Title of Proposal: Heavy Ion Therapy Research Integration *plus* (HITRI*plus*)
Short name: HITRI*plus*

List of participants.

Participant No *	Participant organisation name	Country
1 (Coordinator)	Fondazione Centro Nazionale di Adroterapia Oncologica (CNAO)	IT
2	Bevatech GmbH (BEVA)	DE
3	Commissariat à l'énergie atomique et aux énergies alternatives (CEA)	FR
4	European Organisation for Nuclear Research (CERN)	IEIO
5	Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT)	ES
6	Cosylab Laboratorij za kontrolne systeme dd (CSL)	SI
7	GSI Helmholtzzentrum für Schwerionenforschung GmbH (GSI)	DE
8	Universitätsklinikum Heidelberg (UKHD/HIT)	DE
9	Istituto Nazionale di Fisica Nucleare (INFN)	IT
10	EBG MedAustron GmbH (MEDA)	AT
11	Marburger Ionenstrahl-Therapie Betreibergesellschaft mbH (MIT)	DE
12	Paul Scherrer Institut (PSI)	CH
13	South East European International Institute for Sustainable Technologies (SEEIIST)	CH
14	Universita ta Malta (UM)	MT
15	Philipps-University Marburg (UMR)	DE
16	Uppsala University (UU)	SE
17	Wigner Research Centre for Physics (Wigner RCP)	HU
18	Riga Technical University (RTU)	LV

Third party participation linked to SEEIIST		
Participant No *	**Participant organisation name**	**Country**
19	Ss, Cyril and Methodius University in Skopje, Republic of North Macedonia (UKIM)	MK
20	Clinical Centre of Montenegro (CMSM)	ME
21	Sentronis a.d. (SEN)	RS
22	Jožef Stefan Institute (IJS)	SI

CONTENTS

Abstract

The goal of Heavy Ion Therapy Research Integration *plus* (HITRI*plus*) is to integrate and propel biophysics and medical research on cancer treatment with heavy ions beams while jointly developing its sophisticated instruments.

Cancer is a central health problem for our society. Heavy ion beams irradiate tumours by focussing on the ill tissue while sparing the healthy part around, more effectively than any other irradiation treatment. The wider objective of HITRI*plus* is to provide radiation oncologists with a cutting-edge tool to treat the fraction of tumours that are not curable with X-rays or protons or have better survival rates or lower recurrences with ions.

For this major initiative, HITRI*plus* has gathered a consortium engaging all relevant stakeholders and for the first time bringing together all four European ion therapy centres with leading EU industries, academia, and research laboratories. They all share the ambition to jointly build a strong pan-European Heavy Ion Therapy Research Community. A strategic partner is the South East European International Institute for Sustainable Technologies, which federates eight countries in South East Europe with the ambition to build a next generation heavy ion Research Infrastructure in the area, to boost research and cooperation in a region trying to rebuild after a troubled past.

HITRI*plus* Transnational Access will integrate and open to external researchers the experimental programme of the five European facilities providing therapeutic ion beams. Its Networks will structure and foster the research on heavy ion therapy, including clinical and pre-clinical research. Joint Research Activities will develop new accelerator and beam delivery technologies to extend the reach of the present generation centres and to define a new European reference design, at lower cost and dimensions, to make cancer ion therapy more accessible and to open new markets to European industry.

1. Excellence

INTRODUCTION AND MOTIVATION

This proposal for an advanced **Heavy Ion Therapy Research Integration *plus*** (HITRI*plus*) aims at bringing together, integrating on European scale, and opening up to European researchers from academia and industry, the key research infrastructures for **bio-physics and medical research on cancer treatment with heavy ion beams**, jointly developing at the same time the next generation of its sophisticated **instruments**.

The battle against **cancer** remains a long-term priority for our society, including at this moment when other medical emergencies are mobilising our resources: even under pessimistic assumptions, the death toll of COVID-19 in 2020 will remain below that of cancer[1]. Among the primary tools to fight cancer, X-ray **radiotherapy** (RT) is nowadays a standard and accessible technique, delivered by as many as 3,500 treatment units installed in European hospitals. Besides X-rays, radiotherapy with beams of **protons** that deposit a lower radiation dose in the healthy tissues surrounding the tumour is now flourishing, with 25 units in operation in Europe and other 4 under construction[2]. The next challenge in hadrontherapy[3] consists in a wider use of **radiotherapy using ions heavier** than protons (primarily carbon), which presents many **advantages over X-rays or protons** in terms of dose conformity, effectiveness in particular against radio-resistant tumours[4], and perspectives of integration with modern immunotherapy. In Europe, **only four centres** deliver carbon ion therapy, compared to six in Japan and three in China. Recently, carbon ion therapy received a renewed attention in the US, where the construction of **two new facilities** has been announced[5]. While turnkey heavy ion therapy accelerators can be purchased from Japanese industry, European industry is absent from this potentially growing market.

Two main reasons are limiting the diffusion of heavy ion therapy and the access of a larger number of patients to this advanced treatment technique. The first is the limited availability of **clinical and pre-clinical data**, including experience with different ions, combination of different ions for imaging and treatment, alternative delivery schemes, effectiveness on different types of tumours, etc. The second is the significant cost of the treatment, presently about a factor of four higher than X-ray RT in Germany and Italy, related to the significant **cost and size** of the particle accelerator required to accelerate the ions to the treatment energy.

The HITRI*plus* **Starting Community** initiative aims at gathering a wide multidisciplinary consortium to address both critical issues in a collaborative and structured way. Its Transnational Access will **integrate and open** to external researchers the **experimental and clinical research programmes** of the four European therapy facilities providing heavy ion beams, together with the biophysics programme of the most advanced European centre for research with heavy ions. Its Networks will structure and foster the **research on heavy ion therapy**, including both clinical and pre-clinical research. Its Joint Research Activities will develop accelerator and beam delivery technologies aiming at **extending the reach of the present generation** of European ion therapy centres in terms of experimental programme and therapy techniques. At the same time, HITRI*plus* aims at developing a **new design at lower cost and dimensions** to make cancer ion therapy more accessible and to give to European industry a competing edge in this expanding sector of the cancer care market. The wider objective is, in an optics of advanced **personalised cancer medicine**, to provide radiation oncologists with the **expertise and instruments** to offer a cutting-edge **alternative tool** to treat the fraction of tumours that are not curable with X-rays or protons, or have better survival rates or lower recurrences when treated with ion beams.

[1] Almost 1.2 million persons died from cancer in the European Union in 2016 (source: Eurostat) against 126,757 COVID-19 related deaths in Europe as of 28 April 2020.
[2] Source: https://www.ptcog.ch/
[3] The term "hadrontherapy" covers treatment with protons or ions, both "hadrons", particles made of quarks interacting through the "strong-force".
[4] Tumours resistant to treatment with X-rays or protons, estimated to concern 1 to 3% of all patients presently treated with X-rays, https://gco.iarc.fr/today/home; and Patin S. et al. J. Cancer Epidemiol., 2013
[5] See for example T. Malouff et al., Carbon Ion Therapy: A Modern Review of an Emerging Technology, Front. Oncol., 04 February 2020, https://doi.org/10.3389/fonc.2020.00082

To address these challenges, HITRI*plus* has gathered a consortium spreading across 14 European countries. It involves all four European ion therapy centres, GSI that is a world reference for heavy ion physics and has pioneered particle therapy in Europe, the European Organisation for Nuclear Research (CERN) contributing with its experience in accelerators and project management, together with 8 other world-class research institutions, 5 leading universities, and 3 innovative small and medium enterprises (SME's).

A strategic partner of HITRI*plus* is the **South East European International Institute for Sustainable Technologies** (SEEIIST), which assembled eight countries in the region of South East Europe (SEE) on the project of building there a world-leading institute for tumour therapy and biomedical research with advanced particle beams, open to researchers from the entire Europe[6]. Based on the model of 50% of running time dedicated to research and 50% to therapy to serve the needs of the region and to cover the operational costs, this centre is intended to improve peaceful collaboration in the region and reverse the brain drain in preparation for a successful integration in the European Union. The outcome of HITRI*plus* will become the foundation for the SEEIIST experimental programme and research community, as well as for its advanced accelerator and beam delivery design.

1.1 OBJECTIVES

Starting from its basic motivations, the HITRI*plus* Consortium has identified five strategic objectives to be achieved within the Project, aimed at the advancement of ion therapy research with ions heavier than protons.

1. To **integrate, open up** and **broaden** the leading European Research Infrastructure for the treatment of cancer with **beams of ions,** ranging from helium to carbon and to heavier ions.

2. To **coordinate and strengthen** the research programmes on heavy ion therapy of different European institutions, by promoting synergies, collaborations, innovation, knowledge transfer, new initiatives and sharing of tools and data.

3. To develop in a joint and coordinated way **novel technologies** to improve the accelerators and their ancillary systems that provide particle beams to this scientific community. These technologies will **improve the present generation** of facilities and will be the **foundation for a next generation** European design for ion therapy facilities.

4. To establish a **European multidisciplinary community** for heavy ion therapy research, aiming at improving treatment strategies and modalities by connecting physics and engineering with medicine, biology and biophysics, and to **extend this community** towards emerging European regions, addressing in particular **new initiatives in South East Europe**.

5. To define the main technical features and the scientific programme of a future **pan-European Research Infrastructure** for medical and radiobiological research with heavy ion beams, to be built in South East Europe or in another European region.

Presently, in Europe ion therapy using carbon ions is provided by four facilities, HIT in Heidelberg (DE), CNAO in Pavia (IT), MIT in Marburg (DE), and MedAustron in Wiener Neustadt (AT). These centres started operation between 2009 (HIT) and 2019 (MedAustron). Their design and operation protocols are based on pioneering accelerator design work done at the GSI heavy ion research centre at Darmstadt (DE) and at CERN in Geneva (CH), and on the experience with the first patient treatments delivered by GSI.

[6] https://seeiist.eu/

Since the start of their operation, the priority of these centres has been in administering treatment to cancer patients, to assess and exploit the effectiveness of ion therapy and to cover their operation costs with contributions from the national Health Insurance systems. Pre-clinical experimentation and development of new treatment modalities has received lower priority until recently, when new ideas for improving patient treatment are appearing at a moment when ion therapy is more established and the focus can move from therapy to research. For their new research objectives, some therapy centres are equipping new experimental facilities, as the new experimental room at CNAO that is operational since beginning 2020.
Building on the positive momentum, HITRI*plus* aims at fully exploiting the potential of ion therapy and the large investment related to the construction of the four centres mentioned above, of the order of about 700 million Euros. To achieve this goal, HITRI*plus* will set up a **coordinated research programme** open to all European researchers, especially those external to the therapy centres and coming from industry, accessible *inter alia* to researchers coming from South East Europe and preparing for future research at SEEIIST.

1. The first objective of HITRI*plus* expressed by its Transnational Access (TA) consists in **integrating and opening up the clinical and research programmes** at the four therapy facilities, and in connecting them to the successful biophysics research programme of the GSI laboratory. Biophysicists, medical physicists, medical doctors, pharmaceutical companies, industry and experts developing specialised instrumentation, will all have access to the best European infrastructure for the treatment of cancer with heavy ions. The open access to the therapy facilities, sustaining the patient treatments, will considerably contribute to creation of evidence-based medicine on heavy ion treatments. It will favour a more efficient recruitment of the European eligible patients, and will allow a coherent approach in comparing the clinical trials outcomes. Concerning biophysics research, opening up these infrastructures to external researchers will allow exchange of information, optimisation of resources, and the establishment of common methods and standards. The TA will pave the way for an enlargement of the research community, in particular in the direction of South East Europe favoured by the ongoing SEEIIST programme that will provide connections with the Research Institutions in the area, which will be able to access the best infrastructures gaining an experience that will be vital to the SEEIIST programme.

   Key Performance Indicators (KPI): *HITRIplus will provide to more than 150 users a total of 50 clinical access units (patients) and 448 research units (hours) distributed among its five TA facilities. 20-30% of the users are expected to come from SEE countries institutions that will take part for the first time in ion therapy related research.*

2. The second HITRI*plus* objective is realised by its Networks, which address a large number of partners from the medical and biophysics field with the goal of **coordinating biophysical, pre-clinical and clinical research on heavy ion therapy** at European level. HITRI*plus* will organise workshops and events with the goal of promoting synergies, favour industry engagement and knowledge transfer, and define common approaches and procedures. In particular, collaborative platforms and databases will be set up to share data and experience.

   KPI's: *HITRIplus will gather a community of more than 500 researchers from the medical field, from academia and from industry. A European registry of patients treated with carbon ions will be established, with > 100 patients. To contribute to the dissemination of results, HITRIplus will organise at least one multidisciplinary Workshop per year, and will publish Newsletters for clinicians and for general audience. A Technology Overview committee (WP4) will identify promising HITRIplus technologies that will be advertised to industry at general and dedicated events. The target for social media is >150.000 contacts per quarter.*

3. A crucial objective of the HITRI*plus* Consortium consists in capitalizing from the shared experience of the running centres to advance the existing and develop new **technologies to improve the ion accelerator and the beam delivery systems**. It is of paramount importance to ensure a solid foundation of this starting

community via the joint development of key technologies and innovative solutions of common interest and benefit, with the final goals of improving the services provided by the ion therapy facilities and of reducing costs for both research and therapy. The HITRI*plus* Joint Research Activities (JRA) will develop advanced **beam delivery** techniques to improve the quality of the beam delivered to patients and to experimenters, by enhancing the control of the beam properties and of the dose delivered. On the accelerator side, the goal of the HITRI*plus* JRA's consists in developing new technologies to increase **beam intensity** for faster dose delivery, and to **reduce the dimensions and cost of the accelerator and of the gantry** used to control the position of the beam on the patient. The improvement in both accelerator and gantry will be allowed by an extensive use of superconductivity to generate higher magnetic fields, and will take place in close connection with **European industry** that is a world-leader in the field, to prepare both elements to an industrialisation phase followed by possible commercialisation by a company or a consortium of companies identified in the frame of this Starting Community.

KPI's: HITRIplus will produce a complete design for a new generation of superconducting magnets for medical accelerators and gantries that can operate at 3 T dipole field and 1 T/s ramp rate. These magnets will be used to design a superconducting synchrotron with a circumference about half that of existing ion therapy synchrotrons, and a gantry with weight below 100 tons and a cost not higher than twice that of proton gantries. Injection systems will be developed, to bring the accelerated carbon ions intensity to 10^{10} ions per pulse, an order of magnitude higher than present systems. Additionally, it will prepare accelerators for extraction of different beam energies, will develop new multi-platform software tools to integrate accelerator and beam delivery control, and will develop a chair system for patient positioning on the ion beam.

4. Addressing these challenges requires building a **strong interdisciplinary pan-European community**, joining experts coming from medicine, biophysics, physics, and engineering on a common agenda and in elaborating novel solutions and approaches for a further step in cancer therapy with heavy ions. Although the strong focus of HITRI*plus* is in physics and biophysics, connecting with medicine on one side and with engineering and industry on the other side is one of its primary goals. In this way, HITRI*plus* will exploit the innovation potential of a wide multidisciplinary community that would support the definition, knowledge transfer, construction and exploitation of new European initiatives in this direction such as SEEIIST.

   KPI's: More than 100 stakeholders and researchers from medical field, academia and industry will participate in HITRIplus events, out of a community of more than 10.000 who will receive HITRIplus communications and Newsletters and contribute to the events. The general meetings will connect medicine with physics and engineering and industry, to jointly develop new ideas and explore emerging trends.

5. With a longer-term perspective, one of the objectives of this Starting Community is to prepare for the construction of a **new facility optimised for research** that would provide the amount of beam time and the operational flexibility required to **explore new treatment modalities** and to **define innovative treatment procedures**. A facility based on a new accelerator design would make possible testing with a large variety of ion species and energies, using different intensities including short and strong bursts of particles (FLASH therapy), and possibly combine the production of ions to treat solid tumours with the production of therapeutic isotopes for diffused tumours produced using parasitic cycles of the accelerator. HITRI*plus* aims at defining the main components and the scientific programme of such a new facility, profiting of the knowledge and experience of the therapy centres joined with the competences of the main European laboratories designing and building particle accelerators. The **SEEIIST** is the prime candidate to build and exploit this facility for the benefit of all European scientists; however, the HITRI*plus* programme aims at being openly available to any other institution willing to profit of its results. Other perspective users have already expressed interest, as an

association of scientific institutions from the Baltic countries that is including a medical research and therapy facility with heavy ions in its agenda for the future scientific development of the region[7].

KPI's: HITRIplus will design all the advanced features (injection, extraction, superconducting gantry, beam delivery and software) required to upgrade or build a modern synchrotron for ion therapy and research with 10 times higher beam intensity and more flexible operation for research than present facilities. This option might be used by any facility, as an improved solution with novel features based on normal conducting magnets. In addition, HITRIplus will define a more ambitious superconducting synchrotron design based on a new generation of magnets, with about 1/3 accelerator footprint and lower construction and operation cost. The latter can be adopted by SEEIIST or by any other potential candidate with a timeline compatible with the development time of the magnets. All the components developed and designed in HITRIplus will reach a Technology Readiness Level (TRL)[8] 3 to 4, to be ready for a following phase of industrialisation and prototyping to higher TRL level in collaboration with European industry.

1.2 RELATION TO THE WORK PROGRAMME

HITRI*plus* is addressing all specific requirement of this Call's Work Programme.

Specific objectives of the call	HITRI*plus* approach
Bring together, integrate on European scale, and open up key national and regional research infrastructures to all European researchers, from both academia and industry, ensuring their optimal use and joint development.	The project brings together four national ion therapy centres and integrates their clinical and pre-clinical research programmes on a European scale, opening up their research programmes together with the GSI biophysics research facility. The future upgrades are jointly addressed and the relative developments shared. Preparation is made to integrate a new research institution with the ambition of setting up a new pan-European research centre.
Fostering the potential for innovation of research infrastructures by reinforcing the partnership with industry, public administrations and/or other stakeholders, through e.g. transfer of knowledge and other dissemination activities, activities to promote the use of research infrastructures by industrial researchers or policy-makers, involvement of industrial associations and other stakeholders in consortia or in advisory bodies.	During its execution, HITRI*plus* will use its strong Knowledge Transfer Work Package WP4 to keep the contacts with European industry interested in exploiting the HITRI*plus* results through commercial products, and will promote the HITRI*plus* innovations also through existing Technology Transfer networks. The Advisory Board for Ethical/Legal/Industrial issues (ABELII) will ensure additional interaction with industry on specific topics. Three SME's are part of the HITRI*plus* Consortium, contributing to the development of innovative particle accelerator components. Partnership with the SEEIIST political initiative is a key aspect of the HITRI*plus* project.
Take into account all relevant ESFRI and other world-class research infrastructures to exploit synergies, to reflect on sustainability and to ensure complementarity and coherence with the existing European Infrastructures landscape.	Facilities related to medicine are notably absent from the present list of ESFRI Projects, and only three health related distributed initiatives appear in its landmark list. There is a clear divergence between the focus on health and in particular on cancer care of future European programmes and the European ESFRI landscape. To start filling this gap,

[7] A support letter from the CERN Baltic Group is in Appendix to this document.
[8] Technology Readiness Levels defined accordingly to the Horizon 2020 Work Programme, see for example https://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/annexes/h2020-wp1415-annex-g-trl_en.pdf

	the SEEIIST will submit a proposal for the 2020 update of ESFRI. HITRI*plus* is part of its strategy to prepare for implementation, and shares the same goals of sustainability and green infrastructure.
Organise the efficient curation, preservation and provision of access to the data collected or produced under the project, defining a data management plan, even when they opt out of the extended Pilot on Open Research Data. Data management (including ethics and privacy issues), interoperability, as well as advanced data and computing services should be addressed where relevant.	The structure and objectives of the HITRI*plus* Data Management Plan (DMP) are presented in Section 2.2a. The DMP will be the subject of the Deliverable 1.3 at month 6 of the project.

Relations with other Projects

The HITRI*plus* Consortium has prepared its proposal in consultation with INSPIRE[9] (Integrating Proton Beam Therapy Research across Europe), a complementary ongoing Starting Community Integrating Activity project for the integration of proton therapy research. Although the physics and the biology of heavy ion therapy is different from protons, many subjects of interest are common between the two communities, as well as a fraction of the medical and biophysics community sharing its research interests between the two types of particles. To achieve synergies and to avoid duplication of efforts, cooperation and sharing of tools and information between HITRI*plus* and INSPIRE have been already agreed with the INSPIRE management and are going to be implemented via a close coordination between the management of the two projects and via a crossed membership in the respective advisory boards. Training has been already identified as a priority subject for joint initiatives.

Both INSPIRE and HITRI*plus* are related to the earlier integrating activities project ULICE (Union of Light-Ion Centres in Europe) funded in 2009 under FP7 which was centred on "hadron therapy", i.e. using both protons or ions for cancer treatment. At the time, particle therapy activities were in an initial phase and only one centre was starting treating patients with heavy ions, while now there are two communities rapidly growing one on protons (represented by INSPIRE) and one on heavy ions (represented by HITRI*plus*). While the focus of the proton community is in clinical research using accelerators produced by commercial vendors, the priority of the heavy ion community is more in pre-clinical and biophysics research and in optimising accelerators that are not yet commercial.

Whereas two out of the four clinical facilities engaged in HITRI*plus* Transnational Access were already present in ULICE, only one (HIT) was offering at the time a limited research programme with carbon ions; the other (CNAO) started its carbon ion programme only at the end of ULICE. The Transnational Access of HITRI*plus* is now based on a consolidated basis of four running facilities routinely treating patients with carbon ions, and this Integrating Activity is focused exclusively on the new challenges and opportunities in radiobiology, biophysics and medicine offered by heavy ions.

The accelerator development WPs of HITRI*plus* (WP7, WP8) have been defined in consultation with the management of the ongoing Integrating Activity for particle accelerator R&D "Accelerator research and Innovation for European Science and Society" (ARIES)[10]. In particular, the superconducting magnet developments foreseen in WP8 have been structured aiming at being complementary with the activities foreseen in a new Innovation Pilot H2020 proposal for accelerator R&D, I.FAST (Innovation Fostering in Accelerator Science and Technology). While HITRI*plus* will concentrate on advanced design, the focus of I.FAST is on prototyping with the involvement of industry. Close communication is foreseen between these two initiatives.

[9] https://protonsinspire.eu/. A letter of Support for HITRI*plus* by the INSPIRE Coordinator is in Appendix to this document.
[10] https://aries.web.cern.ch/

1.3 CONCEPT AND METHODOLOGY

Specific advantages of Heavy Ion Therapy

X-rays (photons) radiotherapy (RT) is a widely used treatment modality to fight various types of cancer, exploiting the damage made by radiation to the cells' DNA when the radiation dose is concentrated on the tumour. X-rays have a dose distribution in tissues characterised by an almost exponential attenuation and absorption, delivering a large energy near the beam entrance, reaching a maximum at few cm depth, and then continuing to deposit significant amounts of energy beyond the cancer target, as shown in *Figure 1*. To minimise the radiation dose and the damage to the healthy tissues around the tumour, X-ray RT is usually administered from different angles, which improves the situation but still leaves important radiation doses in the surrounding tissues. The X-rays for RT are produced by relatively small electron linear accelerators installed in hospitals; more than 3500 RT units are presently installed in the EU[11]. This treatment technique has now reached a high level of sophistication, in terms of simulations, planning, delivery and the introduction of high-precision techniques as Intensity-Modulated RT (IMRT) based on 3D computed tomography (CT) and Magnetic Resonance (MR) diagnostic imaging.

The **high radiation dose around the tumour** remains however a major concern, in particular in the treatment of tumours close to critical organs or for young patients that have a high risk of developing secondary tumours in the surrounding organs in their lifetime. Impaired quality of life for patients that have sustained damage to organs close to the tumour is another cause for concern.

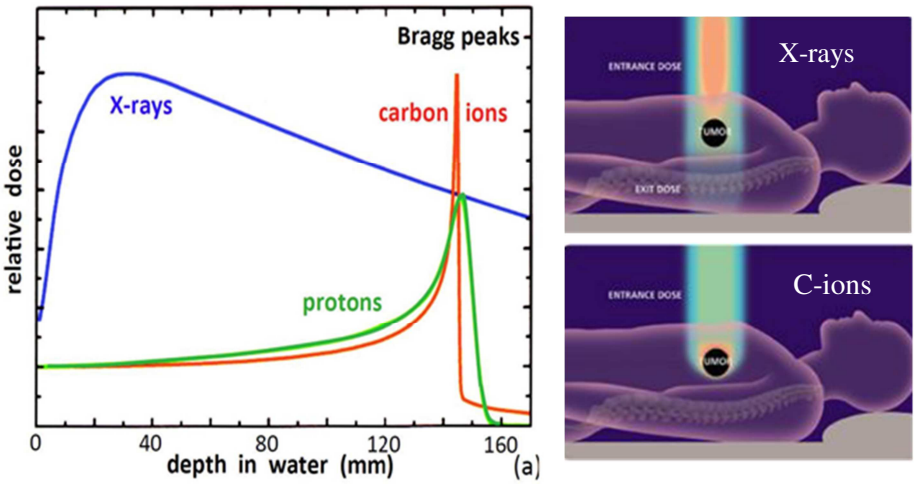

Figure 1 *- LEFT: illustrations of energy deposition for X-ray photons, protons and carbon ions. The energy of the two particles is selected to provide the same range. RIGHT picture shows the different effect of X-rays and carbon ions. Note how carbon ions have minimum radiation deposition on healthy tissue surrounding the tumour.*

To face these problems, direct treatment of tumours with **particle beams** has been proposed already in 1946 and applied in scientific laboratories from the 1950's and in dedicated medical centres from the 1990's. Charged atomic nuclei (ions) like protons or heavy ions have a completely different absorption curve from X-rays, showing the characteristic Bragg peak of *Figure 1*. The absorption is very low after entering the body, and then presents a strong peak concentrated at a depth defined by the energy of the incoming beam. The use of a focussed beam of mm dimensions and the choice of different energies allow spreading the sharp peak along the tumour depth with an almost ideal coverage of the tumour volume in all three dimensions and a very low radiation dose outside of it.

Protons are the easiest ions to produce and accelerate, and proton therapy has been continuously growing since the opening in 1990 in the United States (US) of the first medical centre dedicated to proton therapy[12]. Around 80 proton centres[13] are now in clinical operation worldwide, treating patients with life-threatening tumours where the lower damage to healthy tissues is particularly beneficial as for example at the base of the skull, or tumours in

[11] https://ec.europa.eu/eurostat/web/products-eurostat-news/-/EDN-20171107-1
[12] J.M. Slater et al. in *Hadrontherapy in Oncology*, a cura di U. Amaldi e B. Larsson, Elsevier, Amsterdam-Lausanne-New York-Oxford-Shannon-Tokyo, 1994, p.130
[13] Particle Therapy Co-Operative Group – PTCOG; Particle therapy facilities in operation. 2019. https://www.ptcog.ch/

young children. Another 60 proton centres are under construction or in the planning stage, with one fourth of these spread across Europe. By the end of 2019, over 210.000 patients were treated with protons worldwide.

Beams of **heavy ions**, as **carbon** that is the reference particle for this type of treatment, have a completely different action on the organism with respect to protons or X-rays. The physical difference comes from the **higher energy deposition per unit length**, producing a large number of irreparable double strand DNA breaking that has a much higher probability of killing the cell[14]. On top of this key feature, heavy ions are **more precise than protons**, they have reduced longitudinal range variation (straggling), lower lateral scattering and sharper lateral penumbra[15] (*Figure 1*). These features allow to conform the dose to the tumour and to spare the healthy tissues around it in an unprecedented way. Combined with the use of different energies, this provides a superior coverage of the tumour volume in all dimensions.

These features result in several advantages related to biological processes[16]. The densely ionising radiation is associated with a higher 'Relative Biological Effectiveness' (RBE) for cell killing, with an additional multiplier of about a factor 4 relative to X-rays and protons. This makes it possible to deliver a higher biological dose in the tumour at the same biological dose in the normal tissue, or the same tumour dose with reduced normal tissue damage. The higher fraction of clustered DNA lesions produced by ions, which are difficult to repair, are processed via alternative end-joining mechanisms[17] and open the way for smart radiosensitizers to make tumour cells more sensitive to heavy ion therapy. Another quantitative advantage is that ions have a reduced Oxygen Enhancement Ratio (OER)[18] and are hence less dependent on the availability of oxygen in the tumour tissue. This therefore means that they are effective in the treatment of hypoxia related radioresistant tumours[19] and they can eradicate tumours that are resistant to X-ray therapy[20]. The latter concerns 1% to 3% of all patients treated with X-rays, for which **heavy ion therapy is the only effective treatment**.

Recent data is also pointing towards even more significant biological effects of heavy ion therapy including reduced angiogenesis[21] in tumours, reduced metastasis[22,23] of tumours and increased immune response[24] against tumours following exposure to heavy ions[25]. This means that heavy ion therapy can be used to **enhance the effectiveness of cancer immunotherapy**.

Clinical results from studies conducted a few years ago have indicated carbon-ion treatment advantages for many cancers over photon and proton therapy[26] such as liver cancers (hepatocellular carcinoma), bone and soft tissue sarcomas, head and neck (e.g. adenoid cystic carcinoma), lung, locally recurrent rectal cancer, skin (melanoma), prostate, pancreatic cancer, and cancer during pregnancy, where the low out-of-field dose minimizes the dose to the foetus[27]. Very recent clinical trial results have strengthened the evidence showing the treatment advantages of carbon-ion therapy[28]**,** especially when it comes to radioresistant tumours, tumours in close proximity to vital structures or reirradiation in cases where delivery of a sufficient dose is not possible with X-ray techniques. These studies include skull based chordoma[29], sacral chordoma[30], meningioma[31], adenoid cystic carcinomas of the head and neck region[32], salvage therapy in head and neck cancer[33], and prostate adenocarcinoma[34].

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[14] Suit H, DeLaney T, Goldberg S, et al. Radiother Oncol 2010;95:3–22
[15] Durante M, Debus J, Seminars in radiation oncology 2018 vol. 28:2, 160-167
[16] Durante M, Loeffler JS, Nat Rev Clin Oncol 7:37-43, 2010; Uhl M, Herfarth K, Debus J, Cancer J 20:433-439, 2014
[17] Averbeck N B, Topsch J, Scholz M, et al, Front Onco l6:1-8, 2016
[18] Oxygen Enhancement Ratio: the enhancement of therapeutic or detrimental effect of ionising radiation due to the presence of oxygen
[19] Tumour hypoxia: is the situation where tumour cells have been deprived of oxygen
[20] Chiblak et al. Int J Radiat Oncol Biol Phys 2016;95(1):112–19; Peschke P, Debus J. Int J Radiat Oncol Biol Phys 2011;79(1):239–46; Debus J, Am Soc Clin Oncol Educ Book 2014:e95–9; Klein C, Haberer T, Debus J, et al. Radiation Oncology 2017; 12: 208
[21] Takahashi Y et al, CancerRes 63:4253-4257, 2003; Kamlah F et al, Int J Radiat Oncol Biol Phys 80:1541-1549, 2011
[22] Metastasis: the development of secondary malignant growths at a distance from a primary site of cancer
[23] Ogata T, Teshima T, Kagawa K, et al, Cancer Res 65:113-120, 2005; Rieken S, Rieber J,Brons S,et al, J Radiat Res 56:430-436, 2015
[24] Immune response: the body's response caused by its immune system being activated by antigens
[25] Ebner D K, et al, Front Immuno l8:99, 2017; Durante M, Brenner D J, Formenti S C, Int J Radiat Oncol Biol Phys 96:934-936, 2016
[26] Imai R et al Lancet Oncol 2006;7(Dec 12):1034–5; Matsunobu A et al. Cancer 2012;118(Sep 18):4555–63; Durante M, Orecchia R, Loeffler J, Nature Revs, Clin. Onc. 14, 483-495 (2017); Tsuji et al, ISBN 978-4-431-54456-2, Springer, (2014)
[27] Durante M, Debus J. et al. Fertil Steril 2010;94(Nov 6):2329.e5–9.e
[28] Rackwitz T, Debus J, Seminars in Oncology, 46 (3) June (2019) 226-232
[29] Uhl M, Mattke M, Welzel T, et al. J Cancer 2014;120(21):3410–17; Nikoghosyan A, Debus J. et al. BMC Cancer 2010;10:607; Mizoe JE, Hasegawa A, Takagi R, Bessho H, Onda T, Tsujii H. 2009;19(3):219–24
[30] Imai R et al. Int J Radiat Oncol Biol Phys 2016;95(1):322–7; Uhl M et al. Strahlenther Onkol 2015;191(7):597–603; Uhl M, et al. Radiat Oncol 2014;9:100; Schulz-Ertner D et al. J Clin Oncol 2007; 25(8):953–64; Mima M, et al. Br J Radiol 2014;87(1033):20130512

Existing hadrontherapy centres in the world and focus on European Centres for carbon ions

Therapy with protons or heavier ions is experiencing a strong expansion worldwide, with 78 running proton therapy centres, as reported by the Particle Therapy co-operative Group website[35], and 13 centres exploiting carbon ions beams. Proton centres are located mainly in the USA (34), in Europe (20) and in Japan (13). The carbon ion centres can be found in Japan (6), Europe (4) and China (3); 6 of these produce both carbon ions and protons and potentially other ion species, therefore they are called multi-particle centres, among them all the four European clinical centres: HIT, CNAO, MedAustron and MIT. Presently, three carbon ion therapy facilities are in construction in Asia, all by Japanese vendors, and two are planned in the US, one to be built by a Japanese vendor and one by a new US company. Over 30,000 patients have been treated with carbon ions. Every year 5,000 new patients are added to the carbon therapy cohort. It is important to point out that over the twenty existing treatment rooms with carbon ions in the world, only two are equipped with rotating beam lines (gantry), the rest have only fixed beam lines. This limitation is linked to the size, power consumption and costs of gantry for carbon ions, which are currently prohibitive for hospital standards.

HIT in Heidelberg (*Figure 2*), was designed by GSI and built with the technical support of Siemens Medical. It has been the first hadrontherapy clinical centre in Europe and followed the GSI 'Pilot Project' that treated inside the research laboratory 440 patients with carbon ions in the years across the new millennium. HIT started patients' treatments in 2009 and at the end of 2019 had treated 6200 patients, 50 % with carbon ions. The centre MIT at Marburg (*Figure 3*) was established by the Siemens Company, and is a direct descendant of the pilot project of GSI and of HIT. MIT started treatments in 2015 and, by the end of 2019, had treated 999 patients, 40 % with carbon ions.

The two other European multi-ions centres have their roots at CERN, which was involved in their design. In fact, in 1996, CERN, the TERA (TErapie con Radiazioni Adroniche) Foundation, and the MedAustron group initiated the Proton-Ion Medical Machine Study (PIMMS) with the aim of designing a synchrotron and corresponding beam lines that would be optimized for ion therapy. The centres are CNAO in Pavia (*Figure 4*) and MedAustron in Wiener Neustadt (*Figure 5*).

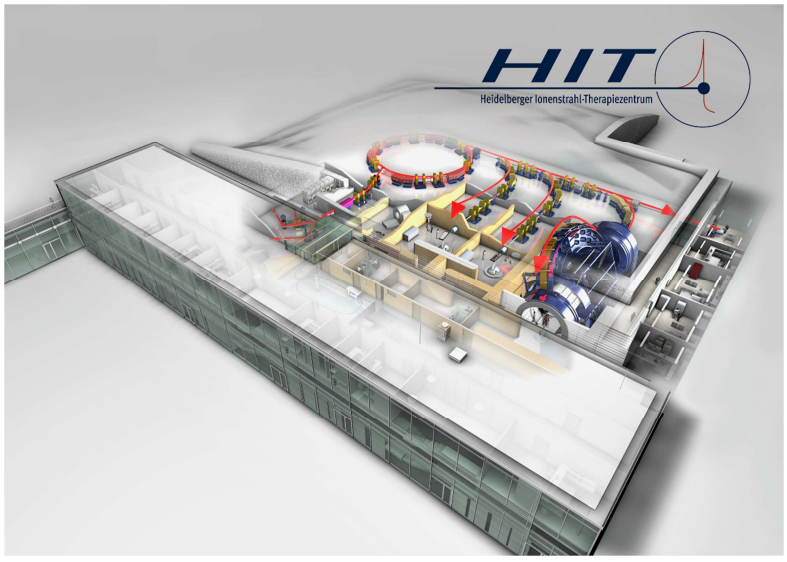

***Figure 2** - Layout of HIT Centre in Heidelberg. By the end of 2019, HIT, which was the first European carbon ion and proton centre, had treated 3100 patients with carbon ions.*

[31] El Shafie RA, et al. Radiat Oncol 2018;13(1):86; El Shafie RAet al. Radiat Oncol 2018;13(1):54
[32] Schulz-Ertner D et al. Cancer 2005;104(2):338–44; Jensen AD et al. Cancer 2015;121(17):3001–9; Koto M et al. 2016;38(suppl 1):E2122–6; Jensen AD et al. Radiother Oncol 2016;118(2):272–80; Sulaiman NS et al. Int J Radiat Oncol Biol Phys 2018;100(3):639–46; Jensen AD et al. Radiother Oncol 587 2015;114(2):182–8; Takagi M et al, Radiother Oncol 113:364-370, 2014
[33] Gao J, Hu J, Guan X, et al. Sci Rep 2019;9(1):4259
[34] Habl G, Hatiboglu G, Edler L, et al. BMC Cancer 2014;14:202; Habl G, Uhl M, Katayama S, et al. Int J Radiat Oncol Biol Phys 2016;95(1):435–43; Mohamad O, Tabuchi T, Nitta Y, et al. Lancet Oncol 2019 pii: S1470-2045(18)30931-8
[35] https://www.ptcog.ch/

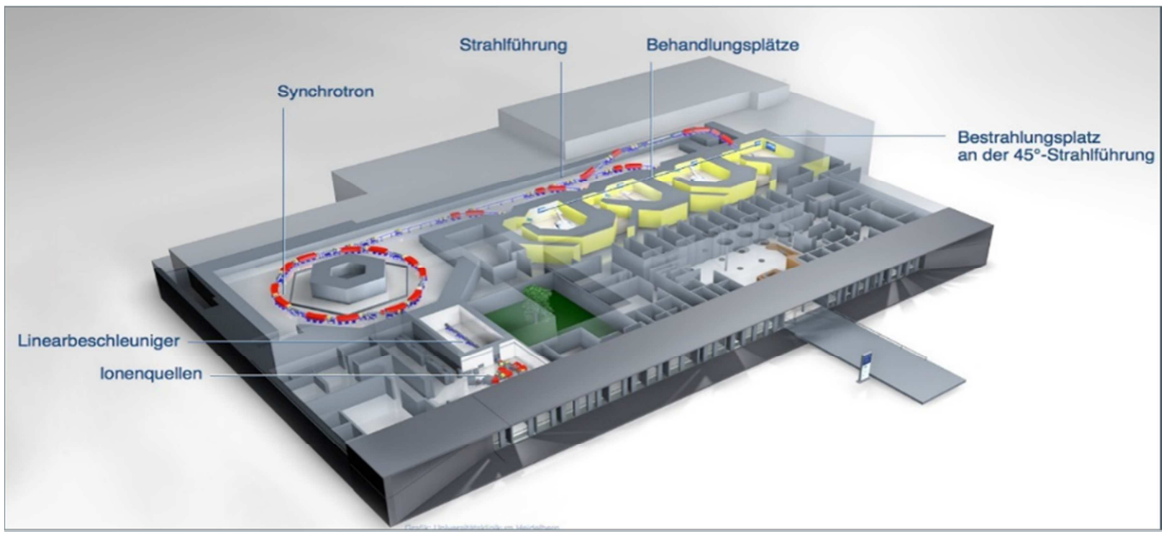

Figure 3 - *Layout of MIT Centre in Marbourg. The facility in addition to horizontal and vertical beamlines has also an oblique beam port irradiating the patient at 45 degrees.*

Figure 4 *- Perspective view of the CNAO, which features 3 treatment rooms with 4 therapeutic beams (3 horizontal and 1 vertical), and 1 experimental room (not represented).*

Figure 5 *- The MedAustron synchrotron feeds 1 proton treatment room with gantry, 2 heavy ions treatment rooms with 3 beams (2 horizontal and 1 vertical), and 1 experimental room.*

By the end of 2019 CNAO had treated 2644 patients (58% with carbon ions) and MedAustron treated 549 patients (5% with carbon ions having started this activity only in the second half of 2019).

The configurations of all the running facilities for carbon ions therapy are very similar. Typically, they feature:

- two (or more) ion sources;
- an injector linac;
- a synchrotron;
- a high energy beam transport line, made of magnets that focus the beam;
- one or more horizontal beamlines and at least one vertical beamline, equipped with instruments that actively 'paint' the tumour and produce dose distributions;
- in the case of HIT also a carbon ion gantry equipped with normal-conducting magnets that rotates around the patient couch and in MedAustron a gantry for protons.

A detailed description of the experimental capabilities of the four ion therapy facilities is given in "Implementation", under the Transnational Access WP6.

In addition to the four European therapy centres, GSI is also supplying carbon beams for research only. GSI operates a worldwide leading accelerator facility for research purposes, including the linear accelerator (Universal linear accelerator, UNILAC), the heavy ion synchrotron (Schwer-Ionen-Synchrotron, SIS) and the experimental storage-cooler ring (ESR). Within the HITRI*plus* project duration, first accelerators of the new FAIR complex will become operational, for higher energies and intensities especially also for radioactive ion beams.

The GSI Biophysics department offers comprehensive experience and capabilities in radiobiology of ion beams and operates experimental facilities at both UNILAC and SIS accelerators dedicated to therapy research. This includes Cave M, constructed for the Pilot Project on patient treatment, where 440 patients have been treated using actively scanned carbon ion beams.

Need for additional common research

To fully utilize the **beneficial radiobiological properties** of ion beams, **a concerted research effort** is called for providing enhanced knowledge on the tumour resistance mechanisms and on the methods to identify them, at the time of the diagnosis, in order to help clinicians in their decision making for treatment. **Systematic radiobiological data** to give guidance to the biologists and physicists on how to properly apply and improve the potential capabilities of particle therapy are also needed.

This need is widely recognized, and the international ion therapy community needs a coordinated access to the existing facilities for radiobiology research and physics research, offering extended blocks of beam time, with beams suitable for **multidisciplinary clinically oriented research**. The **Transnational Access** offered by the existing facilities will respond to this need by providing beam time for systematic radiobiology experiments to better characterize the RBE and its complex dependencies, allowing also improvements of the biophysical models that are required to implement these dependencies in the treatment planning procedures.

In vitro and in vivo radiobiology: open problems

The radiobiological background for ion therapy is described at the beginning of this chapter. While the physical properties of these radiations have been the aim of intense research, less focus has been put on the key point of the actual **biological responses to cell irradiation**.

The radiobiological response to heavy ions radiations is on many levels different from that of photon and proton radiation[36]. Data for determining clinically relevant RBE values are of great importance, but it should also be emphasized that the biological effects of heavy ions radiation is not for all endpoints a question of a dose effect that

[36] M. Durante, *Br. J. Radiol.* **87** (2014) 20130626, https://doi.org/10.1259/bjr.20130626

can be corrected with a RBE factor, but is rather seen as a different biology[37]. To fully exploit the advantages of heavy ion therapy, there is a range of unresolved radiobiological questions that must be answered, and there is a need for more experimental *in vitro* and *in vivo* radiobiological data to support and elaborate on the existing knowledge.

A list of some of the most important topics which are currently under investigation, demonstrating that research in this field is still of the utmost importance, despite the fact that clinical facilities are already in operation, is reported hereunder.

(i) One of the crucial points in particle radiobiology is to establish the RBE of different normal tissues in a systematic, large-scale *in vivo* setup, using relevant particles. This should include simulation of clinical treatment with fractionation as well as different positions in the beam. Relevant normal tissue models should include functional and tissue endpoints, representing both early and late radiation induced reactions. The list is long, however, a number of examples can be given with some relevant bibliography.

1) assays for acute skin reactions[38] and radiation induced fibrosis[39];
2) models of neurological damage of the spinal cord, central nervous system, peripheral nerves, optic nerve, etc.[40];
3) lung injury[41];
4) urinary bladder function[42];
5) cartilage tolerance;
6) different tissue types and position of the irradiated organ along the beam path and the spread-out Bragg peak;
7) cognitive assays, such as novel object recognition (NOR) and novel object location (NOL)[43];
8) dose fractionation.

The normal tissue studies should be accompanied by *in vivo* studies of RBE of a panel of tumours' models with different radio sensitivities to enlighten the therapeutic effect at different Linear Energy Transfer (LET)s.

(ii) Due to the better conformation of the dose, partial volume effects might play a more important role in heavy ion beam therapy; as typically small volumes are involved, these might counteract the locally increased effectiveness. This interplay between partial volume and RBE effects also requires *in vivo* studies, as partial volume effects cannot be mimicked by *in vitro* systems.

(iii) There is increasing evidence that heavy ion beam therapy in combination with a stimulation of the immune system might further increase the effectiveness of the treatment. Also, modulation of the repair capacity in combination with radiotherapy might be beneficial. Systematic studies on all such types of combination treatments are required.

(iv) Stem cells are at the origin of normal tissue regeneration and also represent the major players for the regrowth of tumours after radiotherapy. A better understanding of the peculiar properties of stem cells with respect to radiosensitivity, repair, and regeneration capacity is of high importance for the improvement of any radiation treatment modality.

(v) Drugs, nanoparticles and other agents can modify the radiation response and thus the bio-effectiveness of radiotherapy. There are many open avenues since only a small fraction of the possible choices has been experimentally studied.

[37] M. Durante, R. Orecchia and J.S. Loeffler, *Nat. Rev. Clin. Oncol.* **14** (2017) 483, https://doi.org/10.1038/nrclinonc.2017.30
[38] M.R. Horsman, D.W. Siemann, D.J. Chaplin, *et al*., *Radiother. Oncol.* **45** (1997) 167, https://doi.org/10.1016/S0167-8140(97)00127-8
[39] H.B. Stone, *Int. J. Radiat. Oncol. Biol. Phys.* **10** (1984) 1053, https://doi.org/10.1016/0360-3016(84)90177-9
[40] A.J. Van Der Kogel, *Radiat. Res.* **104** (1985) 208, https://doi.org/10.2307/3576649
[41] H. von der Maase, J. Overgaard and M. Vaeth, *Radiother. Oncol.* **5** (1986) 245, https://doi.org/10.1016/S0167-8140(86)80054-8
[42] F. Lundbeck, *Progrès dans les Rech. sur le Cancer* (1993) **130**:89
[43] M.E. Forbes, M. Paitsel, J.D. Bourland, *et al*, *Radiat. Res.* **182** (2014) 60, https://doi.org/10.1667/RR13662.1

(vi) Cell migration represents one of the key processes leading to metastases. The problems to be tackled are: how far radiation can either enhance or reduce the ability of cells to migrate and affect the occurrence of metastases and whether there are differences in that respect between sparsely and densely ionizing radiation.

(vii) Treatment planning for heavy ion beam therapy requires the use of biophysical models. Although a lot of experimental data are already available, discrimination of different models should be optimized using experimental conditions that are particularly sensitive to model differences and thus frequently require additional experimental data.

Perspectives of different ions for therapy

The carbon ion is the heavy particle that better combines the maximum efficacy on the tumour target and the minimal damage to the healthy tissues upstream the tumour location in the patient. This behaviour brought the radiotherapists in the past to prefer carbon as the elective heavy particle for treating radioresistant tumours[44]. Anyway, it has to be underlined that different particles have different characteristics that could be better suited for treating a particular case, thus going in the direction of a fully personalized medicine approach. The heavy ion facilities in HITRI*plus* are de-facto multi-particle facilities that can deliver different ion species. They are equipped with multiple sources of particles: GSI has the availability of basically all ion species for research purposes and HIT is performing since years experimental activities with helium and oxygen ions. CNAO will be equipped in two years from now with a third ion source for heavy ions different from Carbon (e.g. helium, oxygen, lithium, iron etc.), while MEDA and MIT have already the availability of multiple sources.

Many additional factors need to be considered for the choice of the optimal ion species for a given treatment scenario, and realistic treatment planning comparisons are required for the decision about the optimal ion species. These planning studies should be based on the comparison of the RBE-weighted dose in the target region as compared to the RBE-weighted dose in the surrounding normal tissue. Here, the essentially different radiobiological characteristic of the tumour and normal tissue are of particular relevance, as in general they are connected with different RBE values.

In addition, since RBE also depends on the dose level, the field configuration (1-field vs. 2-field) and fractionation scheme will play key roles in the assessment of the optimal ion. Finally, within the target, hypoxia can substantially alter the radiosensitivity of the corresponding tumour region and with that also the expected RBE, and in these cases even heavier ions than carbon, such as for example oxygen ion beams, may have additional benefits, as they show a more reduced sensitivity to hypoxia.

A large number of well-planned and complementary *in vitro* and *in vivo* studies have to be performed to clarify and define which ion(s) have the largest control probability for which types of tumour with minimal side effects. HITRI*plus* TA will give the opportunity to perform such kind of research activities. In this respect, also the future SEEIIST RI has the potential of greatly contributing to this ambitious program, which will last for decades because the radiobiological results will have to be validated by multicentre phase II and III clinical trials.

Medical physics program

From the medical physics point of view, the success of a tumour treatment depends both on the accuracy of the treatment plan and on the quality, precision and reproducibility of the detectors, which control and ensure that the distribution of the delivered dose is equal (within an accuracy of about 2%) to the optimized output of the treatment planning system (TPS).

To fully expand the therapeutic application of particle beams, there is a range of physics questions that need to be solved, in close collaboration among the centres, in order to:

[44] E. Blakely et al., "Physical and cellular radiobiological properties of heavy ions in relation to cancer therapy applications", *Biological and Medical Research with Accelerated Heavy Ions at the Bevalac*, 1977-1980, LBL 11220 (1980) 73-86

(i) measure very accurately the stopping power of living tissues by new imaging modalities as for example 'proton radiography' (tomography);

(ii) measure the fragmentation of the different ion species, in biological matter. The results will be implemented in Monte Carlo-based TPSs, to enhance the accuracy of the range calculation and fragmentation related dose;

(iii) develop new beam monitors detecting, during and after the treatment with millimetre accuracy, the position where the ion beam stops in the patient body. This is needed to assess, in real time, the accuracy of the dose deposition. This is at present centred on the detection either by Positron Emission Tomography (PET) of isotopes produced in the interactions of the ions with the body nuclei, or of 'prompt gammas', which are also emitted in these nuclear reactions secondary to fragmentation. Other techniques are being developed such as proton radiography and ultrasounds emitted by the beam-let interacting with tissues;

(iv) track moving organs and provide a 3D localization in space of a tumour that moves during the treatment. Many techniques are being developed but none are currently fully satisfactory.

As a whole, many technological achievements will come out and better detectors will be developed and brought from the laboratory to the clinic and industry.

Need for new accelerator technologies

The accelerator technologies and the systems in use at the European therapy facilities have been conceived more than 20 years ago and in some cases even before. The two reference designs have been developed at the end of the nineties by GSI and by CERN, and implemented in HIT and MIT, CNAO and MedAustron, respectively[45]. In the last two decades important technological developments took place both in terms of hardware and software, which could contribute in a significant way to improving performance of the European therapy facilities. Furthermore, the older centres HIT and CNAO are entering in a lifecycle phase in which upgrades of the systems are being considered.

In this perspective, HITRI*plus* can focus on a joint specification, design and development of new accelerator technologies and beam delivery schemes, to improve the present generation of ion therapy centres and to prepare for the next one.

In general terms, the key factors limiting the **performance** of the accelerator systems are:

a) the ion source and the linear injector (linac), which set a limit to the maximum current that can be injected in the synchrotron;

b) the injection into the synchrotron, which is the fundamental bottleneck to the amount of particles that can be accumulated and accelerated in the synchrotron; a larger beam intensity would result in shorter treatment times with clear advantages on patient well-being and throughput;

c) the extraction from the synchrotron that requires a careful control of beam properties up to the treatment rooms;

d) the "gantry", in this context a rotating system for delivering the beam to the patient at the optimum angle position for the specific tumour under treatment;

e) the rapidity of the change in particle energy required to scan the tumour longitudinally;

f) the beam instrumentation required to accurately define position and intensity of the particle beam;

g) the controls and safety requirements.

More than performance, however, the main limitations to the availability of heavy ion therapy are the **cost and dimensions of the accelerator**. The diameter of the synchrotrons used in the present European facilities is between

[45] A. Dolinskii et al., "The Synchrotron of the Dedicated Ion Beam Facility for Cancer Therapy, proposed for the clinic in Heidelberg", EPAC 2000, Vienna, and P. Bryant (ed.), "PIMMS : Proton-ion medical machine study", CERN-2000-006

20 and 30 metres, and the cost of the accelerator and its ancillaries adds up to about **70%-80% of the construction and operation costs** of the facility, gantry excluded.

Improving the accelerator is the key to better **performance**, and in parallel reducing its dimensions and cost is the main avenue to **improving access** to heavy ion therapy. More than twenty years after the design of the present generation of ion therapy facilities, the times are ready for a reconsideration of the accelerator and of its ancillary systems with respect to the traditional designs. In recent years, accelerator science and technology have made an impressive progress pushed by the requirements of **particle physics** and by substantial investments in **accelerator R&D**. The result is that Europe is now the leader in particle accelerator technology, as testified by the successful commissioning and operation of the Large Hadron Collider at CERN, to-date the largest and most powerful accelerator in the world. These developments are related in particular to **superconductivity**, resulting in more than 1.400 high-field superconducting magnets installed and routinely operated in the LHC accelerator. HITRI*plus* will provide the opportunity for a **technology leap** based on the most recent advances in accelerator technologies and in particular of superconducting magnet technology, which will extend the reach of heavy ion therapy and bring to society the benefits of the **investments in fundamental research**.

The HITRIplus concept

HITRI*plus* aims at bringing together a wide multidisciplinary consortium to address the two crucial elements described above:

- define (in the Networks) and implement (in the Transnational Access) an **advanced experimental programme** to improve the quality of radiation therapy treatments to cancer patients; and
- design (in the Joint Research Activities) a set of **innovative accelerator and beam delivery technologies** together with common radiobiological standards, to improve performance and accessibility of ion therapy.

To achieve these goals, HITRI*plus* will gather a consortium of clinical facilities, academic institutions, research centres, and European companies from 14 European countries. Hence, a multidisciplinary Starting Community unites for the first time all European experts in the field of ion therapy in connection with scientists from all over Europe to reach the goals of providing excellent research and high-level treatment to patients., and to improve the related instruments. To this end, the interdisciplinary research programme of HITRI*plus* will address current research challenges and foster innovative approaches in key areas of ion therapy. These span from novel particle beam characteristics, superconducting magnets, treatment planning and delivery technologies, clinical networking, technology innovation network and most importantly using the clinical facilities for recruiting and treating patients Europe–wide, for clinical trials and simultaneously training the physicians and medical physicists.

The breadth of the multi-disciplinary research programme, along with the diverse and complementary composition of the consortium will offer an ideal framework to facilitate the sharing of knowledge for high-level training of the next generation of ion therapy experts while simultaneously offering cancer patients state-of-the-art-treatment.

HITRI*plus* will help to foster the economic development of Europe through joint technological developments and allow faster transfer of the innovative outcome of the JRA activities to the industrial partners for exploitation. In parallel, the advances in the clinical and medical physics research and gained expertise will be transferred beyond the four current therapy facilities and throughout Europe, through the targeted education and training programme provided in HITRI*plus*. In addition, and thanks to the strong engagement of SEEIIST, many opportunities will open to integrate intoto this starting research community new talents from the SEE.

Creating a durable and sustainable research network including the currently existing infrastructures and the newly emerging centres in Europe would optimise sharing knowledge and expertise and would help to integrate the European Research Area for fighting cancer more effectively.

Transnational Access

The HITRI*plus* Transnational Access is a unique opportunity for bringing together, for the first time ever, the four heavy ion centres in operation in Europe and open them in a coordinated way to the medical and research community. A fifth facility providing access is GSI, which contributes by opening its biophysics research programme. High-quality research along the lines defined in the previous section will be possible thanks to this scheme, providing researchers with access to state-of-the-art infrastructure in advanced clinical environments and with a coherent approach to analyse and compare the data produced.

This consortium will also significantly enhance the accessibility to external users with respect to possibilities in each individual facility. Thanks to a unified application procedure, users will be able to have access to the facility that best suits their needs.

Networking and community building

Networking is intended to promote the heavy ion therapy facilities to medical researchers all over Europe in particular by raising awareness about the tumour types that could be treated, and to catalyse the collaboration between the different scientific communities (oncologists, radiologists, biologists, biomedical engineers, physicists and accelerator experts), which is necessary for successful development and improvements in ion therapy at national and European levels.

A European registry of patients treated with carbon ion radiation therapy would provide real world data that could supplement classical trials to build a more solid evidence based medicine. Commons semantics will be developed within the networking activities. Common list of critical OARs will be created, pooled analysis of observed toxicity will be performed and a recommendation for OAR dose constrains will be given in a common effort to build a unified vision of the heavy ions beam therapy.

Accelerator and beam delivery technologies

A recent analysis of the different options for a next generation ion therapy accelerator concluded that because of the relatively high energy required, 430 MeV/u for carbon ions, the synchrotron remains the accelerator of choice thanks to its flexibility, availability of components, and cost[46]. The main improvements to the synchrotron-based accelerator systems that will be analysed in HITRI*plus* are:

- **Magnetic system**: an increase of the dipole bending field in the synchrotron magnets will allow a reduction in diameter and in perspective a reduction in cost because of the lower number of components. This can be achieved by going from conventional resistive magnets to **superconducting magnets** similar to those used in modern accelerators for particle physics.
- **Multiturn or charge-exchange injection**: an increase in the number of particles circulating in the synchrotron thanks to the use of modern improved injection schemes will allow a reduction in the patient treatment time.
- **Linear injector** (linac): a newly designed injector at higher frequency and accelerating gradient, and lower cost, will provide the additional flexibility

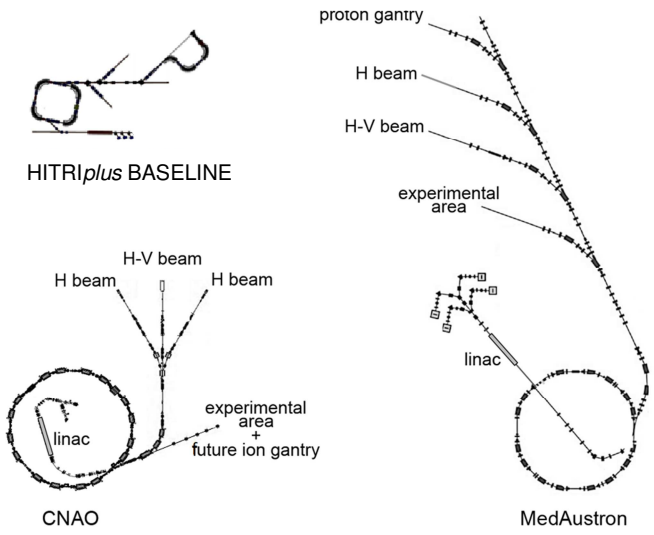

***Figure 6** - Overall size of a reference superconducting synchrotron and gantry design, as compared to CNAO and MedAustron.*

[46] M. Vretenar et al., Accelerator options for a next generation heavy ion therapy and research facility, submitted at IPAC2020 Conference.

required by the improved synchrotron injection schemes. Dimensioning the linac parameters for **production of therapeutic radioisotopes** in parallel with operation as synchrotron injector will open new perspectives for extending the reach of the facility towards treating diffused tumours e.g. with targeted alpha therapy, in parallel with treating solid tumours with direct ion irradiation.

- **Operational modes**, **beam transport and instrumentation**: switching between research and treatment operation modes, and general improvements to the instrumentation required for accurate dose delivery.

These new advanced features for ion therapy accelerators can be combined into a **new accelerator design** integrating lower cost and dimensions and improved performance, for the benefit of **SEEIIST**. A simplified version based on a compact synchrotron operating only for therapy with a limited number of ion species can be transferred to industry to become a product to be commercialised worldwide, in particular in Asia and US where there is an increasing demand for ion therapy centres. A schematic view of a reference superconducting design[47] compared to the present CNAO and MedAustron is presented in *Figure 6.*

Gantry

In radiation therapy, gantries are movable beam lines used to precisely direct the beam on the required position on the patient, who is usually lying on a couch. Due to their cost, size, and complexity, gantries currently represent another limiting factor for the widespread adoption of ion therapy. While different vendors produce gantries for protons, of the four European centres treating patients with ions only HIT is equipped with a bulky and expensive in-house made ion gantry. An ideal heavy ion gantry would be **less expensive** (down to about two times the cost of a €12.5 Million proton gantry), **much lighter** (i.e. within 100 tons, to be compared to over 600 tons for HIT) and require **less power** for operation than the present versions.

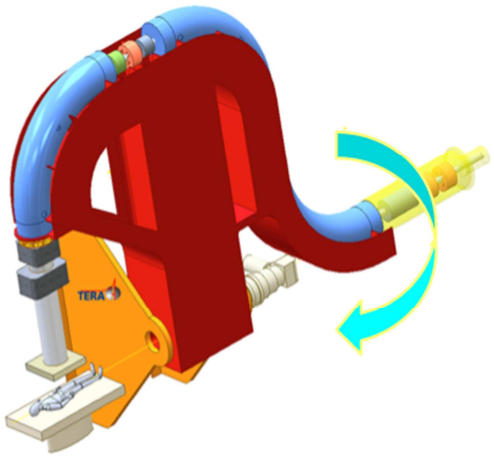

***Figure 7** - Schematics of the compact 180^0 rotating gantry design developed by the TERA Foundation in collaboration with CERN.*

The HITRI*plus* consortium has made the choice of taking a bold step towards superconductivity for both the accelerator and the gantry. For the gantry, the goal is to come to a detailed engineering design with simplified mechanics equipped with superconducting magnets – as similar as possible to the magnets for the synchrotron. This design aims at a **breakthrough in terms of cost, energy consumption, size, weight and complexity**, to allow European industry to become competitive against the aggressive R&D programme on LTS and HTS (Low and High Temperature Superconductors) gantries launched by NIRS, Toshiba and a group of Japanese Universities.

A preliminary innovative gantry design based on CCT magnets (from Ref. 46) is shown in *Figure 7*. HITRI*plus* will consider different gantry options and then concentrate in the detailed integration and mechanical design of the most promising one.

Dose delivery

To make the most of the advanced accelerator and gantry designs, an **active scanning dose delivery system** will be developed, providing unsurpassed delivery speed and accuracy. Supporting this accuracy, state-of-the-art imaging options will be integrated in designs for both fixed beam and gantry treatment rooms. The improved dose delivery system will enable superior patient treatment, but will also open up avenues of clinical and pre-clinical research, such as conformal motion management, FLASH type therapy, and gantry-free, flexible delivery of many beam angles.

[47] E. Benedetto, N. Al Harbi, L. Brouwer, S. Prestemon, P. Riboni and U. Amaldi, "A Carbon Ion Superconducting Gantry and a Synchrotron Based on Canted Cosine Theta Magnets", Submitted to Phys. Med. Biol. (2020)

A key feature of improving scanned beam delivery is the speed and flexibility of dose delivery. Reduced delivery times will help to increase patient throughput and patient comfort by shorter times in fixation. Especially for moving targets such as lung or pancreas tumours, this latter fact is of crucial importance, as it will eventually enable treatment in breath-hold and reduces the so-called baseline drift, inevitably occurring while the patient is lying on a couch. In HITRI*plus*, the dose delivery systems will be further developed to accurately deliver and control scanned treatment plans at very high dose rates.

A recent hot topic in radiotherapy is the possible reduction of side-effects by delivering extreme dose rates > 50 Gy/s, the so-called FLASH therapy[48]. For current particle scanning systems, it seems unlikely that FLASH dose rates of >50 Gy/s are feasible under clinical conditions and for extended volumes. Delivery speed would have to be increased by several orders of magnitude. Current studies use protons at the highest available energy of a cyclotron, which do not stop in the target, but it seems unlikely that the effect of FLASH will compensate the loss of the superior Bragg Peak dose profile. The new HITRI*plus* Dose Delivery System (DDS) will therefore focus on strategies of Bragg Peak FLASH-type delivery using sophisticated range modulators as well as its fast monitoring capabilities. This will enable studies on animal models with orthotropic tumours, providing answers on the impact of FLASH therapy on both side effects and tumour control in the same model system. Research at HITRI*plus* will therefore clarify if the push for FLASH-capable, transformative technology will be worthwhile also, but not only for heavy ions.

Multiple energy operation

The existing European heavy ion therapy centres rely on the three-dimensional intensity-controlled raster scan technique to deliver the dose to the patients[49]. Optimized linac-synchrotron combinations generate libraries of energy-, focus- and intensity-variable pencil-beams for the dose-delivering scanning systems at the various treatment stations[50]. In total, more than 100.000 combinations of beam parameters per treatment room need to be provided. This method allows for the administration of inversely planned and biologically optimized dose distributions having utmost precision. The target volume is dissected into a series of iso-energy slices each of them irradiated using a slowly extracted beam having a constant energy selected during the treatment planning process out of a list of pre-defined beam characteristics. So far, each synchrotron cycle provides a single energy only, even though the circulating beam would allow for the scanning of the next iso-energy slice. Thus, the duty-cycle at the existing heavy ion therapy centres is non-optimal and the treatment duration is unnecessarily long. In order to reduce the total treatment time, it is desirable to shorten the phases without beam extraction. Multiple energy operation is a possible future mode of operating the synchrotron, which is currently investigated at HIT[51]. Instead of dumping remaining particles at the end of the extraction phase they will be accelerated or decelerated to the next energy level. In a typical treatment plan adjacent iso-energy slices (IES) have a distance of a few millimetres only, corresponding to an energy difference of ≤ 4 MeV/u. In such an irradiation scheme, several iso-energy slices can be irradiated with short interruptions only. Phases without beam availability at the treatment room will be drastically reduced saving up to 50% of the irradiation time.

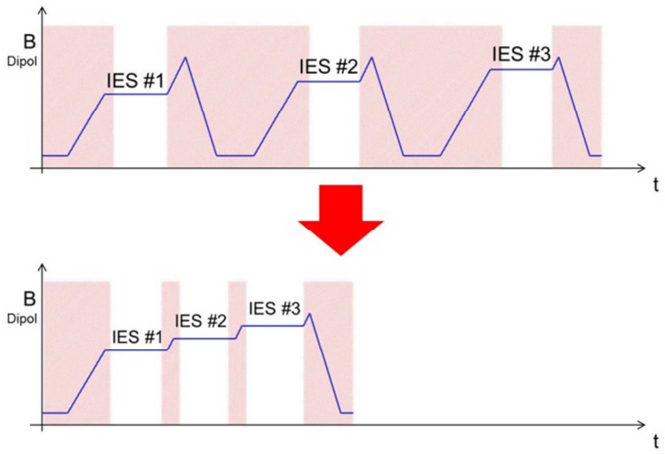

Figure 8 *- Dipole currents as function of time in actual (top) and HITRIplus proposal (bottom) synchrotron operation modes. Phases without beam availability in the treatment room are shown in colored areas.*

[48] V Favaudon et al. Sci Transl Med. 2014;6:245ra93
[49] T. Haberer et al., Nuclear Instruments and Methods in Physics Research (1993) 330, p305-396
[50] T. Haberer et al., Radiotherapy and Oncology, Vol. 73 (Supplem. 2), (2004), p186-190
[51] C. Schoemers et al., Proceedings of IPAC2017, Copenhagen, Denmark (2017)

Accelerator and dose delivery controls

Currently, no companies on the market provide a universal holistic-focused control solution compatible with devices from all major manufacturers/vendors. Furthermore, presently there is no software that is designed with both research and clinical use cases in mind. In HITRI*plus*, frameworks and solutions will be designed that require minimum adaptation to the facility, which leads to lower cost and faster installation. The issues that will be addressed are:

1. *reduction in development effort*: provides core functionality, built for easy adoption.
2. *optimized workflows*: Graphical User Interfaces (GUIs) designed for optimal user experience, based on real clinical usage.
3. *optimized scientific workflows*: GUIs designed in collaboration with scientific users will properly advance also the research usability of the whole system.
4. *compatible* with state-of-the-art imaging and scanning solutions and integration of these solutions.
5. *reduced testing effort*: tests without the hardware, through simulations.
6. *advanced features*: features like Python scripting interface will allow the creation of (research) workflows and increase efficiency of pre-existing Quality Assurance (QA) workflows.
7. *"future proofing" the architecture*: based on a cost-effective modular architecture, to work with novel technologies, like adaptive oncology workflows.

HITRI*plus*' work on control systems will focus on new software architecture that will help to shorten the time a patient needs to spend in a treatment room, where typically most of the time is spent for imaging and positioning, rather than actual irradiation, with an increase in yearly patient throughput.

Need for a new Research Infrastructure

One of the ultimate goals of HITRI*plus*' starting heavy ion research community is to define, building on the experience of all operating heavy ion therapy centres, the basic design of an "optimal" research facility. A new **world-class, innovative, compact, flexible, expandable, pan-European RI**, would produce a heavy ion therapy beam at higher intensity with simpler operation and lower cost. This should allow the clinical and scientific user community to fully exploit, in the future, the advantages of heavy ion therapy, enabling applied and clinical R&D, and providing an innovation and training platform. This new RI will focus on cancer therapy and biomedical research with heavy ions and thus enable scientists from different countries to work together in the fight against cancer.

Building this facility in the SEE region would allow building scientific capacity in the region and enhancing the potential to attract to this starting research community unexploited human resources and potential new talents that could further boost its progress. The proposed SEEIIST business plan is particularly favourable for research because it foresees a 50%-50% split of the beam-time available during day time between applied research ù8including clinical trials, which are – essentially – part of research), and medical treatment[52]. Also, night time and weekends will be devoted to research, as it happens in all existing heavy ion therapy centres. This will allow research communities in SEE and the rest of Europe highly needed access to beam-time and ample time for biological breakthrough research related to cancer. Exploiting the potential of new accelerator designs for producing radioisotopes for imaging and therapy, in parallel with operation for direct cancer irradiation, might open new perspectives in combining different treatment modalities in the same centre. The SEEIIST ambition is of becoming a major European multi-national hub for the development of nuclear medicine techniques to be used in the fight against cancer.

[52] U. Amaldi (ed.), A Facility for Tumour Therapy and Biomedical Research in South-Eastern Europe, CERN-2019-002, https://cds.cern.ch/record/2688922/files/88-73-PB.pdf

SEEIIST and integration with its plans

In October 2017, the governments of eight[53] former adversary states in South-Eastern Europe (the so-called SEE States) signed a Declaration of Intent (DoI) to jointly build a new Research Infrastructure (RI) facility in the SEE region, called the **South East European International Institute for Sustainable Technologies (SEEIIST)**. The core of the RI focusses on Cancer Therapy and Biomedical Research with heavy ions, considered as the most advanced radio-oncological technology for cancer treatment. This DoI was perfectly aligned both in time and sentiment with the Sofia Declaration, in which the Western Balkan states recommitted to the European perspective as their firm strategic choice and to reinforce mutual support. Most recently, a Memorandum of Cooperation Framework was signed by six Prime Ministers of the SEE region in July 2019 at the occasion of the Summit of the Berlin Process at Poznan, Poland to support the establishment of the RI in the SEE region.

The creation of a new RI is meant to show tangible, visible and sustained international cooperation in the Western Balkan region after a period of regional conflict. The RI will gather scientists, engineers, medical doctors, students and technicians within this joint infrastructure with the mission to deliver "Science for Peace" and "Science for Society".

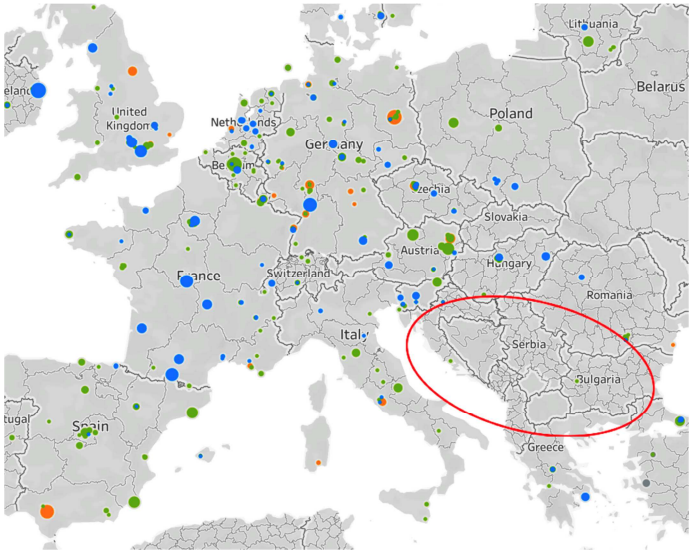

***Figure 9** - Map of RIs in Europe. Notice the very low density of RIs in the SEE region. Source: meril.eu. (blue- distributed; light green-single sited; dark green – mobile; orange – virtual).*

As shown in *Figure 9*, currently the SEE region has very few RIs compared to the EU countries. A new RI in SEE in a scientific field that is still novel in the rest of Europe, well integrated into the starting community that HITRI*plus* is promoting, will become a regional transnational Centre of Excellence and ensure that scientists and institutes from across Europe and from the region assemble critical mass of people, knowledge and investment. As evidenced by the creation of similar capabilities (notably ESO, EMBL in Europe and SESAME in Jordan) the SEE RI has the potential to link regional science, technology and industry and contribute to the slow down and reversal of brain drain, which is a major problem for the SEE region.

HITRI*plus* represents a unique opportunity to **federate** the European research effort in heavy ion therapy and to **connect** it with the starting initiatives in SEE, laying the scientific foundations for an effective construction and exploitation of the new facility.

METHODOLOGY

To achieve its objectives, the HITRI*plus* project is structured in 12 Work Packages as outlined in *Figure 10*. The 22 partners contributing to the Work Plan were selected to reflect the highest level of knowledge available in Europe in ion therapy research and associated instruments, and to provide the best added value to the project in terms of technical research expertise, interaction with the wider hadron community and/or access to running and future facilities. In addition to the academic research community, three European companies participate in the HITRI*plus* Consortium.

The Coordination is provided by the Director General of CNAO, one of the leading centres in ion therapy, with the aim to anchor HITRI*plus* to the day-by-day life of these infrastructures dealing with patients and with the

[53] Albania, Bosnia and Herzegovina, Bulgaria, Kosovo*, Republic of North Macedonia, Montenegro, Serbia and Slovenia (Greece and Croatia so far as observers). The designation "*" is without prejudice to positions on status and is in line with UNSC 1244/1999 and the ICJ opinion on the Kosovo Declaration of Independence.

community of clinicians and researchers. Support is given by a Deputy Coordinator with a wide experience in project management from CERN, the leading European particle physics laboratory with a broad experience in high technology, particle accelerators and their applications, and in project management and organisation.

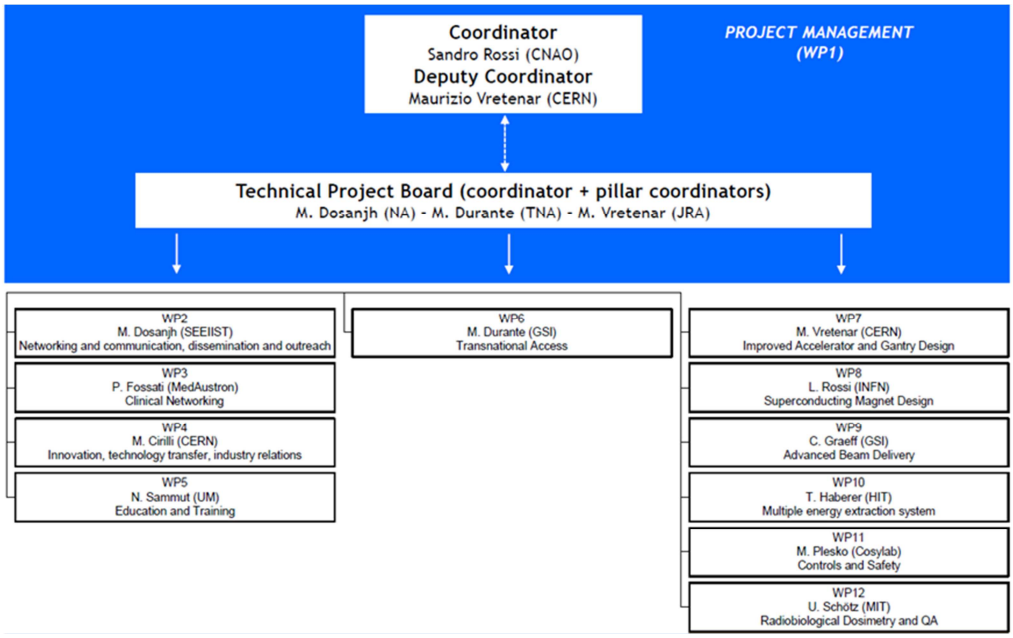

***Figure 10** – Work packages organization.*

A Technical Project Board will support the Coordinator in achieving an effective and strong management and integration among the WPs. The Work Packages are divided into three pillars, which are interlinked:

- Networking Activities (NA, WP2-5): communication, dissemination and outreach (WP2), clinical networking (WP3), innovation technology transfer and industry relations (WP4), education and training (WP5);
- Transnational Access (TA, WP6): to promote the access to the existing facilities of the research and clinical communities;
- Joint Research Activities (JRA, WP7-12): improved accelerator and gantry design (WP7), superconducting magnet design (WP8), advanced beam delivery (WP9), multiple energy extraction system (WP10), controls and safety (WP11), radiobiological dosimetry and Quality Assurance (QA, WP12).

The subdivision in thematic homogeneous Pillars has the advantage of favouring the communication and coordination between NA's, TA's, and JRA's respectively, and to provide via the Technical Project Board a forum for horizontal communication and coordination of the different activities.

The Networking WPs are transversal and useful to TA and JRA. The Clinical Networking is fundamental to establish a "common language" among the medical doctors of the facilities and between them and the rest of the clinical community. It is also important to establish tools to exchange information and standards. It is a fundamental channel to open the existing facilities to the external communities of users, both clinicians and researchers. Also, the developments of the JRA WPs need to be transferred to the industry so to make the deliverables available for the largest community of potential users. At the same time, it is important to safeguard the IP rights of the participating institutions and of the researchers. The education and training is of paramount importance to spread the achievements and create a diffuse culture through the organized involvement of the young generation of students and early stage researchers. The Networking coordination is assigned to SEEIIST, one of the main perspective users for the Networks' outcome.

The Transnational Access is a key pillar of the project, joining for the first time the research programmes of the four European ion therapy centres, and linking them to the biophysics research with ions of the GSI laboratory. The

TA Coordination is ensured by GSI because of its wide experience in research programmes and in successfully running TA activities.

The Joint Research Activity pillar is structured with WPs that have a double goal: first to improve and upgrade the systems already in use at the European facilities and secondly to provide the basic components of a future next-generation design. At the end of HITRI*plus* a new, optimized and up-to-date design of a novel infrastructure will be available, to become the basis of SEEIIST and of all future ion therapy centres to be realized in Europe and possibly in other regions of the world. Strong coordination of the JRA WPs is required to come to a shared and integrated picture of the different technologies and deliverables, which will rely on the CERN experience in dealing with new technologies and management of distributed groups.

Hereunder there is a summary of the content of each WP of the project.

WP1: Project Management

WP1 ensures the implementation of the project and the contractual obligations towards the EC. This activity implies the overall technical, administrative, financial and legal coordination of the project. The role and activities of the overall coordinator concern the monitoring and management of the agreed deliverables and milestones in the contract and the smooth running of the project as a whole.

WP2: Networking and Communication, Dissemination and Outreach

The Dissemination, Communication and Outreach Work Package will organize and implement efficient communications inside and outside the consortium. They should enhance the internal synergies, create databases and provide added value by allowing information flow to/from other projects and the general public as well as within the HITRI*plus*. WP2 will equally support the management for internal communication and follow-up of HITRI*plus* results.

WP3: Clinical networking

The main objective of this WP is a trial design for an innovative use of heavy ion radiation therapy. This will be accomplished through a review of preclinical data to identify promising novel approaches to exploit the heavy ion radiation therapy advantages and the design of one trial as a template for bringing innovative heavy ion radiation therapy approaches in the clinics. Another objective is the creation of a European registry of heavy ion radiation therapy patients by collecting data on rare cancers treated with heavy ion radiation therapy. WP3 has the goal of reaching a European-wide agreement for OARs (Organs At Risk) dose constraints with heavy ion radiation therapy. This will be accomplished by reviewing existing data on OARs dose constraints in use in the clinical facilities and performing pooled data analysis to validate them. Last but not least, WP3 has the task to outline clinical research protocols to favour clinical TA according to the modalities set forth in WP6.

WP 4: Innovation, technology transfer, industry relation

The objective of this WP is to define and implement a roadmap for the exploitation and industrialisation of the HITRI*plus* technologies and innovations. In order to do this, the generated IP will be traced and managed from the beginning of the project, and an adequate dissemination and exploitation plan will be drawn up for each technological innovation. Given the highly collaborative, trans-national nature of the HITRI*plus* project, such plans will look beyond traditional IP protection approaches, such as patenting, and will also consider open innovation schemes such as co-development with industries open-access licensing schemes. The HITRI*plus* innovations will be broadly disseminated to industry through several channels, including using several well-established networks of industry and technology transfer professionals, industrial exhibitions at relevant conferences and dedicated "HITRI*plus* meets industry" events. Technology-transfer opportunities arising from these dissemination actions will be proactively followed up by the HITRI*plus* Knowledge Transfer team, together with the TT offices of the partners.

WP 5: Education and training

The objective of WP5 is to educate and provide hands-on experience to a new generation of researchers *in heavy ion* therapy so that they acquire appropriate skills allowing them to optimally access and exploit (even virtually) all the essential tools of European heavy ion therapy research infrastructures. In addition, WP5 provides researchers from academia and industry of a multidisciplinary background, including researchers not necessarily directly involved in heavy ion therapy, with updated and appropriate knowledge on heavy ion therapy research and the activities and potential of the four major European heavy ion therapy and research infrastructures. Postgraduate students, postdocs, oncology practitioners, and researchers from a wider multidisciplinary community will be attracted, educated and trained to form part of this starting heavy ion therapy research community through specialised courses, masterclasses, e-learning courses, secondments and internships.

WP6: Transnational Access

The TA brings together, for the first time ever, the four heavy ion centres in operation in Europe and opens them in a coordinated way to the medical and research community. Additionally, their programme will be integrated with the biophysics programme at GSI. The WP includes two Access programmes.

The *Clinical Access* will give the opportunity to the hospitals and oncological institutes in Europe to refer patients to the existing hadrontherapy facilities and share clinical prospective investigations and patient follow up. Secondly, it will allow the radiation oncologists to work together with their European colleagues and non-European colleagues in multicentre prospective comparative studies to improve the knowledge both in heavy ion therapy and in classical radiation oncology through clinical research practice.

The *Research Access* will attract universities, research centres, and hospitals, which will connect all the groups to perform research activities in the experimental halls of the existing carbon ion facilities and at GSI. Performing research at a clinical facility will allow researchers to meet different clinical professionals. In direct contact with the real needs of the therapy and of the patient, they will have a clear perception of the feasibility to translate the research from bench to bedside. Industrial partners will be encouraged to take part in the research programme, to be involved in the development of new clinical procedures and new medical devices.

WP7: Advanced Accelerator and Gantry Design

WP7 will develop solutions to enhance performance of existing and future accelerators for heavy ion research and therapy: multiturn injection for higher beam intensity up to 10^{10} carbon ions per pulse, improved extraction and beam transport, and a new linac injector for higher intensity and parallel production of isotopes for research and therapy. The WP will combine the accelerator solutions with the superconducting (SC) magnets developed in WP8 to define the advanced conceptual design of a compact and innovative SC heavy ion synchrotron capable of operating with multiple ion species, from helium to argon, and including protons for testing and calibration. This accelerator design is intended to become the reference for any new ion therapy research facility including the one proposed for the SEE region. A simplified version of the compact SC accelerator with single- or double-ion operation at fixed parameters will be proposed as reference for a new generation of compact ion therapy accelerators to be built by European industry to address the global ion therapy market. Additionally, WP7 will convert the most promising of the existing conceptual designs for superconducting gantries into a detailed technical design integrating all components, and prepare for a final industrialisation and production phase by European industry.

WP8: Magnet Design

The initial list of requirements for new synchrotron designs will be considered followed by a technical and financial assessment of various superconducting magnet designs including different material options. Assessments will be made by: evaluating the technical difficulty of the construction; the financial cost of the different coupling options; and the cooling temperature and energy consumption cost variation estimated over 20 years. Preliminary engineering design of accelerator, gantry and scanning magnets will follow considering the mechanical structure

for the magnets; the field quality during ramp-up and steady state; the losses and consumption and the manufacturing time. The configuration and the most suitable aperture size for testing a small demonstrator will be chosen following the beam dynamic studies of WP7. The construction of a small size superconducting magnet demonstrator will ensue by manufacturing the mechanical components, the winding and the magnet assembly. In the meantime, a test station will be prepared to test the demonstrator magnet performance.

WP9: Beam Delivery

The designs of robotic patient chairs, robotic couches and imaging systems will be evaluated and the rotational stage will be developed after considering different treatment scenarios, beam types, compatibility issues and input parameters from WP7. Treatment planning strategies and a simulation environment for particle arc therapy will be developed and implemented in GSI's treatment planning software TRiP98. Case studies will evaluate the impact of different parameter scenarios and will be fed back to WP7 and WP10 to optimise their respective designs as well as the upgrade of dose delivery and nozzle design in this WP. Novel beam detectors, including a fast Gas Electron Multiplier (GEM) position detector, will enable faster irradiation and capabilities to treat moving targets. A prototype of this system will be installed at GSI to perform a demonstration test of high-dose rate arc therapy using the developed rotational stage. Simulations of arc therapy based on the measured system performance will also be conducted for the gantry design based on input from WP7.

WP10: Multiple Energy Extraction System

A beam characteristics library will be built by defining and combining the existing phase space definitions of new ion species, higher intensities to increase the delivered dose rates, higher energies for some research aspects and a more flexible extraction timing to better support the treatment of moving organs. Furthermore, the multiple energy operation and timing requirements for synchronization capabilities of the next generation accelerator control system will be defined in coordination with WP11. The supply, distribution and quasi real-time generation of patient data systems will be designed in hardware and software after discussions with WP11. Using these results and the outcome of WP7, an architectural model of the accelerator multiple energy extraction system that is capable of multiple energy operation will be conceptually designed as a module to be incorporated in the accelerator and treatment control systems of WP11. The results of WP10 will be used as input for WP11 and WP9.

WP11: Controls and Safety

The machine controls will be designed to ensure fast commissioning and machine QA, optimise ease of use for non-clinical personnel, maximise the reliability of the accelerator and lower the operational cost. This will be done by designing a universally compatible modular design with optimised workflows which will allow easy adaptation and upgrading to work with upcoming technologies like adaptive oncology treatments. The system control requirements and the treatment control system architecture will be optimised by first studying all existing treatment room control systems, and then developing a system which will allow easy integration of all the other systems and can be used ergonomically by the machine operators. Input will be regularly exchanged with other WPs, in particular WP7, to ensure this modular software's performance will meet all other subsystem requirements. The high-level system engineering requirements and basic architecture of the patient safety systems will be designed by following the relevant European regulations and international standards.

WP12: Radiobiological Dosimetry and QA

Treatment planning and beam application technology vary between the European particle therapy centres. WP12 aims to be able to meaningfully evaluate and compare research results, and to standardize radiation dosimetry among the centres. To minimize the variability of results, the partners will share the same phantom specifically dedicated for in vitro dosimetry by means of clonogenic survival provided by GSI. The characterization of mixed radiation field will be done using silicon detectors, Tissue Equivalent Proportional Counter (TEPC), that amongst others could further improve the quantification of the physical uncertainties influencing biological read-outs.

The test plans will be created with the clinical Treatment Planning System (TPS) and re-calculated with Monte Carlo (MC) engines. Different biological models will be chosen and compared both in normoxia and for hypoxic conditions. Model predictions will be compared versus survival experimental data at different depths, LETs, dose levels and hypoxic conditions.

EQUALITY AND GENDER DIMENSION

HITRI*plus* will work to ensure an appropriate gender balance in all its activities. Gender issues will be addressed during the project lifetime to sensitize partners, researchers and the community of TA users. The present inequality in gender balance in sciences is also evident in the HITRI*plus* Consortium. Hence, the project will take measures to ensure gender opportunities by: 1) encouraging women's participation in research and management activities at all levels of the project; 2) promoting the involvement of women as well as men in conferences, workshops and other international scientific events related to the project; and 3) encouraging and supporting the application of women for secondments and internships positions. In particular, will encourage female participation in the management of the Work Packages, as representatives in the General Assembly, and as members of the Advisory Boards. HITRI*plus* will promote gender equality at the selection level and as well in the working environments of the HITRI*plus* partners, complying with the guidelines of the European Research Area gender equality and gender mainstreaming in research (guidance on Gender Equality in H2020[54]).

1.4 AMBITION

The foremost HITRI*plus* ambition is to create a sustainable starting community to integrate and propel European biophysics and medical research on cancer treatment with heavy ions beams. This community will provide a competitive advantage for European research and industry by defining the treatment modalities, the standards, the procedures and the technological instruments that will move ion therapy to its next phase of development. In the long run, the HITRI*plus* ambition consists in providing to European patients, suffering from cancer, an opportunity to have access to the best world-class cancer treatment.

To reach its ambitions, HITRI*plus* needs to realise substantial breakthroughs in community building, in promoting experimental programmes, in clinical networking, in technological developments, and in the definition of common standards. The key elements of this programme are outlined here.

[54] European Commission, "Guidance on Gender Equality in Horizon 2020", Directorate-General for Research & Innovation, April, 2016.

Access to Research Infrastructure

State-of-art	Ambition	Challenges
A limited biophysics research programme is present only in two therapy facilities (HIT and CNAO), pre-clinical research is almost absent, clinical research with heavy ions is not coordinated.	HITRI*plus* will offer access to five state-of-the-art infrastructures providing high quality services, enabling users to conduct excellent research in trans-European collaboration. This will allow research capabilities and expertise in the field to grow, and will expand the potential of researchers that do not normally have access to heavy ion technology. In particular, it will expand this research towards the SEE region. Excellence will be ensured by selecting and supporting the best scientific and innovative experiments accordingly to criteria of equality, transparency, fairness and meritocracy. The TA goal is of providing to more than 150 users a total of 50 clinical units (patients) and 448 research units (hours).	A strong collaboration with the NA WPs will be needed to increase the number of users, inviting new users from different NA events. On top of the normal advertisement of the TA provisions on the project web site and at meetings and conferences, the opportunities will be globally advertised in the SEE region to attract interest from the local research teams.

Building a User Community

State-of-art	Ambition	Challenges
Four facilities in Europe provide ion beams for cancer treatment. There is a limited collaboration among them and with other researchers via some existing channels as the hadron therapy ENLIGHT (European Network for LIGHT ions) Network[55]*. However, this collaboration is limited in scope, there is no common experimental programme, and there are no connections to South East Europe.*	To establish a strong and sustainable heavy ion beam treatment community in Europe and to foster a culture of co-operation between the participants and other relevant stakeholders, by organising, in coordination with the existing structures for proton and hadrontherapy INSPIRE and ENLIGHT, one multidisciplinary Workshop per year, and other topical events. The target is to reach an audience of 100 people.	To address the conservatism of the medical community and increase their engagement with heavy ion therapy. To bridge communities often at opposite sides (medical/ physics; pharma/ accelerators; business/science; laboratories/ health care systems and policy makers) and with different cultures, objectives, agendas and mind-set, and unite them on a common goal. Additional challenge is the possible lack of collaboration between Balkan members.

Establishing a Clinical Network

State-of-art	Ambition	Challenges
Carbon Ion Radiotherapy is used clinically as radical treatment for tumours perceived as radio resistant. Dose and fractionation applied follow either the approach established by GSI/HIT in Germany or the one by NIRS in Japan. All clinical facilities optimize RBE	To explore innovative clinical uses of carbon ions specifically focusing on optimization strategies that go beyond the simple RBE weighted dose, investigating the use of carbon ions to accelerate reoxygenation of tumours that are radioresistant not because of their histology, but	Development of innovative trial design is challenging *per-se*. The creation of a patient registry cannot be funded within this project and will ultimately depend from external cooperation. In the worst case scenario, this project will produce only a registry design and

[55] https://enlight.web.cern.ch/

weighted dose but different RBE models are employed. Carbon ion is used in the attempt to control the most radio resistant tumour clones. *Dose constraints for organs at risk in carbon ion radiotherapy are based on single institution experience. There is no common approach to this critical issue.*	because of an unfavourable baseline signature, and exploring the immunogenicity of carbon ions (alone or in combination with checkpoint inhibitors). To transfer these methodologies to clinical research and define at least one approved trial. To establish the common semantics that will allow to pool clinical data on patients treated with carbon ions and make real world data available for the community as an additional source of evidence. To analyse in a pooled way the observed clinical toxicity, improve and harmonize dose constraints for OAR among European centres.	its implementation will be deferred to a later stage.

Achieve Knowledge and Technology Transfer

State-of-art	Ambition	Challenges
While industry offers several turnkey proton therapy systems, ion therapy centres rely on bespoke solutions. Few EU companies have the capability to build equipment for ion therapy centres (accelerator parts, instrumentation, software). There is not an integrating company. Japanese companies are leading the market and US companies are trying to enter. Currently, the only commercially available solution for ion gantries is provided by Toshiba (Japan).	Drive a major shift in the market of ion therapy technologies, by developing innovative, cost-effective, and manufacturable solutions, thus enabling EU companies to produce turnkey systems for cancer treatment with carbon and heavier ions. Steer the HITRI*plus* technological developments towards transferrable solutions, by fostering a culture of co-operation and co-development between the participants and EU companies. Help EU companies to compete with Asia and US in key markets/technologies by giving them access to the HITRI*plus* innovations in key topics/fields (superconductivity, gantries, etc.).	The uptake of complex and costly technologies by industry is a challenging process. Companies will also need to develop new market strategies and business plans. The HITRI*plus* consortium is well placed to support EU companies in overcoming these challenges, as its partners are not only leaders in technological innovation, but also possess a strong track record in technology transfer and in working with industry.

Standardise Radiobiological Dosimetry and Quality Assurance

State-of-art	Ambition	Challenges
Research centres are conducting their own studies, having implemented their own models for dosimetry due to variations in treatment planning and beam application.	Generate common standards for radiobiological dosimetry, fostering a culture of co-operation between the participants to encourage future joint research.	Finding a shared experimental protocol suitable for all the facilities involved.

Improved Accelerator and Gantry Designs

Technology	State-of-art	Objectives (Technological breakthroughs)
Lattice for superconducting synchrotro.	*Preliminary designs were developed using ideal magnets*[56].	Define a complete layout with injection, extraction, acceleration, based on magnets with 3 T dipole field and 1 T/s ramp rate, which can accelerate 10^{10} carbon ions to 430 MeV/u.
Techniques for high-intensity operation	*Present ion therapy centres operate with maximum 10^9 carbon ions per pulse*[57].	Develop multi-turn and/or charge exchange injection schemes that can be applied to normal conducting and superconducting synchrotrons to increase the ion intensity by an order of magnitude.
Beam transport and instrumentation	*Different beam transport lines are built with limitations in size or performance.*	Define an optimised beam transport layout with minimum length that allows achieving the required beam parameters at irradiation point. Define and standardise the instrumentation required.
Injector linac	*A common injector linac design at 7 MeV/u exists, developed in the 90's*[58]	Design a new linac injector at higher energy (10 MeV/u), with higher accelerating gradient (3-4 MeV/m) and lower cost than the standard design, which can operate at 10% duty cycle for production of therapeutic radioisotopes.
Superconducting ion gantry	*Only one SC gantry developed in Japan, some studies in Europe*[59].	Develop the integrated design (mechanical drawings) of a superconducting gantry with weight lower than 100 tons and length below 16 metres.

Develop new Superconducting magnet designs

Technology	State-of-art	Objectives (Technological breakthroughs)
Canted Cosine Theta (CCT) curved magnet	*At present no demonstrator exists nor an engineering design, of a curved CCT magnet.*	To accomplish a complete design of a strongly curved CCT dipole (curvature radius about 2.2 m), overcoming the engineering, materials and fabrication challenges. This will be a world prima for CCT and for accelerator magnets of slim bore.
Combined function (gradient field super-imposed to a pure dipole) CCT magnet	*Combined function has been proposed but never engineered nor manufactured in CCT type.*	To produce an effective engineering design and implement a coil winding technology on a demonstrator magnet, either as nested winding of 3 T dipole + 2 T quadrupole field, or as combined winding with alternate combined focusing (triplet quadrupole superimposed to a single dipole). This exceptional, innovative, breakthrough would mark the medical system for ion therapy.
Ramped superconducting magnet with 1 T/s and 4 T field	*Ramped magnets exists for fast synchrotrons (like FAIR-SIS100) but only below 2 T level.*	To design an adequate superconducting cable, and demonstrating its applicability, for 1 T/s ramped magnets of 4-5 T field, which is necessary for synchrotron with field quality typical of accelerator magnets (1-10 units).
Indirectly cooled ramped magnet for gantry	*Rotatable gantry with indirectly cooled SC magnets exists (only in Japan) but with low temperature margin and prone to quench.*	To increase stabilization in the indirectly cooled gantry magnet by a factor 10 wrt present state-of-the-art, i.e. increasing the temperature margin to 1.5-2 K, either with LTS and high thermal stabilization or with HTS superconductor working at higher temperature than liquid helium (a novelty in the panorama of medical application).
Zero field magnetic channel for beam extraction	*Zero-field superconductor channel extractor do not exist at present.*	To design a realistic prototype, manufacture and test to experimentally demonstrate feasibility of this concept of zero field magnetic channel for extraction.

[56] E. Benedetto, N. Al Harbi, L. Brouwer, S. Prestemon, P. Riboni and U. Amaldi, A Carbon Ion Superconducting gantry and a Synchrotron Based on Canted Cosine Theta Magnets, Submitted to Phys. Med. Biol. (2020)
[57] S. Rossi, The National Centre for Oncological Hadrontherapy (CNAO): Status and perspectives, Phys. Med. 31, 4, June 2015, p. 333-351
[58] B. Schlitt, U. Ratzinger, A. Bechtold, A. Schempp, Design of the 7 MeV/u, 217 MHz Injector Linac for the Proposed Ion Beam Facility for Cancer Therapy at the Clinic in Heidelberg Contribution to the LINAC2000 Proceedings, Paper ID: MOD10 https://arxiv.org/abs/physics/0008148
[59] Y. Iwata, N. Amemiya, H. Arai, T. Fujimoto, T. Fujita, Superconducting Gantry for Carbon-Ion Radiotherapy, Proc. IPAC 2018 Conference, Vancouver

Develop an Advanced Beam Delivery

Technology	State-of-art	Objectives (Technological breakthroughs)
Treatment chair and imaging system design	*One chair in operation in a proton centre, none in ion beam centres.*	Greatly increase the flexibility and usability of fixed ion beam treatment rooms (11 existing in Europe, only 1 Gantry). Tailored design solution using existing components for each treatment centre, compatible to room layout and robotic positioning systems.
Particle arc therapy	*State-of-the-art in photon therapy, exploratory studies with protons.*	Explore arc therapy on a patient chair in simulations and experiments: Identify treatment sites with significantly improved normal tissue sparing over standard therapy with 2-3 treatment fields. Verify deliverability and reduced dose uncertainty to rotating targets.
Increased delivery speed	*Limited by position detection devices to ~ 3 ms per spot.*	An advanced GEM detector design increases position detection speed by at least one order of magnitude. Average spot durations can be reduced to 1 ms.

Improve Controls and Safety

Technology	State-of-art	Objectives (Technological breakthroughs)
Machine controls	*Present solution's architectures are not optimal and not always built on top of standard and stable commercial off-the-shelf electronic components.*	Design accelerator control system with standard multi-tier control system architecture, based on flexible and maintainable off the shelf platform(s), to ensure fast commissioning and machine QA, ease of use by non-clinical personnel, high reliability of the accelerator and lowering of the total operational costs.
Treatment room controls	*Present solutions are not optimal regarding treatment quality and patient safety, and not user friendly.*	Design a treatment control system, which will increase patient safety, increase treatment quality (adaptive treatment workflow), lower the total treatment time, and ensure easy operation by clinical personnel, thereby also ensuring smooth clinical workflows.
Patient safety systems	*Current implementations have a number of drawbacks:* *- complexity of the system limits optimization options with regard to performance and robustness,* *- not futureproof, limited upgradability and increased effort for maintenance,* *- standardization usually very limited.*	Design patient safety system, which will especially focus on: (1) matching performance of the patient safety system with the performance of the accelerator design; (2) developing a sustainable architecture that can deal with expected technical and medical advancement over the lifetime of a heavy ion therapy facility; (3) low complexity; (4) low effort for maintenance and operation; (5) low investment costs. New solutions will increase patient safety and further lower the total treatment time.

2. Impact

HITRI*plus* has been set up to achieve meaningful and measureable scientific, technical, economic and societal impacts that will ultimately result in establishing a sustainable ion beam therapy Community that joins medical, academic and industrial partners to carry out excellent collaborative research activities that will eventually improve radio-oncology treatment for European cancer patients.

Its key impacts and the related strategic objectives can be summarised as follows.

- Support the development and reinforcement of a **knowledge-based economy** in Europe, and **improve health access** by building unique knowledge and skills through state-of-the-art research and innovative solutions lead by experts in the field. Allow Europe to maintain a leading position in ion therapy in the world. *Related to Objective 4.*
- Provide a **direct transnational access** to ion therapy facilities by offering a free access beam time to the European clinical and research community on ion-based radiotherapy. The wider cancer research community will have a facilitated access to these HITRI*plus* infrastructures, which use state-of-the-art world-class equipment. *Related to Objective 1.*
- Build a **unique multidisciplinary network of experts** from academic, clinical and research institutions, as well as European industry, who will carry out research with a strong translational potential in advanced ion therapy, defining the main features and the design of the next, beyond state-of-the-art generation of ion therapy facilities. It will constitute a **common collaborative European platform** integrating all actors in this rapidly evolving field, allowing sharing information, data, expertise and knowledge in medical, scientific and engineering fields. The collaborative group of professionals in HITRI*plus* will pursue **innovative and cost-effective solutions** in advanced medical accelerator technologies with novel, more efficient accelerators with a smaller footprint and higher ion beam extraction capability, and hence, a faster dose delivery resulting into more efficient, faster and less expensive cancer patient treatment. *Related to Objectives 3 and 4.*
- Accelerate the **pre-clinical implementation**, allowing faster translation of the created know-how to the cancer **patient**. *Related to Objective 2.*
- Foster a **collaborative culture** and provide the tools, procedures and standards for integrated use and knowledge sharing between the ion therapy research facilities throughout the European community for ion therapy research. *Related to Objective 4.*
- Develop **common standards, common treatment protocols, technology development, and common training,** which will allow Europe to advance rapidly in this newly emerging field. The established common treatment platform could be utilised by any future forthcoming ion therapy facility in any European country, which decides to use the available commonly developed standards. *Related to Objective 3.*
- Define a new **common leading-edge European design** for ion therapy facilities that will be transferred to industry to allow European industry to compete with Japanese companies to access the **growing ion therapy markets** in Asia and USA. *Related to Objective 3.*
- Define the **experimental programme**, set up and structure the **research user community**, develop the key accelerator and beam delivery **components**, and establish an **international network** that will support the **construction and exploitation** of a new Research Infrastructure devoted to ion therapy research in South East Europe, the **South East European International Institute for Sustainable Technologies**. *Related to Objective 5.*
- Connect the **most advanced medical and technological institutions** in Western Europe with emerging **medical and scientific communities in South East Europe** and in **other regions** (e.g. the Baltics), contributing to the creation of a wider European Research Area and to the integration of the European Union. *Related to Objective 5.*

2.1 EXPECTED IMPACT FROM THE CALL AND HOW HITRIPLUS WILL ACHIEVE THE IMPACT

2.1.1 a) Impact foreseen in the call

1. **Expected Impact: Wider, simplified and efficient access to the best research infrastructures.**
   HITRI*plus* approach: High quality inter-disciplinary and multi-sectorial clinical and research opportunities will be opened for a wider number of users in order to provide a cutting-edge cancer research and training of the future experts in the ion therapy field. All four European advanced ion therapy centres will participate in the Transnational Access, together with GSI, the largest heavy ion research centre in Europe.
   The HITRI*plus* Consortium covers 14 European countries, and via the SEEIIST is connected to institutions and researchers in eight SEE countries. Through the HITRI*plus* networking and communication platform the ion therapy user community will be able to choose the best site for the research they want to perform. In particular, SEE researches will have access to the best European infrastructure in the field.
   HITRI*plus* will focus on the needs of its users and will provide a Network Facilitator digital platform.
   The JRA's will contribute to improving the facilities so that users will always have access to the best possible research infrastructure.

2. **Expected Impact: New or more advanced research infrastructure services, enabling leading-edge or multidisciplinary research available to a wider user community**
   HITRI*plus* approach: Creating a durable and sustainable research network in heavy ion therapy. Consolidation, interdisciplinary exchange and enhancement of the expertise, clinical and research efforts in ion therapy brings new innovative solutions.
   HITRI*plus*, for the first time, opens the four ion therapy centres in Europe to devote a fraction of their beam time to coordinated research for the advancement of ion therapy, instead of concentrating only on patient treatments.
   An extensive multidisciplinary HITRI*plus* consortium will build up the bridges between leading experts from clinics using the joint communication platform. The research activities will cover clinical, pre-clinical and biophysics research and will be open to participants from the medical, medical physics and biophysics field, and to the related industrial partners. HITRI*plus* will boost frontier research while developing and improving effective knowledge sharing and collaborative culture across Europe and in particular between the major West European players in the field and SEE participants, thus creating a wider user community.

3. **Expected Impact: Operators of related infrastructures develop synergies and complementary capabilities, leading to improved and harmonised services. Economies of scale and improved use of resources across Europe are also realised due to less duplication of services, common development and the optimisation of operations.**
   HITRI*plus* approach: Significant disparities in terms of research and innovation performance among the different member states and regions within the European Union will be reduced by bringing together all four ion therapy centres in Europe. This is particularly important given the growing need and interest for heavy ion therapy, its potential as a cancer treatment and the technological and scientific challenges that still need to be addressed. Europe has been one of the leaders in this expanding area thanks to the individual initiatives of the pioneering institutions in Germany and Italy. Only the creation of a wide multinational Community will now make possible the renovated common effort that will allow Europe to regain its leadership with respect to Japan and to the emerging initiatives in the US.
   Standards produced in HITRI*plus*' JRA will be used for QA, and round-robin experiments will be conducted to ensure inter-comparability between the capabilities of TA providers.
   The HITRI*plus* collaborative approach has huge potential to introduce a paradigm change in the technology and its clinical implementation. This in turn will deliver benefits to patients in terms of outcomes and quality of life and deliver new products and services to enhance EU economy and society. The increased capacity (technical

infrastructure as well as trained staff) will contribute to higher participation in a wide range of EU research programmes. The coordination and integration action among the ion therapy facilities performed by HITRI*plus* will contribute to harmonize the services, reduce the duplications and optimize the outcome of the common efforts.

4. **Expected impact**: **Innovation is fostered through a reinforced partnership of research infrastructures with industry.**
   HITRI*plus* approach: Three industrial companies (SME's) are part of the HITRI*plus* Consortium with key roles (WP Coordination for one of them) and crucial activities. In the ion therapy field, they participate in the effort to innovate the particle accelerators used for ion therapy, together with high-profile academic partners and major physics research laboratories like GSI and international organisations like CERN. This co-innovation effort will lead to new standardised products available to a wide range of potential customers.
   In all other fields where the technologies are not yet mature for co-innovation, the dedicated WP4 Innovation and Technology Transfer is tasked to examine technologies being developed in the project and to assist in the evaluation of the feasibility for technology transfer, by identifying and matching the key European industry players in the corresponding markets of ion therapy technologies. In particular, superconducting magnet technology applied to accelerators for medicine has a vast industrial potential and opportunities in this field will be carefully considered by the Innovation Work Package WP4.
   Pharmaceutical companies will participate in the Network activities and will possibly use the TA opportunities. They are expected to contribute to the integration of ion therapy with immunotherapy treatment towards the definition of future treatment protocols.

5. **Expected impact**: **A new generation of researchers is educated that is ready to optimally exploit all the essential tools for their research.**
   HITRI*plus* approach: The Education and Training WP5 will increase the European pool of trained and well-informed students and researchers in heavy ion therapy science and technology. The subjects will include: clinical practice of heavy ion therapy; accelerator technology and beam physics for heavy ion therapy; accelerated heavy ions in radiobiology and medical physics; heavy ion therapy data platform; safety aspects of heavy ion therapy; compliance to European regulations and standards; certification strategies of medical accelerators; medical physics commissioning; and clinical practice of particle therapy. HITRI*plus* will enhance the communication of achievements and opportunities within the field, as well as increase the flow of trained individuals into industries, laboratories and universities where there is a skills-shortage in Europe.
   Working in eminent academic institutes, participating in the workshops organised by the NAs of HITRI*plus*, and interacting with industrial partners will expand the job opportunities for PhD students a new generation of researchers in academic, health and industrial sectors after completion of the project.
   HITRI*plus* is supporting secondments (for employed researchers/practitioners) and internships (for students). These will provide a first-class unique scientific opportunity to join the day-to-day work of research teams and participate in heavy ion therapy experiments, hence learning best practices.
   All HITRI*plus* education, training and PhD opportunities will be largely advertised across Europe and in particular in SEE countries via the SEEIIST. It is expected that this region will give a strong contribution to the HITRI*plus* activities, and that one of the outcomes of the project will be developing advanced multidisciplinary science and building capacity in the SEE region in addition to Europe as a whole.

6. **Expected impact**: **Closer interactions between larger number of researchers active in and around a number of infrastructures facilitate cross-disciplinary fertilisations and a wider sharing of information, knowledge and technologies.**
   HITRI*plus* approach: More than 100 participants are expected to take part in the HITRI*plus* Annual Meetings, out of the much wider community that will receive the HITRI*plus* Newsletters and will be informed of the events. This number will include clinicians, medical physicists, biophysicists, accelerator and technology

physicists and engineers, and industry representatives from Western European countries and other European regions, such as the South East Europe. In addition, HITRI*plus* will favour secondments and internships that will enable participants to gain first-hand transdisciplinary knowledge on how these facilities can be used for their research in a cross-fertilization process between disciplines. It is expected that HITRI*plus* will create new connections and interactions, among the European ion therapy centres that have rarely collaborated in the past, and between them and new actors coming from different European institutions in particular in South East Europe. The interaction between the medical and medical physics community and the particle accelerator community in particular is expected to identify innovative solutions to reach an overall optimisation of the ion therapy infrastructure, considered as a single process extending from the ion source to the tumour under treatment.

7. **Expected impact**: **The integration of major scientific equipment or sets of instruments and of knowledge-based resources leads to a better management of the continuous flow of data collected or produced by these facilities and resources.**
   HITRI*plus* approach: The integration of ion-therapy centres between them and with the other contributors to ion-therapy research will allow creating common sets of data. An example are the initiatives of the Clinical Networking WP3: a) a review of preclinical data to identify promising novel approaches; b) the first European registry of ion-therapy patients; c) a European registry on rare cancers treated with ion-therapy; d) a review of existing data on organs-at-risk (OAR) dose constraints in use in the clinical facilities. These data will be treated accordingly with the European privacy regulations, as detailed in the Ethics section of this proposal. In addition, standards produced in HITRI*plus* WP12 Radiobiological Dosimetry and Quality Assurance will be used to ensure inter-comparability between the capabilities of the different centres, for therapy and as TA providers. Common treatment and storage of data will lead to a better management of the continuous flow of data collected or produced by these facilities.

8. **Expected impact**: **The integrated and harmonised access to resources at European level can facilitate the use beyond research and contribute to evidence-based policy making.**
   HITRI*plus* approach: The integrated and harmonized access to ion-therapy resources at European level will facilitate the beneficiaries in providing consistent data on results and perspectives of ion therapy to healthcare agencies and relevant government organisations, which will allow for evidence based medicine strategies, optimal usage of ion therapy facilities, and for planning further initiatives in this field.
   HITRI*plus* will provide to EU policy makers data on the extent and perspective of ion therapy research, on the costs and risks of building an advanced accelerator facility for ion therapy, and on the patient throughput of such a facility, which will allow taking decisions on the funding of future new facilities such as the SEEIIST project.

9. **Expected impact**: **The socio-economic impact of past investments in research infrastructures from the European Structural and Investment Funds is enhanced.**
   HITRI*plus* approach: HITRI*plus* will have no impact on past investments from the European Structural and Investment Funds on RI's, but might have an impact on future investments, via its impact on the SEEIIST initiative that aims at receiving funding, among others, from the European Structural and Investment Fund.

2.1.1 b) Additional Impacts

10. **Expected Impact: Improved patient recruitment strategy and quality of life.**
    HITRI*plus* approach: The maximum treatment capacity of the four ion therapy facilities is estimated around 2500 patients per year, a treatment capacity not sufficient to cover the expected number of radio-resistant patients per year in Europe, i.e. about 25,000 patients.
    In addition, the quality of life of the patients is improved by accessing ion beam therapy. In fact, the patient normally feels no pain and suffers very limited side effects. No hospitalization is usually required and the treatments are out-patient treatments. In the case of ion therapy the number of sessions to treat a pathology is

normally reduced with regard to conventional radiotherapy. The hypo-fractionation, the shortening of the overall treatment duration, is positively impacting on quality of life and reducing socio-economic costs.

HITRI*plus* aims at modelling the future demand based on clinical indications and best treatment practice and then mapping this demand across Europe. By combining this study with metrics to determine which patients will derive most benefit from ion therapy, there will be a much better understanding of demand and its geographical distribution. The Networks WP2 and WP3 will better inform the medical community for patient selection criteria and deliver improved treatment outcomes, with better treatment experience of the cancer patients, thus improving their quality of life.

11. Expected Impact: Engagement with the wider medical community.

HITRI*plus* approach: Key to the ion therapy research is engaging with the broader health care community, formed by other professionals such as nurses, planners, bioengineers and radiographers who bring another perspective to the research that is much more patient-centric. Participation of several European hospitals will allow the clinical translation of the research, for patient benefit, from "bench to bedside", again using HITRI*plus*' NA and TA.

2.1.2 Description of Barriers and Obstacles

The following are the potential barriers that may influence the extent of the impact to be achieved.

Obstacle: Research considerations
Description: Medical research by its nature has high financial and economic risk and often has long lead times. Research projects have very variable but often highly valuable outcomes for the society, from no financial or economic benefits to breakthrough discoveries. This may decrease the exploitation time of the ion therapy facilities for research matters.
HITRI*plus* approach: HITRI*plus* will design a joint coordinated beam time management among its ion therapy partners.
Obstacle: Patient selection
Description: Despite past investments and the growing number of treated patients every year, carbon-ion therapy is still relatively new and not broadly known to public, and even more so the related research. Currently there are more patients who would benefit from ion therapy in comparison to the capacity of the existing centres in Europe that can deliver this treatment.
HITRI*plus* approach: HITRI*plus* will design tools common to all therapy facilities to enhance the outreach on ion therapy to potential patients, communicating on the selection procedures, treatment outcomes and living health standards.
Obstacle: Cost implications of ion therapy treatments
Description: The healthcare systems are not prepared to pay for ion therapy treatment because of funding constrains and the lack of clinical evidence.
HITRI*plus* approach: Therapy with ions is primarily offered for tumours which are either radioresistant or difficult to treat by more conventional means. The clinical evidence for treatment of these tumours with ion therapy is constantly improving and will be closely followed in the Network, although it takes several years to prove long-term statistically significant effects. An effort will be made in the JRA's WP7-8 to reduce the construction and operation cost of the accelerator, to reduce treatment costs and increase availability of ion therapy.
Obstacle: Availability of experts for training activities
Description: The training of physicians, medical professionals, applied scientists and engineers is costly and time consuming. Furthermore, even for already qualified oncologists, training requires a broad specialised knowledge. Availability of experts and their coordination may be an obstacle to be taken in consideration for planning networking and knowledge-transfer activities, such as the training workshops.

HITRI*plus* approach: HITRI*plus* will be planning its yearly activities well in advance, in coordination with the experts and their availability. It will access to the national pools of experts of all partners, to increase at the maximum the number of potential trainers.

Obstacle: Shortage in skilled young professionals to be trained

Description: HITRI*plus* aims at inspiring the next generation of leaders in the field. The rapid growth of ion therapy means that there is a shortage of skilled personnel in this highly multidisciplinary and technical field.

HITRI*plus* approach: Although this is seen as a challenge, it is also an opportunity. Secondments (for employed researchers/practitioners) and internships (for students) will provide a first-class unique scientific opportunity to join the day-to-day work of research teams, participate in heavy ion therapy research experiments, learn best practices and thus contribute to building a new generation of skilled young professionals. In addition, some beneficiaries of HITRI*plus* have also submitted a MSCA-ITN proposal. Furthermore, several SEE countries are currently beneficiaries of an IAEA regional project in which about 10 early stage researchers will benefit from 6 months training in heavy ion therapy. All training opportunities will be widely advertised.

Obstacle: Engagement of Medical Community with Heavy Ion Therapy

Description: Radiotherapy treatment using heavy ions is still in its early stages compared to some of the other cancer treatment modalities. The capabilities and the specifics of carbon treatment are still less known/popular in the medical community of European regions such as the SEE and Baltic region.

HITRI*plus* approach: HITRI*plus* has included the dedicated WP3 with the aim to involve the medical user community; the starting point for the design requirements of the next generation facilities will be jointly defined based on oncologists' needs as well as those of researchers. In WP3 and through WP2 the medical user community will be constantly involved and invited to provide feedback. This will also allow HITRI*plus* to establish the training needs that will contribute toward a sustained uptake of the medical potential of each ion therapy facility. The common data sets provided by WP3 are expected to bring evidence on the potential of carbon ion therapy.

Obstacle: Patient Data Sharing

Description: Sharing patient data, even if the project implements all the EU data protection recommendations to be made anonymous, is often a challenging matter. Significant developments have been made through frameworks for distributed sharing of data, such as with euroCAT12. Advances in cloud and distributed computing and related tools are helping with gathering and sharing of patient data and collaborative research.

HITRI*plus* approach: HITRI*plus* will define a Data Management Plan to deal with all the issues related with treatment of critical data within the project.

Obstacle: Transnational Health Care and Research

Description: Further progress in heavy ion therapy is hindered by the lack of experimental beam-time at European ion therapy facilities. A dedicated facility for radiobiological and medical physics experiments with different types of ions, intensities and irradiation times does not exist in Europe.

HITRI*plus* approach: A new facility, such as the one supported by the HITRI*plus* community and planned to be built by SEEIIST in the SEE region will allow a wide range of research including radiobiology, medical physics, pre-clinical research, and clinical trials. The beam time will also be available for technological research to improve particle treatment and for non-medical research in particular space radiation protection research, material research, and detector calibration.

Obstacle: Public acceptance

Description: As a technique, ion therapy has huge potential. The benefits of ion therapy are high especially for some specific tumours, which are difficult or impossible to treat with conventional treatments. On the other hand, the clinical evidence for the advantages of ion therapy are in the early stages. The choice between treatment with ions and treatment with state-of-the-art X-ray or protons technologies is complex and requires consideration of many factors.

HITRI*plus* approach: HITRI*plus* will help shaping public perception, through its range of outreach activities. It will permanently seek innovative ways to deliver the facts about the advantages of the ion therapy and combat the "fear" that often surrounds this treatment, in a fair and coherent way avoiding confrontation with other treatment techniques and instead highlighting the complementarities. Through its website, and the social media HITRI*plus* will inform the public to help them be aware of existing treatment possibilities.

Obstacle: Industrial interest

Description: Ion therapy facilities are still designed and built based on bespoke designs and technologies, contrary to proton therapy for which industrial turnkey solutions are available. Although the industrial players in proton therapy and in accelerators, gantries, superconducting components are well known, the uptake of new, complex, and costly technologies by industry is not straightforward. New market approaches, and possibly new industrial actors, might be needed, also taking into consideration the fact that even big companies are increasingly subcontracting R&D to smaller entities.

HITRI*plus* approach: HITRI*plus* will keep a strong focus on manufacturability and industrialization in its R&D programme, also thanks to a dedicated "industry liaison" work-package. The roadmap to industrialization will also explore the potential for novel companies, SMEs and entrepreneurs, also through the interaction with business and entrepreneurship schools. HITRI*plus* will strive to deliver innovations that also offer cost-effectiveness, size reduction, and standardization.

Metrics for Success:

To assess the impact of HITRI*plus* it will be important to quantify/benchmark at the start of the project and at the end of each year. This methodology for the metrics will be adapted from the balanced scorecard approach developed by the National Physical Laboratory as part of its data standards portfolio. The metrics are listed in *Table 1* below:

***Table 1** - Metrics for success of the impact of HITRIplus, quantified by the number of participants at each HITRIplus project year.*

Metric	Year 1	Year 2	Year 3	Year 4
Number of users	100	150	150	200
Engagement of new users	100	200	200	500
Number of trained early stage researchers	25	45	45	45
Number of trained senior researchers	-	10	10	15
Inspiring outreach events for next generation researchers	5	5	5	10
Number of medical staff involved (doctors)	-	15	15	15
Public engagement (social media, newsletters, video, blogs, scientific online sessions etc.) by using media monitoring tools such as Google Analytics, Google Trends, Sysomos etc.	5.000	7.000	10.000	12.000

2.2 MEASURES TO MAXIMISE IMPACT

a) Dissemination and exploitation of results

Draft plan for dissemination and exploitation of project results

The dissemination and exploitation activities of HITRI*plus* will be coordinated in the frame of WP1 "Project Management" and WP2 "Networking and Communication, Dissemination and Outreach".

Regarding dissemination, HITRI*plus* aims to provide timely information about the results from the NA, TNA and the JRA activities to the medical and scientific community, and in particular for the JRAs to European industry. To this end the dissemination of results will be among and beyond the members of the HITRI*plus* consortium, in a

time span that will go beyond the project duration, in particular for publications and monographs which may be published after the end of the project.

Regarding exploitation, HITRI*plus* aims to promote exploitable results, in particular those that have potential for application on the existing ion therapy facilities, or for commercial applications, and make them available to interested parties within and beyond the consortium, while protecting the legitimate interests of all beneficiaries that have been involved in producing these results. This will be a process that will go well beyond the duration of the project.

To reach these goals, the draft Dissemination and Exploitation Plan of HITRI*plus* includes the following objectives.

Improving the communication among the ion therapy stakeholders for the benefit of the cancer patients: HITRI*plus* will create communication channels among the many actors of innovation in the field of ion therapy, for the final benefit of the cancer patients.

Improving the European innovation human capacities: HITRI*plus* will build on the proven experience acquired by members of its consortium that were the initiators of successful projects such as PARTNER (dealing with medical physics and radiobiology), ENTERVISION (advanced imaging technology for image-guided HT), and the currently ongoing project OMA[60] (Optimization of Medical Accelerators, dealing with medical accelerators and associated technologies). HITRI*plus* is a natural unifier and a follow up to these success initiatives and will greatly contribute to the European innovation capacity by training the much needed new human innovation potential.

Fostering EU leadership in ion therapy innovations: HITRI*plus* will yield a team of leaders in the respective ion therapy related sciences in Europe including the SEE region, convinced of the advantages of pan-European collaborations in innovation and R&D. The collaboration of the renowned European experts along with the young researchers will be an empowered network, strongly linked to research centres, universities, partners from industry and clinical centres. This will strengthen the position of Europe including South-East Europe in the global ion therapy arena. A number of innovations will result from HITRI*plus*, as described in Section 2.2a *Exploitation Measures*.

Fostering innovative solutions for enhancement of the existing ion therapy infrastructures and create the design for the future infrastructures: It is the declared aim of all partners to establish long term collaborations between the consortium members, most of which are linked to the existing infrastructures, but some also linked to the possible future infrastructures such as the SEEIIST facility. HITRI*plus* is designed to support the development of the future infrastructures that will employ innovative solutions and also offer innovative solutions for improving the efficiency and treatment quality of the existing infrastructures. It is expected that HITRI*plus* will create a valuable extension to Europe-wide initiatives in the existing and emerging centres, hence improving the overall innovation institutional potential in Europe.

Enabling two-way knowledge transfer and innovation solutions to non-academic centres: The non-academic HITRI*plus* partners will decisively contribute to the introduction of all participants to the clinical and industrial environments. Some HITRI*plus* Work Packages include joint medical/industry-focused efforts, which are particularly important to train the future users in radiotherapy centres and in innovative industry in biomedical sectors. The innovative HITRI*plus* solutions, could be readily implemented in the existing facilities with the support of the local industries for improving treatment efficiency, thus reducing the cost of treatment, making it accessible to a wider European population.

Fostering entrepreneurship: HITRI*plus* has a dedicated WP on innovation, technology transfer, industry relation lead by CERN for improving the possibilities for helping to identify innovation and generating a market value using the research in the JRA pillar. Some developments such as superconducting magnets and gantry will make market breakthroughs for possible start-up companies.

[60] https://www.liverpool.ac.uk/oma-project/

Dissemination measures

The draft plan for the dissemination and exploitation of the results from HITRI*plus* is outlined below. The HITRI*plus* dissemination strategy dwells on the open science efforts, allowing great visibility and fast access to the research results and raw data of the published material. HITRI*plus* website and other open access platforms will be used for sharing the published research into open access journals. WP Coordinators will ensure that the project results are disseminated internally (among the HITRI*plus* partners) and externally (to the world) as swiftly as possible, in compliance with the protection of the intellectual property rules of the involved participants and ethical rules. Open access publishing will be the norm to ensure that the results are easily available to both the scientific community and to the general public. WP2 oversees the design of a publication policy (as well as communication and exploitation) that will be established during the kick-off meeting of HITRI*plus*. The HITRI*plus* management structure foresees an appropriate roadmap to approve publications and advise on the possibility of exploitation of results. This is especially important for the commercial partners and their future competitiveness. Target groups for dissemination include the research community, decision-makers and leaders of health policy, stakeholders in the area of cancer treatment, health operators, such as hospitals and treatment centres, and secondary disseminators, such as journalists and educators.

Dissemination at the HITRI*plus* level: The project's participants will ensure the dissemination of best practice and exchange of knowledge and experiences through the HITRI*plus* digital communication platform and in person during the regular consortium meetings and joint network events. The HITRI*plus* website will be created as a deliverable in M1. It will consist of two platforms (a) internal platform for the HITRI*plus* consortium members, and (b) public platform. Preliminary research results will be discussed among the members through the internal platform.

Dissemination at the particle therapy community level: This will be facilitated through the links of the HITRI*plus* website and on the existing ENLIGHT site, which also features the "Highlights" journal, distributed digitally and in printed form (twice per year), with a broad outreach to the particle therapy research and general community. One of the annual Highlights will focus and be dedicated to the HITRI*plus* project. The collaborators' communication platforms will also be used for such purposes. ESTRO, PTCOG, Accelerating news, EPTN are existing Societies and communication tools that are already participated by many partners contributing to HITRI*plus* and they will become important vehicles to disseminate scientific results of HITRI*plus*.

Dissemination of scientific raw data and at the international peer reviewed journal level: The main channels for external dissemination in the scientific community will be the publications in international peer-reviewed journals and attendance at conferences and events in the ion therapy field and fields related to accelerators, radiobiology, radiotherapy, medical physics etc. The innovative results on cutting-edge research will be published in broad-field high-impact science and cancer journals, such as Journal of Clinical Oncology and also in specialised journals, such as the International Journal of Particle Therapy. In addition, each hosting institution will include the published work into their own institutional science publications repository on their website. The published results will be further disseminated through science social media such as the ResearchGate, Academia.Edu, Google Scholar, and other alternative platforms.

From the first year of the research activities, HITRI*plus* partners will be encouraged to present their results at dedicated science conferences for accelerators, particle therapy, radiobiology and cancer treatment, such as: (1) ENLIGHT Annual Meeting, (2) PTCOG: Particle Therapy Co-Operative Group annual meeting (3) ESTRO (European Society for Radiation Oncology) meetings, (4) IEEE Nuclear Science Symposium and Medical Imaging Conference (5) International Particle Accelerator Conference, (6) European Conference on Accelerators in Applied Research and Technology, (7) Conferences of the European Association of Cancer Research, (8) Euro-Global Summit on Cancer Therapy & Radiation Oncology, etc. Such participation will help to establish networking activities within the scientific community and make the HITRI*plus* project much more visible and known.

Industrial partners outreach: Research results particularly relevant for industrial exploitation will be carefully identified by the dedicated experts via WP4 that will arrange discussions and meetings with HITRI*plus* and

relevant industrial partners at which they will present their research activities, emphasising the possibilities for business developments and cooperation for the economic benefit of the industry.

***Table 2** - Dissemination activities related to each WP.*

WP#	WP name	Dissemination activities and quantity
WP 1	Project Management	Organization of collaboration meetings (5), participation to external Societies Events (PTCOG, ESTRO…)
WP 2	Networking and Communication, Dissemination and Outreach	Coordination of all HITRI*plus* dissemination activities
WP 3	Clinical networking	Conference papers (10)
WP 4	Innovation, technology transfer, industry relation	Industrial Value Propositions (5)
WP 5	Education and Training	NA
WP 6	Transnational Access	Dissemination via WP2 and WP3
WP 7	Advanced Accelerator and Gantry Design	Scientific publication (1), participation to conferences (>1)
WP 8	Superconducting magnet design	Scientific publication (1), participation to conferences (>1)
WP 9	Advanced beam delivery	Scientific publication (1), participation to conferences (>1)
WP 10	Multiple Energy Extraction System	Scientific publication (1), participation to conferences (>1)
WP 11	Controls and Safety	Conferences, papers and presentations (4)
WP 12	Radiobiological Dosimetry and QA	Scientific publication (1), participation to conferences (>1)

Exploitation measures

Table 3 outlines some of the main exploitable results expected from HITRI*plus*. These results will have a wider impact beyond the specific project targets and objectives, and therefore particular efforts will be made towards their exploitation during and after the end of the project. Since these will constitute the "flagship results" of HITRI*plus* they will be disseminated to larger scientific and public audiences.

***Table 3** - Most relevant exploitable results expected from HITRIplus ("flagship results").*

Description of exploitable foreground	HITRI*plus* Deliverable	How the foreground may be exploited	Further R&D (if needed)	Sector(s) of application or end user(s)	Potential/expected impact (quantify where possible)
Expertise in design of ongoing heavy ion therapy trials	D3.2	Optimized methodology for trial exploring innovative use of heavy ion therapy	Not needed	Clinical use of heavy ion therapy	Expand the use of carbon ions beyond exclusive treatment of histologically radio-resistant tumours
Institutional experience on dose constraints	D3.5	Common European dose constraints for OAR	Not needed	Clinical use of heavy ion therapy	Harmonization of treatments among centres
E-learning course	D5.3	Education and training for new heavy ion therapy researchers	None	Ion therapy research	Provide free education and training for all future heavy ion therapy researchers

New superconducting synchrotron design	D7.4	Compact ion therapy accelerator to be commercially exploited	Prototyping	Ion therapy	Reduce dimensions (50% in radius) and cost (about 20%) of accelerator
New injector Linac design	D7.1	New improved injector for ion therapy facilities	Prototyping	Ion therapy, Radioisotope production, Nuclear and particle physics	Higher beam current (50%) and energy (10 MeV/u) at lower (30%) cost, lower operation and maintenance cost
New superconducting gantry design	D7.3	Design transferred to an industry for production	-	Ion therapy facilities world-wide	Reduction of cost and dimension-commercial opportunities for EU industry in Asia and US markets
Magnet design for SC synchrotron and SC gantry	D8.2	CCT SC magnet design can be used in commercial heavy ion accelerators and gantries and also for high energy physics and synchrotron light sources accelerators	Construction design and full size prototype	Medical Ion therapy, particle physics accelerators, light source rings and FELs	Low cost and energy saving magnets. The required electrical power can be reduced to 25% and energy consumption of 30%
Novel treatment room control systems	D11.2	New improved treatment room control systems	Prototyping	Ion therapy	Faster commissioning and machine QA, higher reliability of the accelerator, lowering total operational costs.
Novel accelerator control system	D11.3	New improved accelerator control system	Prototyping	Ion therapy	Lower cost of treatment room software by an estimated 30%, improve treatment availability by as much as 20%.
Generation of a standardized dosimetry in radiobiology	D12.1	Standard dosimetry to be used in radiobiological research conducted at the centres		Preclinical Research, Translational Research	Crucial for future collaborative studies between the centres

Data collection and management

HITRI*plus* will strictly adhere to the FAIR principles to make data generated or collected in this project Findable, Accessible, Interoperable, and Reusable. In WP1 a Data Management Plan (DMP) will be developed early in the project's life-cycle, following a review of data and knowledge sources, uses, and needs, and will include security standards for access rights and storage, and create guidelines for format, providence, and confidentiality. The DMP will constitute a living document and will be constantly updated throughout the duration of the project. The plan will show how operational project data is collected, processed and stored; also the data management life-cycle of data generated and used during and after the project. The types of data that will be collected and stored will include (not exhaustive list), technical drawings, measurement and characterisation data, simulation and calculation data, analysed data, user specifications, epidemiological data, user community details, design specifications and optimisation parameters, software code, algorithms and workflows, reports and documents etc. Data will be generated, collected, processed, stored and made available to stakeholders, both internal and external to the project, in line with relevant standards and regulations. This procedure and process for sharing information will be governed by a data sharing protocol. The DMP will list details on the different types of data that will be produced, what the data-acquisition process is (when, from where to where and how) and further processing steps (i.e. software, algorithms, workflows, access). Also, data formats; back-up procedures; security measures to protect the

integrity of the toolset and data; quality assurance and control will be described. The DMP will clearly describe management responsibilities for the data and the way and time-period during which the toolset and project-generated data will be preserved, maintained and extended after HITRI*plus* has finished.

Extensive use will be made of free data repositories, as the Zenodo general-purpose open-access repository platform, used for storing and sharing data, software and other research artefacts in a non-commercial environment, freely available to society at large. Zenodo has been developed with co-funding from the European Commission and is operated by CERN, one of the main partners of HITRI*plus* with a long experience in sharing and preserving scientific knowledge for the benefit of all.

HITRI*plus* recognises that sharing research data openly contributes to the impact of research, increasing its visibility and improving its overall quality. HITRI*plus* will incorporate an "Open Access Portal" in its main website, allowing access to all outputs and data, respecting legal and privacy constraints on personal data. Partners will access and download restricted data/information. The DMP will outline which part of the data will be accessible only to the partners and which part will be open to others. Potentially patentable inventions or protectable IP are expected from some of the JRA, and WP4 will examine routes for IP protection before any dissemination. All abstracts will be evaluated prior to submission to international conferences to ensure that IP is not compromised, and due account will be taken of any background belonging to beneficiaries which might be required for successful exploitation of results.

Open source software

Open source software **is not intended to be developed** within the project.

Knowledge management and protection

The principles for dissemination, access and use of results generated through HITRI*plus* will fully comply with the **Rules for Participation and Dissemination in Horizon 2020**. Access to Results and Background and ownership of Results will follow the principles set out in the EC Grant Agreement. The implementation of these principles will be detailed in the Consortium Agreement, which will be signed before the start of HITRI*plus*. In this Consortium Agreement the beneficiaries will identify and agree on the Background needed for carrying out the project and which may have to be made available to other beneficiaries. Access rights to Background or to Results needed for use of HITRI*plus* results for research purposes beyond the project duration by other beneficiaries will be granted on a fair and reasonable basis, with terms agreed in the Consortium Agreement.

HITRI*plus* aims to implement efficient management of Intellectual Property Rights (IPR), which is essential for successfully exploiting the research results of the project and for protecting the interests of the institutes and companies that have produced these results. An experienced staff member of the Knowledge Transfer Group of CERN will coordinate the WP4 "Innovation, Technology Transfer, Industry Relations" and will act as a liaison between the beneficiaries to ensure that ownership of new IP is adequately distributed and protected, with particular attention to those WPs where industrial companies are involved.

The beneficiaries of HITRI*plus* will endeavour **to publish any results from the project as swiftly as possible** in scientific journals and/or other fora as appropriate. The Consortium Agreement will define in detail the procedures for publication, which will take into account the potential for commercial exploitation and/or the need for protection of IPR of the results concerned, with due consideration of the IP practices of all participants.

Open Access to results

HITRI*plus* will make use of both Open Access standards ("Gold" and "Green"), ensuring that readers are granted access to its scientific output without financial, legal or technical barriers:

- Gold standard: The "Gold" standard will be preferred for peer-reviewed publications directly submitted to open-access journals.

- Green standards: The "Green" standard will take the form of self-archiving in an open repository such as ArXiv.org and inSpireHEP.net, widely used by the High Energy Physics community. For articles outside of the scope of ArXiv or inSPIRE, publication will be stored and made available through the CERN Document Server (CDS) platform, which is based on the ZENODO digital repository, developed and hosted by CERN. ZENODO is integrated and used also by OpenAIRE to provide a common platform for Open Access to Horizon 2020 results across various scientific fields.

Dissemination of results to industry

This will be the task of WP4, using the usual Technology Transfer networks and the CERN experience, integrated by TT offices of the other partners, in accessing them. HITRI*plus* aims at involving industry early on in the process of design, testing and prototyping of new components.

b) Communication activities

The communication plan of this project builds upon experience and lessons learned from similar EU projects, and is based on the EC guideline document "*Communicating EU Research & Innovation*"[61].
HITRI*plus* recognises the importance of communicating to the public at large, and implements WP2 to promote initiatives, develop outreach material, and organize the wide spectrum of outreach. The calendar of the outreach events will be published on the web site in advance, at the beginning of each lifetime year of the project.

Table 4 *- HITRIplus target audiences and communication needs.*

Target Group	Communication needs	Methods	Impact	Targeted people
General public	General evidence-based information on ion therapy, and societal implications	Website, new media, audio-visual material, talks, events	Fast Diffusion of the scientific knowledge & Attract students to S&T	**10000**
Industry	Information on new/innovative work, collaboration opportunities	Industry/Academia events	Encourage technology transfer and collaboration	**200**
Media	Notable HITRI*plus* results/events	Website, newsletters, You-tube short clips,	Improve visibility of ion therapy and advancements	**100**
Policy makers	Information and recommendations in support to science, health, and technology policy	Policy briefings, newsletters, CERN Council and SEEIIST events	Justify the funding to decision makers, shape future programmes, standardization and ion therapy related policies	**20**
Students	Basic knowledge in fundamentals of ion therapy, career information	Masterclasses	Inspiring future users	**200**
Medical Personnel	State-of-the-art treatment facility	Website, conferences, Meetings	Transnational Health Care, trained personnel	**50**
Patients	Available treatment alternatives	Brochure, Newsletter, TV, social medias, Website	Better quality of life and life expectancy	**2000**

[61] http://ec.europa.eu/research/social-sciences/pdf/communicating-research_en.pdf

HITRI*plus* project participants and users will be able to communicate with a range of audiences, taking into account their specific needs and modes of communication. *Table 4* depicts the targeted groups, their communication needs, and the expected impact of the HITRI*plus*' communication actions. HITRI*plus* outreach activities are destined to impact on a large part of the population. They will take into consideration ethical issues.

Stakeholders general outreach: HITRI*plus* **Flyer** will be produced at the beginning of the project. A **Brochure** will be published at the end of the project to highlight the research projects and results. Both will be distributed to all stakeholders, at conferences and workshops, science and technology fairs, internationally, and to government representatives in the respective countries. The HITRI*plus* **Website** will give detailed information about all participating institutions and the latest status of all network activities. The website will serve as a central collection point of debates, talks, courses, papers and posters presented by members of the consortium. **Dedicated** HITRI*plus* **Highlights issue** will be produced annually, distributed via email and published on the website.

Outreach to decision/policy makers: Relevant representatives from science/education and health sectors will be invited to the annual meetings of HITRI*plus*. Decision/policy makers in general, and in particular those coming from NE and SEE countries will receive regular HITRI*plus* communications/newsletters.

Outreach to general public through blogging and social media: Social media, especially in SEE, will be continuously used for dissemination. A professional and attractive HITRI*plus* webpage with an attractive **Logo** will be designed. HITRI*plus* NA coordinator will open specific accounts on Facebook, Twitter, LinkedIn, etc. The News-feed will focus on scientific results.

Outreach to general public through short video clips (YouTube) production: Short video stories and interviews of the users will be produced and made publicly available through the HITRI*plus*, ENLIGHT, SEEIIST and other partnering websites; social media platforms will also be used to broadcast success stories and research highlights delivered within the HITRI*plus* project. The early stage researchers will be encouraged to produce a two minutes video-clip using video-editing free tools, and post them through the YouTube channel, publicly available on social media.

Publishing articles/columns in newspapers and/or TV appearance: The project will be promoted through articles in daily/weekly press in the respective countries. Also, some contents about HITRI*plus* progress will be made available on the institutional publications such as the CERN Courier and the communication organs of other partners. ENLIGHT network's publication - "Highlights" will dedicate one issue per year to the HITRI*plus* project outcomes and breakthroughs.

Outreach through Art: The HITRI*plus* outreach program will create dedicated events for the occasion of the European Researchers Night and for Public Open days at the local institutes by public talks of the leading scientists and young researchers from the HITRI*plus* project, presentations, exhibitions, web-stage reading of a theatre play performance or/and other web supported activities.

3. Implementation

3.1 WORK PLAN — WORK PACKAGES, DELIVERABLES

Table 3.1a *- List of work packages.*

Work package No	Work Package Title	Lead Participant No	Lead Participant Short Name	Person-Months	Start Month	End month
WP 1	Project management	1	CNAO	73	1	48
WP 2	Networking and communication, dissemination and Outreach	13	SEEIIST	69	1	48
WP 3	Clinical networking	10	MEDA	94	1	48
WP 4	Innovation, technology transfer, industry relation	4	CERN	47	1	48
WP 5	Education and training	14	UM	22	1	48
WP 6	Transnational access (TA)	7	GSI	68	1	48
WP 7	Advanced accelerator and gantry design	4	CERN	144	1	42
WP 8	Superconducting magnet design	9	INFN	108	1	36
WP 9	Advanced beam delivery	7	GSI	75	1	44
WP 10	Multiple energy extraction system	8	UKHD/HIT	42	1	36
WP 11	Controls and safety	6	CSL	56	1	48
WP 12	Radiobiological dosimetry and QA	15	UMR	36	1	48
		Total persons months		834		

Table 3.1b *- Work Packages description.*

WP number	WP1		**Lead beneficiary**		CNAO		
WP title	**Project Management**						
Participant nr.	1	4	13	7	-	-	-
Participant	CNAO	CERN	SEEIIST	GSI	-	-	-.
Person months	62	5	4	2	-	-	-
Start Month	1		**End month**		48		

Objectives

- Manage and monitor project progress, take corrective actions and assure respect of contractual terms and project deliverables
- Manage decision-making bodies and advisory boards
- Organise meetings to enable collaboration and management of the activities and partners
- Ensure accurate and timely distribution of funds
- Ensure accurate and timely reporting on activities
- Ensure accurate and timely external audits

Description of Work

WP1 ensures the implementation of the project and the contractual obligations towards the EC. This activity implies the overall technical, administrative, financial and legal coordination of the project. The role and activities of the overall coordinator concern the monitoring and management of the agreed deliverables and milestones in the contract and the smooth running of the project as a whole. The coordinator is supported by the Central Project Office (CPO) that will take care of daily activities concerning the administrative and financial aspects of the project.

The Coordinator (CNAO) is supported by a deputy Coordinator (CERN) and by three pillar-coordinators, from SEEIIST, GSI, and CERN respectively. The pillar coordinators will monitor progress inside their pillar and will report to the Technical Project Board, where overall progress is evaluated and the ongoing activities, the deliverables, the milestones, the potential risks rising up are discussed, managed and mitigated.

In case of any serious digression from the agreed deliverables/milestones which may affect the overall aims of the project, the Coordinator will bring the problem and the alternative solutions to the attention of the General Assembly for decision.

Task 1.1: Coordination of Contractual, Financial and Administrative Aspects (*CNAO, CERN*)

In this Task, the Coordinator with the support of the CPO will oversee and coordinate the contractual, financial and administrative aspects of HITRI*plus*, including preparation of the Consortium Agreement. The Deputy Coordinator will provide contact with the EU administrative team at CERN that has a wide experience in dealing with the administrative aspects of H2020 projects. The Task will consist of administrative, legal and financial management including support to partners, management of financial records, fund distribution, coordination of annual cost claims and any contractual coordination. The Coordinator will enforce agreed rules and will support the WP Leaders through the Technical Project Board in ensuring that their WPs proceed smoothly and their respective Tasks are implemented as approved.

Task 1.2: Scientific and Technical Management (*CNAO, SEEIIST, GSI, CERN)*

The Task activities will include (but are not limited to): (1) setting up the General Assembly (GA) and the Advisory Bodies: the External Scientific Advisory Board (ESAB) and the Advisory Board for Ethical/Legal/Industrial Issues (ABELII); (2) checking the scientific relevance of all reports in relation to Grant Agreement requirements and needs; (3) implementing recommendations/inputs and return information to the GA and to the Advisory Bodies, (4) monitoring all technical work and milestones to ensure that timely EC reporting, deliverables and results are achieved with the highest quality. In this Task, the Coordinator will be supported by the Pillar Coordinators.

The preparation, maintenance and enforcement of the working plan will include a monitoring system for use across the HITRI*plus* project to ensure that the technical development follows the "3 O's" principles (Open Science, Open Innovation, Open to the World) and facilitates open innovation across Europe, but also in particular for stakeholders in the SEE countries. In addition, a Data Management Plan will be developed early in the project's life-cycle. Clear guidelines will also be prepared early in the project on open data and data sharing through the European Data cloud in order to promote international cooperation in the research community.

Task 1.3: Coordination of Participants, Communication and Meeting Organisation (*GSI, SEEIIST, CNAO)*

This task will focus on the coordination and consistent implementation of communication tools, in strict relation with WP2, and activities between the project partners. It will also monitor the preparation, maintenance and regularly update of items like access to data, future-proof data filing and storage conventions, data privacy and confidentiality, etc. A common archive repository, real-time communication tools and online workspace for documents (i.e. organisation of agendas, minutes and action lists, knowledge management etc.) will be implemented. The task also involves the organisation (and proper documentation) of the internal project meetings related to the technical work, incl. the Kick-off meeting, the end-of-project conference, the GA meetings, TPB,

ESAB and ABELII meetings and the annual HITRI*plus* meetings. Agendas and meeting minutes will be drawn up for all meetings. An expert in science communication from GSI will lead the Task and will be supported by SEEIIST and by the CPO based at CNAO.

WP1 Deliverables

Title	Delivery Month
D1.1: All governance boards installed	1
D1.2: Plenary meetings reports	3, 13, 25, 37, 48
D1.3: Data Management Plan	6

WP number	WP2		**Lead beneficiary**		SEEIIST		
WP title	**NA1 - Networking and communication, dissemination and outreach**						
Participant nr.	13	1	10	4	14	-	-
Participant	SEEIIST	CNAO	MEDA	CERN	UM	-	-
Person months	52	6	4	4	3	-	-
Start Month	1		**End month**			48	

Objectives

The Networking and dissemination, communication and outreach Work Package will organize and implement efficient communication inside and outside the consortium. These activities shall enhance the internal synergies and provide added value by allowing information flow to/from other projects and the general public as well as within HITRI*plus*. WP2 will equally support WP1 for internal communication and follow-up of HITRI*plus* results. The objectives of WP2 are the following.

- To create and maintain the HITRI*plus* web site as a platform for internal and external communication and dissemination and outreach, and provide linking to the other related networks such as INSPIRE, ENLIGHT, PTCOG through common events and workshops.
- To coordinate and publish a periodic and a final HITRI*plus* report.
- To inform medical and research communities about the existence and actions of Transnational Access and contribute to create awareness on heavy ion therapy.
- To contribute to establishing an efficient clinical network, around the ion therapy centres acting as hubs, for the effective and efficient patient selection and recruitment.
- To maintain and to give evidence and open access to the database of all the scientific publications coming in particular from JRA WPs.
- To promote and communicate outcome of research activities, both of TA and JRA, among the HITRI*plus* WPs and to external community.
- To promote awareness and understanding of heavy ion therapy needs of particle therapy in the community at large, which includes industrial beneficiaries, academics in other related fields and projects, by organizing outreach events such as talks, lectures, webinars, workshops, and wider outreach via the social networks.

Description of work

Task 2.1: Coordination of Communication tools *(SEEIIST, CNAO)*

The purpose of this task is to oversee and coordinate all aspects of the communication activities of HITRI*plus* and ensure its consistency with the project planned timeline (HITRI*plus* Gantt chart). To perform this transversal coordination, an interface among WP2, the other NA WPs and WP1 will be put in place and will be objective of annual reporting.

Website/Communication platform

In order to facilitate the efficient communication among the HITRI*plus* partners a dynamic and interactive website will be provided from the kick-off of the HITRI*plus* project and will be permanently upgraded. The internal HITRI*plus* platform will facilitate exchange of information, documentation, communication, yield access and secure data exchange among all the partners. The public (external) section of the website will reveal a detailed and frequently updated information about the HITRI*plus* project activities for all stakeholders and their role in the project. It will also offer an Open Access Portal so that the outputs, data, and standards resulting from this project will be made available to the wider community and act as an Innovation Gateway for the clinical community, industry and other stakeholders to benefit from its research activities. The electronic communication platform will facilitate the distribution lists for the project participants, Pillar co-ordinators, WP leaders, Committees etc, available to all participants in order to share information. Through the website the project news will be circulated to the external community via a periodic newsletter (Task 2.3).

Monitoring international research activities in ion therapy

Communication/outreach activities across the European and International accelerator community will be pursued. Last scientific communications and publications of the best practices will be shared and disseminated via the web-platform.

Communication improvements

Actions for improving communications/outreach activities will be identified and promoted among the partners creating an internal communication platform within the project, as well as external communications interface, and the www infrastructure for the broader coordinating activities of the WP via tasks 2.2, and 2.3.

Task 2.2: Building the user community *(CNAO, SEEIIST, MEDA, UM)*

The intention of this task is to create a network (all participants) of oncologists, researchers and specialists, present and future users who can become part of the European heavy ion therapy community network and access to TA. To achieve this goal at the very beginning of the project's lifetime, a database of all experts in radiation therapy and potential users of the beam-time for various disciplines of research will be brought together and fed into the internal HITRI*plus* web-site platform.

Multidisciplinary workshops

The most efficient tool for creating a community is to organize multidisciplinary workshops gathering all the different scientific communities (oncologists, radiologists, physicists, biologists, biomedical engineers), which is necessary for brainstorming, bearing new ideas, successful development and creation of technological improvements in ion therapy at a European level. One general workshop will be organized once per year possibly in connection with already existing networks (ESTRO, PTCOG etc), giving the possibility for all the Beneficiaries to meet, discuss common problems and initiatives, and present the results of their collaborations.

Task 2.3. Dissemination and outreach (*SEEIIST, CNAO, CERN*)

This task is dedicated to disseminate the project results outside of the consortium via the following channels: scientific publications of the activities performed, periodic technical reports, conference presentations, journal

publications and monographs. Guidelines will be distributed to all partners early in the project to ensure strict implementation of the three O's, and these will be monitored by examining all the information that is disseminated by the project. Guidelines will include considerations on publication vs IP protection, technology innovations explained to the layperson (starting from the material prepared for industry), technology highlights for general-public reports, etc.

Dissemination of the HITRI*plus* results will be done at project meetings and workshops, and via internal reports. The results will be also shared among the stakeholder using the HITRI*plus* web-portal/platform.

The HITRI*plus* website will be designed to communicate a dedicated calendar of the HITRI*plus* organized outreach events, published for each year in advance. Furthermore, HITRI*plus* Newsletter will be issued twice per year. This publication will give non-expert level details of all actions, events, new technical developments, results and statistics that were delivered by HITRI*plus*. The Newsletter will be available on the website and will be distributed to policy makers interested parties, clinical and industrial stakeholder communities during conferences and workshops.

Outreach will be enabled through the HITRI*plus* public website, disseminated by the powerful social networks such as twitter, Instagram, FB, interviews, short YouTubes, clips and popular publics talks).

Also, the HITRI*plus* participants (especially the early stage researchers and students) will proactively engage in European Researchers Nights, Open days at the ion therapy facilities and at international centres such as CERN, GSI and regional events at participant country national levels, to communicate the HITRI*plus* results and increase the public awareness.

WP2 Deliverables

Title	**Delivery Month**
D2.1: Dissemination to the community about the possibility of the TA and access to clinical and research activities	3
D2.2: Dissemination and outreach plans developed and regularly updated	2, 12, 24, 42
D2.3: Provide an annual activity report for the NA Pillar and final scientific achievements including the use and dissemination of foreground	12, 24, 36, 46

WP number	WP3		**Lead beneficiary**		MEDA		
WP title	**NA2 - Clinical networking**						
Participant nr.	10	8	1	11	-	-	-
Participant	MEDA	HIT	CNAO	MIT	-	-	-
Person months	19	25	33	17	-	-	-
Start Month	1		**End month**		48		

Objectives

- Review preclinical data to identify promising novel approaches to exploit heavy ion therapy advantage
- Design one trial as a template for bringing innovative heavy ion therapy approaches in the clinics
- Establish shared protocols for clinical TA and favour the recruitment of patients at the existing ion therapy facilities (WP6)
- Set up a European registry to collect data on rare cancers treated with heavy ion therapy
- Review existing data on OARs dose constraints in use in the clinical facilities
- Perform pooled data analysis to validate constraints on critical OARs

Description of Work

Task 3.1: Trial design for innovative use of heavy ion therapy *(MEDA, HIT,CNAO, MIT)*

Mature clinical data of heavy ion therapy safety and efficacy are available. This task will focus and document the list of pathologies that are treated at the existing carbon ion facilities participating in HITRI*plus* and will collect from each centre the inclusion criteria for patients recruitments in order to favour the efficient transnational access of patients (WP6) to the existing ion therapy facility. All these data were obtained using heavy ion therapy (alone or as a boost) for tumours that were perceived as radio-resistant and trying to deliver a uniform RBE-weighted dose. Preclinical data suggest that there might be a potential in using heavy ion therapy with different approaches. A non-comprehensive list of promising new concepts includes: optimizing LET distribution besides RBE-weighted dose, using heavy ion therapy to achieve re-oxygenation and/or to deal with residual hypoxia in a negatively selected subset of high incidence diseases not normally considered for heavy ion therapy, exploiting heavy ion therapy immunogenicity with non-conventional temporal and spatial fractionation (with or without immune-modulating drugs). Within this task, potential innovative approaches will be reviewed and the most promising for clinical use will be selected. One prospective study of innovative heavy ion therapy use will be designed and it will serve as template for future studies.

Task 3.2: European registry of heavy ion therapy patients *(CNAO, MEDA, HIT, MIT)*

Heavy ion therapy is a mature and established treatment modality; nevertheless, several aspects (including indications and real advantages in comparison with alternative options) remain controversial. Prospective trials are ongoing, however considering the rarity of some of the disease treated and the scarcity of clinical centres several patients (especially those referred from other countries) are not treated within trials. Each heavy ion therapy patient should also be a learning opportunity. A European heavy ion therapy patients' registry would provide real world data that could supplement classical trials to build a more solid evidence. Within this task commons semantics will be developed focusing on key issues relevant for heavy ion therapy such as: treatment reporting according to ICRU-93, sub-stratification of locally advanced stage tumours (e.g. TNM skull base T4b tumours should be distinguished according to brainstem involvement/compression), toxicity and quality of life reporting. A web based tool will be developed, leveraging on the already existing cooperation between participants and the European Reference Network on Rare Adult Solid Cancers (EURACAN). Follow up data will be collected also through telemedicine approach, in cooperation with the ESMART consortium.

Task 3.3: European agreement for OARs dose constraints with heavy ion therapy *(HIT, MEDA, CNAO, MIT)*

Dose constraints for OARs are critical for the outcome, both in terms of toxicity and of local control. European institutions use different sets of dose constraints based on specific experiences. Comparison between European and Japanese institutions is made more complex by the use of different fractionations schedules and different RBE models. Within this task, institutional internal dose constraints will be reviewed. A list of critical OARs will be created (tentative list includes optic pathways, brainstem, spinal cord and brain parenchyma) and one OAR will be selected for a pooled analysis. Patients relevant for this analysis are those for which: long-term follow up, treatment plan, and consent to use data in anonymized form are available. Treatment plans (and follow up images if needed) will be uploaded in the database created within EC-FP7 project ULICE and managed by HIT. A pooled analysis of observed toxicity will be performed and a recommendation for OAR dose constrains will be given. Toxicity will be analysed not only focusing on dosimetric data, but also considering patient-related factors (for example comorbidities, smoking, previous surgery, etc.) as potential modifiers of the dose-response curve.

WP3 Deliverables

Title	Delivery Month
D3.1: Review of promising innovative heavy ion therapy approaches to be brought to the clinics	24
D3.2: Trial protocol for innovative heavy ion therapy concept	36

D3.3: Web based heavy ion therapy patient registry	36
D3.4: Dose constraints of OARs in use at European heavy ion therapy facilities	18
D3.5: Recommendations for dose constraints on one OAR based on pooled data analysis	48

WP number	WP4		**Lead beneficiary**			CERN	
WP title	**NA3 - Innovation, technology transfer, industry relation**						
Participant nr.	4	9	7	-	-	-	-
Participant	CERN	INFN	GSI	-	-	-	-
Person months	39	4	4	-	-	-	-
Start Month	1		**End month**			48	

Objectives

The overarching objective of WP4 is to devise and implement a roadmap for the industrialisation of the innovative ion therapy technologies developed by the HITRI*plus* project. Indeed, a limiting factor for the broader availability of ion therapy as a treatment modality is the lack of commercial turnkey solutions, while proton therapy is a solid market reality.

In order to ensure a successful uptake by the European industry of the HITRI*plus* developments in accelerators, gantries, superconducting magnets, beam delivery and control systems, WP4 aims at:

- identifying the most promising technical developments;
- devising and implementing the most adequate technology transfer routes, giving due considerations to Intellectual Property matters; such routes will extend beyond traditional approaches (e.g. patents) to open-access licensing schemes (e.g. CERN Open Hardware Licence) and co-development with industries;
- proactively promoting the selected technology innovations in order to gather industrial interest and feedback;
- establishing proactive relationships with the relevant industrial actors in order to successfully industrialise the HITRI*plus* technologies.

All WP4 partners have dedicated Technology Transfer offices with the necessary experience to support the work plan and to achieve these objectives. Tight links with the HITRI*plus* JRA work-packages (WP7-WP12) will ensure an effective internal communication about the technologies being developed.

Description of Work

Task 4.1: Technology overview/assessment *(CERN, GSI, INFN)*

The activities of this task include:

- building a complete picture of the innovations being developed in HITRI*plus*;
- advising on IP matters, including patenting opportunities;
- evaluating the feasibility and optimal routes for technology transfer;
- identifying the key industry players in the corresponding markets for the various technologies;
- providing a list of follow-up actions and recommendations both for the consortium as a whole and for Tasks 4.2 and 4.3 for a successful valorisation of the HITRI*plus* technologies.

The results of these activities will be documented in an internal report that will be periodically updated.

A dedicated HITRI*plus* Technology Overview committee will be organized within the WP4 and will allow to perform the work swiftly and efficiently, and to streamline the internal communication about new technology disclosures. This committee will be composed of the WP4 participants and the leaders of WP7-WP12 (the work-packages where the technologies are developed), it will meet twice a year and exchange regularly.

Task 4.2: Technology promotion *(GSI, CERN, INFN)*

This task focuses on:

- developing "Value propositions" promotional text and visual material highlighting the benefits of the technologies developed and the competitive advantage they have over what is already existing on the market.
- proactively reaching out to the relevant industrial stakeholders identified in Task 4.1.

The marketing and promotion activities within this task will leverage on the instruments (newsletters, websites, events) provided by, inter alia, the TT Offices of the project partners and several networks in which the WP4 partners are already active. These will include: the CERN Knowledge Transfer (KT) Forum, which brings together CERN's KT group, including the KT Officer, and KT representatives from CERN Member and Associate Member States; the Enterprise Europe Network (EEN), an EC network helping small businesses to make the most of the European marketplace; HEPTech, a network operated by TT and KT professionals from large scale High-Energy-Physics projects and research facilities in Europe aimed at enhancing technology and knowledge transfer from fundamental research in physics to society; the TTO (Technology Transfer Offices) Circle, which is an initiative of the Joint Research Centre of the European Commission aiming at connecting Technology Transfer Offices of large European public research organizations.

The HITRI*plus* technologies will also be promoted at selected industry events at relevant conferences (e.g. PTCOG, ESTRO).

Task 4.3: Technology matching *(INFN, CERN, GSI)*

The activities in this task include:

- follow-up of the industrial contacts established through the activities of Task 4.2;
- organisation of an event in year 2 of the project, also in collaboration with design schools, entrepreneurship schools and business admin schools, with the aim of providing input for optimal continuation of the R&D activities in order to optimise the potential for knowledge transfer;
- organisation of an ad-hoc "HITRI*plus* meets industry" event in year 3, to foster the adoption of the HITRI*plus* innovations by traditional companies and entrepreneurs.

WP4 Deliverables

Title	Delivery Month
D4.1: Internal report on the HITRI*plus* technologies and dissemination plan	14, 28
D4.2: Value propositions promotional text	18, 28
D4.3: Organisation of a technology matching event	36

WP number	WP5		**Lead beneficiary**		UM		
WP title	**NA4 - Education and training**						
Participant nr.	14	13	1	7	4	-	-
Participant	UM	SEEIIST (UKIM, CMSM)	CNAO	GSI	All HITRI*plus* partners	-	-
Person months	6	8	1	7	-	-	-
Start Month	1		**End month**			48	

Objectives

- Educate and provide hands-on experience to a new generation of researchers so that they acquire appropriate skills allowing them to optimally access and exploit (even virtually) all the essential tools of European heavy ion therapy research infrastructures.
- Provide researchers from academia and industry of a multidisciplinary background, including researchers not necessarily directly involved in heavy ion therapy, with updated and appropriate knowledge on heavy ion therapy research and the activities and potential of the four major European heavy ion therapy and research

infrastructures.

- Organise specialised courses and masterclasses on heavy ion therapy research delivered by leading scientists and engineers which will broaden the view and increase the understanding in the field.
- Organise secondments and internships for participants to gain first-hand experience in research at the European heavy ion therapy research infrastructures, so that they can become facility users and learn best practices.

Description of Work

Task 5.1: Specialised courses on heavy ion therapy research and infrastructure *(SEEIIST (UKIM, CMSM), UM, CNAO)*

This Task will provide two specialised one-week training courses on heavy ion therapy research and related infrastructure. These will be targeted towards a new generation of researchers that may become part of the starting heavy ion therapy research community. These include postgraduate university students, postdocs and researchers from academia and industry as well as oncology practitioners who are either from a wider multidisciplinary community or who are not directly involved in heavy ion therapy research. Amongst others, the courses will include topics on: heavy ion therapy concepts, clinical practice of heavy ion therapy, accelerator technology and beam physics for heavy ion therapy; accelerated heavy ions in radiobiology and medical physics; the heavy ion therapy data platform; safety aspects of heavy ion therapy; compliance to European regulations and standards; certification strategies of medical accelerators and medical physics commissioning.

To avoid duplication of efforts, the courses' content will complement already existing courses in the fields after conducting a gap analysis. They will be purposely designed to: i) provide a solid foundation of heavy ion therapy; ii) help appreciate the leading-edge and multidisciplinary research potential of the field made available to the wider user community; iii) highlight the new, more advanced, harmonised and complementary services that the European heavy ion research infrastructures provide; iv) inform about the wider, simplified and more efficient access procedures and interfaces to the European heavy ion therapy research infrastructures with particular focus on virtual access to conduct research irrespective of location; v) include innovative industrial applications hence contributing to enhancing the innovation capacity of the field that may ultimately lead to the creation of new market opportunities and the strengthening of competitiveness and growth of companies, and; vi) include discussions on new heavy ion therapy machine designs that optimise power consumption to increase financial and environmental sustainability (including lower impact on climate change).

The courses will be delivered by leading European scientists and engineers from the main European heavy ion therapy research infrastructures as well as other leading European research institutes and universities. They will also be delivered by specialists from associated or other third countries particularly when these offer complementary or more advanced services than those available in Europe. The latter will also help foster the use and deployment of global standards.

The courses will be held back to back with HITRI*plus* annual general project meetings or ENLIGHT meetings to maximise resources and impact. A minimum of 20 participants for each school will be selected through a merit-based equal opportunity (including gender equality) European-wide call, so that the best candidates optimally develop and put to good use their skills and potential for the benefit of society. A joint SEEIIST (UKIM, CMSM), UM, CNAO Programme Committee will define the courses content whilst SEEIIST (UKIM, CMSM) will take lead responsibility for the organisation and marketing of the courses. All HITRI*plus* partners will provide suggestions for courses content and will suggest or provide appropriate leading scientists and engineers to deliver the lectures.

Task 5.2: Masterclasses on heavy ion therapy research and infrastructures *(GSI, UM)*

This Task will complement the specialised courses providing hands-on training in the form of 4 single-day masterclasses sessions on heavy ion therapy research and related infrastructures. Each one will be performed simultaneously in 3 European institutes with about 10 to 15 postgraduate university, postdocs and early stage researchers (i.e. total of between 120 to 180 students/early stage researchers). They will include lectures by leading scientists, mostly from the European heavy ion therapy research infrastructures and institutes, on topics spanning

from the physics of heavy ions and interactions with matter, to their use in medicine, highlighting applications for health, industry, space research and their contribution to an innovation society. This will be followed by hands-on exercises where the attendees perform a task related to heavy ion therapy research, as done in heavy ion therapy infrastructures, based on an open source research toolkit for heavy ion treatment planning. The day will conclude with video conferencing between the 3 participating institutes of the day, moderated by one of the European therapy centres to discuss results and open questions with the experts of the field. Furthermore, another 2 train-the-trainer masterclasses will be specifically dedicated to train early researchers on how to setup and perform the masterclasses, motivating them to deepen their knowledge on the field and on the specific tools and providing them with the expertise to continue organising these masterclasses sustainably It will also provide them with the opportunity to enhance their ability to network and collaborate with each other and with experts from the major European heavy ion therapy research infrastructures to continue organising these masterclasses sustainably. These training sessions will be associated to the specialised courses of task 5.1. Thus another 40 young researchers will be trained Europe-wide and will be ready to also transmit their acquired knowledge on accessing the European therapy centres. The 6 planned masterclasses sessions will be targeted primarily towards students and early stage researchers who show strong promise and interest in becoming part of the starting heavy ion research community and who may then optimally exploit and access the European heavy ion therapy research infrastructures. The participating students and early stage researchers will be selected through a merit-based equal opportunity (including gender equality) open call to the whole European community and to the Balkan states in the context of the new heavy ion therapy research SEEIIST initiative. While the selection of participating institutes will be on a first come first served basis, several institutes, in addition to the HITRI*plus* partners, have already declared interest, among them, in Germany (DKFZ Heidelberg, LMU Munich), Greece (AUTh), Poland (WUT), BiH (UNSA), Lithuania (Vilnius and Kaunas universities). This multifaceted approach has the potential to train the new generation of scientists not only as best equipped researchers and tutors of the next generation but also to become the "messengers" to society and policy makers, clearly demonstrating the benefits of integrated multidisciplinary communities and heavy ion therapy research. GSI will take the lead in organising the masterclasses with input from UM.

Task 5.3: Provide e-learning course material on heavy ion therapy *(UM, SEEIIST (UKIM, CMSM), GSI)*
This Task will convert the specialised courses (Task 5.1) and masterclasses (Task 5.2) on heavy ion therapy research and infrastructure into e-learning courses aimed at a new generation of researchers that may become part of the starting heavy ion therapy research community. This will guarantee the sustainability of these education and training activities. The main elements of the task will be to: study existing e-learning initiatives in relevant sciences and engineering disciplines and draw lessons to guide the design of the proposed course; study e-learning tools and choose the most appropriate tool for the implementation of the courses; record the material of the courses and run the courses in test mode; define the resources needed to launch, maintain and run the courses on a sustainable basis. To improve comprehension, illustration by multimedia content will be utilized. UM will take lead responsibility to draw up the e-learning course with input from SEEIIST (UKIM, CMSM) and GSI.

Task 5.4: Secondments and internships to heavy ion therapy research infrastructures *(UM, CNAO)*
HITRI*plus* will provide opportunities for postgraduate university students, postdocs, researchers from academia and industry, oncologists, and researchers who are close to but who are not necessarily involved in heavy ion therapy, to spend a few weeks at one of the European heavy ion therapy research infrastructures and hence gain hands-on experience. These secondments (for employed researchers/practitioners) and internships (for students) will provide a first-class unique scientific opportunity to join the day-to-day work of research teams and participate in heavy ion therapy experiments and learn best practices. In addition, these secondments and internships will enable participants to eventually become facility users by helping them gain first-hand transdisciplinary knowledge on how these facilities can be used for their research. A combined total of 45 weeks of secondments and internships will be offered. The participants will be selected through a merit-based equal opportunity (including

gender equality) open call to the whole European community. UM will take responsibility of organising the secondments and internships with assistance from CNAO.

WP5 Deliverables	
Title	**Delivery Month**
D5.1: Delivery of specialised training courses	12, 24
D5.2: Delivery of masterclasses and train-the-trainer masterclasses	12, 24, 36, 47
D5.3: Provision of e-learning courses	18, 30
D5.4: Organisation of secondments and internships: calendar of events	6, 24

WP number	WP6		**Lead beneficiary**			GSI	
WP title	**Transnational Access (TA)**						
Participant nr.	1	7	8	10	11	-	-
Participant	CNAO	GSI	UKHD/HIT	MEDA	MIT	-	-
Person months	4	51	4	5	4	-	-

Start Month	1	**End month**	48

Objectives:

WP6 is dedicated to providing TA to research rooms in Heavy Ion centres in Europe. Main objectives are:

- Manage the provision of access to beam time allocation across TA providers
- Review the TA proposals
- Perform TA for selected project
- Facilitate the modality of access for the users
- Describe possible research activities in TA
- Involving TA users from the SEE research community
- Select and support the experiments for TA
- Support new users with little background in Heavy Ion Therapy to undertake experiment

Description of work

Task 6.1 and 6.2 Provision of Access, Review of Proposals, Modality of Access *(GSI, CNAO, UKHD/HIT, MEDA, MIT)*

Each TA provider will have a TA contact researcher of facility who will be responsible for the TA provision on site. The TA researcher will report to HITRI*plus* TA WP leader (Prof. Dr. Marco Durante). The process of getting access to TA for the users starts by filling out an online form (at the HITRI*plus* website). A specific HITRI*plus* TA Helpdesk will be set up within this task to assist users: in case users are not clear of their requirements for the application or which TA provider will best suit their needs. On the online form they will be asked to provide relevant information and will be instructed explicitly on how to most efficiently fill the form including the following details:

a) a short description of the project, including a research hypothesis and why they need access to HITRI*plus*;

b) which TA (s) they require access to, this will also include details of the required experimental parameters, e.g. beam energy(s), beam current, dose rate, fluence(s), end-station and target requirements etc.;

c) expected outputs;

d) next steps, for example possibility for grant applications or commercial exploitation, if the work is successful, potential impact of the project; short lay summary.

When a TA proposal is submitted the TA WP lead will check with the TA provider contact researcher if they have the capacity and infrastructure to perform the experiments described in the application. The users are

advised to select at least two TA in their application form. In a worst case scenario when the first TA provider cannot provide this assurance, the TA lead will contact the next TA provider listed from the user. This will prevent delays on the TA requests. When a TA provider has guaranteed the assurance to the TA WP lead, the application will be reviewed by the User Selection Panel (USP). The USP will be made of international experts nominated by the WP Coordinator, in consultation with the Project Coordinator and the General Assembly. The USP members will be international experts, at least half of them independent from the HITRI*plus* beneficiaries. The Work Package Coordinator will chair the USP. The USP will assess the proposal for TA in terms of technical and scientific excellence, and future potential and impact. The USP will use the TA HITRI*plus* website to conduct their reviews and score the proposals. When significantly different scores are presented from the members of the council, USP will organise a meeting (preferably teleconference) and will discuss to reach a consensus.

Although some of the TA providers (CNAO, HIT, MEDA, MIT) can deliver protons as well as heavy ions, the USP will accept only proposals concerning experimentation with ions (from helium to heavier species). In exceptional cases, for example for calibration purposes, a proton experiment can be considered and in this case the USP will contact the management of the INSPIRE IA project, to verify that the experimentation is not already covered in their programme and to have the endorsement of INSPIRE for the specific proton experiment. In any case, the clinical TA will concern only ions.

The application feedback will be given within 4 weeks after the submission. Once a proposal is accepted it is then transferred to the requested TA provider who will be in touch with the user to arrange a time period for experiments. In the case of declined proposals, users can re-apply for TA by using the feedback to improve their proposals. The local TA researcher at the TA provider is then responsible for its management (allocating beam time etc.), communication with the user and communicating progress with the TA WP leader. In the unusual situation of a major breakdown of the equipment at the TA provider site, the local TA provider will contact the TA WP leader to find another provider where the experiments can be undertaken. Users during their TA experiments will need to be aware of the normal operating rules of each TA provider. Many of the research rooms exist within clinical facilities and so users will need to be instructed about local operation and safety rules and protocols. It is expected that normally outputs resulting from TA will have authors who are users and authors who are TA providers.

Feedback from users will go to the TA Manager who will discuss with the TA provider upon receipt. The TA provider will be expected to provide a response to any negative comments within 10 working days. The TA manager will report on TA management meetings. At these meetings TA will be monitored and discussed, the meeting will also look at the breakdown of TA by member states; industry, academia and clinical usage, user by gender; users in terms of experience (to ensure new users are coming forward).

The main means of communication will be emails, HITRI*plus* website, teleconferences and meetings. In addition, the contact person from the TA providers will take part in the regular management meetings, which occur every six months. These management meetings will combine discussion of NA, TA and JRA activities. The first of these will be at the kick-off meeting. At the mid-term meeting and two subsequent annual meetings, the management meeting could be combined with a workshop of presentations from HITRI*plus* TA users. These meetings will also be attended by the HITRI*plus*' External Scientific Advisory Board (ESAB) some of whom will also be part of the USP. The TPB will provide a critical evaluation, feedback and suggestions on the strengths and weaknesses of HITRI*plus*' TA. The ESAB will also assess the feedback from users and discuss ways in which TA provision can be improved. The ESAB will look at how research from JRA is being made available to TA and when the new providers of TA will come online. The ESAB will also look at the proposals being accepted by the USP and the turnaround times from submission to acceptance and then how long it takes to start TA.

The TA WP leader will prepare reports for each TA related management meeting. Special attention will be paid to the performance of TA activities with respect to the aims, milestones and deliverables set out in the HITRI*plus* proposal. In addition, the following will be assessed in the TA management reports:

- Numbers of proposals submitted, reviewed and approved.

- Reasons why proposals were declined and what is their evolution and current status.
- Hours provided by each TA provider and how it corresponds to the TA outlined in the proposal.
- Attraction of new users across Europe including the ones with little background in heavy ion therapy research such as users from the SEE region.
- Feedback from users.
- Industry / clinical impact: TA participation with industry / hospitals.
- Outcomes (publications / grants / patents etc.) resulting from HITRI*plus* (in later stages of HITRI*plus*).
- Outcomes involving sharing software or data generated through HITRI*plus* (in later stages of HITRI*plus*).
- Transfer of JRA activities into TA portfolio (in later stages of HITRI*plus*).

Description of capabilities and modality of access

The "Research Access" focus is the provision of TA in the research rooms of clinical heavy ion centres in Europe. The TA is offered in unit cost where the unit is 1 hour access time. *Table 5* defines the unit of access offered by each TA provider and the method used for costing. For all TA providers infrastructure the cost includes normal preparatory work and set up, any specific training needed, any subsequent work needed at the TA provider to analyse samples or results and transportation of samples back to the user and actual experimental beam time on target. It also includes the necessary QA. In the case of significant preparation, post irradiation analysis extra units may be charged to accommodate the cost of the work involved, or if significant costs are incurred in setting up the experiments.

The "Clinical" Access will be described in detail in Task 6.3. In this case, access units are "patients" to be treated in the frame of clinical trials, and the "users" are the physicians responsible for the patient. Description of the units are methods for costing are again given in Table 5. Below are listed the TA facility provider with a detailed summary description and

Table 6 provides a list of the services and devices of each TA provider.

Provision of access to the following infrastructure(s):

Description of the infrastructure (Partner 1) CNAO, Italy

Name of the infrastructure (and its installations, if applicable):

Centro Nazionale di Adroterapia Oncologica, CNAO

Location (town, country) of the infrastructure: Pavia, Italy

Web site address: https://fondazionecnao.it/

Description of the infrastructure:

CNAO is one of the four centres in Europe, and six worldwide, offering treatment of tumours with both protons and carbon ions. Besides three treatment rooms with four beam ports (three horizontal and one vertical), a fourth room dedicated to experimental activities is available at CNAO.

The CNAO synchrotron has been designed for particle therapy and provides energies up to 400 MeV/u for carbon ions (corresponding to a Bragg peak depth of up to 27 cm in water) and up to 227 MeV for protons (corresponding to a Bragg peak depth of up to 32 cm in water). The maximum proton energy available is 250 MeV. The minimum extraction energies are about 63 MeV and 115 MeV/u, for protons and carbon respectively, corresponding to particle range of 30 mm.

In all the rooms, the beam is distributed with the same modulated scanning system, providing irradiation field up to 200 x 200 mm2.

A new facility equipped with a proton synchrotron and a proton gantry is presently under construction on the CNAO site and will be operational in 2023 adding a fourth treatment room.

Furthermore, within the same period, the construction and installation of a third source will be completed and additional ions besides protons and carbon ions will be made available for research in the experimental room.

CNAO offers therefore a rare or even unique possibility of clinical and pre-clinical research and a friendly

environment where research can be conducted in a multidisciplinary environment with a broad range of competences.

Services currently offered by the infrastructure:

Research experiments are generally carried out at CNAO in the experimental room but in case of need (e.g. in case a vertical beam is needed) treatment rooms can be considered as well for special activities.

In the experimental room the beamline can be arranged in different configurations according to the needs in term of space downstream the target (e.g. for time of flight measurements) or in terms of field size dimensions.

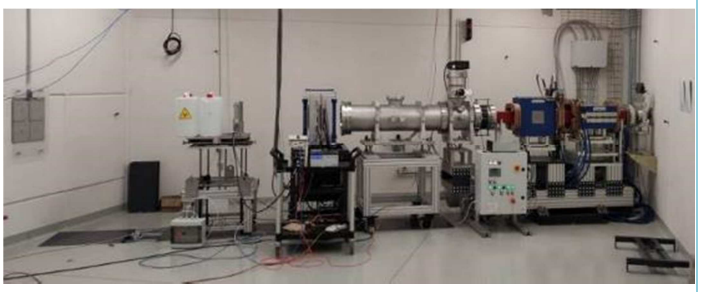

Figure 11 - *CNAO experimental beam line.*

CNAO offers the opportunity to external researchers to use its proton and heavier ion beams to perform basic and pre-clinical studies and to take advantage of the cell culture lab for sample preparation and processing.

In the experimental room a variable height table is available to host the targets and a water phantom for, e.g., in vitro irradiation is also available to users.

A set of water equivalent slabs to vary the particle range locally is also available in case of need.

Standard Farmer and Markus chambers can be made available for calibration and dosimetry on request with unidos and multidos electrometers.

CNAO uses EBT3 radiochromic films for internal use and is equipped with the hardware needed to read and measure them (film scanner).

In the experimental room trigger signals are available for synchronization with the accelerator when needed. Furthermore, point to point connections are available between the experimental room and the control room.

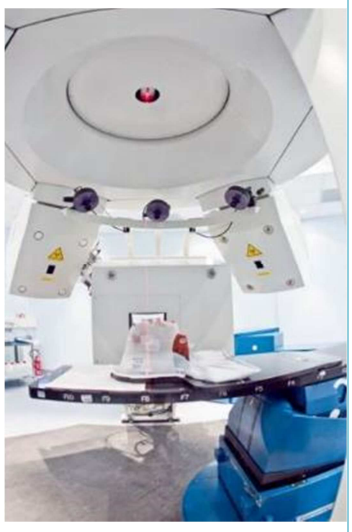

Figure 12 – *Patient positioning and position verification system in CNAO treatment room.*

Details and adaptations shall be discussed case by case starting from simple things like mechanical adapters and reaching even the beam delivery modalities that can be customized to the user needs (or at least it is possible to discuss about it) by modification of the in-house control software.

Access to biological laboratory equipped with laminar flows, chemical hoods, incubators, ultrafreezers, centrifuges, cell counter, etc. is available. In the next 2 years the research area will be expanded and the Radiobiology laboratories foresee new premises for a total area of about 250 square meters. This will include rooms dedicated to microscopy, cell handling, cytology/histology and small animals preparation available for TA.

Thanks to a strong collaboration with the University of Pavia, in CNAO is also possible to carry out in vivo irradiations with small rodents taking advantage of the nearby animal house facility, after technical evaluation and approval by the local ethical committee.

The use of the animal facility is not standard and will have to be considered as an additional cost.

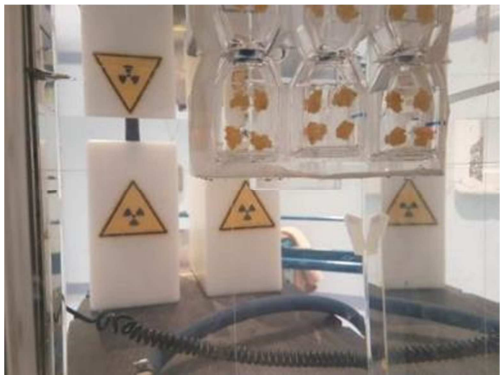

Figure 13 – *Example of in vitro irradiation set up at CNAO.*

Provision of access to the following infrastructure(s):

Description of the infrastructure (Partner 7) GSI, Germany

Name of the infrastructure (and its installations, if applicable):

GSI Helmholtzzentrum für Schwerionenforschung

Location (town, country) of the infrastructure: Darmstadt, Germany

Web site address: https://www.gsi.de/en/work/research/biophysics.htm

Description of the infrastructure:

GSI Helmholtzzentrum für Schwerionenforschung in Darmstadt is a worldwide unique accelerator facility for research purposes. Among approximately 1400 employees of GSI, more than 80 belong to the Biophysics department, which is a unique interdisciplinary collaboration of biologists, physicists, chemists, and technicians, leading in a broad range of aspects of heavy ion biophysics and ion beam therapy, from modelling the effects of ion beam radiation to first development of treatment planning for particles. GSI is the European ground-based lab selected by the European Space Agency (ESA) to perform research in biological effects of space radiation.

Services currently offered by the infrastructure:

Two accelerator facilities (heavy ion synchrotron SIS and linear accelerator UNILAC), providing ions from protons to uranium within a wide energy range, can be utilized for biomedical research.

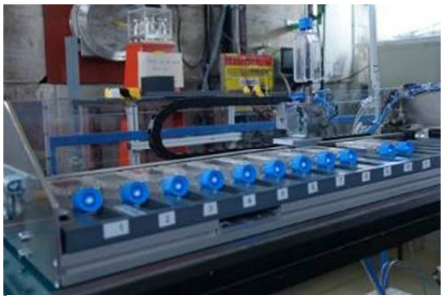

***Figure 14** – Example of in vitro irradiation set up at GSI.*

- SIS Caves A/M: high-energy irradiation facility with a horizontal beam, equipped with a spot scanning system, remote-controlled linear stages, Laser positioning system and optical telescope for sample adjustment, and remote-controlled TV surveillance system. Additional remote robotic system can be used to irradiate of biological samples inside multiple 25 cm^2 tissue culture flasks (see the photos).
- UNILAC: low-energy facility (energies up to 11.4 MeV/u), where cell monolayers samples can be irradiated in the BIBA (Biologische Bestrahlungs-Anlage) facility. Standard irradiations are performed in 35mm Ø Petri dishes. The samples are positioned in the beam by means of an automatic vacuum grabber system and placed back after irradiation in the magazine filled with cell culture medium; the maximum capacity of a magazine is 20 samples.
- X-ray tube (Isovolt DS1, Seifert, Ahrensberg, Germany).
- Fully equipped biological laboratories: cell laboratory (see the photo), tumour laboratory, DNA-laboratory, biochemistry laboratory, microscopy laboratory and qPCR room are located in the close proximity to the irradiation facilities. GSI Animal Facility will be available for TA. All the necessary equipment including laminar flows, chemical hoods, incubators, centrifuges, cell counters (Bio-Rad, Beckman Coulter), etc. is provided.

***Figure 15 –** Cell laboratory at GSI.*

QA equipment available for research:

- Water columns (developed at GSI, higher energies verification possible);
- Calibration tools (Farmer chamber);
- GSI analogue of IBA DigiPhant using a PTW Octavius 1500 XDR IC array detector

QA procedures in place are the beam calibration with Farmer chamber, dosimetry with parallel plate ionization chambers, beam profile and positioning monitoring with scintillation screen.

Provision of access to the following infrastructure(s):

Description of the infrastructure (Partner 8) HIT, Germany

Name of the infrastructure (and its installations, if applicable):

Heidelberger Ionenstrahl-Therapiezentrum, HIT

Location (town, country) of the infrastructure:

Heidelberg, Germany

Web site: : http://www.hit-centrum.de

Description of the infrastructure:

HIT is one of the four centres in Europe, and six worldwide, offering treatment of tumours with both protons and carbon ions, the treatment with helium ions is planned to start late in 2020. Besides two treatment rooms with horizontally-fixed beamlines HIT runs the world-wide first ion gantry. HIT offers an irradiation facility for pre-clinical research that delivers four ion species: protons, helium, carbon and oxygen ions.

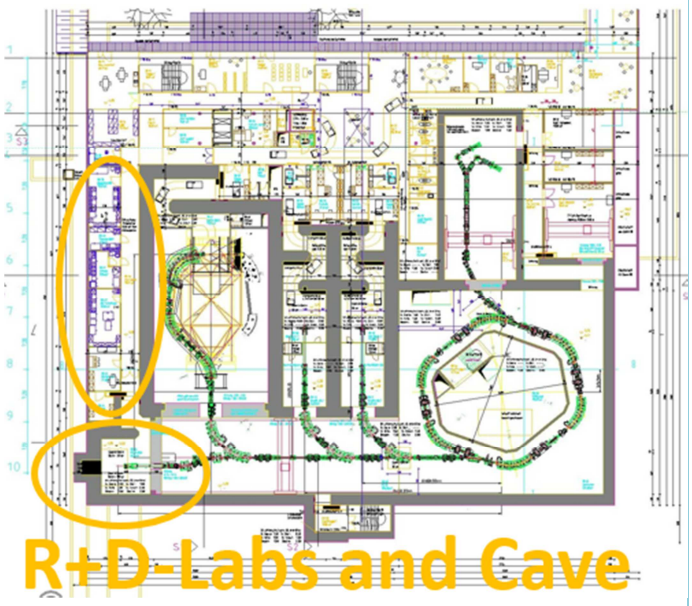

Figure 16 *- HIT layout: experimental room and labs.*

HIT's accelerator system provides energies up to 430 MeV/u for helium, carbon and oxygen ions and up to 480 MeV for protons. For all ions energy libraries are established that allow for millimetre range steps within the therapeutic window (Bragg peak depth between 2 and 32 cm in water). For protons and helium ions higher ranges/energies can be offered for research purposes. At HIT dose delivery is based on the intensity-controlled raster-scanning method. The maximum field size is 200 x 200 mm^2.

Figure 17 *- Nozzle and sample positioning system at the HIT facility.*

Within the centre labs for medical physics and experiment preparation are located directly at the research cave. Labs for radiobiology are hosted in the attached building for conventional radiation therapy.

The HIT facility is operated for more than 8000 hours per year and about 1000 hours are used for research. Groups located in Heidelberg as well as external researchers are running experiments (accelerator physics, beam delivery methods, medical physics, physical beam characterization, in-vitro and in-vivo radiobiology, materials research) using this infrastructure mostly in cooperation with the local team.

Services currently offered by the infrastructure:

HIT's irradiation facility offers the equipment to precisely position targets, detectors. Small samples can be remotely positioned in order to increase the effectiveness of experimental workflow. Large set-ups like telescopes of several meters can be used. The scanning nozzle of the research cave is identical to those being clinically used. The dose rate is adjustable and ranges from 10^3 up to 10^9 particles per second. The experiment support at HIT

helps to plan, test and run the experiment. A variety of planning tools ranging from Monte-Carlo codes to full-blown clinical treatment planning platforms are available to calculate plans for the irradiations.

Provision of access to the following infrastructure(s):
Description of the infrastructure (Partner 10) MEDA, Austria
Name of the infrastructure (and its installations, if applicable): EBG MedAustron GmbH
Location (town, country) of the infrastructure: *Wiener Neustadt, Austria*
Web site address: www.medaustron.at
Description of the infrastructure:
The centre is a limited liability company founded in April 2007 and is in the ownership of the state of Lower Austria, Austria. Around 190 employees from about 20 different countries are currently working on site in Wiener Neustadt, which is located south of Vienna. These include physicians, physicists, engineers, medical physicists, radiology technologists, and administrative staff. The core mission of the facility is the operation of an outpatient clinic for ion-beam therapy. In addition, MedAustron acts as the manufacturer of the medical accelerator providing the particle beams. The whole therapy system including the accelerator itself was certified as a Medical Product according to the EU directive 93/42/EEC. In total, four irradiation rooms are available, i.e. three rooms with different functionalities are used for clinical applications and one room is solely dedicated to non-clinical research. A crucial factor for the treatment is the exact positioning of the patient. For this reason, the irradiation rooms are equipped with a worldwide unique positioning and verification system: a ceiling-mounted robotic system, with industrial robots custom-built for medical use including a unique table mounted ring imaging system. This system makes it possible to position the patients with an accuracy of half a millimetre, and to ensure that the patient stays in this position during the whole treatment. At MedAustron, first proton beams for therapy have been delivered in late 2016. In July 2019, the first carbon patient using the first time the clinical implementation of LEM I within the RaySearch Laboratories treatment planning system RayStation was treated. With beginning of March 2020, MedAustron patient numbers exceeded 600. All treatment rooms and all functionalities including a proton gantry will be fully operational end 2021.
Services currently offered by the infrastructure:
The dedicated non-clinical irradiation room is equipped with a horizontal fixed beam-line and a scanning system providing a field size of 20 cm × 20 cm. Protons and carbon ions can be delivered in the clinically-utilised energy ranges, i.e. 62.4 MeV to 252.7 MeV for protons and 120 MeV per nucleon to 402.8 MeV per nucleon for carbon ions. In addition, protons can be accelerated up to 800 MeV for research purposes, which is far beyond the requirements for clinical applications. The nominal beam intensities are 2×10^{10} particles per spill for protons and 4×10^{8} particles per spill for carbon ions. The patient alignment system, which is used in the clinical irradiation rooms, is also available in the non-clinical irradiation room. This includes a robotic patient positioning system and an X-ray-based verification system.
Several non-clinical research laboratories are fully equipped for performing basic experiments in biology and medical physics. This includes a reference X-ray source (horizontal beam), cell cultures, histology, photometric assays, protein- and RNA work, microscopy, and dosimetry equipment for performing quality assurance of the delivered beams
In addition to the clinical research efforts, MedAustron also supports non-clinical research in strong cooperation with Austrian universities. Three non-clinical research groups are currently located at MedAustron, comprised on radiation physics, medical physics, and radiobiology. The physics orientated research projects focus on the technological facilitation of tumour motion tracking, particle micro- and macrodosimetry and particle imaging, as well as on the investigation of the behaviour of particles within a magnetic field. The biology research focuses on radiation-induced molecular events including reoxygenation and anti-tumour immunogenicity.

Provision of access to the following infrastructure(s):
Description of the infrastructure (Partner 11) MIT, Germany
Name of the infrastructure (and its installations, if applicable):

MarburgerIonenstrahl-Therapie Betriebsgesellschaft GmbH
Location (town, country) of the infrastructure: Marburg, Germany
Web site address: https://www.mit-marburg.de
Description of the infrastructure:
The Marburg Ion Beam Therapy Centre is a facility for tumour treatment of patients using Carbon and Proton beams. Since its start in October 2015 more than 1000 patients have been treated. The beam is provided by a multi stage accelerator (LINAC and Synchrotron) to 4 treatment rooms and the irradiation is performed by a pencil beam and scanning technique. The operation staff consists of about 40 employees with medical, physical and technical professions. The centre is operated at about 320 day a year where the patient treatment takes place mainly on working days. The different beam qualities and the technical infrastructure of a treatment room can be used for non-clinical applications as well. However, our experience in organizational and technical support in conducting experiments has been limited to local external users so far.
Services currently offered by the infrastructure:
The accelerator is delivering protons with energies from 48 to 221 MeV/u and for carbon ions from 88 to 430 MeV/u divided in 290 different energy steps. The spot size is ranging from 4 to 10mm. The maximum fluxes are for protons 2 x 10^9 particles/s and for carbon 1 x 10^8 particles/s. The intensity can be varied over 3 orders of magnitude. All different settings are stored in the accelerator control system and can be requested pulse to pulse. The beam flux is intensity controlled and dose measurement of the beam is available.

***Figure 18** - Main entrance to the MIT Facility.*

Every treatment room is equipped with a moveable robotic table, a laser positioning system and kV-imaging systems. Three treatment rooms have horizontal beam lines, the fourth is equipped with a 45° beam line.
Since August 2019 the facility is open for researchers. Since that time, several national research groups regularly use the facility for biological and physical experiments.
QA-equipment available for research:
- Water column (PTW);
- Dosimetry equipment: Ion chambers (Farmer type chambers, PinPoint chambers, parallel-plate chambers;
- Water phantoms;
- Anthropomorphic phantom;
- Film dosimetry.

Access to biological laboratories is available (on demand).

The unit cost for clinical access has been calculated using the method for clinical access of the EU. All the additional procedures to be performed for foreign patients involved in the Transnational Clinical Access have been listed and divided into tasks following the patient path. Tasks consist in sequential steps, different in terms of procedures and personnel involved. They are identified in screening and evaluation, first visit, planning, follow up, operational aspects directly related to managing of foreign patient. For each task, additional procedures have been detailed, as well as the effort required for category of personnel involved (Doctors, Medical physics, Study nurse, Biostatistic, Foreign patient administration). As shown in the spreadsheet of unit cost calculation Annex to the proposal, a big effort is required to share clinical information, make plans comparison, and studies between doctors (referring physician of the patients and physician operating in the heavy ion facility, medical physics and other categories involved). The completion of databases has the goal to put at the disposal of the community useful information for spreading knowledge of heavy ion therapy and related research. In
*Table 6*5 the clinical and research units of TA providers are listed.

Table 5 - TA units per facility.

	CLINICAL	RESEARCH	TOTACCESS
CNAO	12	80	92
GSI	-	296	296
UKHDIT	10	72	82
MEDA	12	-	12
MIT	16	-	16
	50	**448**	**498**

Table 6 - TA facility summary parameters.

Participant No	Participant Short name	Spot scanning (SS); Passive scattering (PS);	Detectors (PG-prompt gamma), ionization chambers (IC), Semiconductor (SC), Scintillator (SCI)	Imaging	Phantoms (P): anthropomorphic (AM) zoomorphic (Z)	Treatment planning system	Dosimetry	Models and data
1	CNAO	SS	IC, StripIC, PixelIC	X-rays (treatment room)	P: water phantom	RayStation	Clinical QA	-
7	GSI	SS	IC, SCI	X-rays	P, GSI analogue of IBA DigiPhant	TRiP98	Ion Chambers, films	Treatment planning, biological, physics
8	UKHD/ HIT	RS	IC, MWIC	-	Standard QA	RayStation (RaySearch) Syngo Pt Planning (Siemens) MC Tools	Clinical QA	Treatment planning, biological, physics
10	MEDA	SS	IC, SCI	X-rays	AM: CIRS ATOM phantom	RaySearch	Clinical QA	-
11	MIT	SS	IC, MWPC	X-rays	AM	Syngo (Siemens)	Ion Chambers, film	Treatment planning, biological, physics

Task 6.3: Specific TA to clinical activities *(MEDA, CNAO, GSI, UKHD/HIT, MIT)*

The beneficiaries of TA are all the European countries including users with little background in heavy ion therapy research such as the ones from the SEE region. TA partners who will provide clinical research or patient treatment are CNAO, UKHD/HIT, MEDA and MIT. CNAO and UKHD/HIT will provide both the experimental research room and patient treatment. The TA provider will make efforts to best adapt to the users' needs in conformity with their research interest. GSI, where patient treatment was terminated over 10 years ago, will offer only research TA for medical physics, radiobiology and applied nuclear physics experiments of interest or ion therapy. More details of what each facility is making available for TA is described in Task 6.1.

Transnational access of patients to the cutting-edge EU facilities for heavy ion radiotherapy is a high spot of HITRI*plus*. Indeed, part of the TA will be dedicated to treating patients with cancers within the already ongoing research clinical protocols of the ion therapy facilities. The selection of eligible cases and of their connected physician(s) (the TA "users") will be addressed by the same User Selection Panel described in Task 6.1. The users in this case can be clinical researchers, physicians, radiotherapists, oncologists and organ experts belonging to the EU medical community. The scientific goal of opening the ion therapy facilities through the clinical TA is

to engage the medical community in the capabilities, outcomes and advantages of ion therapy, sharing with them all the phases that bring the patient from the first visit to the follow-up. HITRI*plus* offers a unique opportunity to treat patients from different countries with heavy ions, to connect the medical community from different countries, and to educate them on the effectiveness of the treatment with practical clinical cases. The impact of this TA will be very high both on the research and societal benefit side.

The patient access rules will be defined among the partners according to the specific procedures valid for each centre. Each clinical facility will provide a list of pathologies that are treatable with carbon ions, based on the running clinical research protocols. The TA user will be the physician responsible for a patient that may be eligible for treatment with carbon ions. This physician will then engage his activity in the research protocols available at TA provider sites. It should be noted that this procedure is already implemented in the four centres providing clinical TA, as they already treat patients coming from foreign countries. The dissemination and outreach activities in HITRI*plus* are essential to improve the awareness of the oncologists in different EU countries, and especially in countries with less experience with related possibilities, such as SEE, and will lead to an increase in TA of patients to carbon ion therapy.

The process of getting access to TA for the users will start by filling an online form (at the HITRI*plus* website) or contacting the HITRI*plus* Helpdesk for assistance. On the online form they will be asked to provide the following documents:

1. "Access to treatment" form signed and filled out by the patient;
2. copy of medical report;
3. treatment plan of previous radiotherapy, if any;
4. copy of histologic outcome;
5. copy of diagnostic imaging, reports and images,(CT, PET, MRI, Bone scintigraphy);
6. updated and detailed clinical history;
7. an application letter submitted by referent physicians, preferably not exceeding 3 months, that contains the following information: diagnosis, tumour stage, non-oncological history, detailed oncological history, therapies in progress, drugs, comorbidities;
8. any other document useful to evaluate the case.

The documents have to be in English, up-to-date (not older than 3 months), essential and informative. To ensure the security of data transmission, the documents have to be sent through an encrypted channel.

When a TA proposal is submitted, the following procedure will be followed:

1. The User Selection Panel (USP) makes a first evaluation on the eligibility of the request, on the expected amount of TA units necessary and travel expenses.
2. In case of positive evaluation, the USP, following the recommendation of the responsible doctor and the available TA in the four TA providers, forward the documents to one of the four centres. The USP acts then as the first filter on the applications, regulates its number and the distribution in the different centres, and will eventually reject them when the TA are all used.
3. The ion therapy facility selected by the USP will then evaluate referrals within 5 working days.
4. If the documentation is adequate a preliminary judgement on eligibility will be issued, otherwise further diagnostic work-up will be requested.
5. The facility will issue a preliminary judgement on eligibility within 5 days of receiving the requested additional exams.
6. After preliminary acceptance a first visit will be organized within 14 days and necessary preliminary procedures (and dedicated) will be scheduled within 5 days from the first visit. This time frame can be delayed according to clinical needs to allow completion of, or recovery from, ongoing or newly planned medical or surgical therapies.
7. Final evaluation on treatment feasibility will take place at first visit. In exceptional cases final decision may require treatment plan evaluation (7 days after first visit). If the case is finally accepted, the patient will be

scheduled for the treatment in within 7 – 10 days from simulation.

The objective of the Clinical TA is to inform and involve the responsible oncologist in the treatment activities that can be summarized as:

- immobilization devices simulation CT;
- imaging for contouring such as MR or CT PET;
- treatment planning with dedicated software;
- dosimetry plan verification;
- treatment sessions on subsequent days according to clinical protocols;
- visits and eventually imaging during treatment course.

A medical report will be issued on the final day of treatment. It will report all the listed parameters, moreover the DICOM files (simulation CT, simulation MR and when necessary simulation CT PET, registration matrixes, RT plan RT dose and RT structures), eventually sent through a dedicated ftp.

All follow-up treatment will be arranged in accordance with the clinical protocols; most common is MR and visit every 3 months. Additional procedures may be necessary according to tumour site. Follow up will be performed in direct contact with the referring doctor(s)/user(s). Each clinical facility has an International Patients Office that will assist the patients for any need concerning travel, accommodation, interpreter services etc.

All patient data will be collected and included in the HITRI*plus* clinical database and in the local TA provider clinical trial protocol.

Task 6.4 and 6.5: Outreach to new users, SEE involvement *(GSI, CNAO, UKHD/HIT, MEDA, MIT, SEEIIST)*
In order to support users and facilitate the choice of the best TA provider for each proposed project a dedicated HITRI*plus* TA Helpdesk will be setup by this Task with the contribution of all TA providers. As described in Task 6.1, the TA Helpdesk is the first point of contact for new users guiding them through the process. To support users and enhance awareness HITRI*plus* will provide a platform to allow many more users to benefit from TA access to heavy ion facilities. In addition, HITRI*plus*' NA's will bring in new users, will train and inspire them and then provide a route for dissemination and communication to the scientific, industrial and clinical communities, consumer and government stakeholders and the public at large. In order to make sure users are aware of the capabilities within HITRI*plus* the TA offered by the project will be promoted by Task 6.3 at relevant international conferences, national meetings, workshops and through mailing list and meetings relevant to HITRI*plus*.
In particular, the HITRI*plus* project will work as a bridge for collaboration between the different TA facilities and the SEE research community. The SEEIIST will participate in the Task 6.3 activities, to facilitate the access of researchers of this region to the European centres of ion therapy in order to gain experience and create scientific collaborations before the proposed SEEIIST facility is built. The HITRI*plus* TA will help integrate scattered scientific efforts across Europe in a strong heavy ion research community providing practical tools to perform experiments, to obtain training from leading experts of the field, share experience and establish collaborations. The experience gained within HITRI*plus* will help in the future the users to fully exploit the benefits and the advantages of heavy ion therapy.

WP6 Deliverables

Title	Delivery Month
D6.1: HITRI*plus* delivers 160 units of TA by month 24	24
D6.2:HITRI*plus* delivers 498 units of TA by month 48	48
D6.3: Treatment of 50 patients with heavy ion therapy in TA	48
D6.4: Publication of an overview article or a focus issue on the results of the TA - financed activities	48

WP number	WP7		Lead beneficiary			CERN	
WP title	**JRA1- Advanced accelerator and gantry design**						
Participant nr.	4	13	7	1	18	10	2
Participant	CERN	SEEIIST	GSI	CNAO	RTU	MEDA	BEVA
Person months	14	48	4	8	40	2	28
Start Month	1		**End month**			42	

Objectives

The WP7 objectives are:

- To design solutions that could improve performance of the existing accelerators for heavy ion research and therapy: multiturn injection for higher beam intensity, improved extraction and beam transport – in particular for new FLASH therapy modality, and new linac injector for higher intensity and parallel production of isotopes for research and therapy.
- To combine these accelerator solutions with the superconducting (SC) magnets developed in WP8 to develop the advanced conceptual design of a compact and innovative SC heavy ion synchrotron for cancer research capable of operating with multiple ion species, from protons to argon as required for research projects, particularly helium, carbon and oxygen.
- To propose a simplified version of this compact SC accelerator (with single- or double-ion operation at fixed parameters) as the reference for a new generation of compact ion therapy accelerators to be built by European industry to address the global ion therapy market.
- To convert the most promising of the existing conceptual designs for superconducting gantries into a detailed technical design integrating all components including diagnostics and beam delivery, and prepare for a final industrialisation and production phase by European industry.

The components and the full accelerator design will aim at increasing the beam intensity for carbon, the reference ion for the accelerator design, up to 10^{10} ions per pulse at the final energy of 430 MeV/u. In terms of dimensions, the SC reference design aims at a reduction by a factor >3 in the accelerator footprint as compared to the present normal-conducting designs, thanks to the higher field by more than a factor 2 provided by SC magnets in comparison with warm magnets. The higher beam intensity together with the small synchrotron dimensions leads to an unprecedented beam density that represents a challenge for beam optics design.

Other key components to be developed in this WP are a novel linear accelerator (linac) injector design for higher energy and current, a new multi-turn injection scheme for ion synchrotrons, and a combined slow and fast extraction for increasing the research reach towards alternative experimental and treatment modalities (e.g. FLASH therapy). The accelerator and gantry design work will be done in close collaboration with the European heavy ion therapy research centres, to profit of their operational experience and to integrate in the design licensing and operational requirements.

Description of work

Task 7.1: Coordination and Communication (*CERN, SEEIIST, GSI*)

This Task focuses on the WP7 management and internal and external communication. Specific activities include:

- coordinating the WP-activity with the other WPs and making sure that the accelerator work is in line with the specifications coming from the scientific and medical community and is coordinated with the developments taking place in other JRAs (CERN, SEEIIST);
- organising meetings and documentation exchange to keep close relations especially within the WP (GSI);
- organising dissemination of the WP results in coordination with WP1, and receiving feedback from other external partners on technological benefits of proposed solutions and costs (CERN, GSI);
- taking care of the WP schedule and organising reviews of the work in the tasks and writing reports (GSI);
- coordinating with WP4 the Technology Transfer to industry of the technologies developed in WP7 (CERN).

Task 7.2: SC Synchrotron and Advanced Components Design (*SEEIIST, CERN, CNAO, MEDA*).
The activities of this Task will be performed by a joint CERN-SEEIIST team based at CERN, with contributions from the other partners. It includes definition of the components for a SC synchrotron and the final analysis and tracking for the reference SC synchrotron design. It is divided in 4 sub-tasks:

- *Sub-Task 7.2.1, Lattice for a SC synchrotron:* definition of an appropriate lattice using the SC magnet design defined in WP8, including modelling of magnets and particle tracking for long-term stability (SEEIIST, CERN).
- *Sub-Task 7.2.2, Multi-turn injection in resistive and SC synchrotrons*: conceptual design of the multi-turn injection of 10^{10} ions per pulse into a reference synchrotron with resistive magnets, and in the SC synchrotron (SEEIIST, CERN, CNAO).
- *Sub-Task 7.2.3, Extraction and beam transport:* conceptual design of slow and fast extraction for different treatment options and for experimental research, in coordination with beam transport and delivery teams, for a synchrotron with resistive magnets and with SC magnets (SEEIIST, CERN, CNAO).
- *Sub-Task 7.2.4, Longitudinal and transverse beam dynamics studies and assessment*: preliminary analysis of acceleration, collective effects, space charge, intra-beam scattering and collimation (SEEIIST).

Task 7.3: Operational modes, beam transport and instrumentation (*SEEIIST, CERN, CNAO, MEDA*).
The activities of this Task will be performed by a team based at CERN, integrating the experience from two operating heavy ion therapy facilities. It is divided in 3 sub-tasks:

- *Sub-Task 7.3.1, Operational modes:* identification of specific requirements and challenges in operation due to switching between therapy and research operation modes (for the sources, injector linac, ring and transfer lines) (SEEIIST, CNAO, MEDA).
- *Sub-Task 7.3.2, Beam transport lines*: definition of improved layouts of the transport lines to the experimental and clinical treatment areas, with special attention to safety due to switching between the 2 modes, e.g. beam-dump, shielding (SEEIIST, MEDA, CNAO).
- *Sub-Task 7.3.3, Beam instrumentation and QA:* identification of advanced beam instrumentation options and of their possible application to present and future medical synchrotrons (SEEIIST, MEDA).

Task 7.4: Injector Linac Design (*BEVA, CERN, SEEIIST*).
The activities in this Task will be performed by a CERN-BEVA team, with the contribution of SEEIIST:

- analysis of heavy ion source options for high ion intensity and selection of new designs to improve performance of present and future ion therapy and research infrastructures (BEVA, CERN);
- conceptual design of a 325 MHz 10 MeV/u multiple ion injector: stripping energy optimisation, RFQ energy, RF system design, accelerating structure design and preliminary beam optics design. Comparison with layout, cost and performance of a 217 MHz injector with improvements against the existing standard injector (BEVA, CERN, INFN, SEEIIST);
- detailed design of the preferred option (325 MHz or 217 MHz), with final beam optics design and overall design of RF accelerating structures, of amplifier system, and of instrumentation layout. Analysis of the impact on the design of a double operation mode, for injection into the synchrotron and using additional beam pulses for production of experimental radioisotopes for imaging and therapy (BEVA, CERN, SEEIIST).

Task 7.5: Integration of an innovative superconducting gantry: optics, mechanics, beam delivery (*CNAO, CERN, SEEIIST, INFN, MEDA, RTU*).
This Task will be carried out in close collaboration with WP8. After an initial examination and comparison of the different existing conceptual gantry designs and of their performances and limitations, a specially appointed WP7

Committee will select the most promising option for further development. A risk management analysis (CNAO, MEDA) will be included to consider safety, security, reliability and performance factors so that the outcome is transferable toward a clinically usable machine subsystem.

- *Sub-Task 7.5.1, Basic structure and mechanical design*: After having identified the baseline conceptual design, the mechanical structure and the technical solutions of the beam transport and the magnets will be investigated in detail. This sub-Task will start from a general mechanical and optics design of the gantry to integrate actual magnet designs, beam instrumentation, dose delivery, cryogenics aspects, etc. into a detailed mechanical design. (CNAO, RTU, CERN).
- *Sub-Task 7.5.2 Simulation of optics, scanning techniques*: This phase of the design will consist in a global simulation and optimisation of the gantry considering the main aspects like optics (CNAO, CERN, SEEIIST), magnets (INFN, CERN), power converters (CNAO, CERN, INFN), beam diagnostic (CNAO, SEEIIST), mechanics (RTU, CNAO, CERN), dose delivery (CNAO, INFN). An integration study will highlight interferences between different items. The design shall be flexible enough to adapt the gantry optics to the existing (CNAO, MEDA) and future (SEEIIST) facilities, and to be easily industrialised and reproduced in several units.

WP7 Deliverables

Title	**Delivery Month**
D7.1: Advanced conceptual design of an optimised linac injector for multiple ions at 10 MeV/u	24
D7.2: Report on operational modes, beam transport and instrumentation	36
D7.3: Report describing the main optics parameters and integration features of the gantry	36
D7.4: Design of an optimised synchrotron with SC magnets and advanced features: high beam intensity, fast and slow extraction, multiple ion operation, optimised linac injector, optimised instrumentation and QA procedures	40

WP number	WP8		Lead beneficiary				INFN	
WP title	**JRA2 - Superconducting magnet design**							
Participant nr.	9	4	3	5	16	12	13	17
Participant	INFN	CERN	CEA	CIEMAT	UU	PSI	SEEIST	Wigner RCP
Person months	32	4	20	22	8	2	8	12
Start Month	1		**End month**				36	

Objectives

The objective of WP8 is to perform a first technical and financial assessment of various magnet designs for a novel type of carbon ion synchrotron and gantry complex. This includes a preliminary engineering design for the new concept accelerator magnets (mainly dipoles with combined function) and an innovative gantry magnet. The WP8 will eventually manufacture and test a small size demonstrator magnet that will give important feedback, useful for accelerator as well as a gantry final magnet design. A novel compact zero field superconducting magnetic channel for extraction from the synchrotron will also be designed and tested.

Description of work

Task 8.1: Coordination and assessment of magnet design (*CEA, INFN, CERN, CIEMAT, PSI*)

This Task focuses first on the coordination between different tasks towards the designated objectives and with other WPs (INFN, CEA, PSI). The task starts by carefully assessing recent developments in Asia (INFN, CEA) and must deliver a set of parameters to be used in the design of magnets for synchrotrons and gantry (INFN, CERN, CIEMAT, PSI). The assessment will take into account also future reasonable evolution of HTS superconductors that is a field in very fast evolution (CEA). The work will be carried out in close collaboration with WP7 (Advanced Accelerator and Gantry Design). The result of this assessment will be a set of parameters that will be an input to Task 8.2. Tentatively we aim at 60-90 mm aperture, 5 T peak field, with coils indirectly cooled and should allow a gantry of weight of about 100 tons (which is 15% of the present reference ion gantry in Heidelberg (600 tons) and less than half of the best world gantry for ions at Chiba (Japan) of about 350 tons. This task will also provide input in the industry workshop organized by WP4 to make sure the proposed magnet parameters and the design features (Task 8.2) will integrate in the EU industry capability in terms of engineering optimization and manufacturability at affordable cost.

Task 8.2: Technical and financial evaluation of various magnet designs for synchrotron and gantry (*INFN, CEA, CIEMAT, CERN*)

Following the preliminary assessment and selection of target parameters carried out in Task 8.1, various conceptual designs of the accelerator magnets will be developed with different layouts both for accelerator and gantry (by INFN, CEA, CIEMAT and CERN), all based on superconducting coils, considering LTS (Nb-Ti as baseline and Nb_3Sn as possible alternative, by INFN and CERN). An advanced novel superconductor solution (MgB_2, REBCO tape or cable, BSCCO tape or cable) in the 4.2 – 30 K operation range will also be investigated (CEA, CIEMAT and INFN). The technical difficulty of the designs and the financial cost of the different options will be evaluated and scored. This includes the cost variation in cooling temperature (cost of operation for 20 years and energy consumption) that is possible with different superconductors. The complexity of the analysis is due also to the fact that superconductor choice and magnet lay-out are strongly inter-dependent. The result of the evaluation carried out in this task 8.2 will indicate the best route to select among the various practical options. This will feed directly into WP7 and Task 8.3 for the accelerator and gantry engineering magnet design. It will also be critical for the decision on the type of demonstrator to be designed and built (Task 8.1 and 8.4). The technology readiness assessment will also be carried out for each type of considered solution.

Task 8.3: Preliminary Engineering Design for Accelerator and Gantry magnets (*Wigner RCP, CIEMAT, CEA, CERN, INFN, UU)*

A preliminary complete design will be carried out for both accelerators (limited to main dipoles with or without combined gradient) and gantry (dipoles and focusing magnets, in a combined function). The design will aim at a 60-90 mm aperture magnet with field of about 5 T (possibly 4.8 T peak field for gantry and 4.6 - 5 T for accelerators, when dipole and gradient field are summed). The coils are indirectly cooled, and the design will address the mechanical structure for the accelerator magnets, the field quality during steady state and during ramp up/down (ten time faster for synchrotron than for gantry), the losses and consumptions (including exploitation for 20 years), magnetic components of the extraction system (accelerators) and ancillary magnets for gantry. It will cover also the manufacturing time, the magnet safety systems and a cost estimation (INFN and CERN). This will result in a set of engineering drawings (CIEMAT, CEA, UU, Wigner RCP and INFN) and a concept for energy exchange between the accelerator and power converter to minimize the energy consumption from the grid (CERN, UU). The output is a report (CIEMAT and INFN) with concept, calculations and technical drawings that will feed into WP7 for global accelerator and gantry design and into Task 8.4 for the detailed design of a relevant demonstrator. Wigner RCP will take care of the novel extracting system design based on superconducting zero-field magnetic channel as well as of other features especially regarding the CCT lay-outs, while CERN and INFN will also explore an alternative CosTheta design as back-up plan in case CCT would encounter problems.

Task 8.4: Construction of a small size magnet demonstrator for accelerator and gantry (*CIEMAT, INFN, SEEIIST [SEN], CEA, CERN, UU, Wigner RCP*)

Once the WP collaboration has decided which configuration is the most suitable for testing in a small demonstrator, this task will pursue the manufacturing design (INFN and CEA), the manufacture of the mechanical components (INFN) and the winding and magnet assembly (CIEMAT) of at least one 4 T demonstrator. The demonstrator will be useful for both the accelerator and the gantry. The aperture of the magnet demonstrator will be defined following the beam dynamic studies of WP7 and WP9 of the first year. A test station, possibly with variable temperature, will be prepared with suitable power leads and protection and the magnet will be tested to assess performance (CERN, UU and Wigner RPC). SEEIIST [SEN] will prepare the magnetic measurement system for warm measurements and will carry out the field quality assessment, both at CIEMAT and at CERN (and/or UU). Wigner RCP will also take care of the test of a zero-field superconducting magnetic channel model to prove this new beam extraction device for ion synchrotron.

WP8 Deliverables	
Title	**Delivery Month**
D8.1: Report on assessment of magnet types, suitable for fast SC synchrotron and for SC gantry and preliminary evaluation	14
D8.2: Final report on Magnet design for SC synchrotron and SC gantry, with indication of time, cost and technology readiness assessment	32
D8.3: Magnet Demonstrator completed	36

WP number	WP9		**Lead beneficiary**			GSI	
WP title	**JRA3 - Advanced beam delivery**						
Participant nr.	7	1	-	-	-	-	-
Participant	GSI	CNAO	-	-	-	-	-
Person months	66	9	-	-	-	-	-
Start Month	1		**End month**			44	
Objectives							

- Develop a comprehensive modular design for treating and imaging patients in a sitting position
- Develop a particle arc therapy based on the rotating chair in a fixed beam treatment room
- Investigate potential scenarios for applying particle arc therapy for different tumour locations and delivery modalities, including a comparison of Bragg peak and shoot-through therapy
- Investigate ultra-fast beam delivery (Flash therapy) to reduce side effects in shoot-through arc therapy

Description of work

In addition to gantries becoming more compact and cheaper, the existing and future fixed beam lines should be exploited for the best possible patient care, by providing a means of more flexible beam delivery. In this WP, a patient chair and associated vertical imaging will be investigated to enable particle arc therapy. Novel detector technology will be used to speed-up beam delivery, and potentially allow a combination of flash and arc therapy. The basis of this study will be the CNAO DDS, which is in clinical use at CNAO, MEDA and was recently installed at GSI.

Task 9.1: A modular patient chair and imaging design (*GSI, CNAO*)
Based on literature data and data from the participating clinical partners, different treatment scenarios will be developed for seated and lying down patients, irradiated with fixed beam lines as available in the European heavy ion beam centres. Based on these scenarios, existing commercial and research designs of robotic patient chairs and couches as well as compatible imaging systems will be evaluated. A set of criteria based on technical capability, availability, space requirements, intercompatibility and safety will be developed. The final layout will aim for rapid and precise patient setup, as well as capabilities for plan verification and possible adaptive radiotherapy through volumetric imaging and motion monitoring.

Task 9.2: Particle arc therapy for fixed beam lines (*GSI, CNAO*)
In photon therapy, arc delivery of a continuously moving gantry enables the highest degree of flexibility and dose conformity. First studies on proton arc therapy show its feasibility at comparable or shorter delivery times and comparable or better plan quality. In this task, a simulation environment for particle arc therapy will be developed to derive efficient treatment planning strategies. The resulting plans will consist of a large number of discrete beam angles with a single energy each and will rely on the fast dose delivery capability as well as the feedback control of the chair rotation during delivery. A demonstrator rotational stage will be developed and interfaced to the DDS at GSI, to permit a dynamic rotation for arc therapy (CNAO). Outside of the scope of this project, this stage will be usable also for precision irradiation of orthotopic tumours in small animals (note: there will be no animal studies performed within the project itself). The DDS itself will be modified to be able to deliver plans to a continuously rotating chair.

Task 9.3: Clinical scenarios for particle arc therapy on sitting patients (*GSI,* CNAO)
Based on the data gathered in 9.1 and the performance achieved in 9.2, a comprehensive set of simulations will be performed to assess the potential clinical benefit and usability of particle arc therapy to sitting patients. This includes target locations, such as brain, head-and-neck, thoracic or abdominal, as well as different treatment modalities. In a technically more challenging strategy, the Bragg Peak can be used in arc therapy as well, demanding for angle-dependent energy changes. While strategies exist to reduce energy layers, fast energy changes will still pose a challenge to the technique. Moreover, range uncertainty for a sitting patient might be considerably higher, depending on the treatment site. An alternative could be to use the plateau of the beam in a shoot-through therapy, which would eliminate the need for energy changes as well as most of the range dependence, but would also reduce the inherent benefit of particle therapy. This drawback could be overcome by combining arc therapy with strategies to reduce side effects, such as Flash therapy.

Task 9.4: Particle arc therapy at high dose rates (CNAO, GSI)
Based on novel GEM detector technology for faster position detection, the CNAO DDS will be capable of

handling average spot delivery times of < 1 ms. In this way, the DDS will fully exploit the advanced capabilities provided by WP7 and WP11 of high and flexible dose rates. The DDS will be modified in collaboration with WP12 (CNAO). This will enable advanced motion handling strategies including phase-controlled rescanning or synchronised delivery of conformal plan libraries. A prototype installation at GSI will permit experimental exploration and validation of achievable delivery speed, and consideration of clinical safety parameters adapted to such speed (GSI). The possibility of shoot-through flash therapy will be investigated using the demonstrator rotary stage aiming for dose rates in excess of 50 Gy/s per beam angle.

WP9 Deliverables	
Title	**Delivery Month**
D9.1: Conceptual Design Report for a patient chair capable of rotating the patient around a vertical axis as well as a vertical in-room imaging system	9
D9.2: Particle arc therapy delivery to a small scale demonstrator of a rotational patient positioning system for gantry-free delivery with a position feedback integrated to the DDS	24
D9.3: Identification of beneficial patient arc therapy scenarios by lesion location and delivery mode	36
D9.4: Experimental validation of arc therapy treatment plans through patient QA-like procedures	42

WP number	WP10		**Lead beneficiary**			UKHD/HIT	
WP title	**JRA4 - Multiple energy extraction system**						
Participant nr.	8	7	1	-	-	-	-
Participant	UKHD/HIT	GSI	CNAO	-	-	-	-
Person months	36	3	3	-	-	-	-
Start Month	1		**End month**			36	

Objectives

- Review realistic treatment plans
- Generate a library of optimum beam characteristics
- Analyse the critical timing threshold for in-spill energy changes
- Define the data volumes, the typical rates and the essential reaction times
- Describe a strategy to generate the process data in quasi-real-time
- Build an architectural model of the control system layer

Description of Work

Task 10.1: Generation of Beam Characteristics Library *(HIT, GSI, CNAO)*

The existing ion beam therapy centres were designed for patient treatments using proton and carbon ions. Typically, physical doses less than 5 Gy are delivered at dose rates of 1-2 Gy/l x min. The maximum range of 32 cm water equivalent thickness translates into energies up to 430 MeV/u for carbon ions. In order to support the clinical as well as the research use cases, within HITRI*plus,* the pencil beam library being produced by the accelerator system extends the parameter space presently used. New ion species like oxygen, higher intensities to increase the delivered dose rates, higher energies for some research aspects and a more flexible extraction timing to better support the treatment of moving organs will be defined and combined with the existing phase space definitions. Based on realistic treatment plans, static as well as moving organs, the optimum time structure of the pencil beams will be deduced using the research treatment planning platforms at GSI (TRiP98) and HIT (RayStation). This task will be carried in cooperation with GSI, CNAO and WP9.

Task 10.2: Multi-Energy Operation and Timing Requirements *(HIT, CNAO)*

The raster scanning dose delivery method relies on the consecutive irradiation of target volume slices. Each slice represents a constant and predefined beam energy. Currently a new synchrotron cycle is started for each energy level and typically takes 5 – 8 seconds. The number of particles available in the synchrotron typically exceeds the number of required for a single iso-energy slice.

A new idea to operate the synchrotron is the multi-energy operation mode. Instead of dumping the left-over particles at the end of the extraction phase, they will be accelerated to the next energy. After the first partial extraction the beam that remained in the synchrotron is no longer in a feasible condition for further acceleration as it is transversally blown-up. Due to Liouville's theorem this is irreversible. All accelerator devices must now be tuned carefully to find the best conditions to reaccelerate such a beam. This procedure can be executed several times, until the synchrotron is empty. In contrast to the so far used single-energy operation mode that uses precalculated process data for a large number of devices the multi-energy operation mode requires the calculation of process data just in time at the frontend. This task will define the data requested by the therapy control system and the distribution of these to the front-end of the numerous accelerator devices. Furthermore the data volumes, the typical rates and the essential reaction times will be analysed.

Task 10.3: Quasi Real-Time Data Generation Strategy and Architectural Model *(HIT, CNAO)*

To realize the multi-energy operation mode, a data supply model for almost all accelerator components is required that generates patient-specific patterns for all synchrotron and beamline devices according to the individual treatment plan. This level of flexibility leads to a challenging complexity for the calculation and storage of accelerator settings. The generation of individual patterns (e.g. power supply currents) based on machine parameters (tune, energy etc.) can either be done in advance or online. That means for all possible sequences of beam-energies the data are either stored in the front-end controllers, which leads to a large amount stored data, or the calculation is done in a running cycle while the beam circulates in the synchrotron.

Both flavours require a massive upgrade of the hard- and software frontend parts compared to the existing systems. Data storage as well as process data computing capabilities of the frontend controllers will be defined. The new design shall be based on standard components instead of proprietary solutions.

Using the results of Tasks 10.1 to 10.3 and the outcome of the synchrotron design work package an architectural model of an accelerator control system that is capable of multi-energy operation will be defined.

WP10 Deliverables

Title	Delivery Month
D10.1: Beam characteristics library	8
D10.2: Data distribution and synchrotron timing requirements	22
D10.3: Real-time data generation strategy	36

WP number	WP11		**Lead beneficiary**			CLS	
WP title	**JRA5 - Controls and Safety**						
Participant nr.	6	10	13	-	-	-	-
Participant	CSL	MEDA	SEEIIST (IJS)	-	-	-	-
Person months	45	7	4	-	-	-	-
Start Month	1		**End month**			48	

Objectives

The goal of this WP is to analyse and determine the best solutions for an upgrade of current and future facilities

in terms of performance and cost. Using experience from past research results in previous projects, as well as clinical users' experience, future trends and market needs, a novel design for the control software and safety systems will be elaborated. Existing state-of-the-art solutions for machine and treatment room controls and patient safety systems will be used as baseline on top of which novel solutions will be proposed – unique solutions which will facilitate both research and clinical users at the same time.

Description of work

Task 11.1: Technical Coordination *(CSL)*

This Task concerns the coordination between different tasks and the incorporation of inputs from other WPs as well as transfer of WP-results (CSL). This Task will also provide input in an industry workshop to make sure the design directions defined in the tasks can be well integrated in the EU industry in terms of design and manufacturability at affordable cost.

Task 11.2: Machine controls *(CSL, MEDA, SEEIIST [IJS])*

Concepts and solutions will be studied to ensure fast commissioning and machine QA, ease of use by non-clinical personnel, high reliability of the accelerator and lowering of the total operational costs (CSL). This will be achieved by concentrating on the design of a "future proof" control system architecture, which will facilitate both clinical and research requirements (MEDA, SEEIIST [IJS]). Specifically, Cosylab will leverage upon the best concepts from the state-of-the-art solutions used in other facilities (both research and clinics). This task will result in a set of system engineering requirements and a multi-tier control system architecture.

Task 11.3: Treatment room controls *(CSL, MEDA)*

This Task will propose solutions to increase patient safety, increase treatment quality (adaptive treatment workflow), lower the total treatment time, and ensure easy operation by clinical personnel (CSL). This task will first study all possible treatment room control systems in existence today (and in the near future). Then it will propose a treatment control system which will make it easy to integrate all those together and be used ergonomically by the radio-therapy technicians (MEDA, CSL). Making the system simpler, medically safe and easier to integrate will lower the cost of the treatment room software by an estimated 30% and improve treatment availability by as much as 20%. This task will result in system engineering requirements and a treatment control system architecture and design. The results will not only benefit future facilities, but all collaborators of HITRI*plus* project who are treating patients (CNAO, MEDA, UKHD/HIT, etc.).

Task 11.4: Patient safety systems *(MEDA, CSL)*

Task 11.4 will propose comprehensive system engineering requirements as well as design and architecture for safety systems relevant for safety as required by European regulations, in particular related to patient safety (MEDA). The aim is: (1) to match the performance of such systems to the performance of the accelerator design; (2) a sustainable architecture with respect to expected technical and medical development over the lifetime of a heavy ion beam therapy system; (3) low complexity; (4) low effort for maintenance and operation; (5) low investment costs. Applicable international standards will be considered, e.g.: IEC 60601-1; IEC 60601-2-64; IEC 60601-1-2; IEC 60601-1-6; IEC 60601-1-8; IEC 62304; IEC 82304; IEC 62366-1; IEC 61217. The work is based on MedAustron's and Cosylab's experience in design and clinical operation of such systems. Experience of other partners within the HITRI*plus* community will be included. The results of this task are relevant for WP7, WP10, WP11 and are also directly relevant to all other HITRI*plus* partners who are treating patients like CNAO; MedAustron and UKHD/HIT.

WP11 Deliverables

Title	Delivery Month
D11.1: Report on the state-of-the-art TCS, ACS and patient safety systems	18
D11.2: Design study on novel treatment room control systems	42
D11.3: Design study on novel accelerator control systems	46
D11.4: Design study on novel patient safety systems	46

WP number	WP12		Lead beneficiary			UMR	
WP title	**JRA6 - Radiobiological Dosimetry and QA**						
Participant nr.	15	8	1	10	7	-	-
Participant	UMR	UKHD/HIT	CNAO	MEDA	GSI	-	-
Person months	12	12	8	2	2	-	-
Start Month	1		**End month**			48	

Objectives

The objective of the WP is to create a dosimetry standardization for radiobiological experiments. One main aim in radiobiology is to establish associations between various doses and their effects induced on cellular level. Treatment planning and beam application technology vary between the European ion therapy centres, and to be able to meaningfully evaluate and compare research results, standardization of radiation dosimetry is a very important step. It requires precise dose measurements and detailed information about how measurements were performed, to create a dosimetry standard operating procedure. Additionally, the characterization of mixed radiation field using silicon detectors, TEPC, amongst others could further improve the quantification of the physical uncertainties influencing biological read-outs. Furthermore, this WP creates an objective and quantitative approach to compare treatment plans.

Description of Work

Task 12.1: In vitro joint experiment for Radiobiological dosimetry and quality assurance *(UMR, HIT, CNAO, MedAustron, GSI)*

As first approach, a survey among the participants will be circulated in order to create a common standard operating procedure (SOP). A commercial cell line selected according to its wide use for radiobiological studies, its proliferating times, and plating efficiency will be purchased by the participants from the same provider. The experiment will be done by researchers from each participating institute at their own facilities.

Each participating centre will also carry out additional X-ray clonogenic assay experiments to produce a reference survival curve for the carbon ion experiment.

To minimize the variability of results, the institutes will share the same phantom specifically dedicated for in vitro dosimetry by means of clonogenic survival provided by GSI. The phantom will be positioned at different depths for simultaneous irradiation at different positions inside the SOBP.

Together with RBE calculation and comparison in normal conditions, also hypoxic conditions, different oxygen environments will be tested and evaluated at all facilities.

Task 12.2: Modelling joint experiment for radiobiological dosimetry and quality assurance *(HIT, CNAO, MedAustron, GSI)*

Initially, a survey of the planning software and options available among the centres will be carried out in order to harmonize the planning process. Once defined the cell line in Task 12.1 and its characterization with X-rays, creation of the biological database for treatment planning systems will be carried out. The plans will be created with the clinical TPS and re-calculated with Monte Carlo (MC) engines when available. Additionally, direct inter-comparisons with the same calculation engines could be made possible by using RayStation (RaySearch Labs) and FRoG (Fast dose* Recalculation on GPU). This choice decreases the variability between the calculation engines which could affect the predicted biological response. The chosen biological models in normoxia are: Local Effect Model IV (LEM IV), modified Microdosimetric Kinetic Model (mMKM) and UNIVERSE (UNIfied and VERSatile cell/tissue response Engine). For hypoxic conditions, dose-averaged LET(LETd)-based phenomenological approaches together with mechanistic frameworks (for mMKM and UNIVERSE) will be implemented in research TPS and MC engines. Model predictions will be compared vs. survival experimental data at different depths /LETs, dose levels and hypoxic conditions.

WP12 Deliverables	
Title	**Delivery Month**
D12.1: Conceptual design report and proceeding; joint radiobiological experiments in all facilities	36
D12.2: Modelling of the joint results	40
D12.3: Final report and summary	46

The following *Figure 19* reports the Gantt chart of HITRI*plus* with evidence, within the time plan, of Deliverables and Milestones.

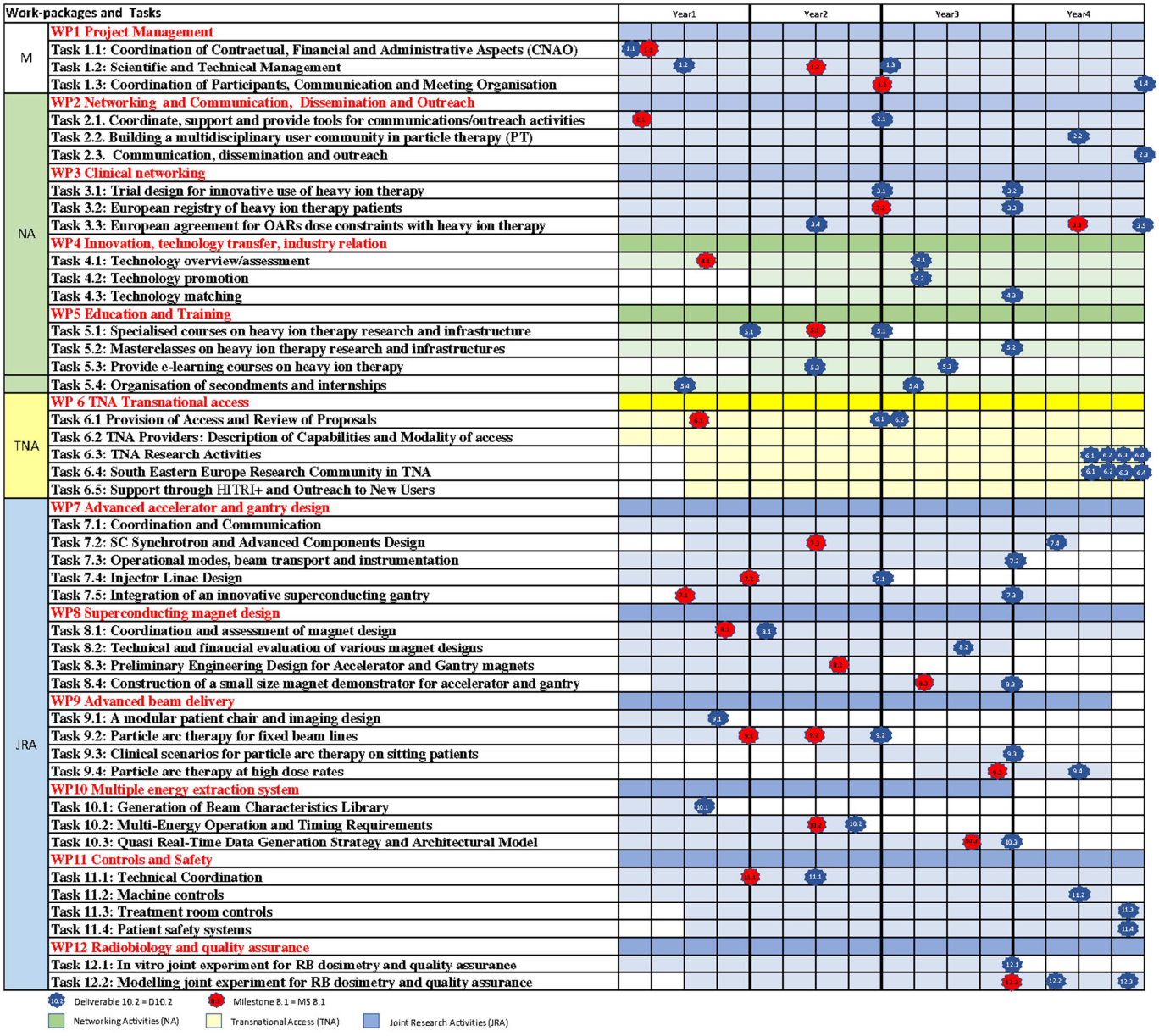

Figure 19 *- Timing of the Work Packages and their components (Gantt chart, red = Milestone, blue = Deliverable).*

Table 3.1c and Table 3.2a report the complete list of Deliverables and Milestones, respectively.

***Table 3.1c** - List of Deliverables.*

Deliverable (number)	Deliverable name	Work package number	Short name of lead participant	Type	Dissemination level	Delivery date (in months)
D1.1	All governance boards installed	1	CNAO	R	PU	1
D1.2	Plenary meetings reports	1	CNAO	R	PU	3, 12, 25, 37, 48
D1.3	Data Management Plan	1	CNAO	R	PU	6
D2.1	Dissemination to the community about the possibility of the TA and access to clinical research with patients from EU - through out	2	SEEIIST	R	PU	3
D2.2	Dissemination and outreach plans developed and regularly updated	2	SEEIIST	R	PU	2, 12, 24, 42
D2.3	Provide an annual activity report for the NA Pillar and final scientific achievements including the use and dissemination of foreground.	2	SEEIIST	R	PU	12, 24, 36, 46
D 3.1	Review of promising innovative heavy ion therapy approaches to be brought to the clinics	3	MEDA	R	PU	24
D 3.2	Trial protocol for innovative heavy ion therapy concept	3	MEDA	R	PU	36
D 3.3	Web based heavy ion therapy patient registry	3	CNAO	DEC	CO	36
D3.4	Dose constraints of OARs in use at European heavy ion therapy facilities	3	UKHD/HIT	R	PU	18
D 3.5	Recommendations for dose constraints on one OAR based on pooled data analysis	3	UKHD/HIT	R	PU	48
D4.1	Internal report on the HITRI*plus* technologies and dissemination plan	4	CERN	R	CO	14, 28
D4.2	Value propositions promotional text	4	GSI	R	PU	18, 28
D4.3	Organisation of a technology matching event	4	INFN	R	PU	36
D5.1	Delivery of specialised training courses	5	SEEIIST	DEC	PU	12, 24,
D5.2	Delivery of masterclasses and train-the-trainer masterclasses	5	GSI	DEC	PU	12, 24, 36, 47
D5.3	Provision of e-learning courses	5	UM	DEC	PU	18, 30,
D5.4	Organisation of secondments and internships: calendar of events	5	UM	DEC	PU	6, 24
D6.1	HITRI*plus* delivers 160 units of TA by month 24	6	GSI	R	PU	24
D6.2	HITRI*plus* delivers 498 units of TA by month 48	6	GSI	R	PU	48

D6.3	Treatment of 50 with heavy ion therapy in TA	6	GSI	R	CO	48
D6.4	Publication of an overview article or a focus issue on the results of the TA -financed activities	6	GSI	R	PU	48
D7.1	Advanced conceptual design of an optimised linac injector for multiple ions at 10 MeV/u	7	BEVA	R	CO	24
D7.2	Report on operational modes, beam transport and instrumentation	7	SEEIIST	R	PU	36
D7.3	Report describing the main optics parameters and integration features of the gantry	7	CNAO	R	CO	36
D7.4	Design of an optimised synchrotron with SC magnets and advanced features: high beam intensity, fast and slow extraction, multiple ion operation, optimised Linac injector, optimised instrumentation and QA procedures	7	SEEIIST	R	PU	40
D8.1	Report on assessment of magnet types, suitable for fast SC synchrotron and for SC gantry and preliminary evaluation	8	CEA	R	PU	14
D8.2	Final report on Magnet design for SC synchrotron and SC gantry, with indication of time, cost and technology readiness assessment	8	INFN	R	CO	32
D8.3	Magnet Demonstrator completed	8	INFN	DEM	CO	36
D9.1	Conceptual Design Report for a patient chair capable of rotating the patient around a vertical axis as well as a vertical in-room imaging system	9	GSI	R	PU	9
D9.2	Particle arc therapy delivery to a small scale demonstrator of a rotational patient positioning system for gantry-free delivery with a position feedback integrated to the DDS	9	GSI	DEM	PU	24
D9.3	Identification of beneficial patient arc therapy scenarios by lesion location and delivery mode	9	GSI	R	PU	36
D9.4	Experimental validation of arc therapy treatment plans through patient QA-like procedures	9	GSI	R	PU	42
D10.1	Beam Characteristics Library	10	UKHD/HIT	R	CO	8
D10.2	Data Distribution and Synchrotron	10	UKHD/HIT	R	CO	22

	Timing Requirements					
D10.3	Real-Time Data Generation Strategy	10	UKHD/HIT	R	CO	36
D11.1	Report on the state-of-the-art TCS, ACS and patient safety systems	11	CSL	R	PU	18
D11.2	Design study on novel treatment room control systems	11	CSL	DEM	PU	42
D11.3	Design study on novel accelerator control systems	11	CSL	DEM	PU	46
D11.4	Design study on novel patient safety systems	11	CSL	DEM	PU	46
D12.1	Conceptual design report and proceeding; joint radiobiological experiments in all facilities	12	UMR	R	PU	36
D12.2	Modelling of the joint results	12	UKHD/HIT	R	PU	40
D12.3	Final report and summary	12	UMR	R	PU	46

The *Figure 20* is a graphical presentation of the HITRI*plus* structure showing the inter-relation among the different WPs. It outlines the structure in pillars of the project: Networking Activities, Transnational Access and Joint Research Activities. The pillars refer to a unique management coordination represented by WP1 (on top in orange, connected with a single bar to all three pillars) that acts as supervisor and integrator of the entire project. This coordinating action is guaranteed by the TPB.

The NA pillar, shown in green on the left, is organized in four WPs that act as services for the other two pillars. The transversal action of NA is represented by the green arrows, going back and forth, right to left and left to right across JRA and TA, giving inputs, defining procedures and rules, but also getting results, information and feedbacks. The mutual process cross-feeds and permeates the whole project and favours exchange integration among WPs. This same process guarantees visibility and openness to the external world. WP2 and WP3 in NA are particularly important for TA, because they contribute to open the access of the facilities to the external medical and research communities. In addition WP3 contributes to define the clinical content of the information spread outside the project via the communication activities of WP2.

The JRA pillar, in light blue, is composed of different WPs, from WP7 to WP12, that are all integrated and coordinate in a common strategy. The influence of the NA's green arrows on the JRA is bi-directional: one way to favour the essential collection of input data and specifications from the potential users; the other way to share the outcome results of the single WPs with the existing infrastructures in HITRI*plus* to improve their performances at the advantage of the users. Last but not least, the overall outcome of the JRA consists in a novel design of a new generation RI facility that will be at disposal of the EU community and in particular of SEEIIST.

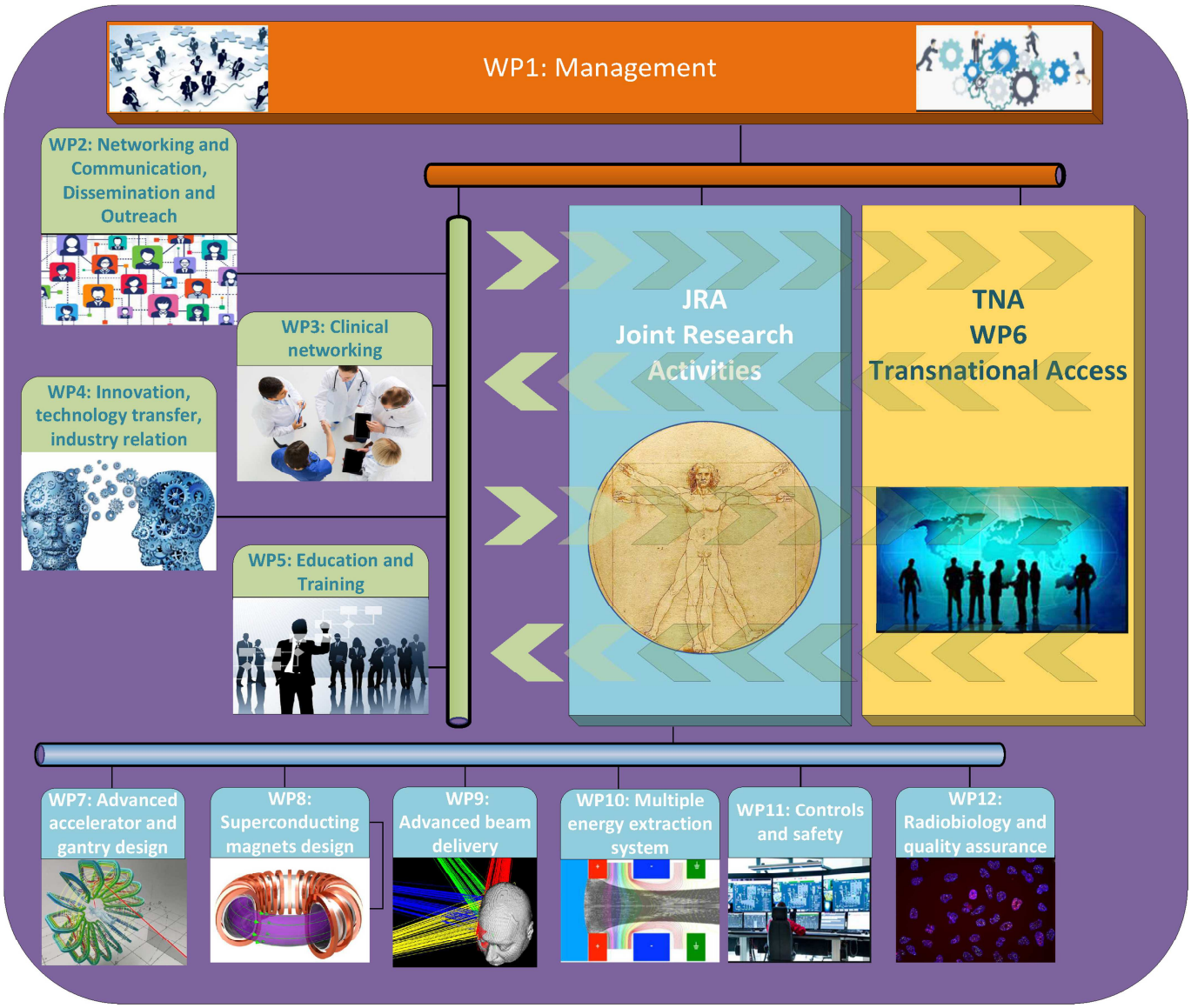

Figure 20 *- Graphical presentation of the components showing how they inter-relate.*

3.2 MANAGEMENT STRUCTURE, MILESTONES AND PROCEDURES

The general set-up of the HITRI*plus* project management consists of three functional and hierarchical layers: the General Assembly, the Coordinator, the Technical Project Board interfacing the WPs thematically organized in three types of activities: Networking, Transnational Access, Joint Researches Activities. The management structure of the project is presented in the *Figure 21*.

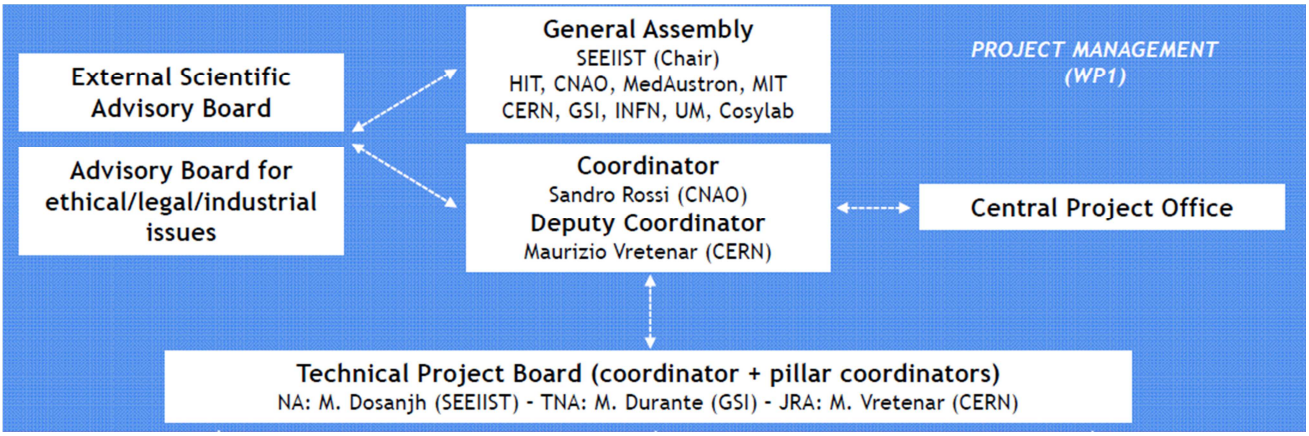

Figure 21 *– Project Management organization.*

General Assembly

The General Assembly (GA) is the highest decision-making and arbitration body of the project and consists of one senior level representative for each beneficiary in the project, including Third Parties. Coordinator and Deputy Coordinator are ex-officio members, without voting rights. The Chairperson appointed for the first year will be ex-officio the Chair of the SEEIIST Steering Committee, while for the following years the Chair will be elected by the GA members. Each beneficiary or Third Party has one vote, and decisions are taken by a majority of the votes. The types of decisions and the corresponding voting procedure and rules will be described in the Consortium Agreement. The GA will meet twice per year, one in person during the Yearly meeting and one by videoconferencing. The GA is regularly informed by the Coordinator about overall project progress and other matters that may have a structural impact on the goals and/or deliverables of the project. The GA will appoint the members of the External Scientific Advisory Board (ESAB) and the Advisory Board for Ethical/Legal/Industrial Issues (ABELII) and consult with them at least once per year.

Project Coordinator

The Project Coordinator (PC) is responsible for the technical management and scientific coordination of the project, assisted by the Deputy Project Coordinator. The PC will chair the Technical Project Board meetings, lead the Central Project Office, define the principles for internal and external communication, monitor the overall progress of the project, follow and verify the deliverables, represent the project vis-à-vis the European Commission, be responsible of preparing contractual reports, organise and transmit relevant project information, manage potential conflicts, communicate with external stakeholders, and monitor and promote gender equality.

Administrative and financial tasks and responsibilities include managing the financial administration of the overall project expenses, and reporting the overall budgetary situation of the project to the European Commission.

Technical Project Board

The Technical Project Board (TPB) represents the technical focal point for the project activities. The TPB is chaired by the Coordinator and will consist of the three WP Coordinators selected by the Coordinator to represent their own Pillar.

The TPB, supported by the Central Project Office, is in charge of the technical coordination management of the project. The TPB will meet remotely to discuss progress and coordinate joint activities. When strategic technical decisions have to be taken the TPB meets to define the issues and gather all the information and data needed, preliminary evaluate criticalities, obtain partner opinions and consider different options and possibilities. In situations where decision may affect the structural aims and deliverables of the project, the Coordinator will present the TPBs' conclusions to the General Assembly for a vote.

External Scientific Advisory Board

The External Scientific Advisory Board (ESAB) is composed of three outstanding and internationally recognized experts in the field of radiation therapy (both medical and technical). The members are proposed by the Coordinator and must be approved by the GA. The composition of the ESAB may change during the duration of the project. The initial members may resign and new members are elected to replace them. The ESAB will meet annually and will examine the project progress and their link with the continuously evolving scenario of cancer care and associated research. The ESAB will designate a Chairperson among its members. The Chair will be the link with the GA and the Coordinator that may consult him/her on specific issues.

Advisory Board for Ethical, Legal, Industrial Issues

The Advisory Board for Ethical, Legal and Industrial Issues (ABELII) provide advice to the Coordinator on special ethical, legal and relations with industries matters indicated by either the Coordinator or the Technical Project Board. Special and sensitive issues may arise as a result of - for example - performing clinical trials, privacy matters, secure treatment and storing of sensitive data, treatments entailing risks to human health or any other ethical or legal implication or definition of IP and relations with industries of activities in order to achieve the aims

of the project. The ABELII will meet with the Coordinator twice a year unless requested more frequently. It is indicatively composed by three members, but it may be complemented if needed by external experts to address specific issues.

Central Project Office

The project Coordinator will create and manage a Central Project Office (CPO), in charge of overall day-by-day administrative management and coordination of the project, design and implementation of project reporting procedures, design and implementation of all templates, forms, presentation formats etc., used in the project, definition, monitoring and on-going revision of the detailed Project Work Plan, supervision of all activities necessary to ensure compliance with EC reporting and administrative requirements, detailed organization of meetings, and revision and final editing of all Project Deliverables.

The CPO will set up a common-workspace on the internet which will act as the common archive for all project documents, accessible to partners at any time.

***Table 3.2a** - List of Milestones.*

Milestone number	Milestone name	Related work package(s)	Due date (in month)	Means of verification
M1.1	Kick-off meeting completed	1	1	Start of HITRI*plus*
M1.2	Mid-term General Assembly Meeting completed	1	18	Agenda, attendance, minutes
M 2.1	Project website launched	2	2	Public website
M3.1	Evaluation of web based registry development status	3	24	Report
M3.2	Evaluation of impact on European centres OARs constraints	3	42	Report
M4.1	First meeting of the Technology Overview committee with definition of the work plan	4	8	Meeting minutes
M5.1	Specialised Courses and masterclasses content definition	5	18	Report
M6.1	Implementation of a USP structure and Website Communication Platform	6	8	Users can apply for TA and these are evaluated by USP. Public website.
M7.1	Choice of conceptual design and basic parameters of the innovative superconducting gantry	7	6	Report
M7.2	Selection of basic linac design: frequency, layout	7	12	Report
M7.3	Definition of key parameters for the superconducting synchrotron, including magnet field and type	7	18	Report
M8.1	Decision on layout of demonstrator magnets Task 8.1	8	10	Report
M8.2	Engineering Design of synchrotron-gantry dipole Task 8.3	8	20	Report
M8.3	Manufacturing readiness of demonstrator Task 8.4	8	28	Report
M9.1	Small scale rotary stage finished and linked to DDS	9	12	Report

M9.2	Finished simulation environment for particle arc therapy	9	18	Report
M9.3	Installed GEM detector in GSI beamline,	9	24	Report
M10.1	Data Distribution and Timing Requirements	10	18	Report available
M10.2	Real-Time Data Generation Strategy	10	32	Report available
M11.1	Intermediate report on the state-of-the-art treatment room, accelerator control systems, and patient safety systems.	11	12	Report
M12.1	Generation of a standardized dosimetry for collaborative radiobiological experiments between the facilities	12	40	SOP completed, data of all participants integrated and validated

Table 3.2b - *Critical risks for implementation.*

Description of risk (indicate level of likelihood: Low/Medium/High)	Work package(s) involved	Proposed risk-mitigation measures
Luck of collaboration or interaction between partners (Low)	all	Continuously ensure coordination among pillars and regular meeting and exchange in the Technical Project Board, involvement of the Advisory Boards, discussion with partners to find a solution
Unexpected pandemic (e.g. Covid19) or other events impacting working environments and travels (Low)	all	Introduce modalities based on smart working and videoconferencing. Reconsider funding allocations between partners to maintain agreed global output of HITRI*plus*
Termination of the support from the SEE countries to the project (e.g. one or more countries leaving the SEEIIST) (Low)	1,2,5,7,8,11	The SEEIIST as a collaboration of Universities and Institutes in SEE can continue even with low political support. In case of major problems, activities, personnel and budget of SEEIIST in HITRI*plus* can be transferred to another partner, e.g. CERN that is hosting and supervising the SEEIIST team.
The web based registry in Task 3.2 cannot be established within the framework of this project because of lack of cooperation from partners (Medium)	3	As mitigation strategy, the task will focus on providing a commons semantic of heavy ion therapy relevant outcome and toxicity data for future registry implementation.

Not enough candidates register for the specialised courses and the masterclasses (Medium)	5	Advertisement will be improved, via different contact points and media. Course content will be made as engaging as possible to keep the students committed.
Failure to engage a strong HITRI*plus* community in Networking (Medium)	2, 3	Increase the commitment of the HITRI*plus* project team that has strong and varied backgrounds in engaging with national and international networks and conferences to promote HITRI*plus* and the offered capabilities.
Under estimation of demand for TA, the amount of positively evaluated proposals exceeds TA capacity (Medium)	6	Limit hours initially available to each project. Only allocate more hours to the very best projects once they have met first milestone. Evaluate and optimise scheduling and ensure that TA provision equates with where the demand is.
Overestimation of demand for TA (Medium)	6	Increase advertising and networking possibilities to attract new users through different events dedicated to networking.
SC Magnets for synchrotron not viable or very expensive (Medium)	7	Design with optimized normal conducting magnets.
Magnet demonstrator too complex and expensive for the allocated budget (High)	8	Increase the matching funds of some Institute and/or reduce the target parameters of demonstrator.
Delivery speed increase misses goal of <1 ms per spot (Medium)	9	Impact for most clinical cases is small, as delivery similar to existing facilities. A speed-up would facilitate several motion mitigation strategies (breath-hold), which could be replaced by alternative strategies (gating+rescanning)
Arc therapy delivery takes too long or is impracticable in combination with patient chair (Low)	9	Fast multi-field delivery pursued instead, or delivery on gantry system
Beam instable after reacceleration (Low)	10	Rework synchrotron timing
Ethernet-based timing not precise enough (Low)	10	Define a hardware-based timing system
Existing facilities too busy treating patients to dedicate enough personnel to give crucial feedback on the proposed solutions (Medium)	11	Organize dedicated workshops and discussions with clinical facilities.
Phantom design cannot be equivalently used at all participating centres due to variation in beam application (Low)	12	Evaluation of another one phantom among the ones available at GSI.

3.3 CONSORTIUM AS A WHOLE

The beneficiary-consortium consists of 2 major European heavy ion physics laboratories, 4 European ion therapy centres, 8 world-class research institutions, 5 leading universities, 3 innovative SME's (two of which from SEE region). Some partners are active in the field of heavy ion therapy since many years and form the core of Europe's expertise and capacity in this field. Their commitment to the HITRI*plus* project is clearly evidenced by the substantial voluntary co-funding that each of them is willing to bring into the project. Their combined knowledge and background, grounded in experience of running four state-of-the-art treatment facilities and committed user communities, constitutes the core of this proposal. Some Consortium partners have also previously been involved in challenging European projects, The project will benefit from the complementary experience and expertise of the beneficiaries in the following ways.

Management of the project is ensured by CNAO, which has the requires structure and expertise, supported by CERN, GSI, and SEEIIST.

The HIT, CNAO, MEDA, MIT facilities are central players for the clinical and research activities and the related networking and to favour the trans-national access of patients and medical professionals. These facilities provide also the technological, medical, research and economic benchmarks against which SEEIIST will base the new RI in the SEE countries. They also bring to the project their operational experience in designing, constructing and running a particle therapy facility. Their expertise is also crucial to the project's effort to create a future medical user community in the SEE countries. Together with GSI, which has extensive expertise in biophysics, medical physics, radio-biology and heavy ion accelerator systems and that was the place where first Europeans patients were treated with heavy ion therapy, they will allow access of the international research community to the heavy ion beams and related research infrastructures.

CERN's expertise lies in designing, constructing and operating accelerators and their subsystems, including superconducting magnets, synchrotrons, ion sources, beam dynamics, control systems and diagnostics. In these activities CERN will partner with the accelerator design team of SEEIIST and CNAO, and specifically for the linac design with the crucial expertise of BEVA, a spin-off company of Frankfurt University. RTU will contribute to the gantry design with its expertise in mechanical engineering. The activity (WP8) on superconducting magnets will access the competences of the main European players in the field, with a consolidated tradition of collaboration in the CERN projects (LHC, HL-LHC) and in other European initiatives (ARIES, EUCARD2): INFN, CERN, PSI, CIEMAT, CEA, UU and Wigner RCP. The SME SEN will contribute in designing and building magnetic measurement instrumentation for magnet characterisation. CSL is a world-wide renowned company for control system, with a specific expertise in the control of medical accelerators, having designed for example the control system of MEDA. It will exploit this experience and jointly with MEDA and the research centre IJS will design and develop modular accelerator and therapy control systems. GSI and CNAO have a decade-long expertise in heavy ion beam delivery systems that they will bring into the project. Similarly, HIT, GSI and CNAO have a long experience in extraction system that will be made available to the project. UMR, HIT, CNAO, MEDA and GSI have all a long experience in QA and treatment planning.

A particular case is the SEEIIST institution, which is one of the initiators of this Starting Community but as an institution has been set up only recently and does not have specific experience in the field. However, its first priority since inception has been to set up an accelerator design team made of experienced accelerator designers, to be hosted at CERN. This team is already active since Spring 2019, thanks to the support of the European Commission via an initial Service Contract. The team is supervised by an experienced CERN staff member former project leader of a project of similar size and complexity, and has already produced important results that have allowed a more precise definition of the SEEIIST design. In addition, SEEIIST has started a communication team that deals with the communication issues of the project and with the contact with the ion therapy community, supervised by a retired CERN staff member.

CERN is also contributing with its Knowledge Transfer team and experience, and with support to the management of the project via the Deputy Coordinator.

The University of Malta is a long-standing partner in accelerator projects (EuCARD2, ARIES), which is engaging now in an activity related to its key competences, education and training in an advanced technical field.
The expertise of the different partners on the core competences required by the project is graphically represented in Figure 22.

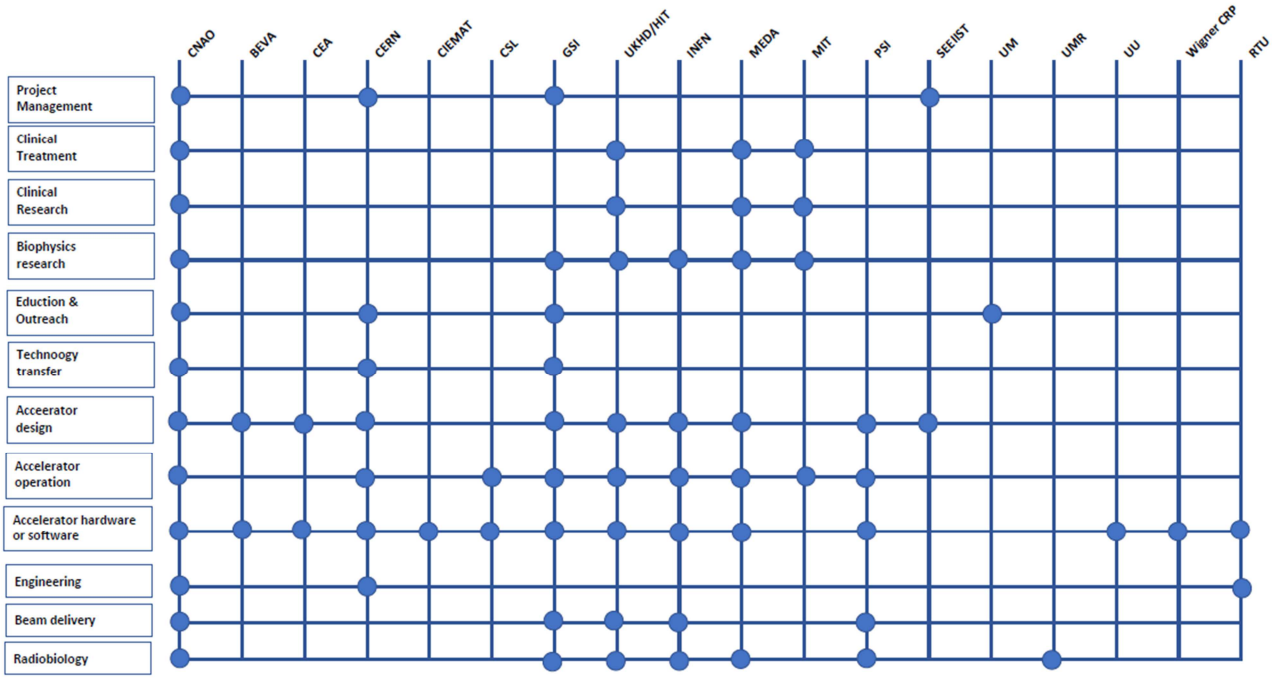

***Figure 22 -** HITRIplus expertise.*

3.3.1 Support Letters

The Letters of Support (LoS) for HITRI*plus* are in Annex I. LoS are available from: TIARA Consortium; Central European Initiative; European Network for Light Ion Hadron Therapy; CERN Baltic Group; INSPIRE Consortium.

List of Abbreviations	
ABELII Advisory Board for Ethical/legal/Industrial issues	**NOL** Novel Object Location
ARIES Accelerator research and Innovation for European Science and Society	**NOR** Novel Object Recognition
CCT Canted Cosine Theta	**OAR**s Organs At Risk
CERN European Organisation for Nuclear Research (Conseil Européen pour la Recherche Nucléaire)	**OER** Oxygen Enhancement Ratio
CT computed tomography	**OMA** Optimization of Medical Accelerators
DDS Dose Delivery System	**PET** Positron emission tomography
DMP Data Management Plan	**PIMMS** Proton-Ion Medical Machine Study
EC European Commission	**PTCOG** Particle Therapy Co-Operative Group
ENLIGHT The European Network for Light Ion Hadron Therapy	**QA** Quality Assurance
ERA European Research Area	**R&D** Research and Development
ESA European Space Agency	**RBE** Relative Biological Effectiveness'
ESAB External Scientific Advisory Board	**RFQ** Radio Frequency Quadrupole
ESFRI European Strategy Forum on Research Infrastructures	**RI** Research Infrastructure
ESR Experimental Storage Ring	**RT** Radiotherapy
ESTRO European Society for Radiotherapy and Oncology	**SC** Superconducting
FAIR Facility for Antiproton and Ion Research	**SEE** South East Europe
GDPR General Data Protection Regulation	**SEEIIST** South East European International Institute for Sustainable Technologies
GEM Gas Electron Multiplier	**SIS** Schwer-Ionen-Synchrotron
GUIs Graphical User Interfaces	**SME** Small Medium Enterprise
HITRI Heavy Ion Therapy Research Integration	**SOP** Standard Operating Procedure
HTS High Temperature Superconductors	**TEPC** Tissue Equivalent Proportional Counter
IAEA International Atomic Energy Agency	**TA** Transnational Access
IES Iso-Energy Slices	**TERA** Terapie con radiazioni Adroniche
IEIO International European Interest Organisation	**TPB** Technical Project Board
I.FAST Innovation Fostering In Accelerator Science and Technology	**TPS** Treatment Planning System
IMRT Intensity-Modulated Radiation Therapy	**TRiP** Treatment Planning for Ion Beam Radiotherapy
INSPIRE Integrating Proton Beam Therapy Research across Europe	**UNILAC** Universal Linear Accelerator
IP Intellectual Property	**USP** User Selection Panel
JRA Joint Research Activities	
KPI Key Performance Indicator	
KT Knowledge Transfer	
LEM Local Effect Model	
LET Linear Energy Transfer	
LHC Large Hadron Collider	
LoS Letters of Support	
LTS Low Temperature Superconductors	
MC Monte Carlo	
mMKM Microdosimetric Kinetic Model	