Brussels, 17 May 2024

COST 045/24

DECISION

Subject: Memorandum of Understanding for the implementation of the COST Action "Magnetic Particle Imaging for next-generation theranostics and medical research" (NexMPI) CA23132

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action Magnetic Particle Imaging for next-generation theranostics and medical research approved by the Committee of Senior Officials through written procedure on 17 May 2024.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA23132
MAGNETIC PARTICLE IMAGING FOR NEXT-GENERATION THERANOSTICS AND MEDICAL RESEARCH (NexMPI)

The COST Members through the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action, referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any document amending or replacing them.

The main aim and objective of the Action is to foster the development of MPI and help its translation from pre-clinical to clinical applications. The Action will enhance technology accessibility, advance collaboration and sharing of technical innovations, standardize measurements, broaden the scope of applications, increase the visibility of MPI in other scientific fields, to the clinicians, and the general public. This will be achieved through the specific objectives detailed in the Technical Annex.

The present MoU enters into force on the date of the approval of the COST Action by the CSO.

OVERVIEW

Summary
Non-invasive assessment of the inner-body is one of the major medical advances in the 20th century. Magnetic particle imaging (MPI) is a young biomedical imaging modality offering opportunities for clinical diagnosis, therapy, monitoring and prediction of treatment outcomes, which are unattainable with other imaging modalities. MPI employs non-toxic magnetic nanoparticles and involves non-ionising radiation. The technique offers detailed, real-time, quantitative imaging of the location and concentration of the nanoparticles, their flow state, binding state, local viscosity and temperature. Moreover, using bespoke nanoparticles with distinct properties enables the extraction of supralinear information, facilitating truly theranostic approaches.

Preclinical MPI has already been implemented in oncology, stem cell research, vascular imaging, neuroimaging, imaging of lung perfusion, in vivo tracking and quantification of inhaled aerosols, imaging of the heart, on-the-spot biopsies etc. With the current developments, MPI has the potential to give a new impetus to nanomedicine, whose successes have yet to match early expectations.

The Action NexMPI is the **first** European network of MPI scientists, including physicists, chemists, biologists, engineers, clinicians and others, employed at hospitals, academic institutions, and small and medium enterprises. The network will **enhance access to the limited number of MPI systems** available in Europe; **foster close collaboration** among the small but rapidly growing MPI community; put Europe at the forefront of MPI research and development; help **define a roadmap** for the translation of pre-clinical research to the clinic; and raise public **awareness of MPI enabled opportunities**, including its application in the field of nanomedicine.

Areas of Expertise Relevant for the Action	**Keywords**
● Nano-technology: Electromagnetism for nano-technology applications ● Nano-technology: Nano-technology for pharmaceutical applications ● Medical engineering: Diagnostic tools (e.g. genetic, imaging) ● Clinical medicine: Radiology, nuclear medicine and medical imaging ● Physical Sciences: Databases, data mining, data curation, computational modelling	● Magnetic Particle Imaging ● Magnetic Nanoparticle ● Image reconstruction ● Theranostics ● Computational modelling

Specific Objectives
To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination
● To evaluate the level of harmonisation between MPI measurements
● To assess the suitability of various MNPs for different applications
● To establish the framework for conducting large-scale analysis of MPI data
● To disseminate, communicate, and exploit the Action outcomes

Capacity Building
● Institutions will be supported by fostering the adoption of MPI and facilitating widespread knowledge transfer in both ITCs and non-ITCs
● Device development will be advanced by enabling the initial community testbeds for comprehensive

validation of MPI, particularly in the field of nanomedicine applications. Additionally, the progression towards MPI commercialization and widespread clinical adoption will be expedited

● Address human resources by enabling staff exchanges. Support approaches to account policy towards ITCs, gender balance, YRIs in leading positions and Action activities (encourage some WGs to be led by an ITC, substantial number of leading positions held by YRIs, network activities predominantly held in ITCs and tailored for YRIs).

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. SOUNDNESS OF THE CHALLENGE

1.1.1. DESCRIPTION OF THE STATE OF THE ART

Magnetic Particle Imaging (MPI) is a relatively young biomedical imaging modality that does not rely on ionizing radiation. It presents a distinct set of advantages, allowing for precise clinical diagnosis and therapies that were previously inaccessible through traditional imaging methods. MPI utilizes safe magnetic nanoparticles (MNPs) as superparamagnetic tracers, achieving remarkable sensitivity, specificity, and impressive spatio-temporal resolution. MPI serves as a ***versatile theranostic platform*** with several capabilities: (a) offering real-time, in vivo imaging of tracer location and concentration; (b) providing additional insights like MNP flow, binding state, local viscosity, and temperature; (c) enabling active tissue heating (hyperthermia); (d) allowing MNPs to be labelled with other agents for diagnosis or treatment. Since its introduction in 2005, significant efforts have gone into developing MPI technology (both hardware and software). Various scanner designs and reconstruction techniques[1] have been demonstrated, with two types of preclinical scanners currently on the market. Additionally, self-built MPI scanners are in use in numerous labs. Each approach has its own strengths and weaknesses, making different devices ideal for specific tasks.

Despite variations in instrumentation, certain principles are consistent across all MPI scanners. They rely on specific magnetic fields to generate a signal from MNPs within the patient. ***MNPs emit a signal when subjected to a time-varying excitation magnetic field in conjunction with a strong gradient magnetic field***[2-3]. The non-linear magnetic response of MNPs results in a signal that contains detailed information about their location, concentration, and local conditions (e.g., temperature, binding state, viscosity). This high-quality information is obtained without interference from surrounding tissue or the drive field. However, there are currently various acquisition approaches regarding e.g. frequency, trajectory, and acquisition time, while image reconstruction often depends on the type of MPI scanner in use. Consequently, there is a need for optimisation when it comes to particular applications. MPI offers numerous potential applications as a ***non-ionizing radiation alternative*** for ***molecular imaging,*** including interventional radiology procedures[4]. MPI-guided hyperthermia, a powerful adjuvant to radiotherapy and chemotherapy[5], provides a ***distinct advantage*** that surpasses other techniques[6]. Unlike current hyperthermia systems with invasive temperature measurements at a single point, MPI can heat the tumour while simultaneously offering real-time, three-dimensional temperature distributions[7-8]. Furthermore, MPI stands out by its capability to heat deep-seated tumours, a feature not commonly found in other systems.

Different kinds of MNPs have been employed as MPI tracers. However, designing a tracer customized for specific goals is a complex undertaking, i.e., ***the choice of MNP impacts several crucial aspects including signal strength, spatial resolution, tissue absorption, necessary dosage, imaging time frame post-injection, and the potential for multiple functionalities***. Additionally, the necessity for a stable tracer, consistently reproducible in magnetic properties across batches, poses an added challenge in creating clinically viable materials. Consequently, the development of MNPs calls for a wealth of experimental data to reach an economically viable production[9] and compatible hardware/software setups.

Nanomagnetism plays a leading role in nanomedicine, as demonstrated by the successful preclinical testing of various MPI scanners and tracers, establishing them as potent theranostic tools for a range of applications, including: cardio-vascular imaging[10-12], cell tracking[13-14], oncology[15-18], neurology[19-21], atherosclerosis[22], inflammation[23], drug delivery[24], photothermia[25] etc. This also involves employing multiple MNPs with unique properties concurrently where the combined information surpasses their individual performance[10]. ***Given the extensive potential of MPI in translational medicine, the COST Action (NexMPI) is structured to foster the environment for this expansion.*** Its goal is to furnish the resources necessary to turn the promise of MPI into a tangible, effective, and clinically accessible approach in translational medicine. Hence, bringing together experts and professionals at a European and global scale is crucial for advancement in this field.

1.1.2. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Despite its initial development in Europe, there is now a growing global interest in MPI. However, despite demonstrated pre-clinical applications, its full potential remains untapped. To unlock MPI's capabilities, a collaborative effort between physicists, engineers, mathematicians, and computer scientists is required to design and simulate crucial components like coils, topology, acquisition patterns, and the induced signal. This involves solving complex equations and developing image reconstruction algorithms. Additionally, chemists and biologists must delve into MNP biodistribution, pharmacokinetics, and toxicity. Collectively, they must engineer MNPs with optimal signal strength, spatial resolution, tumour/tissue absorption and retention, and application-specific properties like heat transfer efficiency. Clinicians also play a vital role in characterizing diseases and defining treatment objectives. Despite the field's undeniable dynamism, several challenges must be addressed.

Challenge 1: Scanner availability. The current limitation of operational scanners to specific regions not only hinders the progress of MPI but also impedes the advancement of related emerging biomedical technologies that could significantly benefit from a well-established MPI platform for successful clinical integration. This situation presents a significant obstacle to the widespread dissemination of MPI technology knowledge, restricts access to MPI equipment for interested researchers, limits opportunities for collaboration with field experts, and hampers the spread of knowledge to those looking to develop their own MPI setups or applications.

Challenge 2: Lack of standardization and interoperability. Currently, a variety of MPI systems exist alongside various data formats, image reconstruction software, and laboratory-scale MNPs. This diversity hinders interoperability and experiment reproducibility. Therefore, there is a pressing need for quality assurance phantoms, protocols, and procedures.

Challenge 3: Lack of MNP characterization. It is evident that there isn't a one-size-fits-all MNP for every application. Various applications will demand MNPs with distinct magnetic properties. For instance, hyperthermia addresses larger tumours affected by abnormal vascularization, making route of administration and heat transfer efficiency crucial. In contrast, these considerations are irrelevant in stenting or perfusion imaging.

Challenge 4: Fragmentation of knowledge. The fundamental progress of MPI hinges on three essential components, each necessitating distinct scientific expertise: (a) hardware (physicists, engineers), (b) software (computer scientists), and (c) tracers (biologists, chemists). While certain groups may partially integrate some of these components (e.g., hardware/software), the overall proficiency within each group is inherently constrained. MPI stands to gain significantly from an initiative like this Action, which would assemble experts from each of these disciplines and facilitate enduring collaboration between them.

Challenge 5: Visibility and Exposure. While the MPI community has advanced enough to establish its own dedicated journal (International Journal of MPI) and conference (International Workshop on MPI), its relatively small size hinders widespread recognition among researchers in other scientific fields, clinicians, and the general public. This is evident in the challenges faced in recruiting Young Researchers and Investigators (YRIs) and in the hesitancy of YRIs to engage with a medical device that lacks established clinical recognition, potentially limiting their professional growth.

NexMPI will serve as a platform and conduit to tackle these challenges. It aims to establish a new network that facilitates the dissemination of MPI knowledge and expertise across the EU and beyond. This initiative will enhance technology accessibility, standardize measurements, and broaden the scope of applications. This aligns with the EU programs Horizon 2020 and Horizon Europe, particularly in line with the EU's mission to "Beat Cancer." ***The overarching objective of NexMPI*** is to create an interdisciplinary and intersectoral network dedicated to cutting-edge research in basic and translational sciences, fostering collaboration and sharing technical advancements in MPI. It will also develop and promote standardized protocols within the community, while broadly disseminating the outcomes to all stakeholders. ***NexMPI will play a pivotal role in ensuring that Europe's initial advantage in MPI expertise is sustained, securing the EU's position in the market for years to come.***

1.2. PROGRESS BEYOND THE STATE OF THE ART

1.2.1. APPROACH TO THE CHALLENGE AND PROGRESS BEYOND THE STATE OF THE ART

NexMPI will leverage the full potential of MPI for nanomedicine applications and tackle the current challenges (Section 1.1.2) via the following activities:

1. **Fostering collaboration** between parties with scanner access and researchers exploring MPI-related subjects. This encompasses physicists and engineers (hardware), computer scientists (software), biologists and chemists (tracers), as well as clinicians (nanomedicine).
2. Advancing **standardization and interoperability** through procedures, protocols, phantoms, and reference samples with well-defined MPI signal characteristics that will be deployed for cross-laboratory investigations. These assessments will gauge the level of alignment in MPI measurements conducted at different locations and timeframes, ultimately contributing to the development of standardized protocols for MPI measurements. Currently, there are no certified reference materials for the MPI-related physical properties of NPs, nor is there a certified acquisition protocol for evaluating the magnetic properties of MNPs. While some initial work has been initiated to evaluate the temporal stability of MPI scanners[26], no study has yet examined the harmonization between MPI scanners. Similarly, preliminary studies detailing devices for assessing the magnetic properties of MNPs[27-28] have not progressed towards standardized protocols.
3. **Fostering knowledge transfer** among the crucial specialties in MPI development will be achieved through meetings, networking events, training schools, and educational resources like coursework from the training schools. There will be a special focus on Short-Term Scientific Missions (STSMs) involving YRIs from Inclusiveness Target Countries (ITCs) as these facilitate direct knowledge and expertise transfer from more MPI-advanced nations.
4. **Establish a platform involving all stakeholders** to convene and deliberate on the specific MNP-requirements for various applications. This encompasses considerations like pharmacokinetics, administration route, tissue specificity, uptake, retention, heat transfer efficiency. Industrial partners will provide insights into the feasibility of large-scale production of laboratory-grown MNPs. Trade-offs between desirable properties must also be assessed to strike an optimal balance.
5. **Enhance the visibility and exposure** through network activities aiming at established researchers and YRIs pivotal for the technical advancement of MPI, but also clinicians, industry, and the general public. Clinical involvement is crucial for offering guidance regarding clinical requirement for new applications in nanomedicine. NexMPI aims to educate industry and Small and Medium-sized Enterprises (SMEs) about the potential of MPI, encouraging their active participation in the field. Additionally, the general public will be informed about this specific facet of nanomedicine progress, and through patient and non-profit organizations, support for its further development will be sought.

1.2.2. OBJECTIVES

1.2.2.1. Research Coordination Objectives

NexMPI aims to promote MPI by uniting the inherently diverse areas of scientific expertise required for its progress in the life sciences. This will be achieved through the Research Coordination Objectives (RCO) summarised below which will be carried out by five Working Groups (WGs) detailed in Sec. 4:

RCO 1: To evaluate the level of harmonisation between MPI measurements	
S	Assess the alignment of MPI measurements conducted using various types of scanners.
M	Development of reference materials, establishment of standard operating procedures, and 1-3 scientific publications mirroring the current state of the community.

A	Reference materials and protocols defined; best-practices described.
R	Harmonisation will contribute towards standardization and interoperability.
T	The evaluation will take place between M10 and M44, in WG1 and WG2.
RCO 2: To assess the suitability of various MNPs for different applications	
S	Assess the magnetic properties of at least 10 MNPs to ascertain their suitability for specific applications, with a particular focus on hyperthermia and cardiovascular uses.
M	Report/publication.
A	Definition of optimal MNP properties for different clinical conditions.
R	Selection of the optimal MNP for each application will significantly improve the clinical results.
T	The implementation will take place between M10 and M44 (WG3).
RCO 3: To establish the framework for conducting large-scale analysis of MPI data	
S	Establish a universally applicable method for large-scale analysis of MPI data.
M	Coordination for creating open database of experimental setups and establishing a database for reconstructed images.
A	Development of the analysis roadmap.
R	Large-scale analysis of MPI data will help advance the robustness of MPI.
T	The database of experimental setups will be operational by month 36 (WG2), the database consisting of reconstructed images will be operational by month 36 (WG2).
RCO 4: To disseminate, communicate, and exploit the Action outcomes	
S	Enhancing networking capability and scientific prominence through planned dissemination and outreach efforts targeting the general public, scientific community, and industry.
M	A minimum of 2 publications/reports per year; Disseminating knowledge to the local and regional community of stakeholders (e.g., industry, pharma and medical environment); Specific dissemination/communication activities (see Sec. 3.2.2)
A	Endorsement from medical and industrial teams, along with backing from media outlets.
R	Dissemination and communication of outcomes will engage stakeholders with MPI values.
T	The data management plan will be ready at M6; the dissemination will take place between M1 and M48, in WG5

1.2.2.2. Capacity-building Objectives

1. Institutions will be supported by fostering the adoption of MPI and facilitating widespread knowledge transfer in both ITCs and non-ITCs. Long-term collaborations among NexMPI participants will also be established.
2. Device development will be advanced by enabling the initial community testbeds for comprehensive validation of MPI, particularly in the field of nanomedicine applications. Additionally, the progression towards MPI commercialization and widespread clinical adoption will be expedited.
3. Addressing human resources will involve enabling staff exchanges. Support approaches to account policy towards ITCs, gender balance, YRIs in leading positions and Action activities ; such as encouraging WGs to be led by an ITC (possibly two), substantial number of leading positions to be held by YRIs (possibly 25%) and gender equity in as well leading positions, and network activities to be predominantly held in ITCs, and specifically tailored for YRIs..
4. The extensive network of partners will facilitate collaborative efforts to secure both private and public research funds.

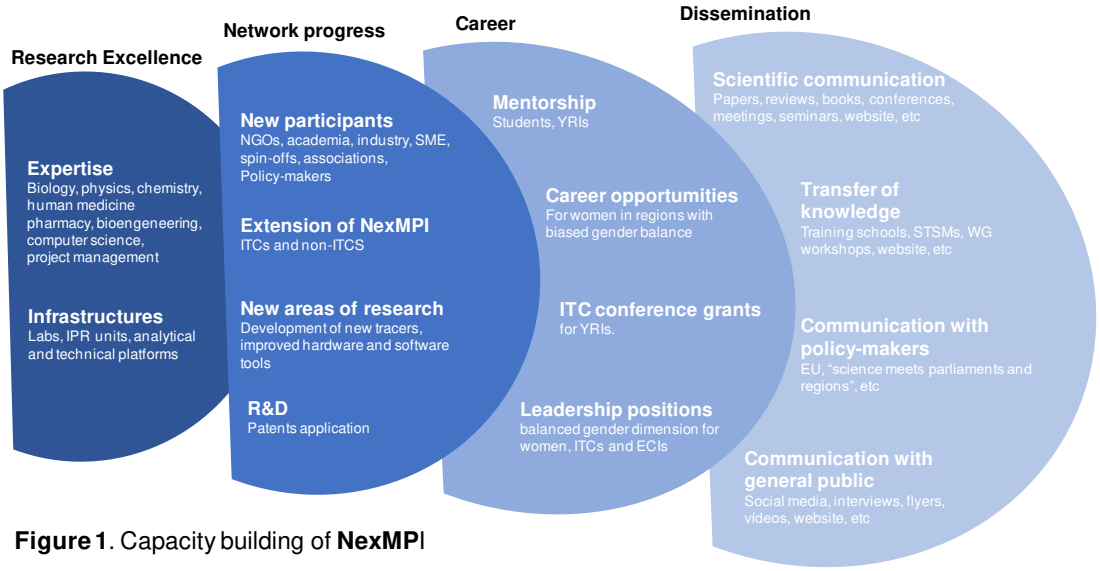

Figure 1. Capacity building of **NexMPI**

2. NETWORKING EXCELLENCE

2.1. ADDED VALUE OF NETWORKING IN S&T EXCELLENCE

2.1.1. ADDED VALUE IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

The **NexMPI** network represents a timely and essential initiative aiming to address global challenges:

- Facilitate connections among stakeholders in the expanding field of MPI.
- Align technical and clinical advancements for the betterment of patient well-being.
- Encourage collaborative research, particularly emphasizing the integration of ITCs.

NexMPI adopts a comprehensive and pragmatic approach, grounded in a bottom-up methodology that encompasses clinical needs. The network is dedicated to offering essential training and providing accessible foundational knowledge through its network. This is all geared towards the goal of defining and launching innovative collaborative research ventures on a global scale, crucial for the development of a clinical MPI device. Consequently, the **NexMPI** network aligns with the majority of the objectives outlined by the COST Action. It promotes scientific excellence, encourages interdisciplinary research, enhances European research and development capabilities, facilitates knowledge exchange, and provides support for capacity building.

Numerous European projects have tackled various aspects of nanomedicine. These include exploring the ethical, social, and economic implications of nanomedicine through initiatives such as the NANOMED ROUND TABLE (FP7-CSA-SA), as well as efforts to upscale nanoparticle production with projects like NANOFACTURING (H2020-RIA). Others have focused on specific targets such as cancer (NoCanTher, H2020-RIA) or brain conditions like NanoStem (H2020, MSCA-ITN). Additionally, the NanoPilot project (H2020-RIA) aimed to ensure production under stringent quality control measures. Despite these endeavours, there remains a notable gap in implementing rigorous quality control in the production of MNPs, particularly those intended for high-volume applications.

Under the Horizon Europe scheme, the advancement of medical devices geared towards harnessing the potential of MNPs for imaging has been progressing gradually. This involves the projects integrating specific agents (DIASHUTTLE, TMA-MSCA), along with bioinspired synthesis methods as ProteNano-MAG (AG-UN, ProteNano-MAG (AG-UN), BacToMagicle (ERC), and MAD Control (ERC). However, in the realm of sensing and imaging, the number of projects is diminishing. For instance, PCAVISION (AG) relies on ultrasound, while XheranoXome (TMA) leverages MRI, both of which exhibit a high degree of non-specificity for their intended purpose.

Evidently, there is a deficiency in the establishment of networks for sharing consolidated expertise, experience, know-how, achievements, tools, and data across multidisciplinary and interdisciplinary, pan-

European (or international) perspectives to expedite research and enhance the diagnosis and treatment methods relying on specific sensing and imaging using MNPs. The ***NexMPI*** initiative fills a crucial gap by incorporating a wide range of expertise, spanning from fundamental research to application (involving clinical and industrial experts). This multidisciplinary approach has been notably absent in recent COST Actions related to medical diagnostic imaging: CA17121, CA18206, CA17140, CA17104, and CA19138. Therefore, ***NexMPI*** represents a significant leap toward translating nanomedicine from the laboratory to clinical practice, specifically in the diagnosis and treatment of prevalent causes of mortality in Europe.

2.2. ADDED VALUE OF NETWORKING IN IMPACT

2.2.1. SECURING THE CRITICAL MASS, EXPERTISE AND GEOGRAPHICAL BALANCE WITHIN THE COST MEMBERS AND BEYOND

The interaction among stakeholders has been limited, hindering the progress of MPI development. Researchers were often unaware of others with specific expertise in technological advancements, creating barriers to communication and slowing down progress. **NexMPI** aims to address this by forming a diverse consortium of members and participants from COST member countries, Near Neighbour Countries (NNCs), and International Partner Countries (IPCs). This initiative brings together world-class scientists specializing in the development and use of MNPs for nanomedicine and imaging. It also facilitates research collaborations between multidisciplinary groups and SMEs with shared objectives. The network includes members leading national and international research projects, and industrial partners capable of providing comprehensive solutions. **NexMPI** encompasses expertise in technology development, translational and clinical research, and business value creation. The collaboration in interdisciplinary workgroups will foster strong teams even beyond the duration of the Action, such that the CBOs and RCOs are met with the highest standards. Each member will actively participate in planned events and scientific dissemination activities. The wide geographical spread of the network ensures the efficient distribution of knowledge across European countries, benefiting healthcare professionals, SMEs, large companies, and society at large. This extended network of experts also enhances technology vigilance, enabling faster and more precise implementation of updates. By involving a vast number of countries, **NexMPI** aims to increase the capacity to attract research funding from both private and public sources. The integration provided by this pan-European network is crucial for advancing MPI as a widely adopted medical technology. The ambition of **NexMPI** is to create a pan-European and multidisciplinary network of experts across academia, healthcare, and industry, including SMEs, for the optimal utilization of MNPs in nanomedicine. This initiative will be the first to cover a comprehensive perspective of MPI, inviting members from existing European initiatives to join and collaborate through working group meetings and other network activities.

- Gain deeper insights into participant countries' current status regarding the adoption of MPI and related techniques for diagnostics, theranostics, or adjunct therapies in diseases like cancer and cardiovascular conditions. This aids in achieving Action milestones and streamlining the design of a practical research-to-bedside roadmap.
- Optimize the use of research resources, reducing experiment times and enabling complex, multidisciplinary experiments that would otherwise be infeasible.
- Prevent redundant research efforts through seamless communication and data exchange. This accelerates screening processes, identifies protocol pitfalls, and facilitates knowledge transfer.
- Improve alignment between technical advancement and clinical challenges, bridging the gap between pre-clinical testing and medical practice by involving more clinicians and physicians in a robust multidisciplinary network.

2.2.2. INVOLVEMENT OF STAKEHOLDERS

NexMPI welcomes new interested groups and SMEs globally, actively seeking new participants to expand the network as needed. Additionally, all scientific events like training schools, workshops, and conferences will be open for participation by individuals outside the network, regardless of their career stage. The following stakeholders will play explicit roles in this Action:

Researchers: NexMPI members, especially YRIs, will gain advanced technical knowledge and skills in designing nanomagnetic tracers, hardware, software, clinical evaluation, and intellectual property. They will use social media, tutorials, and webinars for visibility and networking. The network's wide reach ensures

MPI technology accessibility across European countries.

Healthcare professionals: Identifying reference centres for specific pathologies and hosting focused events will enhance awareness and application of MPI in medicine.

Industrial partners: The MPI industry structure is accessible, combining hardware, software, and nanoparticle tracer manufacturers. Engaging key private partners aims to establish industry standards and expedite reliable healthcare technologies. They will actively participate in network activities, including technical meetings, research visits, conferences, and workshops.

Government agencies & policy makers: NexMPI aims to support ambitious health programs like EU4Health 2021-2027 and Europe's Beating Cancer Plan. It offers insights into diagnostic imaging's short-term future to accelerate access to advanced medical technologies for European citizens.

Patients and associations: NexMPI engages with the ecosystem of MPI, collaborating with key actors in related disciplines. Regular meetings with patient associations will facilitate advice and technology updates.

The general public: The program will collect, discuss, and disseminate information through various formats tailored to different audiences such as social media platforms.

3. IMPACT

3.1. IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAKTHROUGHS

3.1.1. SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS (INCLUDING POTENTIAL INNOVATIONS AND/OR BREAKTHROUGHS)

MPI is a new theranostic platform whose possibilities have yet to be explored. As described in Sec. 1.1.1, MPI has the potential to give a new boost to nanomedicine, whose successes have yet to match early expectations. Thus, if a suitable network is in place to correctly nurture MPI, the future impact is anticipated to be even more diverse than the points already discussed.

Scientific and technological impact

Short-term perspectives: NexMPI will drive forward MPI research throughout Europe and beyond: (i) Development of the first European network on MPI; (ii) Criteria for non-biased comparison of different MPI scanner types; (iii) Coordination for the creation of open-source systems (hardware and software) repository; (iv) Software tools for simulation environments; (v) Synthesis methods for tracers designed specifically for MPI; (vi) Reduction of production costs for tracers; (vii) Coating and functionalisation of MNP; (viii) Criteria for non-biased comparison of different tracers; (ix) Harmonisation of tracer characterisation protocols; (x) Biosafety of MNP; (xi) Harmonisation of pre-clinical imaging protocols.

Long-term perspectives: (i) Development of new specialised tracers for specific diseases; (ii) Creation of academic-industrial synergies for the future mass-production of tracers; (iii) Development of clinical imaging protocols; (iv) Creation of long-term academic-clinical collaborations towards a roadmap to clinical translation and trials; (v) Demonstration of the potential of MPI in the theranostic realm to spearhead investments and resources; (vi) Technology transfer especially to ITCs, which are hindered by the cost of commercial systems. In sum, NexMPI will help pave the way for various stakeholders to move MPI towards an established medical theranostic technology.

Socioeconomic impact

Short-term perspectives: End users of MPI devices are on all continents and the market is enormous. NexMPI forsees: (i) Increased medical clinic and public knowledge of MPI and its potential; (ii) Demonstration of a tangible application of nanomedicine; (iii) Public awareness of new diagnostic tools and therapeutic options (e.g. magnetic hyperthermia).

Long-term perspectives: (i) Translation of pre-clinical research to the clinic; (ii) Use of MPI, instead of ionising radiation, for various diagnostic and interventional procedures; (iii) Reduction of health care costs due to the elimination of the requirements for ionising radiation installations (e.g. shielding), and occurrence of radiation imaging induced cancer; (iv) Reduction of environmental and security concerns by the

substitution of radioisotope-based imaging with MPI; (v) Development of new theranostic procedures using specialised tracers; (vi) Harmonisation of practices across Europe.

3.2. MEASURES TO MAXIMISE IMPACT

3.2.1. KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

The cost and scarcity of MPI equipment hinders scientific and technological progress, particularly in ITCs. Therefore, the Action is committed to promoting and supporting the participation of researchers from ITCs in Action activities and the transfer of knowledge to them.

Knowledge creation: The Action NexMPI includes physicists, chemists, engineers, clinicians, materials scientists, biologists and others. They are employed at hospitals, academic institutions, public research institutes, industry and commercial entities. Their interaction through a well-organized network will help create knowledge in all aspects of this nascent field. This includes equipment design and operation, software for simulations, image reconstruction and post-processing, and MNP fabrication and characteristics. The Action will perform systems intercomparisons, develop protocols and procedures, study the properties and characteristics of MNPs and contribute towards standardisation and interoperability. Crucially, the Action partners are well-suited to pose clinical questions, propose specific applications and describe the systems and MNP requirements for each clinical condition.

Transfer of knowledge: At the same time, NexMPI provides excellent opportunities for knowledge transfer. The MPI community is concentrated, with just a handful of operational systems in Europe. NexMPI will provide access to these systems. Databases of measurements will be created; language- agnostic data formats will be defined; protocols, reports and descriptions of MNPs will be provided to all stakeholders. Through these open-access pathways, as well as direct personal collaborations (e.g. STSMs, Training Schools) and other forms of exchange, knowledge will be transferred from the more experienced groups to the less experienced ones. At the same time, since the technology development of MPI is far from being saturated, cross-fertilisation will also take place; for example, MNP synthesis practices established at a given institution can be adapted to MPI, even if that institution has no prior MPI experience. The participation of industrial partners means that knowledge transfer will not be limited to academic issues, but will involve commercial and regulatory concerns; for instance, how a novel MNP or a device can be taken from the lab to the market, MNP mass- production issues, how laboratory experiments and developments can be translated to the clinic etc.

Career development: MPI is currently in a pre-clinical phase with several challenges and opportunities that require further research. There exists fully-functional commercial pre-clinical equipment; however, the technology is not mature enough and various groups are developing devices for specialized applications or exploring new design approaches. Thus, there are tremendous opportunities for career development, for both experienced researchers and YRIs. NexMPI will provide enhanced opportunities for career development in a new field through: (a) STSMs, Training Schools, workshops, Virtual Mobility, ITC Conference grants and (b) leadership positions in WGs, organizing events, development of international network associations for future career advancement.

3.2.2. PLAN FOR DISSEMINATION AND/OR EXPLOITATION AND DIALOGUE WITH THE GENERAL PUBLIC OR POLICY

The Action members realize the importance of dissemination, especially for a technology still in its early stages of development for which new applications are constantly being added. Because expeditious dissemination of **NexMPI** breakthroughs to both specialised groups and the general public is crucial for optimised exploitation of the results, the Action will establish as soon as possible a detailed data management plan (D5.1) in coordination with all network participants to organise data collection, curation, sharing, and archiving, complying with the “FAIR” (Findable, Accessible, Interoperable, Reusable) principles.

Under the direction of the Science Communications Coordinator, the Action communication, dissemination and exploitation plan will be specialised for each specific target audience.

A website and social media will be used to reach ***all stakeholders***. The website will have a public and a private section, containing clear and accessible information on the project, impacts, partners, workplan, funding source, and results. The private section will host internal Action documents, such as reports,

meeting minutes etc. The project page will also host downloadable brochures, flyers, posters and videos and will have different pages for each the audience categories. The website will be updated monthly or more often, starting from M6. The aim is to average 20 visits per month by M36. In addition, a project LinkedIn account will be created for engagement with the scientific and academic communities, clinicians, industry experts and the general public. The account will be updated regularly (tentatively every two weeks), and the target is possibly reaching above 500 followers by M36.

The ***scientific community*** will be reached through publications in peer-reviewed high impact open access journals (e.g., Biomaterials, Nanomedicine, Physics in Medicine and Biology, Medical Physics, International Journal of Hyperthermia) and the EC´s publishing platform Open Research Europe; presentations in national and international scientific conferences (e.g., if possible International Workshop on Magnetic Particle Imaging; European Congress of Medical Physics; British Society of Interventional Radiology Annual Meeting; European Society for Hyperthermic Oncology; and European Society of Therapeutic Radiology and Oncology Annual Meeting); organization of workshops, seminars and webinars about MPI and its applications; and online courses describing the science and technology of MPI. Subject to institutional or professional approval, these courses could also provide academic or continuing education credits.

The key dissemination tools for YRIs are Training Schools (two are planned, at years 1 and 3) and STSMs. The latter are extremely important as the number of MPI laboratories is limited. Thus, within the framework of an STSM, YRIs and PhD students will be able to gain valuable hands-on experience, which they will bring back to their countries (technology transfer). YRIs and PhD students will be supported to give presentations at conferences as well as intra- and inter-institutional workshops and seminars. For example, a physics or engineering YRI or PhD student working on hardware development could describe MPI to other students and researchers in the biology or nanomedicine department of the same or another institution.

To communicate to the ***general public***, the Action will use articles, posters, flyers and brochures written in laymen's language. In addition to describing the science and technology of MPI itself, communication will take the form of "success stories" and specific non-technical examples, e.g. how MPI can be used in lieu of ionizing radiation. Video clips will be created and hosted on the Action website and/or YouTube and other video hosting platforms to maximise outreach. Webinars will be organized regularly (tentatively every six months) to present key achievements and discuss specific topics through Teams/Zoom platforms. Special attention will be given to newsletters and press releases targeting patient associations and medical doctors. The aim is to have two newsletter issues per year. Finally, WG 5 will maintain a database with outreach events in the partners' cities (e.g., if possible, Pint of Science, European Researchers Night), and foster the participation of the partners. Moreover, WG5 will make the most of partner meetings to organise dedicated outreach events in the host-cities. The target is to encourage each participating country to organize regular local outreach event.

Clinicians are a special target audience, since they constitute the main group of end-users. NexMPI will promote contact with presentations, seminars, workshops to acquaint clinicians with MPI, but also in an effort to actively engage them to define and describe clinical problems suitable for MPI. Depending on the situation, the message will be adapted to the specific clinicians, departments or hospitals. For example, Interventional Radiologists performing angiographic procedures would be particularly interested in human-size MPI units (that are currently at their latest stages of development) as a replacement for standard ionizing radiation producing angiographic equipment. It should be pointed out that, to date, most applications using MPI have focused on certain selected fields, such as Oncology, whereas the majority of other fields has received little attention.

Dissemination to ***industry*** is crucial, as the advancement of MPI technology occurs in significant leaps. Currently, two commercial entities produce MPI equipment for preclinical research, and numerous companies specialize in MNPs. The Action will extend a warm invitation to industrial stakeholders to actively engage in Action initiatives. This includes involvement in systems evaluations, contributing to the development of protocols and procedures for MNP characterization, participating in working groups, offering demonstrations, providing hands-on training in specialized workshops and training schools, as well as organizing parallel sessions in conferences and meetings. Through these interactions, industry members will gain a deeper understanding of the clinical and research challenges under exploration. Commercial participants within NexMPI will showcase MPI technology and its applications at conferences and trade shows. Industry representatives will also be invited to address regulatory considerations, discuss mass production of MNPs, and explore the journey from a laboratory prototype to market readiness. These engagements will enable them to connect with a broader industrial audience, refine product designs for

specific applications (such as MNPs with distinct attributes), and enhance overall product offerings.

Special attention will be given to industry conferences and trade shows identified by technology transfer and innovation hubs of the participating institutions, publications in industry journals, company visits and pilot demonstrations, industry-specific forums and online communities.

4. IMPLEMENTATION

4.1. COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

4.1.1. DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

The **NexMPI** Action will be managed by the Management Committee (MC), supported by WG leaders and coordinators to address challenges and facilitate decision-making. Four working groups (WGs 1 to 4) are dedicated to scientific advances and one WG (WG5) deals with regulatory issues, Intellectual Property Rights (IPR), dissemination, and educational programmes, including towards ITCs and YRIs. The Action MC will support the following policies to help achieving the Action objectives: (1) Fair regional contribution (with possibly 50% ITCs at all levels of Action management), (2) Balanced generational representation [enrichment in YRIs (with possibly 25%) at leading positions] and (3) Gender and diversity equity (with possibly 50% females in decision-making bodies). The interrelations between all WGs will promote information sharing during WG meetings and the annual Action conference. To achieve Action goals (section 1.2.2), the scientific work plan of NexMPI will be structured in five tightly interconnected WGs (Fig. 2).

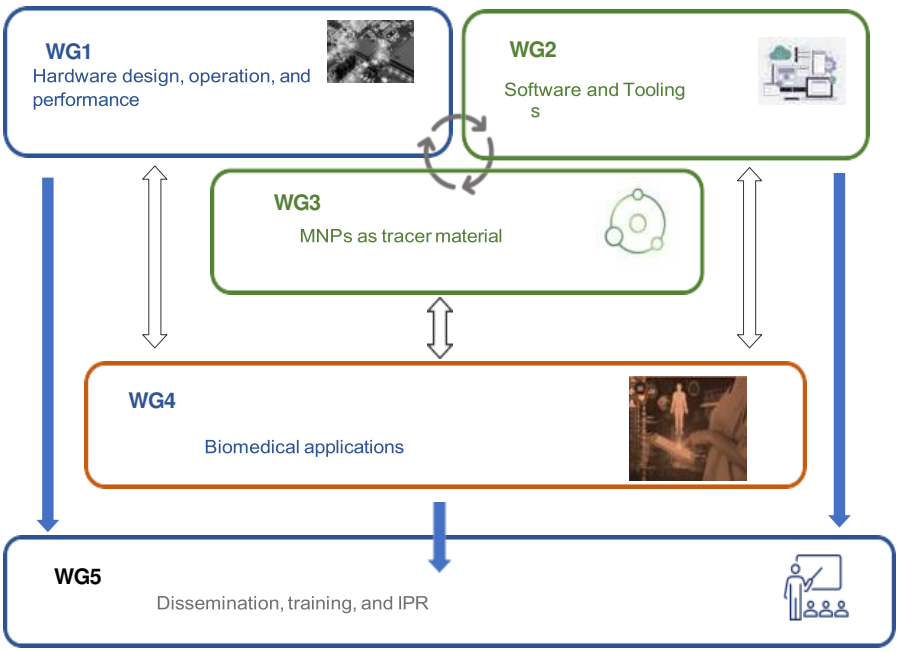

Figure 2. NexMPI workplan

WG 1: Hardware design, operation, and performance

This WG will evaluate the performance of different MPI scanners by developing common criteria and procedures. It will also create an open-source database of MPI/MPS (Magnetic Particle Spectroscopy) systems, components, and control software to reproduce and optimise future MPI and MPS systems. Specifically, WG1 will focus on the following tasks:

- *Task 1.1 Currently available MPI hardware*. Collect information on currently available MPI hardware inside and outside of the action (M1.1). This will result in a publication (D1.1) and help advance WG 4 objectives.
- *Task 1.2 Comparison of MPI systems.* Compile a protocol for non-biased comparison of different MPI scanner types. This will allow the establishment of phantoms and protocols for the first tests (M1.2) on WG4 (D1.2).

- *Task 1.3 Data collection.* Collect data based on the comparison protocol from all setups available to members of the Action. This roadmap represents a crucial tool to understand data obtained from the NexMPI members and thus advance with best practice for future studies (D1.3).

WG 2: Software and Tooling

WG 2 will investigate software related topics, such as the simulation of particle physics and scanner instrumentation (e.g. magnetic fields, signal induction, coil coupling); image reconstruction; and pre-processing/postprocessing of the resulting MPI images. The aim of WG 2 is to define proper interfaces of software components that allow the combination of different software packages across research groups. Of particular importance, WG 2 also aims to bring together software developers with users (e.g. application researchers) in order to improve the functionality and output of the software. The tasks of WG2 are:

- *Task 2.1 Software packages.* Identify currently available MPI software packages and categorise them according to their functionality, development status, performance and the programming language used (M2.1). Publish the results (D2.1) and integrate them in the Training School.
- *Task 2.2 Lack of functionality.* Use the gathered data for identifying a lack of functionality in the MPI software landscape and include additional end-user feedback (M2.2).
- *Task 2.3 Data formats & interfaces.* Develop programming-language agnostic file formats for simulation environments (e.g. coil setup, MNP parameters, sequence parameters), raw MPI data (e.g. voltage signals, measurement parameters), and data reconstructions. Additionally, implement interfaces to the new data formats for software packages inside and outside of the Action (D2.2).
- *Task 2.4 Inter-operability.* Develop unit tests that are performed with continuous integration (CI) services and test the inter-operability of different software packages (D2.3, D2.4).

WG 3: MNPs as tracer materials

This WG will focus on the optimization of MNPs as tracer materials in MPI. This includes their magnetic properties, in order to produce a strong MPI imaging signal and also be clinically feasible. For some advanced MPI applications additional characteristics/functionalities may be required, e.g. heat-transfer efficiency for hyperthermia. WG 3 will focus on the following tasks:

- *Task 3.1 Review literature.* Map current technological advances relating to MNP synthesis relevant for MPI applications. This will include considerations such as shape/size of MNPs, coating design, biosafety and biocompatibility (D3.1).
- *Task 3.2 MNP synthesis.* Assess MNP synthesis methods specifically for use in MPI. This includes functionalization with specific biomarkers in order to increase target uptake (M3.1, D3.2).
- *Task 3.3 Characterisation and evaluation of MNPs.* Magnetic and structural characterisation of MNPs regarding MPI efficiency, in cooperation with WG1, WG2 and WG4 (D3.3).

WG 4: Biomedical applications

WG 4 will foster development of novel (pre)clinical applications and translation of existing preclinical approaches to the clinic, focusing primarily on cancer and cardiovascular conditions. That includes mapping of (pre)clinical requirements, such as biodistribution, pharmacokinetics, pharmacodynamics, biological effects, active/passive targeting, as well as application-specific considerations. Specifically, WG 4 will include the following tasks:

- *Task 4.1 Survey MPI preclinical groups.* Investigate state-of-the-art research groups employing MPI in (pre)clinical research and map their specific research topics (D4.1).
- *Task 4.2 Preclinical studies.* Develop guidelines for preclinical studies using MPI (D4.2, D4.3).
- *Task 4.3 Clinical challenges.* Suggest MPI clinical trials, define metrics to assess the efficacy of MPI, and compare with established molecular imaging techniques, e.g. PET, SPECT (M4.3, D4.4).

WG 5: Dissemination, training, and IPR

NexMPI aims to become a think tank and a business incubator for technology related to patentable valuable products, as new hardware, software or MNP tracers. This requires a conduit for permanent information

flow between academia and industries under the guidance of regulatory bodies. Moreover, the development capacity of NexMPI lies in the opportunity for academic laboratories and industrial partners to develop an educational programme together with a clear dissemination strategy as follows:

- *Task 5.1 Data management plan.* Develop data management plan for data produced by the Action (D5.1).
- *Task 5.2 Dissemination.* Develop Action website; produce newsletter, videos, podcasts and tutorials; keep archive and manage recordings of talks, seminars, workshops etc (e.g. on YouTube). Organize NexMPI participation and promotion in science events, e.g. if possible European Researchers' Night, Nanomedicine Day, Pint of Science, World Cancer Day (D5.2, D5.3)
- *Task 5.3 Training*. Organize and manage STSMs and Training Schools. Set up seminars/workshops with world-leading scientists, industrial partners, and young scientists (PhD students and early/mid-stage researchers) to stimulate exchange of information, networking, mentorship spirit, and career development (D5.4)
- *Task 5.4 Intellectual Property Rights.* Develop IPR management plan in accordance with: (a) the COST rules, (b) national laws, and (c) institutional procedures and rules of the parties involved. Address confidentiality issues, strategies to avoid early disclosure, procedures for data sharing and access of unpublished data (D5.5).

4.1.2. DESCRIPTION OF DELIVERABLES AND TIMEFRAME

The MC will continuously monitor progress on the basis of the Gantt chart (in section 4.1.4), as well as the milestones and deliverables in Tables 4.1 and 4.2, respectively. The milestones, being major control points, have been defined to provide easy verification of progress towards the achievement of the final goals.

Table 4.1. List of NexMPI milestones

No	Milestone name	WG	Date (Mo)
M1.1	All work groups and corresponding scanner types have been identified	1	12
M1.2	Phantoms and protocols for first test defined	1	18
M1.3	Phantoms and protocols implemented at all participating sites	1	30
M2.1	Categorisation of currently available MPI software packages	2	12
M2.2	Software functionality requirements determined	2	24
M3.1	Mapping of MNP synthesis expertise	3	12
M3.2	Identification of optimal MNP for MPI	3	24
M4.1	Information collected on preclinical MPI	4	18
M4.2	Symposium on harmonisation of guidelines for preclinical MPI	4	30
M4.3	Symposium on clinical MPI challenges	4	38

Table 4.2. List of NexMPI deliverables

No	Deliverable name	WG	Date (Mo)
D1.1	Open-access publication on MPI hardware	1	24
D1.2	Catalogue of protocols and phantoms for non-biased comparison	1	30
D1.3	Open-access publication on protocol for non-biased comparison	1	42
D2.1	Open-access publication on MPI software packages	2	20
D2.2	Data file format specifications shared in open-access repository	2	32
D2.3	Publication on interoperability between software packages	2	36
D2.4	Documentation and unit test published on open-access repository	2	44
D3.1	Open-access publication on MPI tracers	3	18
D3.2	Standard Operating Procedures (SOP) for synthesis of MNPs	3	24
D3.3	Open-access report on the characterisation and evaluation of MNPs	3	44
D4.1	Open repository of MPI preclinical research groups and topics	4	20
D4.2	White paper on mapping end-users and (pre)clinical requirements	4	24
D4.3	Open-access report on guidelines and requirements for in vivo MPI	4	36
D4.4	Open-access publication of clinical applications of MPI	4	44
D5.1	Data management plan	5	6

D5.2	Website creation	5	6
D5.3	Communication, dissemination and exploitation plan	5	8
D5.4	STSM reports (M12, M24, M36, M48)	5	48
D5.5	IPR plan	5	12

4.1.3. RISK ANALYSIS AND CONTINGENCY PLANS

NexMPI is a large interdisciplinary and intersectoral network with top experts, opinion leaders, outstanding clinicians and industry partners of various sizes, which will ensure the feasibility of the work plan and the resilience of the network. However, as a large, distributed entity, **NexMPI** will have to tackle challenges at the individual, WG and network scales.

General Issues Relevant to the Whole Action

Type of Risk	Mitigation measures
Organizational	
Size of the network inadequate (Likelihood: low, Impact: low)	A sufficient critical mass is foreseen, and any required expertise not found in Europe may be looked for overseas. If the size of the network becomes too big, the management structure could be reinforced by adding Task Coordinators
Temporary or permanent absence of a participant (Likelihood: medium, Impact: medium).	For research tasks, a substitute will be appointed and, if needed, invited to the network. For management tasks, MC substitutes will become available before the kick-off meeting.
IPR	
IPR transfer among participants inadequate (Likelihood: medium, Impact: high).	Participants will sign non-disclosure agreements to undergo a project that requires the use of background IP. Any foreground IP generated during the Action shall remain the property of the involved parties.
Issues referring future use of results (Likelihood: high, Impact: high).	IP access rights under fair conditions shall be granted to participants willing to exploit the results generated.
Scientific	
Failure to access the research infrastructures (Likelihood: low, Impact: high).	Depending on the available budget, reinforce funds to support researchers who need to use those facilities; alternative paths will also be looked for.
Progress insufficient (Likelihood: medium, Impact: high).	Joint WG meetings focused on the problem or topic of interest will be organized.
Economic	
Reduction in funding of individual research groups or in COST Association budget (Likelihood: medium, Impact: medium).	Given the size of the Action, reductions in local funding may be counterbalanced by other Action nodes and the possibility to access European (or international) resources in the frame of collaborative projects and geographical mobility programs. If funding reduction affects networking activities, STSM and WG meetings will be prioritized.

Work Group Specific Risks

Type of Risk	Mitigation measures
WG 1: Hardware design, operation, and performance	
The interlaboratory data collection and protocol refinement upon the pertinent analysis take more time than expected (Likelihood: low, Impact: medium).	Lower the intended geographical spread or operating principles of the machines included and re-evaluate the suitability of the proposed protocol.
Access to scanners is less than anticipated (Likelihood: medium, Impact: high).	Recruit other groups into the Action. If the number of scanners is still inadequate, adjust the experiments and measurements planned.

WG 2: Software and tooling	
Different file format requirements for different MPI scanners may impact on the interoperability and efforts to evaluate interlaboratory reproducibility and establish best operating procedures (Likelihood: medium, Impact: high).	A data file format with custom fields for allowing implementation-specific extensions will be established.
WG 3: Tracer materials	
New nanoparticle synthesis processes prove not to be robust and reproducible (Likelihood: low, Impact: medium).	Adapting a manufacturing process following well-tested and currently used standard operating procedures.
WG 4: Biomedical applications	
Insufficient realisation of new MPI applications or progress towards clinical trials (Likelihood: low, Impact: medium).	Ensure recruitment of appropriate stakeholders from the network or reassess the studies expectations downwards and redistribute the tasks accordingly.
MPI scanner capable of whole-body imaging not ready in time for use in clinical work (Likelihood: high, Impact: medium).	Use head-and-neck scanner and leg scanners that have already been demonstrated in operational prototypes.
Whole-body MPI scanner developed but regulatory approval is pending (Likelihood: high, Impact: medium).	Use phantoms or extend pre-clinical studies to experimental animal studies with the new devices
Novel MNPs are not approved in time for use in clinical trials (Likelihood: high, Impact: high).	Use tracer materials with existing regulatory approval instead.
WG 5: Regulatory, education, disseminating and technology transfer	
Delayed activities, tasks and deliverables (Likelihood: low, Impact: medium).	Examine progress twice a year. If necessary, postpone deliverables.

4.1.4. GANTT DIAGRAM

		Year 1				Year 2				Year 3				Year 4			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
	Management																
	Kick-off meeting	x															
	MC meetings	x				x				x				x			
	MC teleconferences			x				x				x				x	
	WG meetings	x				x				x				x			
	WG teleconferences			x				x				x				x	
	Training Schools				x					x							
	STSMs		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
WG 1	**Hardware**																
T1.1	Currently available MPI hardware				M				D								
T1.2	Comparison of MPI systems						M				D						
T1.3	Data collection										M				D		
WG 2	**Software**																
T2.1	Software packages				M			D									
T2.2	Lack of functionality								M			D					
T2.3	Data formats & interfaces												D				
T2.4	Inter-operability															D	
WG3	**MNPs as tracer materials**																
T3.1	Review literature						D										
T3.2	MNP synthesis				M				D								
T3.3	MNP characterisation and evaluation															D	
WG4	**Biomedical Applications**																
T4.1	Survey MPI preclinical groups						M	D									
T4.2	Preclinical studies										M		D				
T4.3	Clinical challenges													M		D	
WG5	**Dissemination, training, IPR**																
T5.1	Data management plan		D														
T5.2	Dissemination		D	D													
T5.3	Training				D				D				D				D
T5.4	Intellectual Property Rights				D												

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