

EURO-BIOIMAGING ERIC: General and Technology-Specific Review Criteria for Euro-BioImaging Nodes

Biomedical Imaging Technologies

Introduction.

This document describes the resources which are either required or desirable to enable user access to integrated Animal/Plant Imaging and Human Imaging Technologies in Euro-Biolmaging Nodes.

At the date of application for Euro-Biolmaging Node, resources described here can either be already provided by the applying Institution or Consortium, or planned to be built up as a part of Euro-Biolmaging Node construction. In order to submit a successful application, each Node applicant is invited to provide as many resources listed here as possible. However, Eols by technology providers who plan to only offer a selection of resources will also be considered.

In addition to the individual resources listed here, future Nodes are expected to have capacities available to handle the often complex administrative matters associated, in particular, with imaging probes/contrast agents, radiotracers, animal facilities, model organisms, cell culture, microscopy and biobanking where required.

In the framework of Euro-Biolmaging, it is expected to have considerable diversity between users of biomedical imaging Nodes, depending on their expertise and availability of certain technology(ies) at their home institutions. In order to successfully host all users, a Node should provide an infrastructure together with specially trained and experienced staff who will support the user at all levels of the Imaging experiment, including project planning, experiment preparation, animal handling, protocol optimization, patient or subject recruitment, ethics management, data acquisition & storage/curation/annotation, data processing, analysis and interpretation, and training. Experienced staff to support users in all these activities and through all steps of the research project with the offered imaging modalities will be necessary. This mandatory comprehensive support will ensure that the facility and all its resources are utilized in the best possible way and that data is recorded under optimal technical conditions.

The feasibility and scientific value of the project should be evaluated and a detailed project plan agreed prior to user access. It is essential to have in place a project assessment and planning process that includes input from experienced technical and scientific staff. These staff should have the time and resources to contribute to this process. The process should include sign off of the agreed project plan by the user, scientific contact and where appropriate facility manager.

Types of Nodes:

Technology providers can express their interest to become a “Single Technology Flagship” or “Multi-Modal Technology” Euro-Biolmaging Node.

Multi-Modal Technology Nodes would provide excellence by the integration of multiple imaging technologies at one Node. Multi-modal technology nodes can include all Euro-Biolmaging technologies including biological, animal/plant or human imaging and image data analysis.

Multi-modal in-vivo Imaging deals with the “in vivo” visualization, characterization and measurement of biological processes at the molecular, cellular and tissue levels by combining several tools and techniques with complementary characteristics in terms of sensitivity, specificity, temporal and spatial resolution. The imaging techniques include PET/SPECT, MRI/MRS, optical imaging, ultrasound, CT and other advanced and combined technologies such as PET/CT or PET/MRI or Photoacoustic Imaging to enable insights into anatomical, functional, metabolic and molecular processes in an integrative fashion, most often in combination with applied specific imaging agents. Molecular Imaging agents can be endogenous molecules

or exogenous probes that use nuclear, magnetic, optical or other measures to generate image contrast. Quantification of the regional distribution of the image contrast is a central feature in multi-modal molecular imaging experiments and requires specific and standardized protocols for probe administration, image acquisition, processing, co-registration and analysis. In vivo Multi-modal Molecular Imaging results are validated by established in vitro molecular, genetic or histological tests. Multi-modal Molecular Imaging is interdisciplinary as it involves skills from general fields, including physics, chemistry, pharmacology, biology, imaging technology, medicine.

Multi-modal molecular imaging can tackle highly diverse scientific questions including among others: (i) development and test/validation of a novel imaging probe on state-of-art Imaging technology; (ii) test/validation of a new animal model with state-of-art probes/Imaging technology; (iii) monitor the therapeutic effects of a new drug using state-of-art probes/Imaging technology; (iv) compare/validate a new development in imaging technology with state-of-art imaging/models technologies; (v) compare/validate new developments in Image analysis with state-of-art imaging/models technologies both in preclinical and clinical settings. Thus, taking into account the broad application field and the interdisciplinary nature of multi-modal molecular imaging, it appears clear that a Multi-modal Molecular Imaging Node has to be implemented on an existing large Center or a consortium of highly qualified, complementary centers able to provide the wide scientific bases in terms of expertise and available instrumentation to tackle a wide-spread range of Multi-modal Molecular Imaging studies.

A Multi-modal Molecular Imaging Node provides excellence by the integration of multiple Imaging Technologies (Table 1). The Node may be single-sited or it may be multi-sited (see general eligibility criteria). The Node lists the procedures offered to the users outlining the ones the Node claims its excellent uniqueness.

Common Technology Review Criteria for Biomedical Euro-BioImaging Nodes

All criteria listed here are defined as High/Medium Priority for each technology individually in Table 1.

Experienced staff to support users throughout all the research project, from project planning to data analysis and interpretation, is needed.

Staff at the infrastructure should be capable of advising users on the most appropriate choice among the portfolio of imaging modalities and validation experiments to deliver the research objectives for all project types that a Multi-modal Node will accept. In particular, Node Staff should help decide which imaging modalities they offer are best-suited for a particular experiment or sample type or help the user to test different modalities in a comparative manner at the beginning of the project.

Staff should also be able to maintain the different devices, guide measurements and help in interpreting data recorded across the range of imaging modalities offered. Tools for performing these analyses should be installed at the Node or be easily available from on-line resources.

As the duration of projects may vary (from ½ day to 1 year or more) nodes should be able to facilitate repeated visits by the users to the infrastructure at different stages of the project.

In addition to imaging technologies and skilled personnel to maintain and provide the imaging services at the highest level of quality and scientific excellence, the following expertise or resources should be provided:

- 1) Animal and cell culture facilities.
- 2) Molecular probes associated to the technologies provided by the Node, (e.g. magnetic resonance, nuclear, optical - bioluminescent, fluorescent, combined - and ultrasound imaging probes, as well radiotracers and biological reporters) should be available at the facility, either through own production or commercially acquired. The infrastructure should offer a clear guidance on the specific probes to be used in order to fully exploit the potential of the selected imaging techniques.
- 3) Chemistry/radiochemistry labs for analytical/physico-chemical characterization and/or production of the imaging probes, together with the ability to store and distribute these probes will be considered as a strength of the Node.
- 4) Facilities for image validation (ranging from simple sample staining over immunohistochemistry to autoradiography) are considered as an added value to the Node.
- 5) Skilled staff to advise users on the most appropriate technology(ies), among their portfolio of imaging modalities, to deliver the research objectives for all project types that the Node will accept.
- 6) Competence, both scientific and technological, in application development
- 7) Expertise in image acquisition, processing, co-registration and analysis, either by commercial or in house built software, together with the experience to customize standard protocols to the specific user needs.
- 8) High level of integration among the available imaging platforms and between the imaging platforms and the additional infrastructure/resources.

To attain the high standards required in the Euro-BioImaging Infrastructure, the application for a Biomedical Imaging Node should provide sufficient information concerning the following items:

- i. A detailed description of all the resources which are considered required or desirable to enable user access to the Node, including access to a probe/tracer repository, available analytical tools for physico-chemical characterization of the imaging reporters, description of the facilities for handling and preparation of small animals and list of specific animal models that can be made available to users.
- ii. Experiments with animals must be approved by the local (national institution) regulatory bodies and performed by personnel trained and skilled in laboratory animal anaesthesia and surgical support. Regulatory approvals need to be handled by the Node, prior to start of the user access.
- iii. Animal transport and shipping: the animal facility should be equipped and staffed by appropriately trained personnel who have the capacity to plan for and deal with incoming animal models from, and their return to, international locations. All such processes will be carried out with close adherence to the local regulations at the Node concerning animal experiments.
- iv. Facilities for the handling and preparation of model organisms are often necessary for users to culture and propagate specific model organisms required for experiments. The biobanking facilities should be located within easy working access in the same building as the imaging facility.
- v. Nodes providing human imaging must ensure that, when patients or volunteers are involved, the required study complies with the national and local ethical rules by obtaining the related authorizations and that image data management and storage is performed in compliance with general data protection regulations. Information about how the Node will handle subject recruitment will also be needed.
- vi. Nodes should have the capacity to offer a basic workstation to all users accessing their facility, and where necessary, high-powered workstations with sufficient processing, memory and storage capacity to enable users to efficiently perform image processing and analysis and achieve their experimental aims.
- vii. Nodes should have the capacity to offer server space to users for storage of images and results. Data storage requirements vary greatly depending on the imaging technique used, but in general, capacity to store several tens to hundreds of Gigabytes is routine, and in certain cases, larger capacities will be necessary. In general, sufficient capacity to store both original and processed datasets from several users will be necessary.
- viii. Accommodation may be required by some users, particularly those who have travelled internationally to access a facility. Where a node can offer accommodation on site, this should be made clear to the user during the pre-visit preparation phase. If no accommodation is available on site, the Node should have the capacity to offer assistance in finding affordable accommodation.
- ix. Nodes should offer the capacity for planning on-site experiments with the applicant prior to access by the user. Assistance should include guidance on methodological set up required to obtain appropriate images, and provision/procurement of materials required for image acquisition (contrast agents, probes, anaesthetics etc). For some technologies more detailed project planning should be provided.
- x. Nodes should offer a general induction or training programme for all visiting researchers. The induction should include documented safety and QM procedures for use of the technology and the supporting infrastructure to be accessed by the user.
- xi. Nodes should have the capacity to support user access and provide expert support for operation of the imaging technologies being accessed. Facilities should offer documented procedures and expert assistance for operation of the technology and image acquisition. All staff offering support should be fully trained in the operation of the instrument. Since multi-modal pre-clinical and human imaging implies utilization of sophisticated machines and protocols, and animal handling is allowed only to specialized and appointed personnel, it can be foreseen that in most cases users will not be able to run the instruments personally: Nodes must therefore guarantee that the staff committed to user access will be able to dedicate all the necessary amount of time to the preparation of experiments, acquisition and processing of images.

- xii. Nodes should have the capacity to support users in data curation and annotation, image processing, co-registration and interpreting results. Documented guidance and expert advice on image processing, co-registration and analysis using offered technologies is essential.
- xiii. To ensure that users achieve the objective of the requested access, thorough project planning by the Node staff will be required. Planning should also include safety and regulatory considerations.
- xiv. Some user projects could last several months and sometimes even beyond one year. This may require repeated visits of the users to the infrastructure at different stages of the project or multiple iterations as users gain experience and redesign or optimise their experiments. The feasibility of longer term projects needs to be regularly reviewed, particularly during early stages, and projects could be refined or postponed until required preparatory work has been carried out or gaps in user training has been filled by Euro-BioImaging measures, as necessary. It is therefore essential to have in place a project management planning procedure and experienced staff able to over-see the project through all stages to support users.
- xv. Nodes need to be able to support multiple users over extended periods and need dedicated flexible staff to support projects with diverse aims. Node staff needs to be knowledgeable about the biological and biomedical applications as well as their range of imaging techniques in order to be able to judge the capabilities and commitment of potential users.
- xvi. With open access, the application of new instruments to new applications may be common and there could be a difficult learning curve for users as well as node staff. Nodes need to be able to support users over extended periods and to have appropriate staff, who have the time and resources to learn new skills or knowledge for specific projects. Staff will not be leading the user projects, however, and so must get appropriate recognition and career development in these support roles that will take up much of their time.
- xvii. A node should provide a friendly and expert infrastructure with specially trained and experienced staff who help to run the experiments, help with the interpretation of the acquired data and who host and train its users and teach them to use the facility in the best possible way. This comprehensive support is a mandatory quality control in order to ensure that data is recorded under optimal technical conditions.

Table 1: Technology Review Criteria for animal and plant Multi-modal Imaging Nodes

Facility / Training	High priority	Medium priority
Chemistry Lab.	X	
Radiochemistry Lab.	X	
Cell Culture / Microscopy	X	
Probes/tracers repository	X	
Animal facilities	X	
Ethics management	X	
Biobanking		X
Repository of molecular probes	X	
Workstations / ICT Access / Data Storage	X	
Accommodation		X
General Training Courses		X
Methodological set-up	X	
Technical assistance to prepare experiments and run instrument(s)	X	
Image Processing and analysis	X	

21	Project planning and management	X	
22	High level of infrastructure integration	X	

Technology specific criteria for MRI, Phase Contrast Imaging, PET-MRI, Magnetoencephalography, and Population Imaging

In addition to the general eligibility and review criteria and the above listed resources for Euro-BioImaging Biomedical Nodes, additional specific criteria are considered critical for providing efficient access to **MRI, Phase Contrast Imaging, PET-MRI, Magnetoencephalography and Population Imaging**.

Magnetic Resonance Imaging (MRI)

1. The infrastructure should be able to support users at all levels of MRI-based projects. These are: measurement sequences suitable and optimized for the addressed field of application, RF coils and other pertinent hardware, data management and handling, tools for image analysis, processing and evaluation (e.g. for statistical analyses and presentation of results or correction of systematic errors during image acquisition). Experienced staff to support users in all these activities will be necessary.
2. High impact MRI projects typically last several months and sometimes even beyond one year. This may require repeated visits of the users to the infrastructure at different stages of the project. At early stages the feasibility of large-scale projects needs to be evaluated and if necessary terminated or postponed. Therefore, it is essential to have in place a project management and planning procedure and experienced staff able to oversee the project at all stages to support users.
3. Infrastructures need to be able to support multiple users over extended periods and need dedicated staff to support projects with different aims. A node should provide a friendly and expert environment that helps to run the experiment, helps in the interpretation, hosts and trains its users and teaches them to use the facility in the best possible way. Staff at the infrastructures needs to be knowledgeable about pertinent fields of application of UHF-MR as well as their range of imaging techniques in order to be able to judge commitment expertise and required support level of potential users.
4. With open access, the application of new instruments to new applications may be common and there could be a difficult learning curve for users as well as node staff. Nodes need to be able to support users over extended periods and to have appropriate staff, who have the time and resources to learn new skills or knowledge for specific projects. Staff will not be leading the user projects, however, and so must get appropriate recognition and career development in these support roles that will take up much of their time.

Phase Contrast Imaging (PCI)

1. The infrastructure must be able to support the users in all aspects during an entire PCI based project, including:
 - method selection,
 - preparation of sample or experimental animals,
 - experimental data collection,
 - data processing and image calculation

- mathematical evaluation of the data.

For PCI, data analysis is complex and methods are not yet standardized. Special attention should be paid to this circumstance by allowing extra time and resources for user support in this aspect. Nevertheless, specially trained and experienced staff in the facility should warrant all aspects of support.

2. Since PCI is an innovative technique, users may often be inexperienced. Therefore, proper discussion of projects ahead of start may be necessary. Multiple visits for each project are usually planned: a first short visit to run preliminary tests of the applicability of methods on targeted samples or sample animals, followed by more elaborately planned visits for data collection. The infrastructure should provide a clear project plan as a mandatory and structured preparation phase before the first user's visit: during this phase, the user is provided with information about the different assessments and analysis technologies available and it is assessed which of these methods is the best in order to tackle the given questions. For example, images with reference methods such as CT and MRI should, if applicable, have been recorded upfront to show the limitations of the conventional techniques. This requires sufficiently trained and experienced staff for project management and project planning.
3. With open access, the application of new instruments to new applications may be common and there could be a difficult learning curve for users as well as node staff. Nodes need to be able to support users over extended periods and to have appropriate staff, who have the time and resources to learn new skills or knowledge for specific projects. Staff will not be leading the user projects, however, and so must get appropriate recognition and career development in these support roles that will take up much of their time.

PET-MRI

1. The infrastructure should be able to support users at all levels of a PET-MRI- based project, including: definition and setup of bimodal protocols, selection of the radiotracer appropriate for the specific question to be studied, application for legal approval of studies using radiotracers in human research, selection and optimization of adequate MR sequences, optional equipment for blood sampling, optional equipment for metabolite correction, data management and handling, tools for image analysis, framework for quantitation and kinetic analysis of PET data, processing and evaluation (e.g. for statistical analyses and presentation of results or correction of systematic errors during image acquisition). Experienced staff to support users in all these activities will be necessary.
2. The feasibility of a PET-MRI project might depend heavily on the availability of PET- radiotracers adequate for the specific question to be studied. Infrastructures can either rely on commercially available tracers or develop and produce tracers. Therefore, studies can be realized in an infrastructure in which the required radiotracer is already available or can be made available in short time and it has the legal approval for studies using ionizing radiation and radiotracers in animal/human research. The infrastructure should be able to take responsibility for these applications. Thus, the preparation phase of PET-MRI projects may last even beyond one year if non-standard radiotracers are required. Repeated visits of the users to the infrastructure at different stages of the project might be necessary. At early stages the feasibility of such large-scale projects needs to be evaluated and if necessary reviewed, postponed or terminated. Therefore, it is essential to have in place a project management and planning procedure and experienced staff able to over- see the project at all stages to support users.
3. Infrastructures need to be able to support multiple users over extended periods and need dedicated staff to support projects with different aims. A node should provide a friendly and expert environment that helps to run the experiment, assists in the analysis and interpretation, hosts and trains its users and

teaches them to use the facility in the appropriate way. Staff at the infrastructures needs to be knowledgeable about pertinent fields of application of PET-MRI as well as their range of imaging techniques in order to be able to judge commitment of potential users.

4. With open access, the suggestions for new applications may be common and there could be a difficult learning curve for users as well as node staff. Nodes need to be able to support users over extended periods and to have appropriate staff, who have the time and resources to learn new skills or knowledge for specific projects. Staff will not be leading the user projects, however, and so must get appropriate recognition and career development in these support roles that will take up much of their time.

Magnetoencephalography (MEG) for human neuroimaging

1. The infrastructure should be able to support users at all levels of MEG-based projects. These are: measurement settings, actual measurements, stimulators, and basic data analysis, artefact suppression, management and handling. Experienced staff to support users in all these activities will be necessary.
2. High impact MEG projects typically last several months and sometimes even beyond one year. This may require repeated visits of the users to the infrastructure at different stages of the project. At early stages the feasibility of large-scale projects needs to be evaluated and if necessary terminated or postponed. Therefore, it is essential to have in place a project management and planning procedure and experienced staff able to oversee the project at all stages to support users.
3. Infrastructures need to be able to support multiple users over extended periods and need dedicated staff to support projects with different aims. A node should provide a friendly and expert environment that helps to run the experiment, helps in the interpretation, hosts and trains its users and teaches them to use the facility in the best possible way. Staff at the infrastructures needs to be knowledgeable about MEG experiments and data analysis as well as their potential use in research in order to be able to judge commitment expertise and required support level of potential users.
4. With open access, the application of new instruments to new applications may be common and there could be a difficult learning curve for users as well as node staff. Nodes need to be able to support users over extended periods and to have appropriate staff, who have the time and resources to learn new skills or knowledge for specific projects. Staff will not be leading the user projects, however, and thus they must get appropriate recognition and career development in these support roles that will take up much of their time.

Nodes providing human neuroimaging in MEG must ensure that, when patients or volunteers are involved, image data management and storage is performed in accordance with general data protection regulations and ethical statements are available from an appropriate Internal Review Board. The Node may also provide assistance in subject recruitments, e.g., by providing email lists.

Table 2: Technology Review Criteria MRI, Phase Contrast Imaging, PET-MRI and MEG

Technology	Facilities								Training						
	1. Probes / tracers	2. Animal Facility	3. Biobanking	4. High Biological Safety Level	5. Workstations - Desk, ICT access	6. Data Storage - images	7. Accommodation		9. Patient / Subject recruitment	10. Methodological set up	11. Facility Induction	12. Technical assistance to run instrument	13. Image acquisition	14. Image processing and analysis	15. Project planning
Phase Contrast Imaging	N.A.	High*	Med.	Med.	High	High	Med.		Med.	High	High	High*	High	High	High
MRI	High	High*	N.A.	N.A.	High	High	Med.		Med.	High	High	High*	High	High	High
PET-MRI	High	High*	N.A.	N.A.	High	High	Med.		Med.	High	High	High*	High	High	High
MEG	N.A.	High	N.A.	N.A.	High	High	Med.		Med.	High	High	High*	High	High	High

*Remark: for biomedical imaging it is unlikely that the external users will actually run the instrument

** for Nodes that will offer access at the preclinical level. N.A. for human imaging.

Population Imaging

The population imaging infrastructure contains three interconnected main parts: 1) imaging facilities 2) access to image handling platforms and 3) access to image data. The main aim of the infrastructure is to support harmonized data acquisition and analysis and data sharing.

Specific Technology Review Criteria for Population Imaging Euro-Bioimaging Nodes are the following:

1. The infrastructure connects at least two imaging facilities which acquire image data for epidemiological cohort studies. An overarching infrastructure which provides Standard Operating Procedures (SOP), image protocols, quality control, data storage, data analysis and data access is available.
2. The imaging facilities normally serve an epidemiological cohort in the vicinity of the image facility. It is not the main aim of the imaging facilities to provide open access to remote cohorts or studies but each facility give access to image acquisition for local epidemiological cohorts. The purpose of the infrastructure is to support users (which could be existing or new epidemiological studies) at all levels of the design and execution of a population imaging study. Support includes access to optimized imaging protocols, quality assurance protocols, data management and handling protocols, automated image analysis pipelines of large data sets, data mining infrastructure, evaluation tools (e.g. for statistical analyses and presentation of results or correction of systematic errors during image acquisition), ethical issues protocols. Experienced staff to support and educate users in all these activities will be necessary. Support and education for optimization of imaging protocols, quality assurance protocols, and data acquisition can be provided at the imaging facility of the user. This includes both users who acquire image data at imaging facilities being part of the Node, as well as users who acquire data in their own imaging facility and who wish to use the image analysis infrastructure of the Node.
3. Population Imaging projects last several years due to the inclusion of thousands of participants, to the serial (longitudinal) acquisition of imaging data, and to the assessment of clinical endpoints during a long follow-up period. In addition, the wealth of information in the imaging data leads to repeated analysis of the imaging data with new algorithms and new methodologies. This may require a longstanding use of the image analysis infrastructure at different stages of the project. Therefore, the infrastructure must have in place 1) data storage capabilities that is able to receive and store imaging data and to provide remote access to imaging data (and vice-versa) 2) high performance computing systems.
4. Semi-automated image analysis requires a pipeline of validated algorithms for different tissues/structures/organs. The infrastructure provides physical access to a broad selection of validated image analysis algorithms interconnected into pipelines. Experienced staff to support in the execution of the image analysis pipeline is available. Semi-automated image analysis requires frequently visual evaluation of results and manual adaption of registrations and segmentations. Users are trained to perform these tasks. It is not the staff who is executing these quality checks.
5. The infrastructure has regulations in place for access to image data and other relevant data acquired in the population cohort studies. Access to image data may require visits of the user to the infrastructure and on site analysis in case image data can only be accessed physically due to local data protection regulations.

Table 2: Technology Review Criteria for Population Imaging Euro-Biolmaging Nodes

Technology	Facilities			Training					
	1. Workstations - Desk, ICT access	2. Data Storage - images	3. Accommodation	4. Methodological set up	5. Facility Induction	6. Technical assistance to run instrument	7. Image acquisition	8. Image processing and analysis	9. Project planning
	Priority								
Population Imaging	High	High	Med	Med	Med	High	High	High	High

