general requirements for all projects in Systems Medicine, the funding of projects specifically dedicated to improve utilisation of existing data will be considered to facilitate Systems Medicine approaches. This includes among others:

- Facilitating the provision of data from existing data repositories through
  - Data standardisation and curation;
  - Overcoming fragmentation by integration of different data types;
  - Merging of data from different studies;
  - Research into data compatibility and analysis of heterogeneous data sets;
- Continuous enrichment and Expansion of databases with data from new of research projects.

Similar projects are currently funded in the framework of the Innovative Medicines Initiative (IMI) with the goal of a standardized knowledge management (KM) and analysis platform for biomedical data sets (eTRIKS project) and the streamlined re-use of existing health data (EMIF project) for all other IMI projects and beyond. Also the Joint Programming Neurodegenerative Diseases has set out to improve the data basis for research in neurodegenerative research by defining standards and investigating possibilities to merge existing cohort data.

Multidisciplinarity

Project consortia

One of the central cornerstones of Systems Medicine is the variety of disciplines, which ideally engage together in a research project consortium. As clinical benefit should be at the heart of all Systems Medicine projects, the participation of clinicians is mandatory. Molecular approaches and experimental models to derive and test hypothesis requires a range of biologists. Even in the computational field, mathematical modelling needs theoretical scientists, while data integration and analysis is to be covered by computer scientists from the bioinformatics, medical informatics and biostatistics field.

It has been a key success factor for systems biology to incentivise or even demand the formation of such cross-disciplinary consortia for systems-oriented projects. The composition of consortia with the relevant disciplines will therefore be implemented through the eligibility criteria.

The same requirement for the expertise composition of the consortia applies to the reviewer panels that perform the evaluation. Only the representation of all disciplines can guarantee that the selected projects do not fall short in exploiting a full systems medicine approach and that the projects have the necessary competitive edge. Therefore, apart from biologists, the presence of clinician scientists as well as experts in computational modelling is necessary, same as experts in bioinformatics and medical informatics, which are needed to cover the whole complexity of data involved.

Training the new generation of medical doctors and scientists in systems approaches

Training of young and experienced researchers and clinicians will play an instrumental role for an efficient implementation of Systems Medicine as a common everyday approach. As pointed out above, there is an eminent need to bring together experts from various disciplines to make Systems Medicine a reality. However, in order to work together, a common understanding of principles and problems is needed. Clinicians that are in need of new tools and approaches for existing and novel medical problems must be able to understand, what cutting edge systems biology approaches and computational modelling can do for medicine to tackle and finally understand how to best react to medical conditions. In turn, computational and biological scientists should learn to understand and ultimately address real world clinical problems and challenges.

Hence, training programmes should be foreseen that allow scientists and clinicians to better understand each other's challenges and language. A continuous and concerted effort in such cross-disciplinary training will lower borders between the disciplines, allow mutual understanding and finally strongly facilitate

collaborations and building of truly cross-disciplinary consortia. This central need of new trainings and educative measures should be reflected whenever possible in future Systems Medicine funding measures.

Scientific Implementation of Systems Medicine

Community building

Common projects

Community building is an essential element for a successful implementation of Systems Medicine. As described above, Systems Medicine requires a multitude of different disciplines and expertise integrated for both, developing the right questions to improve medicine and to develop new diagnostic, therapeutic and preventive approaches. Therefore a constant exchange between the different research groups is needed to develop an understanding for each other's competence and contribution for a common research across the different disciplines.

Systems biology, whose development has been and still is successfully supported both by national funding agencies as well as the EU, is a positive example how community building was triggered through funding initiatives. A similar commitment will be needed from the side of funding stakeholders in order to incentivize multidisciplinary, cross-border research. Calls for projects will develop the field of Systems Medicine as well as the building up of strong, international multi-disciplinary consortia and the community-building amongst the different expert groups.

European Association for Systems Medicine (EASyM)

The scientific community needs an exchange platform on Systems Medicine. Currently this opportunity is created through the Coordination and Support Action CASyM. However, due to the restricted lifetime of EU coordinating actions, the foundation of a European Association for Systems Medicine (EASyM) can take over this role from CASyM. EASyM is supposed to serve as a sustainable structure fostering the further implementation of Systems Medicine in Europe.

Such organization will serve as an important networking tool between disciplines and all relevant scientific stakeholder groups involved in Systems Medicine. Tools for community building of the Society are the organisation of an annual conference and the publication of a Journal of Systems Medicine. If EASyM succeeds in drawing in the different clinical and scientific stakeholders, it can become an opinion leader in Systems Medicine, representing the European Systems Medicine community to the outside world.

The initiative of a self-organisation of the scientific community is welcome by the funders and will complement concerted actions of funders in common initiatives.

The Systems Medicine web hub

Another activity has recently been implemented, which might serve as a future tool for the community building: the Systems Medicine web hub (www.systemsmedicine.net). This website has the potential to become the central resource to gather all information relevant for Systems Medicine and the relevant interest groups. Although websites in the realm of Systems Medicine do exist, they all appear to be directed to or concerted by a specific project or stakeholder group. The new Systems Medicine web hub is supposed to circumvent this problem by providing an independent, overarching infrastructure that channels information from other resources. The provided information includes sections about events, current and past research projects, open positions, important research resources and databases in the field.

It is appreciated that the web hub will help in increasing the overall visibility of Systems Medicine activities in Europe next to its expected function in networking and community-building aspect.

Infrastructures

Overarching research infrastructures´ functionalities are instrumental in order to allow full leveraging on existing biomedical resources such as biobanks and data repositories. Such relevant infrastructures provide open, standardized, and fair access to data, samples, and expertise, which are of value for research, development, and application. However, rather than creating dedicated Systems Medicine infrastructure, the existing resources should be utilised first. Currently, there exist nine research infrastructures at various stages in the ESFRI framework, which Systems Medicine can benefit from:

BBMRI - Biobanking and Biomolecular Resources Research Infrastructure

BBMRI is facilitating the access to European biobanks and related biomolecular resources including biomedical samples and corresponding data sets from patients and populations. BBMRI virtually bundles European bio-banks and bio-molecular resource centres in sixteen Member States.

Infrafrontier – Mouse Disease Models

Infrafrontier provides animal models to test hypotheses before entering human testing. Central activities of this infrastructure include (i) the archiving and distribution of Mouse Models, the (ii) systemic phenotyping of Mouse Models, and the (iii) mouse production from embryonic stem cells. Furthermore, training and consulting services are being provided that relate to the above-mentioned activities. Infrafrontier is currently offering pan-European services in its six founding Member States.

ECRIN – European Clinical Research Infrastructures Network

ECRIN provides the clinical infrastructure for academic clinical testing with patients in hospitals and clinics. It coordinates national clinical trial infrastructures and partners to allow multinational trials. ECRIN's services are based on the connection of national hubs providing services to multinational clinical studies and on the provision of services to investigators and sponsors in the conduct of multinational studies, as academic institutions often lack the capacity to fulfil the sponsor's responsibilities in foreign countries. France, Germany, Italy, Spain, and Portugal are ECRIN members whereas Czechia and Hungary participate as observers.

ISBE – Infrastructure for Systems Biology Europe

ISBE is currently in the process of creating a pan-European infrastructure for systems biology that facilitates the use of model-driven approaches to understand complex biological systems, thereby enabling their function to be altered in a rational and predictive way. Its coordinated activity will comprise the provision of four main types of services to European researchers: (i) modelling and data integration, (ii) standardization of data, (iii) model-compliant data generation, and (iv) education and training in systems biology.

EATRIS – European Infrastructure for Translational Medicine

EATRIS provides access to a network of 70 academic institutions across Europe renowned for their individual skills and high-end research facilities for translating research results into clinical applications. It is open to researchers and companies in need of support for advancing biomedical innovations from bench to bedside and back. EATRIS expedites the innovation development process by offering a single point of access to the right expertise.

ELIXIR – A distributed infrastructure for life-science information

ELIXIR provides a secure pan-European platform for the standardized collection, quality control and archiving of large amounts of -omics and biological data produced by life science experiments. The inclusion of clinical data is currently under development. Through its services, the use and re-use of existing life science research

data can be greatly facilitated. ELIXIR also provides tools to the research community, which facilitates the management, use and integration of big data.

EU-OPENSCREEN - European Infrastructure of Open Screening Platforms for Chemical Biology (in preparation, transition phase)

EU-OPENSCREEN integrates public national networks in 16 European countries in the field of compound screening and drug development. Building on their diverse expertise and compound collections, which contain up to 300.000 commercial and proprietary compounds, EU-OPENSCREEN aims at accelerating the discovery of all kinds of biologically active substances in the life sciences with a major focus on systems and network biology, structural biology, pharmacology, and plant biology. All newly discovered tool compounds will be made available publically.

EuroBioImaging - European Research Infrastructure for Imaging Technologies in Biological and Biomedical Sciences (in preparation, transition phase)

EuroBioImaging provides open user access to a complete range of state-of-the-art imaging technologies in biological, molecular and medical imaging for life scientists in Europe and beyond. Its services will include image data support and training for infrastructure users. 14 countries participate in EuroBioImaging together with EMBL towards the implementation of the infrastructure and governing EuroBioImaging development.

Other infrastructures

Systems Medicine uses models to describe and predict the development of diseases. To build such models, high quality clinical phenotypic data is needed. Especially longitudinal data is required to capture the disease progression, ideally already from early stages on. Therefore longitudinal disease and population cohorts with high quality phenotyping provide an important infrastructure relevant for Systems Medicine.

Longitudinal cohort studies are currently gaining and increased interest by the clinical and scientific community. Especially large population studies promise to give answers to many questions related to widespread, potentially life-style related diseases with increasing incidence such as diabetes, metabolic syndrome, and neurodegenerative diseases. However, through the longitudinal cohort design, extensive financial efforts over long periods of time are needed to make full use of their potential. Moreover, a lack of standards between different cohort studies hampers full utilization of potentially valuable data and prohibits comparison of data.

Unifying existing cohorts to standardise procedures, data management and access could therefore prove to be instrumental for exploiting their full potential. Next to this, many longitudinal cohorts lack sustained funding, which poses an eminent risk for study survival. Therefore sustainably funded longitudinal cohorts are an important contribution towards a successful Systems Medicine. In addition, harmonisation and integration efforts for creation of pan-European cohort data as currently already done within the Joint Programming Neurodegenerative Diseases can further increase the power of the existing data.

Implementation of pan-European initiatives for Systems Medicine

Instruments for common initiatives

As stated above, gaining critical mass in Systems Medicine will benefit from cross-border collaboration of funders in common initiatives for funding. Currently, the following EU instruments for common initiatives are being actively employed. In the following they are briefly characterised with regards to their potential impact on the implementation of Systems Medicine in the European Research Area:

(1) ERA-Net/ERA-Net cofund
(2) Article 185 (ex 169) Activities
(3) Joint Programming Initiatives (JPI)
(4) European Research Infrastructure Consortia (ERIC)

ERA-Net/ERANet cofund

Characteristics

ERA-Nets are among the most common instruments for the coordination of national and regional research programme funding on the European level and the launching of common calls. Within the European Framework Programmes 6 & 7 (FP6 & FP7), more than 100 ERA-Net and ERA-Net Plus actions have been implemented. Within ERA-Net cofund actions, the European Commission provides a "top-up" financial support to one call budget.

In the fields close to Systems Medicine, the ERA-Net ERASysBio, the ERA-Net Plus for Systems Biology (ERASysBio+) and the ERA-Net for Systems Biology Applications (ERASysApp) have been successfully running in FP7. ERASysAPP is still active and will run until the end of 2015

Central aim of ERA-Net actions is the setting up of joint calls in their area of scientific interest, where each country covers the cost of their national researchers in the European consortia. An important and interesting feature of ERA-Nets is their openness: even after the action has started, further members can join and participate in the following calls. The initiation of ERA-Nets is typically based on calls issued from the European Commission, now being included in H2020 societal challenge work programmes, which define a top-down approach and impact of the future ERA-Net. Proposals with more specific actions and plans for research calls are being rendered from bottom-up, self-organized consortia of funding organisations, which apply for being awarded the status ERA-Net and the associated funding of the coordination activity. In the new European research framework programme Horizon 2020, a new funding initiative instrument has been developed, which is based on the ERA-Net scheme of the previous framework programmes. The so called ERA-Net co-fund scheme directly includes EU top-up funding for research projects in one selected call and additional activities (included non-co-funded calls in the type B) and is thus a further development of the two previous schemes (ERA-Net and ERA-Net Plus). However, in the ERA-Net co-fund scheme the coordination costs are not covered by community funding, a clear drawback compared to the previous schemes.

Dis-/Advantages

As pointed out before, ERA-Nets are among the most common instruments. Therefore, a lot of experience could be gained in the last decades for its utilisation. Advantages of the participation in ERA-Nets are: (i) supporting of internationalisation efforts both in research projects and funding agencies, (ii) enlarging the scope of potential collaborations, and (iii) the EU financial contribution towards networking and the funding budget.

On the downside, ERA-Nets do pose certain disadvantages, many of which do actually apply for other instruments as well: Time-consuming management and coordination efforts often go together with slowness due to the application process, sometimes diverse discussions, and complex decision-making due to high numbers of partners. Moreover, due to limitations in the scope of ERA-Nets, there is sometimes a lack of flexibility in the scope of calls. In terms of budgeting, strong differences of the financial set-up between partners can complicate the financing of the selected consortia. All these aspects contribute to the fact that consortium partners might feel they have to make suboptimal compromises in a number of aspects during the setup of an ERA-NET.

ERA-Nets have a fast impact on the research landscape due to calls that can directly follow the ERA-Net's establishment. Therefore, they are a good solution to provide limited, but almost immediate impact and assess the quality and responsiveness of a defined area of research. The new ERA-Net co-fund encourages

participation due to the top-up fund but is impacted due to the lack of coordination cost coverage. As pointed out before, the ERA-Net co-fund scheme does no longer cover any coordination costs, which can hamper the engagement of partners and the consistency of the programme development, thus impacting the quality of the network.

Conclusion

ERA-Nets require some initial efforts for setting up, but can easily be implemented and provide openness for further partners during its lifetime, thus ERA-Nets are good tools for a concertation of a larger group of funders across borders. Therefore they are ideal instruments to develop a common research programme.

Article 185 (ex-Art. 169) Activities

Characteristics

Compared to the ERA-Net scheme, Article 185 activities represent a substantially different kind of scheme for an integrated scientific programme as it aims at a more permanent scheme requiring a legal framework.

Similar to the ERA-Net Plus or co-fund, Article 185 allows the EU to participate in the funding and research initiatives jointly performed by several Member States. The establishment of Article 185 initiatives requires the setup of a legal body of its own (Society, European Economic Interest Grouping, Association or similar), which needs to take into account the rules of H2020 not specifically derogated and the national programmes to be included as well as a dedicated implementation structure. Moreover, the scope of the programme needs to be detailed before legal implementation and a clear definition of the objective to be pursued must be given, and its relevance to the objectives of the Framework Programme needs to be defined. Art. 185 may only be established by decision of the European Parliament and the Council upon an initial proposal by the European Commission, if a clear EU added value and critical mass can be proven.

Within both past framework programmes, there have been a total of only five Article 185 initiatives. Among these, the European and Developing Countries Clinical trials Partnership (EDCTP) and the EUROSTARS, which deals with supporting market-oriented research projects with SMEs, and the AAL, which deals with supporting market-oriented ICT research projects (for ageing) with both SMEs end user participation appear to be closest to the subject of Systems Medicine. The limited number of Article 185 initiatives indicates that only selected subjects are envisaged that require a tool for stabilizing and sustaining the research funding actions and that are of specific strategic interest and with substantial added value for the EU.

Dis- /Advantages

The firm, long-term national and EU commitment, both financially and politically, the clear programme priorities and the existence of a dedicated implementation structure (Art. 185 secretariat/central management unit) are beneficial for the sustainable development of the chosen research field.

A disadvantage is the required long-term commitment of member states that can be hard and lengthy to obtain. In addition, the need to create a legal entity where the countries funders become members creates difficulties. Questions of liability, ratification in parliament are only some of the obstacles that have to be overcome.

Due to the low number of total Article 185 initiatives few funders have experience in participating. However, the EU financial contribution is clearly a substantial stronghold and, due to the funding size and impact, also advantages for the respective economies can be observed.

Conclusion

Art. 185 initiatives have substantial impact on a given field of research and local economies. However, this scheme is only suitable, if there is a substantial political commitment of a critical mass of countries together with the European Union.

Joint Programming Initiatives (JPI)

Characteristics

JPI combine a strategic framework, a bottom-up approach and high-level commitment from Member States: following a consultation of stakeholders, a High Level Group on Joint Programming identifies areas for JPIs and the Council approves each of them. Member States can decide in which JPI to participate. The goal is alignment via developing a common vision and an associated Strategic Research Agenda. The implementation of the Strategic Research Agenda can be done through various instruments; among these are common calls to support European research projects.

As for Article 185, JPIs are directed at major societal challenges, but does not require a legal framework for its establishment. JPIs aim at focussing national efforts on topics of overarching interest by bringing together the diverse national funding activities into a common framework for a better coherence and use of synergies in research. So far, 10 JPIs have been established. JPI Neurodegenerative Diseases (JPND) and JPI Healthy Diet for a Healthy Life (JPI – HDHL) are the two JPIs that have most overlap with the topic of Systems Medicine.

Dis- /Advantages

A clear advantage of JPIs is the possibility to establish a longer-term political commitment of Member States to coordinate their funding without the necessity to establish new legal structures. Similar to ERA-Nets, a consortium agreement is sufficient to lay down the guidelines for the JPI participation.

The more loosely defined framework, however, may lead to a lower level of commitment of the members. Especially the lack of a financial support structure can impact the efficiency of the JPIs. Coordination and support actions of the European Commission to fund the organisational structures of JPIs have been beneficial. Through the ERA-Net co-fund, now the launch of common calls is further incentivised, thus overcoming some of the disadvantages of the scheme.

Similar to ERA-Nets, JPIs suffer from the different financial commitments that hamper the funding of all selected European consortia, as each country only finances their own research groups. The high number of partners can lead to a complicated decision-making and the discussions in the preparation can become lengthy.

The preparation time for launching a JPI can also be of disadvantage. Rather than just through a bottom-up process and only after the development of a strategic research agenda, first actions can be taken for an integration of the research activities.

Conclusion

JPIs can be the initiative of choice, in case collaborating Member States do want to commit themselves on a longer term to support an area of interest, but try to avoid the strict legal guidelines of Art. 185 initiatives. Ideally a first roadmap as basis for the Strategic Research Agenda should be in place to allow a timely implementation.

European Research Infrastructure Consortia (ERIC)

Characteristics

A European Research Infrastructure Consortia (ERICs) is a legal framework to set up cross-border research infrastructures based on European law. Thus it is substantially different to the other instruments as it aims at integrating infrastructure rather than research programmes. Commitment is made on the level of the participating country. Governance, funding and access conditions for the infrastructure must be determined on the level of the statutes. No European co-funding is foreseen. The suitability check concerning the ERIC legal entity for the infrastructure consortium is performed by the European Commission. In order to achieve

ERIC status, a clear added value for the development of the European Research Area needs to be demonstrated and the European research community needs to be granted access to the specific infrastructure.

Within the last years, 10 ERICs have been created. Three of these have functionalities to serve the topic of Systems Medicine: the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), the European Advanced Translational Research Infrastructure in Medicine (EATRIS), and the European Clinical Research Infrastructure Network (ECRIN).

Dis- /Advantages

An advantage of ERICs is the provision of a legal European framework for common scientific initiatives across Europe. The commitment on the country level ensures financial sustainability of the scientific services but not of self-service projects. On the other hand, this can complicate participation in some countries that require ratification of membership in international organisations through parliament.

A disadvantage of this instrument is the limitation on infrastructures.

Conclusion

The implementation of an ERIC specifically directed to Systems Medicine does not appear appropriate on a short to medium term perspective, since most infrastructural needs of the field are covered by existing infrastructures.

Barriers & Challenges

While all above-mentioned instruments are being used for the implementation of common scientific programmes in Europe, there are barriers and challenges in the implementation of such programmes that have already been partly addressed among the disadvantages. These barriers mostly originate in the diversity of national legal frameworks, financial scope, and scientific strategies. They all share the fact that they can have a negative impact on the research landscape in individual countries.

Lack of common budgets

The principle that each country only covers their own national costs can lead to complicated situation, that the budget allocated by the individual countries to a call is not sufficient to cover all research groups that are in the projects selected for funding. In consequence, some projects may not survive the selection process due to a shortfall of individual partners.

This can lead to reluctance to involve researchers from these countries where money is likely to run out. Smaller countries that can only afford limited amounts could be put at disadvantage. Also those countries that could contribute a larger share of excellence in the field may not be able to match this excellence with the necessary funding, thus the full potential in research cannot be utilised. While the EU top-up fund could in principle ameliorate the situation, there is concern that such utilisation of the top-up funding could encourage the underfunding by the countries.

Legal differences

Funding in the instruments described above is executed according to the national legal framework of the individual funders. Differences in the rules for funding and accountability lead to the impossibility to fund the full scope of activities needed for Systems Medicine. As an example, not all research funding bodies can support training activities such as summer schools. Another inequality is the funding of public-private partnerships. In some countries, the funding of public research is separated from the support of companies. Thus in some countries, small and medium enterprises (SMEs) cannot become consortium partners despite their innovation potential. While in principle, the use of top-up funding by the European Commission could

cover these costs, there are still administrative hurdles how to implement the transfer of funds to the companies.

Research landscapes and strategies

Common initiatives of funding bodies in Europe have a high impact on the community building in the corresponding research field. However, participation depends on the national strategies of the individual funding body. There may be a discrepancy between the research performance of the scientific stakeholders and the priorities of the country for participation in European initiatives. Excellent research groups of high relevance for Systems Medicine may be cut off from their European colleagues and put at a serious disadvantage despite their qualification. On the other hand, the full potential of Systems Medicine projects may not be realised as it will not always be possible to include the most suitable research groups in Europe. Here, common programmes of national funders cannot reach the same impact as a central European funding.

Working with industry

In order to implement Systems Medicine on all relevant levels, the active participation of both small and big enterprises in PoC projects will be of central importance. On the long-term it is expected that industry will sustain Systems Medicine implementation by employing and further developing its approaches in R&D but also in their commercial product portfolios.

Large enterprises vs. SMEs

Depending on the company size, different modes of interaction with public partners and hence funding schemes should be considered. Big companies tend to engage in precompetitive research with the aim of knowledge gain in research consortia. If potential for the generation of intellectual property (IP) for their business is developing they prefer to enter bilateral collaborations with a stronger control on IP rights. In contrast, small and medium sized enterprises (SMEs) often depend on external funding to maintain their business. Hence, they tend to use PPPs to gain a proof-of-concept for their developments or to derive income from service provision. These strongly differing concepts of participation public-private partnerships (PPPs) demonstrate that defining roles and expectations during the set-up of such mixed consortia is of high importance in order to achieve the maximum output in terms of translating research results into practice and market application.

Role of TTOs

To allow efficient balancing of the different partners' needs and prospects, the inclusion of technology transfer offices (TTOs) both in the process of consortium preparation as well as during the succession of a project is recommended. Taken together, participation of industry representatives are seen as important in the definition of call programmes. Ideally, industry should be part of the decision making of consortia and TTOs must be centrally integrated in PPPs to allow balancing of interests and needs.

Mandatory industry participation

The participation of companies as partners in research consortia as a mandatory pre-condition for funding has to be critically evaluated on a case-by-case basis since not all topics require an active industrial partner. In such cases the enforcement of participation might lead to "token SME / industry partners", which are only part of the consortium to fulfil the eligibility criteria. In such cases, the option to include industry as an observer or in an advisory board could be more effective to reach the expected goals.

As an example, the ERANet EuroNanoMed already now launches annual joint calls and funds projects with mandatory industrial participation as partners

Integration of private foundations

Private foundations could offer a solution for the hurdles in common national funding initiatives. They could play a key role in providing and sustaining project funding where for strategic, budgetary or legal reasons the national (or regional) funding body is unable to provide the necessary funds.

Regarding the landscape of potentially collaborating foundations, there are strong differences between the Member States, which can be partially explained by factors such as differences in charity tradition and tax law. For example, annual donations vary from about 175 EUR per year and person in the UK to 60 EUR in Austria. Also some countries favour endowments over donations, leading to a more fragmented landscape of foundations. Moreover, the focus on funding research projects varies between countries, with again the UK being in the lead with more than 1 Billion EUR health research funding from private foundations in 2013.

Modes of participation

Different modes of participation of private funders could be considered to increase the chances for successful co-funding. The potential modes include (i) back-up funding by private funders in case of insufficient public funding budget to support projects, which could otherwise not be funded, of through funding of activities or stakeholders that are not eligible under public funding (ii) the substitution of public funding agencies in a common call, if no public agency can participate, and (iii) increasing the national budget for a common call, where foundations would fund alongside with public agencies. Several disease charities have reported to have been previously engaged in the latter two constructs. However, in most cases, private foundations do yet engage in funding on a national level and mostly in the framework of self-organized programmes and calls.

Barriers and challenges

Potential barriers and challenges in the inclusion of private foundations in joint funding initiatives need to be taken into account and specific national aspects apply. Next to the sheer lack of foundations or private funding capacity in some countries, legal obstacles might apply, which prohibit the participation of private foundations in funding consortia. It has to be noted, however, that on a European level such participation has already successfully taken place in the case of the ERA-Nets E-Rare and TRANSCAN.

Whereas commitment of public funding agencies is usually backed by national budgets, private foundations could go bankrupt during a course of a funded project, with all related consequences. Next to this potentially harmful aspect, private charities and foundations often have a substantially different scope than public funding agencies, for example by focusing on a specific disease or condition. This specific scope would limit the possibility for collaboration and might interfere with decision-making processes and definition of calls, in case private foundations would engage as an equal partner in funding consortia.

Conclusion and Outlook

The Horizon 2020 ERA-NET ERACoSysMed

Recently the ERA-NET ERACoSysMed was established based on an ERA-Net co-fund call by the European Commission. It integrates 14 European funding bodies from 13 countries in a joint effort to further Systems Medicine in the European Research Area. It is a first promising step towards joint funding initiatives in this complex yet promising field at the intersection of biomedical research and clinics. It will help gathering experiences and allow a first alignment of strategies between public and potentially private funding bodies in Systems Medicine funding.

ERACoSysMed started official operation in January 2015 with the first call for proposals (JCT-1) already being closed in March 2015. This call is co-funded by 33% EU contribution with a total budget of more than 12 Mio.

EUR. Funding bodies from Austria, Belgium, France, Germany, Ireland, Israel, Italy, Luxembourg, Netherlands, Norway, Slovenia, Slovakia, and Spain have agreed on a call aiming at demonstrator projects in Systems Medicine that are oriented towards a clearly defined medical need and can be successfully completed within 3 years. This important first step to further the implementation of Systems Medicine in the EU follows the recommendations of the CASyM roadmap

In the future, further non co-funded calls are foreseen, which may also be based on the CASyM road map recommendations. Further funding bodies are invited to join the ERACoSysMed in the upcoming months in order to achieve maximal impact and coverage in the EU. It has been agreed that public funders as well as private charities and foundations can join the consortium for common funding of excellent research in the field of Systems Medicine. This model of interaction would seem specifically appropriate in case either the future calls would be dedicated to a specific disease field or research consortia would apply with project proposals that focus on an area of interest for the participating private foundations. Inclusion of private foundations, however, will be subject to the individual national situation in the respective country, considering already participating public funders and their position.

Indicators for success

In order to critically review the success of the ERACoSysMed, indicators for its success need to be defined. Next to the obvious output of successful Systems Medicine projects, which fulfil the expected results and are able to demonstrate the added value of Systems Medicine compared to existing approaches, the ERACoSysMed has the ambition to have an impact on both the funding body community as well as the scientific communities. Given the scarce national programmes in Systems Medicine in Europe, the ERACoSysMed is expected to drive the development of cross-disciplinary research consortia on disease modelling on a systems level. Over the course of issuing calls, it will be likely that a development towards more balanced, highly skilled, and comprehensive research consortia could be observed. Moreover, the scope and quality of proposed projects is expected to rise in case the ERACoSysMed has sufficient impact in the field. On the other hand, the composition of the ERACoSysMed itself over the course of it life-time will give information about how successfully additional funding bodies could be attracted, which directly allows to infer the overall visibility of the initiative and the topic of Systems Medicine per se.

A test case for the implementation of Systems Medicine

The ERACoSysMed has been instigated as a first important initiative towards a sustainable common initiative in the field of Systems Medicine. It has been decided that it will serve as a test case for supporting Systems Medicine implementation in the EU, the impact such measures can have, and the potential for networking and collaboration among the funding bodies. Its success will provide an important reference for many funding bodies before deciding on the potential national commitment in common Systems Medicine funding initiatives to support the implementation of Systems Medicine in the EU. Dependent on the experiences gained in ERACoSysMed and the succeeding of funded research, these might comprise the initiation of another future ERA-Net, the launching of a European Joint Programme (EJP), a JPI activity or preparing the grounds for an Article 185 initiatives. In any case, it has become apparent that an efficient implementation of Systems Medicine will require concerted action amongst funding bodies both in the short as well as the long-term perspective.

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