Mid-Size Instrumentation in the Life Sciences:

V. Final Report – Results and Impact

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Content

Preface

In the last century, promotion of research policies was still conducted with a predominantly national view. Given increasing world-wide competition for the best scientists and the most promising projects, restricting the view to a national level is no longer tenable. Today there is growing awareness and acceptance that concepts and strategies for research infrastructure (RI) funding should be harmonised and coordinated within the European Union (EU). The ERA-Net, *ERA-Instruments* set out arguing that national funding and research organisations can no longer afford to remain at the national stage and need to follow scientists to the European level.

Summary

ERA-Instruments brought together stakeholders such as funding agencies, ministries, charities and research performing organisations with an interest in mid-sized instrumentation and centres for mid-size research instrumentation in the life sciences.

Accompanied by a Scientific Advisory Board, *ERA-Instruments* started out with a portfolio of activities ranging from comparison and analysis of funding schemes and RI road maps, over user meetings and workshops with invited scientists and policy makers, surveys of specific instrumentation and questionnaires, to study tours to non-European countries. A cost-neutral extension of the project allowed to discuss issues in more depth, to address new issues such as facility management, and to disseminate the results in the form of “recommendation” papers to interested parties or to present them directly to a wider audience.

Major results of *ERA-Instruments* relate to funding schemes, RI road maps, access and operation of RI. Policy makers and funders should take an inclusive view to the issue of RI for the life sciences and should emphasize the visibility of distributed RIs, in form of networks or as European Strategy Forum on Research Infrastructure (ESFRI) projects. A balance between different levels in size and organisation of RIs should be kept to be economically efficient and scientifically effective. In the life sciences networking and optimizing existing decentralised facilities seems more promising in this respect than installing new centralized RIs.

Impacts of *ERA-Instruments* can be seen in changes introduced to the daily practice of national research organisations and funders, and contributions to international discussions on RI. A well working network of stakeholders is now in place which successfully interacts with other European initiatives such as the Member Organisation Forum on Research Infrastructure or with ESFRI projects.

ERA-Instruments' main results and foregrounds

Context in brief

It has become obvious that concepts and strategies for research infrastructure (RI) funding should be harmonised and coordinated within the European Union (EU). In the past, promotion of research policies has been mostly restricted to national efforts without managing these actions with a European view. The European Strategy Forum on Research Infrastructures (ESFRI) has formulated requirements for European RI funding and has presented a roadmap, which increasingly has been influencing national planning for RI.

The ERA-Net, *ERA-Instruments* set out with the conviction that funding and research organisations can no longer afford to remain at the national stage, while there is increasing world-wide competition for the best scientists and the most promising projects. As frontier research has been conducted in an international context for long, funding organisations need to follow scientists to the European level.

Clearly, action is needed in the interdisciplinary area between physics, chemistry, biology and medical sciences as cutting edge instrumentation becomes increasingly expensive and, yet, indispensable for world-class research. There is growing awareness that the life sciences tend to rely more and more on RIs, albeit of a less centralised and more networked dimension. Therefore *ERA-Instruments* has placed its focus on bioanalytical instrumentation (incl. high-throughput techniques) such as NMR, mass spectrometry, microscopy, DNA-sequencing platforms etc. Research based on mid-range equipment - here defined as instrumentation costing in the range of 0.5-10 Mio. € - has become an essential and a strategic strength of European countries.

Objectives and further context

The core aim of the project was and still is information exchange between national funding agencies on infrastructure funding for life sciences that can optimise access to and scientific output from existing and future instrumentation. Networking and coordination

can improve the efficiency of national programmes. The driving force behind these activities is the need to maximize the access of scientists to leading edge instrumentation within the limits of the national budgets and minimize the bureaucracy in the granting procedures. Well-informed programme managers are a prerequisite for appropriate funding policies and procedures that best benefit the scientists. *ERA-Instruments* tries to contribute to improving existing national procedures while avoiding bureaucratic hurdles.
ERA-Instruments' focus is on “midsize” equipment (typically in the range of 500 k€ to some million €), which can still be purchased by national funds but is worth to be discussed on a pan-European level. In this context, *ERA-Instruments* is based on strong experience with national funding schemes, seeking for solutions where solely a national view seems to be no longer suitable, and thus filling the gap to the truly European infrastructures defined by ESFRI. In so far, *ERA-Instruments* can be regarded as complementary to the ESFRI projects but with some overlap and thus opportunities for exchange.

ERA-Instruments has its focus on funding agencies, research organisations, charities, and ministries since it aims at establishing an active and sustainable network of organisations for infrastructure funding, but with close contacts to the companies and the scientific community. *ERA-Instruments* aims at fostering the collaboration between scientists, companies, and funding organisations, especially on the working level (as opposed to e.g. EUROHORCs). Backed-up by European partner organisations, the participating organisations are placed in a stronger position at the national level for supporting scientists.

The instrumentation needs of the life sciences are more fully recognised, as all partners are widening their knowledge base by European treatment of the respective topics. A major objective of *ERA-Instruments* was to improve funding schemes and decisions. The development of (national) roadmaps as well as research policies in general obviously benefit from transnational discussions and measures.
A bottom-up approach and the close contact to the scientific communities were chosen to ensure that the classes of instrumentation and

the emergent technologies that are chosen for the *ERA-Instruments* activities, such as pan-European inventories, are most relevant for strengthening the European position in world-wide competition in science and research. The dialogue between scientists, funding organisations, and industry is regarded as essential. Vendors and enterprises are important partners of science as they are mainly developing and providing new techniques. Manufacturers are vital partners when defining emerging RI needs.
Summarising, the *ERA-Instruments* goals are balanced research policies providing better access to midsize facilities with an emphasis on defining transnational standards. Thus the support for national and European funding activities should be improved with all the stakeholders involved.

Networking stakeholders

ERA-Instruments brought together stakeholders such as funding agencies, ministries, charities and research performing organisations with an interest in mid-sized instrumentation and centres for mid-size research instrumentation that meet the needs of the scientific community. The stakeholders, such as research performers or funders, from countries of different sizes and diverse approaches to research funding, did not only inject various aspects and interests to the discussions, but also contributed and exchanged expertise and experiences gained in specific contexts. This rich texture joined by common interest in improving instrumentation based research proved very fertile. In particular the exchange of "good practice" and sharing of information was very useful and productive. The continuing contact and exchange among partners within *ERA-Instruments* and beyond demonstrates the successful networking achieved during the course of the project.

Our initial conviction that there is a need and interest for networking stakeholders was confirmed by the strong positive feed-back received from partners and scientists. A major out-come of *ERA-Instruments* can be seen in the impact the project had on the partner organisations by providing recommendations and good practice examples which inform the process of improving national funding schemes.

Moreover *ERA-Instruments* has generated wider interest with international consortia such as ESFRI projects and other European Initiatives, especially the Member Organisation (MO) Forum on Research Infrastructures.

Direct contact between stakeholders and scientists generated valuable input and feedback. In particular, the contribution of the *ERA-Instruments* Scientific Advisory Board, assembled from scientists recommended by each partner organisation, proved highly valuable for the project. Also the direct discussions with scientists held at workshops and user meetings provided important input which informed the "recommendations" derived from the project.

Instruments and Research Infrastructures

ERA-Instruments bears the term "instruments" in its name and title, however, early on in discussions, it became obvious that instrumentation should not be considered in isolation. Any usage of instrumentation implies many aspects besides the instruments themselves such as technical personnel, running costs, handling data etc. Hence in the widest sense mid-sized instrumentation is mostly run in facilities forming "research infrastructures".

The term "research infrastructure" (RI) comprises a broad variety of facilities, resources or services that are needed by the research community to conduct research in any scientific or technological fields. The definition we adopt here is similar to those used by ESFRI[1] and the European Commission[2] and includes, besides major equipment and other hardware or IT components, the associated human resources. RIs may cover the whole range of scientific and technological fields. They may be "single-sited", "distributed", or "virtual". An important characteristic of an RI is that it provides access or service for a research community based on an assembly of techniques and know-how.

There is a clear tendency in the life sciences to share usage of instrumentation and to run it in

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[1] *ESFRI defines RI e.g. in the ESFRI-Roadmap 2008, page 10, on* http://cordis.europa.eu/esfri/

[2] *The European Commission describes RI:* http://ec.europa.eu/research/infrastructures/index_en.cfm?pg=what

centres like core facilities. Once such a core facility has grown to a certain size and developed an organisational structure, it is quite reasonable to consider it a research infrastructure in the full sense of the definition adopted above. The resulting research infrastructures may or may not grow to the level of a mid-size facility. So far there are no agreed criteria to mark the transition from local to mid-size RI and the factors promoting or hindering the foundation of mid-size centres need to be investigated more deeply.

Access and Operation

There is an increasing tendency to run mid-size instrumentation in core facilities that can provide valuable service to the regional or wider scientific community. Naturally the first discussions and results of *ERA-Instruments* related to issues such as access to and operation of RI.

Access to instrumentation does always imply not only access to cutting edge instrumentation by itself, but rather the provision of expertise of experimental methods as well as data treatment. Although service provision is a cost-effective way to realise access to a wider community, scientific facilities should not only provide service but rather need a high quality research programme of their own in order to achieve and maintain highest scientific standards. Excellent facilities are usually overbooked and therefore require suitable selection procedures for proposals requesting access.

While the expertise of core staff at the facility is essential for its operation, sharing of expertise in form of courses and training at the facility would be highly desirable. Data analysis, but also access, transfer and storage of the primary data are of increasing importance.

Centres or consortia of excellence can develop best practices which are then passed on and distributed. For a smooth interaction between facility and user, information on access conditions must be easily accessible and potential legal or practical problems should be clarified early on. In the life sciences access to cutting edge techniques is often realised in form of co-operations rather than pure service provision. Co-operations are by definition more than access to technologies, but rather require an engaged collaborative effort on the side of the facility.

The majority of the life scientists appear to be in favour of a graded user fee model, in contrast to the physicists' community. Additionally, exploiting available research instrumentation in companies by academic researchers might be beneficial to both sides.

Decentralized or distributed research infrastructures that comprise many relatively small centres instead of one very large facility are increasingly recognised in their relevance for establishing the European Research Area (ERA). This should be accompanied by implementing quality standards for mid-size facilities across Europe.

While some fundamental aspects of providing and gaining access to RI in the life sciences do generally apply, it is clear that many minor and major differences exist between different kinds of RI and for different organisational structures that provide access. This diversity may be an asset for exploring, evolving and defining best practice models. Irrespective of all this variability, it is clear that procedures and conditions for obtaining and exploiting access to an RI always need to be clearly defined.

Management of facilities

Facility management is gaining importance in the life sciences. Facility management is a key success factor for a research facility. However, various aspects of facility management in the life sciences are still in need of improvement. Research facilities need to be evaluated by a different matrix than pure research proposals. Standards of good practice need to be further disseminated and ultimately enforced. Hereby funders could play a larger role. The need for longer term sustainability of facilities needs to be further recognised by funders.

The contribution of facility managers to research efforts needs to be more explicitly appreciated by scientists and research councils. At the same time, facility management should be further professionalised. Larger organisations experienced in facility management and training managers, such as ESRF, are willing to share their experience.

Personnel running instrumentation

Qualified personnel are indispensable for running modern research instrumentation. However there is a perceived difficulty for scientists charged with running equipment and providing service to develop their careers. Recruitment of instrumentation specialists can be problematic and competition for talented scientists is increasing globally. Longer term contracts, developing well defined career paths with a long-term perspective and providing attractive working environments are therefore necessities for successfully recruiting such talent.

Forecasting of and access to new developments in technology

Incremental improvement of instrumentation can be foreseen by scientists and manufactures who are close to the technological cutting edge in cases where pieces of equipment such as NMR, Electron microscopy or MRT undergo continuously improvements. The life time of a state-of-the-art instrument is many years and early access is of importance for prestige, but less so for cutting edge research.

On the other hand, break-through innovations cannot be anticipated (or only in the last moment) before they occur. Hence a systematic process, e.g. “Foresight”, appears to be of little help to identify upcoming break-through innovations. Therefore, an appropriate strategy for research funders appears to be staying in close contact to academia and industry in the respective area and to “react” quickly and flexibly when a new technology is emerging. This may require establishing programmes focussed on technology development and assessment alongside hypothesis driven research funding programmes. Close cooperation with industrial partners is another interesting way to gain better insight and early access to new technologies.

Access to new developments in technology

Use of the very latest emerging technologies is invaluable in advancing scientific discovery. Analysis of biological systems with higher specification equipment or novel instrumentation can lead to new insights and knowledge that keep researchers at the forefront of their fields. Interactions between instrumentation companies and EU academic researchers are key where scientific progress is strongly coupled to technological developments that in turn are moving forward quickly or are undergoing dramatic change. In some fields, lack of access to state-of-the-art RI prevents researchers from addressing leading edge questions. Although European scientists actively contribute to developing new technologies in many fields, commercial R & D is mostly located in the USA and preferred partners of those companies are few in Europe. This seems to result in a time lag of approximately two years between Non-European instrumentation companies developing the latest cutting edge technology and EU academic scientists getting it into their labs. Fortunately, this time lag does not exist in all scientific fields as international companies are choosing academic cooperation partners not only on a local but rather at a global scale. Moreover, in some cases the developments have in good part taken place in Europe. For instance, in advanced light microscopy new disruptive technologies such as single molecule observation or sub-wavelength microscopy are driven by European scientists and companies, allowing European researchers early access.

A comprehensive insight into relationships between instrumentation companies and EU academic users whose research would benefit from early access to the emerging technologies still needs to be developed.

For early access, lack of funding is considered to be an issue, followed by some difficulty in dealing with procurement regulations. As most cutting edge instrumentation is not purchased, instead being borrowed or accessed at pre-market stage through collaborations, the potential impact of the tendering process may be reduced. Partnering with companies or major instrumentation centres is viewed as a successful mechanism for accessing new technologies. There are few available funding streams to allow fast access to new instrumentation. Difficulties in obtaining money through peer review arise as very new equipment is often unproven, which necessitates obtaining pilot data. Dedicated funding streams can enable these initial studies. Direct funding can be relatively short term, but should be available quickly to ensure rapid access to instrumentation is enabled. Some funding schemes are (or were) available for industrial interchanges which may support some partnering activities. Awards could comprise an initial short contact, followed later by regular project funding.

The joint development of new technologies by academic researchers and industrial partners is valuable both in terms of early access for researchers as well as innovations and new products for companies. Barriers to partnering outside funding are lack of understanding of industry working practices (such as timelines) by academics, and excessive legal or administrative restrictions, and disputes around intellectual property. Certainly, there is a growing perception among scientists and academic institutions that pecuniary benefits from research results can and shall be reaped and there might be some associated overreactions, such as overvaluing IP or unrealistic expectations as to returns. However, companies can no longer expect to exchange free software licences or some accessories for full access to any IP generated. A fair balance needs to be established. Throughout this process, all involved parties must recognise the importance of relationship-forming between the academics and industry to access new technologies. These working relationships are usually formed between individuals and less between organisations. Appreciating this is very important in forming industry-academic partnerships for both sides.

Funding instrumentation and RI

Stakeholders influence the availability of instruments by directly funding instrumentation or RI via specific calls or permanent funding programmes.

Many fields in the life sciences depend upon expensive instrumentation to carry out competitive research projects. Special attention should therefore be given to investment programmes for funding research. Continuity of funding is an important prerequisite for building an efficient infrastructure that scientists can use and rely upon.

The very best equipment should be provided to leading researchers while still maintaining access to basic or regular instrumentation for the broad research community. Joint applications and mixed funding should be supported to allow the formation of groups or consortia that can flexibly join forces to pursue an investment. Procedures should be in place for multidisciplinary proposals. Applications should explicitly address international context, human resources and management aspects in addition to the scientific case and the scientific merit of the applicants. When the requested instrumentation is operated in a shared facility, additional aspects of shared access need to be addressed (see above "Access and Operation"). Public-private partnerships could be an attractive way of pooling resources provided that facilities can clearly separate industrial and academic use.

A major short-coming of many funding schemes still is that instrumentation is often funded in isolation from running costs (personnel, consumables, up-grades). This bears the risk that instrumentation is run ineffectively due to lack in essential resources. Hence, funding programmes should take a more comprehensive view and should include personnel, running costs, installation costs, maintenance and upgrades as cost items eligible for funding. The diversity of funding schemes and programmes throughout Europe requires funding organisations to respond flexibly to the diverse needs of the scientists. This is especially true for user fees, because financial models for operating shared facilities vary broadly in the life sciences.

Mid-size instrumentation should basically always be accessible to external users and shared usage and access should be stimulated by funding schemes that support and promote access to centres including travel expenses and other costs. Maximal scientific output can be achieved by granting access to the highest quality projects of internal and external applicants. Funding organisations have to develop appropriate indicators for assessing the productivity, quality, community impact and other benefits of running instrumentation. In any case, the usage or service of a facility has to be acknowledged by the users in appropriate ways.

RI Road Maps

The European Strategy Forum on Research Infrastructures (ESFRI) has, like no other initiative, set off and promoted the discussion and consideration of research infrastructure in Europe. The publication of the ESFRI roadmap and its updates has had an enormous impact on both scientific communities and policy makers. Although the initial focus was on large scale facilities that are required only by some scientific fields - many of them in the area of physics - ESFRI had already for the first roadmap broadened the scope to cover all scientific fields including the life sciences. The updates of the ESFRI roadmap have even emphasized those fields that have only recently begun the discussion on research infrastructures. Almost half of the new ESFRI projects of the 2008 and 2010 updates are in the life sciences. It is a major achievement of ESFRI to have raised awareness on the political level for the importance of RI also in the life sciences. Additionally, distributed and virtual RIs have been brought to attention.

A comparison of national RI roadmaps reveals some variation in terms of procedure of establishing and aims. However, major similarities become evident. Firstly, national funding policies have a strong international orientation. Participation in international facilities is considered necessary as RIs become more and more expensive, while it remains fundamental to achieve or maintain high standards in research quality. Secondly, the importance of life science research is widely recognised. The RIs in the life sciences constitute a significant portion of the total RIs included in national roadmaps and often receive a considerable portion of the available funding.

Most roadmaps further recognise two necessary key factors for research infrastructures: operation costs and personnel. This view is confirmed by facility managers who consider purchase of equipment in many cases not as the major bottle-neck for research infrastructures; rather costs for operation, maintenance and upgrades, and costs for personnel running equipment and increasingly for processing data, have become the limiting factors.

International cooperation is seen as essential to reach or maintain a competitive level in research. Although national roadmaps generally do not explore concrete options for cooperation and exchange of knowledge, they all clearly indicate that international research infrastructures are considered as important vehicles to realise these. In fact, they attract the most talented researchers from abroad and they encourage international cooperation. For the same reasons, hosting a facility is highly desirable, as this translates into brain-gain for the hosting country in terms of attracting scientists and knowledge exchange via attracting cutting edge projects. In addition, RIs usually attract other R&D activities, in particular in the high-tech industry, favouring its cooperation with the scientific community and providing an impulse to the local and national economy.

For these reasons there is a strong incentive for all countries to host an international RI or in case of distributed facilities to host a node of an international RI. This usually also allows connecting national facilities to international networks in a specific research area. In particular the latter can be interpreted as a decentralization of infrastructures in Europe. This process is certainly a reality in the life sciences (including biomedical infrastructure) which mostly have distributed character. Cost issues, and also the need to create focus and mass, lead to coordinated efforts to optimise the distribution of equipment in Europe, thereby creating decentralized research infrastructures.

The European context

As life science research is increasingly dependent on sophisticated instrumentation, costs and complexity of operation are constantly growing and thus have promoted the aggregation of instrumentation into centres and core facilities. In Europe this process is typically self-organized and the creation of centres depends in a self-regulatory manner on the scientific needs and institutional commitments. This bottom-up approach can be contrasted to the top-down installation of large scale facilities in other regions of the world, for instance in Canada, China and Japan. While telescopes, particle accelerators and research vessel are by their nature large scale facilities, research infrastructure for the life sciences can typically vary in the degree of centralisation. The extremely rapid and often unpredictable development of new technology for the life sciences asks for correspondingly fast adaption of existing research infrastructures. The bottom-up approach is probably more flexible in this regard, while the top-down installations allow for strategic planning, can emphasize professional management and provide higher visibility.

The European Strategy Forum on Research Infrastructures (ESFRI) has been instrumental in extending the discussion on research infrastructure to all scientific fields including the life sciences. The distributed nature of life science research infrastructures is explicitly acknowledged and reflected by the ESFRI projects in the biomedical section of the ESFRI roadmap that has also strongly influenced national roadmaps. However, the process for establishing them and the expected governance models seem to originate from a large scale facility perspective.

Existing facilities and centres vary widely in size and outreach. A discussion of life science requirements should take a comprehensive view and take into account all levels of distributed infrastructures: from networks of regional centres to the hub-and-spokes model with a strong centralized component. Networking of and optimizing access to existing instrumentation and expertise should be cost-efficient and, thus, attractive to funding organisations. New installations, e.g. from structural funds, should be integrated into existing networks wherever possible to facilitate training and exchange of experience. Sharing best-practice models for efficient operation and management of facilities on all levels will be beneficial to the scientists that make use of the research infrastructure. Crucial components for successfully establishing and operating RI facilities are – independent from size - qualified scientific and technical personnel, professional management and sufficient financial support.

Our focus is on mid-size instruments and centres in the life sciences, but our results do apply also to other scientific areas and to larger facilities such as those determined by ESFRI.

Conclusion

The life sciences require a broad spectrum of research infrastructures, from the lab equipment to international large scale facilities. A recent development is the increasing use of mid-size facilities that allow access to leading edge instrumentation and that provide the expertise and experience for making the best use of the expensive equipment. Cutting edge research in these fields is more and more depending on the availability of the latest technologies. The importance of these facilities does not depend on whether they are stand-alone, part of a network or part of a European RI consortium, as long as they offer excellent scientific service and support.

Policy makers and funders should take an inclusive view to the issue of RI for the life sciences and should emphasize the visibility of distributed RIs, in form of networks or as ESFRI projects. A balance between different levels in size and organisation of RIs should be kept to be economically efficient and scientifically effective. In the life sciences networking and optimizing existing decentralised facilities seems more promising in this respect than installing new centralized RIs (maybe even from scratch) although the latter is clearly a more visible measure and, thus, potentially more attractive to politicians. However, the goal should always be providing the best resources to scientists, not prestige and status.

Scientific research is an international endeavour. Many mid to large scale RIs cannot be supported by a single country. Hence international collaboration in establishing and running RI is increasing. A vision of a global research area should envisage international exchange allowing the best researchers to make use of the best research infrastructures world-wide.

Specific results

Right at the beginning it became obvious that the various kinds of instrumentation that *ERA-Instruments* meant to cover separate naturally into two categories. On the one hand, there are expensive single pieces of equipment, such as NMR, Electron microscopy or MRT, that require a major investment for installation and that remain state of the art for many years. On the other hand, there are platforms, such as proteomics assemblies or sequencing facilities that comprise many instruments that individually are less expensive.

NMR spectroscopy

NMR has been an instructive example for many issues that have been discussed in the *ERA-Instruments* project. NMR spectrometers are among the most expensive single pieces of equipment that are used in the life sciences (>10 million Euros for one spectrometer). They are usually operated in local or regional core facilities, but open access to external users is often based on cooperation based on personal contacts rather than general access policies.

This section is summarizing some specific results for NMR that have been obtained during the various meetings, an inventory and the other actions, including the study tours.

In the life sciences applications of NMR are to a large fraction in structural biology and drug discovery. Structural biology is moving from descriptive to functional analysis. Targets are proteins in more natural environment (including membranes) and more natural states (complexes, post-translational modifications, weakly folded). The integration of data from structural biology, imaging and proteomics becomes more and more relevant. Integrated Large Scale Facilities (LSF) that focus on a kind of application such as structural biology rather than a kind of instrumentation are seen as new and promising development to meet future needs. Automation and remote control will increasingly support and facilitate external access. Sample preparation is a critical step in structural biology and centres need to take this into account. RIKEN's NMR complex at Yokohama that was visited during a study tour provides an example of operating an Integrated Large Scale Facility, unknown for Structural Biology in Europe, which is internationally visible but also controversial.

The development of NMR spectrometers (high field magnets, high frequency electronics) is almost exclusively done by vendors. Nevertheless, important accessories such as dedicated probes or advanced software tools are often developed in close cooperation with scientists. Availability of new equipment is mostly based on the scientific standing of a research group rather than the geographic location. The persistent strive for ever higher magnetic fields is certainly an incremental development from the view of the life science applications, but there have been break-through innovations in technology in the past (superconducting magnets). An important step to magnetic fields beyond 1 GHz is on the horizon (and will likely be realized before 2020) with magnets using high-temperature superconductors. Notably, the development of wire for NMR magnets consisting of high-temperature superconductors would not be economically feasible if it were only for NMR spectrometers. Potential applications in the energy sector justify these investments for the company.

Probes have also been continuously improved, but the advent of the cryo probe with its sensational sensitivity improvements has certainly been a major step forward. DNP-NMR (NMR enhanced by dynamic nuclear polarization) is a current development with potential for a breakthrough innovation.

NMR does not generate excessive amounts of data, at least according to nowadays scales. Software development is traditionally fragmented and many (incompatible) tools co-exist. Vendors software has in the past failed to provide leading edge methods in their software packages so that many individual developments have taken place, some of them close to a standard, but basically all of them lacking sustained support.

The NMR survey showed that some countries in Europe are blessed with high densities of modern NMR spectrometers. While NMR instrumentation is not rapidly out-dated, it is difficult to keep track of the new installations.

Open access to leading edge NMR methods and instrumentation has very effectively been supported since some time via the transnational access scheme of the European Commission. The NMR consortia involved (EU-NMR, BIO-NMR, EAST-NMR etc.) provide access and expertise to users throughout Europe, usually in a single access point manner. Funding from Brussels supports both travelling of external users as well as operational costs of the centres. A recurring shortcoming of this scheme is that user and provider need to be in different countries, irrespective of the distance. National schemes to fill this gap are lacking.

Advanced Light Microscopy (ALM)

Light microscopy has recently seen an incredible boost in technology and methods development. The degree of sophistication of the instrumentation is often such that specialized expertise is required for efficient and successful operation as well as for productive use of the resulting image data. It has become not only inefficient, but impossible that every user of light microscopy may acquire in-depth experience with all the diverse techniques that have become available. Consequently, core facilities are installed for pooling instrumentation as well as expertise. These microscopy facilities provide state-of-the-art technologies and methods for a broad range of scientific users. They can also act as a link between various user groups, the technology oriented developers and the commercial instrument providers. Sufficient funding, not only for instrumentation, but also for expert personnel, maintenance, upgrades etc. has to be provided to the core facilities allowing them to provide high quality scientific service to users, including external users whenever possible. User fees for academic users will typically cover some running costs, but full costs can only be charged to users from industry. Research grants have to allow for these user fees.

Mature instrumentation should normally be integrated in such core facilities, whereas dedicated or specialized microscopes will still be run by individual expert groups. Development of new technologies is mostly done in the laboratories of physicists or engineers. They can also benefit from links to the core facility that can provide a testing ground for new developments or prototypes and can convey the expectations of the biological user community. The communication between developers and biomedical researchers should be fostered, so that methods development is accepted as integral part of life science research while the developers should be aware of the biologically relevant questions.

A funding gap is identified at the transition from a new development to a commercial prototype: The market potential that is a prerequisite for the engagement of a company can hardly be tested with only the original set-up at the optical bench of the inventor or developer. Duplicates need to be provided to the user community and tested for their usefulness regarding biological questions, ideally in cooperation with a core facility. A lack of funding for these duplicates can block the innovation pipeline at this point.

IT infrastructure and bioinformatics should be seen as integral parts of advanced microscopy facilities or platforms and need to be included also in early stages of planning. Sufficient human and financial resources need to be provided to meet the data challenge. Interoperable software tools and standardized data formats are required to transform the laboriously acquired image data into scientifically valuable results. Funding organisations should promote and support open source developments that are increasingly recognized also by the companies.

Next Generation Sequencing (NGS)

Next generation sequencing (NGS) can been described as a disruptive technology creating unforeseen possibilities for research, but also a series of challenges. The capacities of instruments are still growing rapidly, while costs for nucleotide base pair sequenced are falling as rapidly. On the other hand, the costs for large instruments are increasing, while the life span of instruments is only a couple of years, before they need to be up-graded or are superseded by newer instruments. The demand for bioinformatics, data processing and storage capacities is considerable and growing.

ERA-Instruments has addressed some of these issues in various activities, ranging from a questionnaire based survey to user meetings. The activities produced the following results. A balanced mix of larger centres, capable of executing large projects, and smaller facilities specialised on serving the regional community or niche applications is desirable. NGS in clinical research may also be run in local or regional facilities. The expected reduction in cost effectiveness in smaller facilities should be further counter-weighted against benefits such as regional academic or industrial contacts. Moreover, competition between facilities may be productive and aid improving quality. However, data for standard experiments can perhaps most cost effectively be generated by private sector service providers. Though, in some cases outsourcing to private service providers is not an option due to specific experimental or legal requirements.

Standards need to be further developed for sample preparation and data analysis, annotation, and sharing. Larger projects and consortia, such as the International Cancer Genome Consortium (ICGC), Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), Sharing capacity across Europe in high-throughput sequencing technology to explore genetic variation in health and disease (gEUVADIS), and the European Sequencing and Genotyping Infrastructure (ESGI), take a leading role in establishing these.

The results of the instrumentation survey/questionnaire and discussions with scientists suggest that, besides the considerable running costs in terms of chemicals, the major challenges and possible bottle-necks for NGS are the analysis of data and difficulties in recruiting bio-informaticians. This is underlined by the notion that about half the staff of larger facilities is dedicated to data analysis. Given the crucial role of data analysis in NGS, data analysis can be regarded as a product per se. Hence the costs of data analysis and not so much the generation of primary data may become the major cost limiting factor in the future. As in many other fields in the life sciences the data challenge is perceived as the greatest current and future challenge posed by NGS.

The Data Challenge

The storage and analysis of the vast volumes of data being generated by advanced instrumentation for genomics, proteomics and microscopy pose critical challenges. At the same time, there are tremendous opportunities for data integration across fields, but this depends on standardised formats. The demands of data management may increasingly become a constraint for instrument distribution and access.

Data sharing poses challenges at multiple levels: infrastructural, technical, professional and legal. Sustaining the infrastructure for long-term data storage and curation requires long-term planning and commitment by research funders. Incentives for and recognition of researchers, who share their data, is needed for motivating and engaging the scientific community. Furthering interoperability of software is an important issue, as long as proprietary instrument formats require proprietary software for analysis, which still can be a barrier. Emerging standards of data storage and curation need to be defined and implemented.

Training and career development of data specialists needs to be professionalised and extended. A major obstacle at national and, even more so, at international level in the bio-medical field can be posed by the legal requirements protecting the confidentiality of research participants. Broad ethical and legal agreement at national and international level needs to be achieved in order to allow exchanging and making use of the ever increasing amounts of research data.

International efforts, such as the ESFRI project ELIXIR, which aims to develop a data infrastructure for managing and safeguarding the massive amounts of data being generated by publicly funded research in the life sciences, will play a central role for dealing with the data challenge.

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The impact of ERA-Instruments

Impact at national level

ERA-Instruments' overall goal was to generate information exchange and networking among partner organisations and to contribute to improving national funding schemes and policies. In order to assess the impact *ERA-Instruments* had on the partner organisations, feed-back from the partners was collected via a questionnaire. A broad range of impacts and various examples of implemented changes influenced by the project were reported.

A clear benefit from knowledge exchange was perceived. Partner organisations received a wealth of input which may come to fruition in various ways and over a broad time scale, but which cannot be described here in a succinct way. However, several issues did strongly resonate with all partners and will lead to changes in the daily practice of the partners. Issues, set out in the *ERA-Instruments* work plan were considered as highly relevant, such as funding/costs and access issues in relation to running of instrumentation facilities, good practice in conducting funding schemes and many specific recommendations concerning specific technologies. In addition, further issues have come into focus; in particular, facility management has been recognised as a crucial point for improvement, and the issues concerning data analysis, as a major and growing challenge for the present and future. There was common agreement that awareness about the need for improvement of RI management and securing the effective longer-term running of RI are going beyond the LS and need to be raised and spread further.

The project helped reflecting the partner organsiations' directions and let to implementing some concrete changes to funding schemes.

The Dutch funding organisation NWO now contributes to covering costs for five years in large instrumentation/facility. During grant application evaluation special emphasis is now given to the quality of facility management.

The DFG has introduced a core-facility programme for funding core-facility activities and networking with calls in 2011 and 2012. This programme is exclusively aiming at establishing management structures and best practice.

Furthermore, the DFG started to include some running costs as eligible in project grants and now explicitly asks for a “Nutzerordnung” (a document detailing access policies and cost model).

In France, CNRS and INSERM introduced the IBiSA (Infrastrutures en Biologie Santé et Agronomie) label which can be given to national facilities in some life sciences areas (for example proteomics).

ERA-Instruments activities benefited partner organisations by helping to formulate or further develop national RI road maps. For example, Archimedes reported that the discussions and results of *ERA-Instruments* were helpful in establishing the Estonian RI roadmap and NWO, who conducted the *ERA-Instruments* analysis of RI road maps, has thereon been put in charge of up-dating the Dutch RI road map.

ERA-Instruments results have been disseminated within the partner organisations and at discussion fora at national level. For example, ENEA organised a meeting dedicated to disseminate and discuss *ERA-Instruments* results within its organisation. At the DFG, the *ERA-Instruments* recommendations have been endorsed by the DFG “Apparateausschuss”, (board for scientific instrumentation) and influenced the recommendations derived from expert round table discussions on specific instrumentation.

Other consequences derived from outcomes of *ERA-Instruments* perhaps may take longer to implement. As the information exchange among partner organisations will continue so will the impact of *ERA-Instruments*. The active participation in *ERA-Instruments* also aided partner organisations to position themselves and to take up new roles in European discussions on RI. For example some partners are engaged in ESFRI projects such as ELIXIR (BBSRC) or EuroBioImaging (DFG, BBSRC, Helmholtz).

International impact

In addition to the impact on the respective project partners as described above, *ERA-Instruments* has had (and still has) a remarkable influence on the role national research organisations do have in the context of research infrastructures and their European discussion. Most importantly, the EUROHORCs and ESF have published their "Vision on a Globally Competitive ERA" and their "Road Map for Actions"[3]. The document describes the role the organisations wish to play in shaping the ERA. Out of the ten vision points, "world- class research infrastructures" is one of the relevant topics. Ten actions have been derived from the vision points, one of them dealing with: "Develop shared funding and exploitation of medium-sized research infrastructures". This should be done by:

- "Establishing an ESF Member Organisation Forum;
- Continued updating of the inventory of national research infrastructures with European significance;
- Using *ERA-Instruments* as a pilot project for collaboration in medium-sized research infrastructures."

The Road Map acknowledges explicitly the impact of *ERA-Instruments* "providing research infrastructure focussed platforms for their stakeholders".

The Member Organisation Forum on Research Infrastructures[4], launched in 2010, has been mandated to the DFG and can provides a platform for 30 national research organisations plus a number of observers. The Forum will develop comprehensive tools for the adequate treatment of research infrastructure related topics (funding procedures, access rules, running costs, personnel, replacement, etc.). The aim is to gradually evolve the Forum into a network through stakeholder workshops by initiating research infrastructure specific user-meetings and interaction with scientists including ESF Committees and instrument suppliers to identify new developments. The

[3] http://www.eurohorcs.org/SiteCollectionDocuments/ESF_Road%20Map_long_0907.pdf

[4] http://www.esf.org/activities/mo-fora/research-infrastructures.html

Forum will develop recommendations on requirements for research infrastructures. Results of *ERA-Instruments* have had a direct impact on first results of the MO Forum, namely the recommendations for “Basic requirements for Research Infrastructures”[5] that have been adopted by the EUROHORCs and implemented by national organisations, as it aims at identifying a minimum quality standard for access to RIs at the European level.

Through the MERIL project[6], the Forum is looking forward to updating and upgrading the inventory of national research infrastructures with European significance which was initiated by the EUROHORCs, the European Commission and the ESF. Again, results from *ERA-Instruments*, namely with the inventories on NMR and NGS, have a direct influence on the design of the MERIL project; for instance partner CNRS who has been in charge of the *ERA-Instruments* inventories is the working group chair for mapping in the MO Forum.

Through these projects the national organisations have committed themselves to take over responsibility for RI issues. At a European level, these developments have been recognised, and the national organisations are present at the relevant discussion groups. For instance, EUROHORCs has agreed to a Declaration of Common Intent between European research funding organisations, major stakeholders and advisory boards on RIs. The declaration is addressing:

[5] http://www.dfg.de/download/pdf/foerderung/programme/wgi/basic_requirements_research_infrastructures.pdf

[6] http://www.esf.org/activities/science-policy/research-infrastructures/meril-mapping-of-the-european-research-infrastructure-landscape.html

- Developing a common approach for the evaluation of RIs (including *e*-Infrastructures) at national or European level (based on excellence, management, impacts)
- Development of coherent projects and initiatives on the basis of national and European priorities for world-class quality research infrastructures and research services
- Identifying and promoting best practices for RI governance, including cost control and long-term sustainability of resources
- Attraction of human resources, notably of high quality technical, engineering and managerial staff, and support to their training and mobility
- Promoting best practices for the optimal use of RIs by the research community, and for implementation of open access policies ensuring scientific excellence
- Improved interactions between the RI providers and the user communities, including industry as user and supplier, to fuel the research-innovation cycle
- Increased development and use of e-infrastructures as building blocks of pan-European RIs, in particular to improve access, availability and archiving of data as well as to build virtual research communities.

A very good example of new collaborations emerging from these developments is a joint workshop on criteria for European Relevance of RIs, organised jointly by the MO Forum on RI, ESFRI, and MERIL (to take place in spring 2012).

About ERA-Instruments

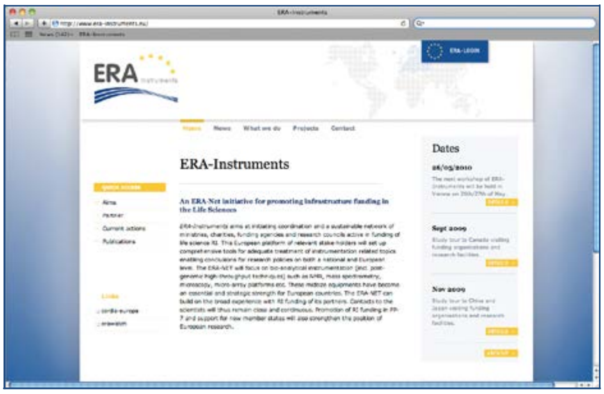
The Programme

It has become increasingly obvious that concepts and strategies for research infrastructure (RI) funding should be harmonised and coordinated within the EU. ESFRI has determined requirements for European RI funding and has presented a roadmap. Growing attention is paid to life sciences that rely on RIs of a less centralised, but more networked dimension. There is a clear need for action in the interdisciplinary area between physics, chemistry, biology and medical sciences as cutting edge instrumen-tation becomes increasingly expensive and, yet, indispensable for world-class research.

However, promotion of research policies, apart from the ESFRI projects, has been restricted so far to national efforts without managing these actions with a European view. Funding and research organisations cannot afford to remain at the national stage with world-wide competition for the best scientists and the most promising projects. Frontier research is international since long and funding organisations have to follow scientists to the European level.

The ERA-Instruments website

www.era-instruments.eu



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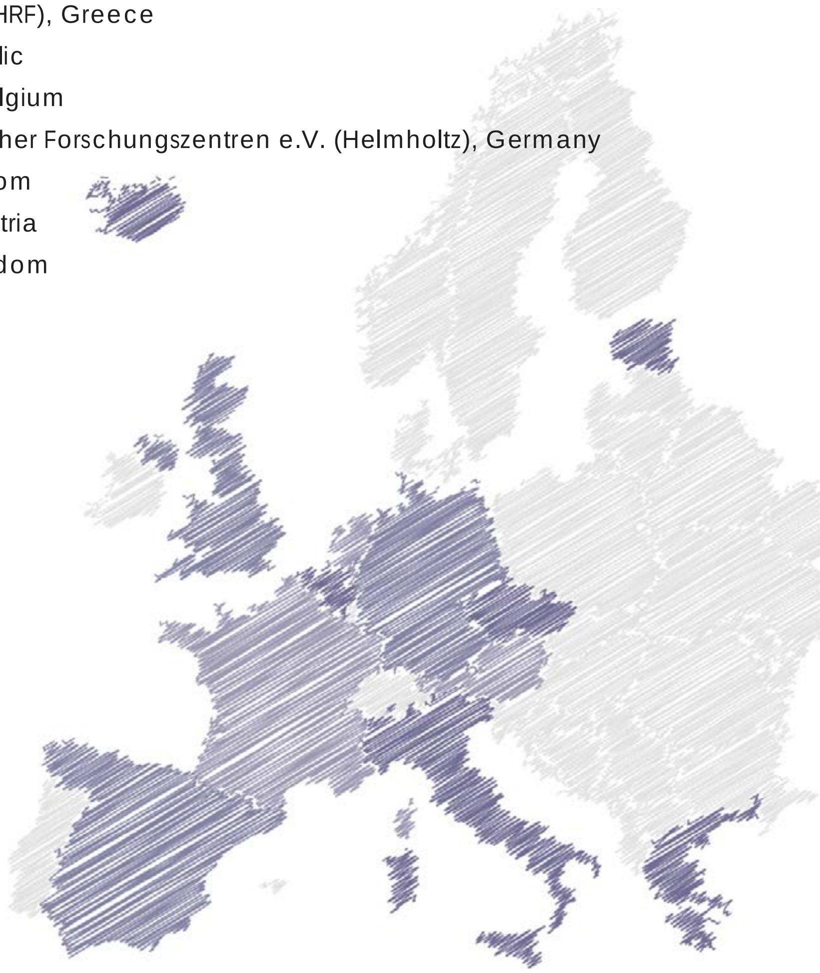
- Centre National de la Recherche Scientifique (CNRS), France
- Biotechnology & Biological Sciences Research Council (BBSRC), United Kingdom
- Consiglio Nazionale delle Ricerche (CNR), Italy
- Ente per le Nuove tecnologie, l'Energia e l'Ambiente (ENEA), Italy
- Netherlands Organisation for Scientific Research (NWO), Netherlands
- Consejo Superior de Investigaciones Científicas (CSIC), Spain
- Archimedes Foundation, Estonia
- The Icelandic Centre for Research (RANNIS), Iceland
- The National Hellenic Research Foundation (NHRF), Greece
- Grantova agentura CR (GACR), Czech Republic
- Fonds Wetenschappelijk Onderzoek (FWO), Belgium
- Hermann von Helmholtz-Gemeinschaft Deutscher Forschungszentren e.V. (Helmholtz), Germany
- Wellcome Trust (Wellcome Trust), United Kingdom
- Ministry for Science and Research (BMWF), Austria
- Medical Research Council (MRC), United Kingdom



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SEVENTH FRAMEWORK
PROGRAMME