The Laser-hybrid Accelerator for Radiobiological Applications

R&D proposal for the preliminary, pre-construction phases

The LhARA collaboration

This author list was taken from the Frontiers publication and must be updated.

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Executive summary

LhARA [1, 2], the Laser-hybrid Accelerator for Radiobiological Applications, is conceived as the new, highly flexible, source of radiation that is required to explore the vast "terra incognita" of the mechanisms by which the biological response to ionising radiation is determined by the physical characteristics of the beam [3]. The LhARA collaboration's concept is to exploit a laser to drive the creation of a large flux of protons or light ions which are captured and formed into a beam by strong-focusing plasma lenses. The triggerable, laser-driven source allows protons and ions to be captured at energies significantly above the proton- and ion-capture energies that pertain in conventional facilities, thereby evading the current space-charge limit on the instantaneous dose rate that can be delivered [4]. The plasma (Gabor) lenses provide the same focusing strength as high-field solenoids at a fraction of the cost. Post-acceleration, performed using a fixed field alternating gradient accelerator (FFA), will preserve the unique flexibility in the time, energy, and spatial structure of the beam afforded by the laser-driven source.

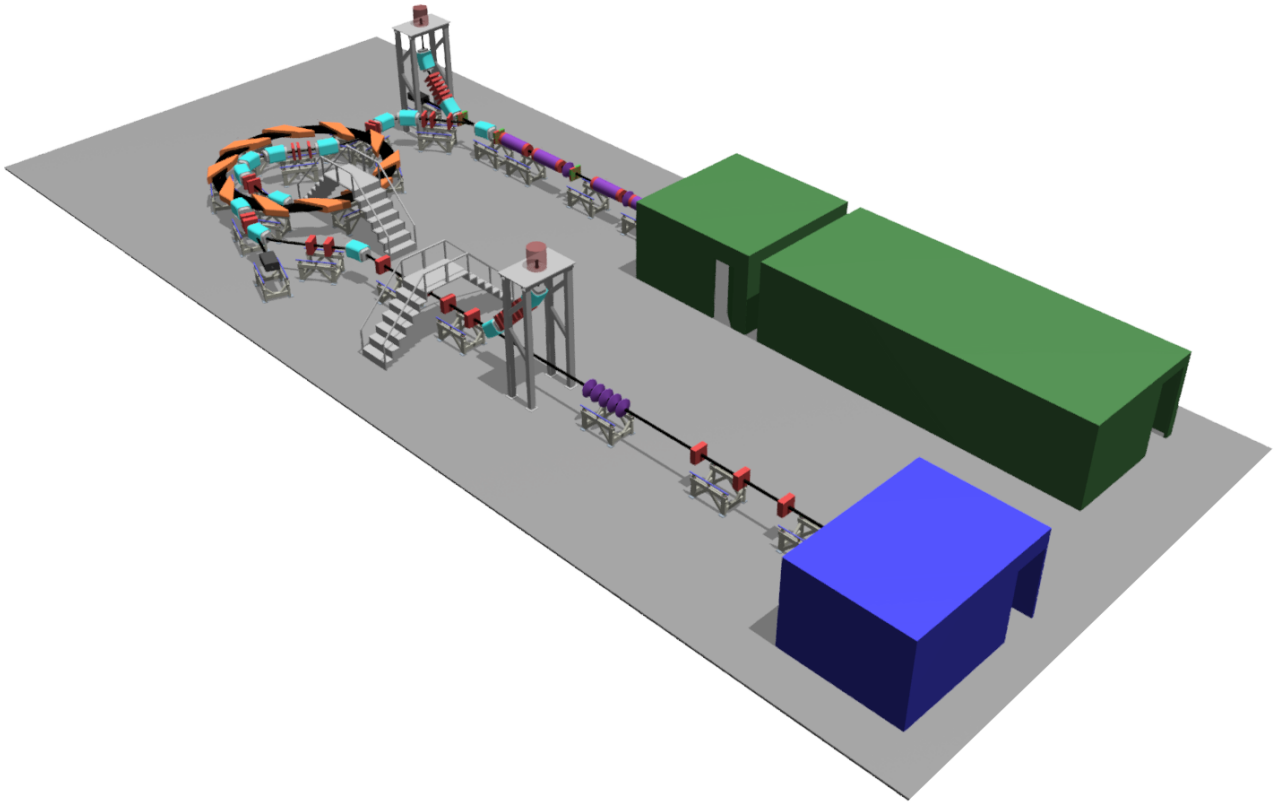

Figure 1: LhARA—the Laser-hybrid Accelerator for Radiobiological Applications.

The LhARA collaboration's vision [5] is to radically transform the clinical practice of proton- and ion-beam therapy (IBT) by creating a fully automated, highly flexible system to harness the unique properties of laser-driven ion beams to:

- Deliver particle-beam therapy in completely new regimens by combining a variety of ion species from proton to carbon in a single treatment exploiting ultra-high dose rates and novel temporal-, spatial- and spectral-fractionation schemes; and
- Make "best in class" treatments available to the many by reducing the cost of IBT per patient. The system we propose integrates patient, soft-tissue, and dose-deposition imaging with real-time treatment planning in an automatic system that triggers the delivery of dose tailored in real time to the individual patient. Our

system will reduce the cost per patient by removing the requirement for a large gantry, thereby reducing the size (and therefore the cost) of a clinical IBT facility and increasing patient throughput by reducing the time spent in treatment.

We have created the multi-disciplinary collaboration [6, 7] of clinical oncologists, medical, particle, plasma, laser, ultrasound, and optical physicists, accelerator, computer, and instrumentation scientists, radiobiologists, industrialists, and patient representatives required to realise our vision. With this proposal the collaboration seeks to initiate its broad and ambitious, multi-disciplinary programme to:

- Demonstrate the feasibility of the laser-hybrid approach in a facility dedicated to biological research; and
- Create the national and international partnerships necessary for LhARA to become a multidisciplinary research centre of excellence in the UK.

LhARA formed the basis of a recent proposal to the UK Research and Innovation (UKRI) Infrastructure Advisory Committee to create an "Ion Therapy Research Facility" (ITRF) [8]. The proposed ITRF "*... will be a unique, compact, single-site national research infrastructure delivering the world's first high-dose-rate ions from protons through oxygen and beyond, at energies sufficient for both in-vitro and in-vivo studies.*" The ITRF proposal notes that a "*... laser-hybrid proton/ion source, as proposed by the existing, UK-led, international LhARA collaboration (see figure 3), can deliver this and meet the needs of the ITRF.*" The proposal is for a two-year Preliminary Phase activity and identifies the need for a subsequent three-year pre-construction phase. The timeline for the development of the ITRF defined in the proposal is shown in figure 2.

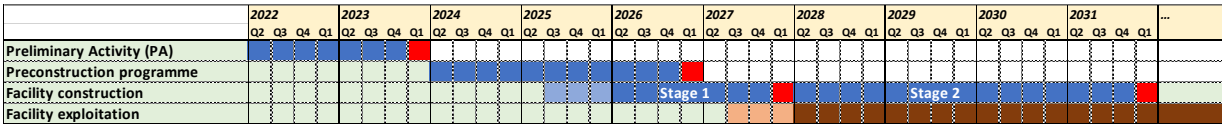

Figure 2: Timeline for the development of the Ion Therapy Research Facility presented in the proposal to the UKRI Infrastructure Advisory Committee [8].

We propose that LhARA be developed to serve the ITRF in two stages [1, 2]. In the first stage, the laser-driven beam, captured and transported using plasma lenses and bending magnets, will serve a programme of *in-vitro* experiments with proton beams of energy of up to 15 MeV. In stage two, the beam will be accelerated using an FFA. This will allow experiments to be carried out *in vitro* and *in vivo* with proton-beam energies of up to 125 MeV. Ion beams (including C^{6+}) with energies up to 30 MeV per nucleon will also be available. The beam energy at LhARA has been specified to allow *in-vitro* experiments and *in-vivo* studies using small mammals. The LhARA collaboration's hybrid approach will allow the unique properties of the laser-driven source—extremely high instantaneous flux in an extremely sort pulse over a tiny area—to be preserved and exploited to deliver radiobiological investigations in completely new regimens.

LhARA will not be developed or operate in isolation. Proton and ion beams for radiobiological research are available at a number of laboratories in Europe, the Americas, Africa, and in Asia. A number of clinical proton- and ion-beam centres (e.g. [9–17]) also provide beams for research. A small number of laboratories in Europe actively seek to develop laser-driven sources for biomedical applications (e.g. [18]). The LhARA collaboration's vision is to build on this work to demonstrate the feasibility of capturing and manipulating the flux created in the laser-target interaction to provide a beam that can be accelerated rapidly to the desired energy. The collaboration recognises the scientific imperative of engaging with partners in the UK and overseas to develop a state-of-the-art programme of research into the biological effect of ionising radiation. Therefore, an integral part of the programme we propose is the exploitation of existing proton- and ion-beam facilities at home and abroad using techniques co-created by the collaboration and its partners. Modest resources to support this aspect of the collaboration's programme are requested.

With this proposal we seek the resources to deliver the Preliminary and Pre-construction Phases of the programme necessary for LhARA to serve the ITRF. Over the first two years the Preliminary Phase will deliver:

- CDR ...

The Pre-construction Phase will be carried out over years three to five of the programme we propose and will deliver:

- TDR ...

The five-year programme we propose will lay the foundations for the establishment of an entirely new technique for the automated delivery of personalised, precision, multi-ion IBT, place the UK at the forefront of the field, and establish UK industry as a key player in the delivery of novel clinical equipment. In addition, by partnering with proton- and ion-beam providers for biomedical research at home and overseas, our research programme will allow significantly enhanced access to and exploitation of state-of-the-art IBT research facilities for researchers across the UK.

Lay summary

Lead authors: H. Hall, G. Jones
Indicative page count: 1

Contents

1 Motivation

In the UK it is anticipated that 1 in 2 people will develop cancer [19]. The present incidence of 17 million new cases per year globally is predicted to increase to 27.5 million new cases per year by 2040 [20]. Radiotherapy (RT) is used in 50% of cancer patients and is already involved in 40% of cancer cures [21]. The NHS long-term plan [22] to increase the rate of diagnosis of cancer in the early, curative stage, implies an increasing need for therapeutic interventions including RT.

Photons are used most frequently to deliver external-beam RT. There is increasing emphasis on the exploitation of proton and ion beams in proton- and ion-beam therapy (IBT) for which the bulk of the beam energy is deposited in the Bragg peak that occurs as the beam comes to rest. This allows dose to be conformed to the tumour while sparing healthy tissue and organs at risk. The benefits of IBT are widely recognised. The NHS has invested £250M in proton-beam therapy [23] and the Particle Therapy Co-Operative Group (PTCOG) [24, 25] currently lists 90 proton therapy facilities and 12 carbon-ion-therapy facilities [26]. These facilities are located predominantly in high-income countries[26]. Nearly 70% of cancer patients in low-and-middle-income countries globally do not have access to RT [21].

The beam characteristics that can be exploited in IBT facilities today are restricted to low dose rates ($<$ 10 Gy/min), a small number of temporal schemes (a typical treatment is delivered in "fractions" of 2 Gy per day over several weeks) and a small number of spatial distributions (predominantly large beams delivering a homogeneous dose over several square centimetres). Clinical efficacy is dependent on the dose delivered which in turn is limited to minimise damage to the healthy tissues. The use of novel beams with strikingly different characteristics has led to exciting evidence of enhanced therapeutic benefit, e.g. therapy using very high dose per fraction [27], very high dose rate ($>$ 40 Gy/s, "FLASH") [28], and "mini-beam" (MBRT) [29, 30]. This evidence, together with developments in our understanding of personalised medicine based on the biology of individual tumours, now provides the impetus for a radical transformation of IBT.

Laser-driven proton and ion sources are disruptive technologies that offer enormous potential to satisfy the anticipated growth in demand for IBT by providing more flexible, compact and cost-effective high energy particle sources. We propose to develop a laser-hybrid system, in which novel strong-focusing electron-plasma (Gabor) lenses capture and focus the large flux of protons or ions created when a short pulse, high-power laser strikes a target, thereby delivering a wide variety of ion species in almost arbitrary time, spatial, and spectral structures. The laser-hybrid approach will also evade the instantaneous dose-rate limitation of current sources and deliver ultra-high dose rates of up to 10^9 Gy/s in pulses that can be as short as 10–40 ns [1, 2]. These short, intense pulses allow novel techniques such as proton- and ion-acoustic imaging to be used to determine the position of the Bragg peak for each pulse in real time. The capability of the system we propose cannot be delivered through incremental development of cyclotron-, synchrotron-, or linac-based IBT facilities.

1.1 Scientific case

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1.2 Technological advancement

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Indicative page count: 2

1.3 Impact

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Indicative page count: 2

2 LhARA; the Laser-hybrid Accelerator for Radiobiological Application

2.1 Overview

High-power lasers have been proposed as an alternative to conventional proton and carbon-ion facilities for radiotherapy [31–33]. The capability of laser-driven ion beams to generate protons and high-LET ions at FLASH dose rates will provide a significant step forward in the provision of local tumour control whilst sparing normal tissue. High-power lasers have also been proposed to serve as the basis of electron, proton and ion-beams for radiobiology [34–39]. More recent projects (e.g. A-SAIL [40], ELI [41] and SCAPA [42]) will also investigate radiobiological effects using laser-driven ion beams. These studies will also address various technological issues [43–47].

The LhARA collaboration's concept is to exploit a laser to drive the creation of a large flux of protons or light ions which are captured and formed into a beam by strong-focusing plasma lenses. The laser-driven source allows protons and ions to be captured at energies significantly above those that pertain in conventional facilities, thus evading the current space-charge limit on the instantaneous dose rate that can be delivered. Rapid acceleration will be performed using a fixed-field alternating gradient accelerator (FFA) thereby preserving the unique flexibility in the time and spatial structure of the beam afforded by the laser-driven source.

Modern lasers are capable of delivering a Joule of energy in pulses that are 10s of femtoseconds in length at repetition rates of $\gtrsim 10$ Hz. At source, a laser-driven electron beam is reproducibly well collimated and has a modest ($\sim 5\%$) energy spread. By contrast, laser-driven proton and ion sources create beams that are highly divergent, have a large energy spread, and an intensity that varies by up to 40% pulse-to-pulse. Multiple ion species, from proton to carbon, can be produced from a single laser by varying the target foil and particle-capture optics. The realisation of LHARA requires that each of these issues be addressed.

The LhARA consortium's vision is that LhARA will prove the principal of the novel technologies required for the development of future therapy facilities. The legacy of the LhARA programme will therefore be: a unique facility dedicated to the development of a deep understanding of the radiobiology of proton and ion beams; and the demonstration in operation of technologies that will allow particle beam therapy to be delivered in completely new regimens.

The LhARA facility, shown schematically in figure 3, has been designed to serve two end stations for *in-vitro* radiobiology and one end station for *in-vivo* studies. Proton beams with energies of between 12 MeV and 15 MeV will be delivered directly from the laser-driven source to the low-energy *in-vitro* end station via a transfer line. The high-energy *in-vitro* end station and the *in-vivo* end station will be served by proton beams with energy between 15 MeV and 125 MeV and by ion beams (including C^{6+}) with energies up to 33.4 MeV/u. This configuration makes it natural to propose that LhARA be constructed in two stages; Stage 1 providing beam to the low-energy *in-vivo* end station and Stage 2 delivering the full functionality of the facility. The development of LhARA Stage 1 will include machine performance and optimisation studies designed to allow *in-vitro* experiments to begin as soon as possible.

2.2 Conceptual design

To do:

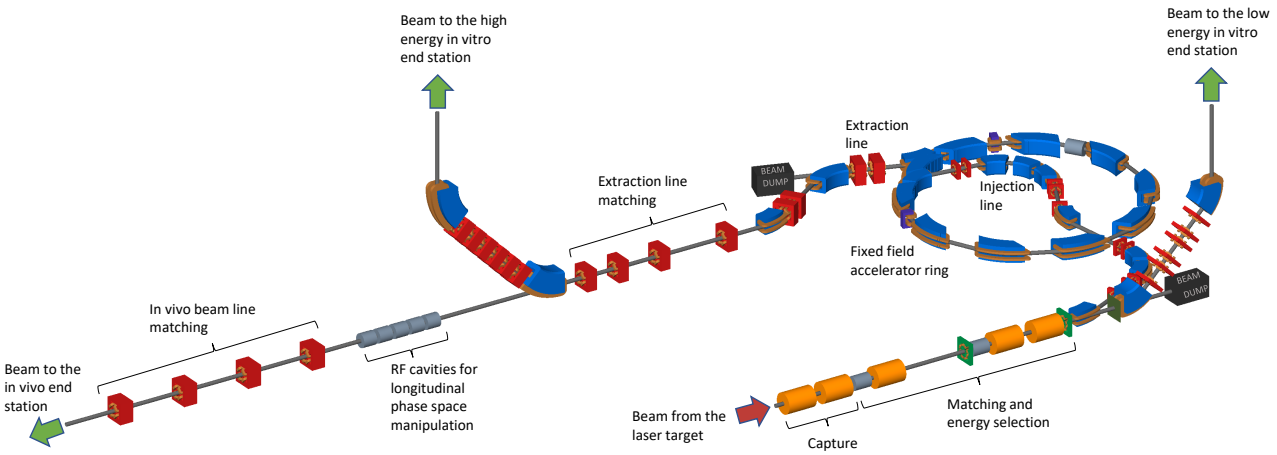

Figure 3: Schematic diagram of the LhARA beam lines. The particle flux from the laser-driven source is shown by the red arrow. The 'Capture' section is followed by the 'Matching and energy selection' section. The beam is then directed either into the 90° bend that takes it to the low-energy *in-vitro* end station, towards the FFA injection line, or to the low-energy beam dump. Post acceleration is performed using the 'Fixed field accelerator ring' on extraction from which the beam is directed either to the high-energy *in-vitro* end station, the *in-vivo* end station, or the high-energy beam dump.

- Add cross references to proposal physics sections;
- Add figures.

The protons and ions for LhARA will be produced through "target normal sheath acceleration" (TNSA) [48, 49] when a high power pulsed laser strikes a thin foil target with a typical thickness above 0.1 μm and up to a few 10's μm. The TNSA mechanism exploits the intense electric field that is created on the surface of the foil by the focused laser beam to accelerate surface electrons into the foil. The most energetic electrons traverse the material ionising it as they go. As the fast electrons exit the target's rear surface, a strong space-charge electric field, the "sheath", is generated which accelerates protons and ions deposited on the surface. Such a sheath acceleration scheme has been shown to produce accelerating gradient $\gtrsim 10\,\mathrm{GV/m}$. Proton pulses that feature broad exponentially decreasing spectra with cut-off energies in excess of 85 MeV have been produced through the TNSA mechanism [50] or hybrid schemes [51]. **Comment on ion production energies.[** Medium energy femtosecond class lasers were previously used to investigate the acceleration of carbon ions and generate maximum ion energies of approximately 5 MeV/u for relatively thin ($\sim$ 100 nm) solid targets [52]. Higher maximum energies in excess of 30 MeV/u were obtained from femtosecond class lasers with the use of ultra-thin targets ($\sim$ 10 nm) to selectively accelerate carbon ions [53, 54]. In the TNSA regime, target surface cleaning techniques were shown to enable the acceleration of heavier ions including carbon and oxygen to maximum energies of a few MeV/u [55, 56]. Proof-of-principles experiments aimed at the generation of oxygen ions investigated the same technique of controlling and removing contaminants from targets that can be used at high repetition rates [57].] For LhARA, a commercially available multi-TW laser has been identified as a suitable candidate for producing the desired flux of 15 MeV protons. Such a system will deliver $> 2.5\,\mathrm{J}$ in $< 25\,\mathrm{fs}$ pulses, at a 10 Hz repetition rate with shot contrast of $> 10^{10} : 1$. The laser will serve a tape target system or an alternative advanced targetry developed and optimised as outlined in subsection 3.2.

Simulations of the TNSA interaction have been determined to estimate the typical bunch profile and proton-energy spectrum. The 2D simulations, performed using the particle-in-cell (PIC) code SMILEI [58], modelled a focused laser pulse incident on a thin plastic film at a 45° angle [59]. A large spread of proton kinetic energies

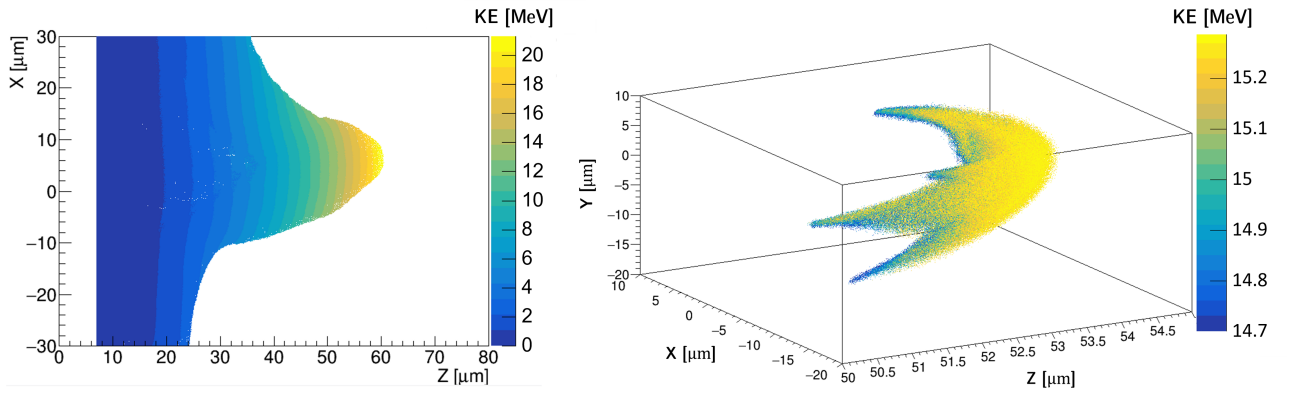

Figure 4: Left: Proton macroparticles at the final timestep of 1 ps of the 2D simulation of the TNSA interaction between the laser and the target. Right: 3D sampled proton beam generated from the 2D simulation on the left. Only protons with a kinetic energy of 15 MeV $\pm$ 2% are shown as they will not be stopped by the energy selection section of the LhARA beamline. Colours in both plots correspond to the kinetic energy.

up to 20 MeV was observed primarily in the direction of the target normal. The majority of the accelerated protons have low ($<$ 5 MeV) kinetic energy. The flux of protons with energies larger than 10 MeV which are of interest here were found to emerge at an angle to the target normal. Simulations to date have been restricted to 2D PIC codes as full highly resolved 3D simulations are computationally expensive. A sampling method that generates 3D momentum distributions from the 2D simulation has been developed and is described in [59]. Figure 4 shows a typical spatial distributions of protons according to a 2D PIC simulation of the TNSA interaction and the result of the sampling procedure by which a 3D proton beam is generated. **Need a figure.**

To capture the beam, we propose to use a series of Gabor lenses developed as outlined in subsection 3.3. Such devices provide transverse focusing from an electron cloud confined within the lens using a long cylindrical anode placed inside a uniform solenoidal magnetic field, a configuration commonly known as a "Penning-Malmberg trap". The lens consists of a trapped non-neutral electron plasma that creates a radially focusing force in both transverse planes simultaneously. The magnetic field required to confine the plasma is significantly reduced compared to that of a conventional solenoid with the same focusing strength. The focal length of the plasma lens is proportional to the energy of the particles entering the lens in contrast to conventional solenoid or quadrupole lenses in which the focal length is proportional to the square root of the particle energy. Thus, the Gabor lens is even more advantageous for focusing heavier ions like carbon. Five identical Gabor lenses will be used; two for beam capture, and a further three for matching and energy selection. A collimator before the first lens will also contribute to energy selection.

In LhARA's matching and energy selection section, two rebunching cavities will be installed to provide longitudinal phase space manipulation. An octupole and collimator will subsequently shape the beam to improve transverse dose uniformity. The parallel beam will then be transported to the stage 1 *in vitro* end station through a 90° vertical matching arc consisting of 2 dipoles and 6 quadrupoles. The vertical arc will contain a collimation system in a high dispersion region to provide further momentum-selection capabilities.

Start-to-end simulations have been performed in BDSIM and GPT (General Particle Tracer) [60], which includes the modelling of space-charge forces. A short distance after the laser-target interaction is simulated without space-charge as we anticipate the electron cloud created in the interaction to neutralise the ion-bunch charge. Subsequently, space-charge effects are simulated as the higher energy protons of interest will have separated from the low energy electrons. Whilst an immediate emittance growth is observed due to the high proton charge density, the impact on the subsequent beam transport performance is not severe, with the beam at

the stage 1 *in vitro* end station displaying similar characteristics to idealised simulations without space-charge. We anticipate that further optimisation of the Gabor Lens strengths can counteract any space-charge induced emittance growths.

For stage 2 operation, the Gabor lens strengths are modified to provide the lower Twiss beta necessary for injection into the FFA ring. The 14.6 m long injection line is comprised of a switching dipole after the final Gabor lens, 10 quadrupoles, 6 dipoles, and an injection septum magnet. Space for a collimation system in a dispersive region is provided for further momentum selection. Simulations of the modified Stage 1 and injection line have shown that the early space-charge induced emittance growth remains present [61] despite the modified Gabor lens settings. The focusing to a smaller spot size in the matching section compared to nominal stage 1 configuration is susceptible to further space-charge forces. Whilst the beam transport performance is adversely impacted, it is anticipated that further ongoing optimisation efforts will resolve such issues.

The Stage 2 FFA ring is comprised of 10 symmetric cells each containing a single combined function spiral magnet. The design of the ring is a compromise between the size of the orbit excursion and the length of the straight sections to accommodate injection and extraction systems. Simulations show that the rings dynamic acceptance for 100 turns is significantly larger than the beam emittance, with a working point of (2.83, 1.22) chosen for the ring's tune in the x and z directions respectively. A full aperture, fast injection of the beam will be performed using a magnetic septum installed on the inside of the ring, followed by a kicker magnet in a consecutive lattice cell. The small emittance beam at injection limits the maximum intensity due to space-charge forces which will be severe immediately after injection, however these will diminish due to debunching of the beam. Fast beam extraction will be performed using a kicker magnet followed by a magnetic septum installed in a consecutive lattice cell close to the extraction orbit. We propose to use normal conducting spiral-scaling FFA magnets based on a variation of a design recently proposed in studies of the ISIS neutron and muon source upgrade. Acceleration of the beam to 127 MeV will be done using an RF system operating in a frequency range of 2.89 to 6.48 MHz. The systems will be operated up to a voltage of 4 kV which provides an energy acceptance of $\pm$ 2%. Two cavities are proposed to provide greater operational stability.

The FFA extraction line is designed with significant flexibility to serve a wide spectrum of beam conditions to the *in vitro* and *in vivo* end stations, as well as to accommodate uncertainties both in the beam distribution originating from the Stage 1 beam transport and space-charge effects during acceleration in the FFA ring. The first section of the extraction line consists of two dipoles and four quadrupoles. This section is designed with closed dispersion to minimise the impact of off-momentum particles on the downstream beam profile. The second section of the extraction line contains four quadrupoles and transports the beam up to the first dipole of the vertical *in vitro* beam line. The quadrupoles provide flexibility to produce a range of beam sizes over three orders of magnitude. Beam transport simulations at both 40 and 127 MeV beams showed the optics and geometric acceptance of the extraction line are similar at both energies.

High energy beams are delivered to the *in vitro* end station in a vertical matching arc consisting of two dipoles and six quadrupoles. This beam line is a scaled version of the Stage 1 low energy vertical arc but with longer magnets to ensure peak magnetic fields are below the limits of normal conducting magnets. The arc length difference compared to the Stage 1 *in vitro* line will be offset by adjusting the length of the final drifts that transports the beam to the end station.

If the first dipole in the vertical arc is not energised, the beam is instead transported to the *in vivo* end station. This beam transport line provides space for five RF cavities for longitudinal phase space manipulation and installation of diagnostic devices. A subsequent section contains four quadrupoles to perform final focusing adjustments prior to end station delivery. A further straight section is reserved for magnets used in spot scanning techniques. The *in vivo* beam line also offers flexibility in the beam sizes that can be delivered, with simulations successfully transporting beams between 1 and 30 mm in size to the end station. Providing a parallel sub-mm beam remains an ongoing challenge that may also be susceptible to space-charge effects at the lowest energies.

The dose deliverable by LhARA was estimated in performance evaluation simulations with BDSIM. Beams of various energies were delivered to a water volume corresponding to the sensitive volume of an ion chamber, thus the stated doses and dose-rates are comparable to those of operational facilities. For simulation of the low-energy *in vitro* end station, proton beams with a 7.0 ns bunch length at a 10 Hz repetition rate delivered a maximum dose rate of 71 Gy/s and 128 Gy/s for 12 MeV and 15 MeV beams respectively. For the high-energy *in vitro* end station, a 127 MeV proton beam delivered an average dose rate of 156 Gy/s. A 33.4 MeV/u Carbon ion beam delivered a maximum average dose rate of 730 Gy/s.

2.3 Staging the LhARA project within the ITRF

The staging of the LhARA initiative was first discussed in the preparation of the pre-CDR [1]. The pre-CDR identified the need for a five-year R&D programme to develop critical aspects of the laser-driven proton and ion source and the Gabor-lens proton- and ion-capture system as well developing full designs for the novel end stations and the associated instrumentation. The need for detailed simulation of the facility that included appropriate consideration of space charge effects was recognised. Further, the pre-CDR included little consideration of the implementation of the facility or any consideration of site-specific issues.

LhARA formed the basis of the transformative vision presented in the proposal to establish an Ion Therapy Research Facility (the ITRF) in the UK [8]. The ITRF proposal identified a two-year Preliminary Phase followed by a three-year Preconstuction Phase. The staging scenario presented in the present proposal maps the five-year R&D programme defined in the LhARA pre-CDR onto the Preliminary and Preconstruction Phases identified in the ITRF development plan. An overview of the schedule for the development of the LhARA initiative in the Preliminary and Pre-construction Phases is shown in figure 21.

2.4 Timeline for the LhARA initiative

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Indicative page count: 1

3 Preparatory, pre-construction phase proposal

3.1 Project Management

The overarching goal for the LhARA five-year project described here is to prepare for the start of the LhARA construction phase. The key technical risks that arise in the implementation of LhARA will be addressed through the:

- Validation of the simulated laser-generated proton and ion fluxes in test measurements using a representative laser source;
- Validation of the simulated properties of the confined electron gas that is the basis of the Gabor lens and the subsequent design and construction of a second lens prototype as a pre-cursor to an operational system;
- Development of a direct, real-time, non-destructive dose-profile measurement system based on the acoustic signals generated by the deposition of energy in the Bragg peak; and
- Development of fully automated *in-vitro* end station, its instrumentation, and the necessary ion-beam diagnostics.

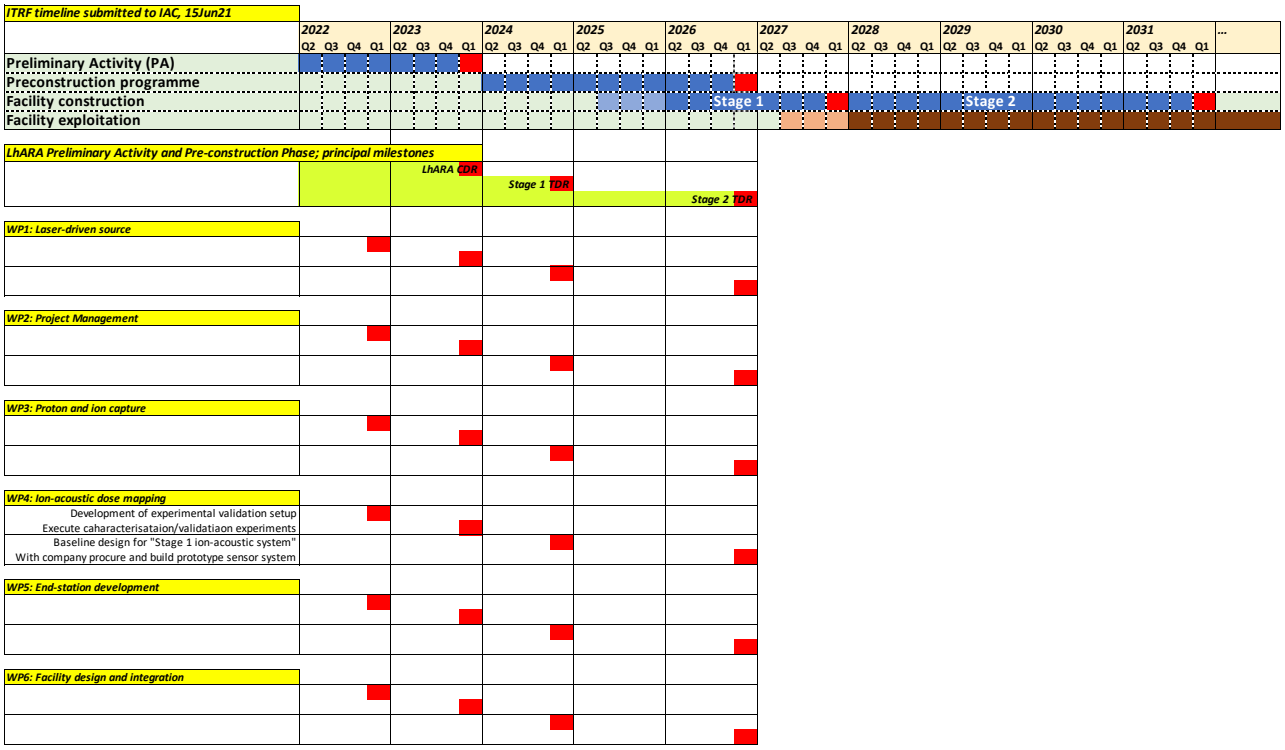

Figure 5: Waterfall chart showing the principal milestones that define the project proposed herein. The block entitled "ITRF timeline submitted to IAC, 15Jun21" shows the timeline for the development of the ITRF submitted to the UKRI's Infrastructure Advisory Committee. The block entitled "LhARA Preliminary Activity and Pre-construction Phase; principal milestones" shows the principal milestones of the LhARA Preliminary Activity and Pre-construction Phase proposed here. The subsequent blocks present the principle milestones that serve to specify each of the work packages.

The project will be managed by the LhARA Project Manager. Management information is presented in the Annex to this report (see section A.8.3).

The five-year activity proposed here is defined with reference to the larger LhARA Programme which encompasses the implementation of LhARA, the development of the capabilities necessary to exploit the unique features of the facility, and the identification of opportunities to spin out elements of the full LhARA system as the R&D programme matures. The LhARA Programme is managed by two Programme Managers: the LhARA Project Manager who is responsible for the delivery of the LhARA Project and the Biological Science Project Manager. The Programme Managers, supported by an administrator and the Project Spokespeople form the LhARA Programme Office.

The LhARA project is divided into six work packages, one for each of the elements of the risk-management programme outlined above, one for facility design and integration, and one for the overall project management. These work packages will support the preparation of the CDR for the full facility and Technical Design Reports for LhARA Stages 1 and 2. The work-package definitions are detailed in the sections which follow.

Resources for the management of the LhARA project proposed here are identified in "Work package 1: Project management". Together the project management team has responsibility for:

- Project management and planning;
- Reporting to STFC, other funders and stakeholders, including financial reporting. This task includes planning, organising and supporting all oversight activities requested;
- Risk management, tracking and deprecation or escalation as appropriate;
- The maintenance of sufficient technical & scientific documentation and drawing repositories to accurately record the project activities and results.
- Stakeholder engagement; and
- Patient and Public engagement.

The work of the project management team will be driven by the Project Managers supported by the administrator. The Spokespeople have wider responsibilities and should not be unduly loaded by day to day tasks. The LhARA project will be organised through the following tasks:

- The development and continuous monitoring of the programme, schedule and cost. In the first two years of the project spend will be dominated by University salary commitments and will therefore be predictable and easily controlled. As the project moves to the purchase of more equipment and STFC TD commitments to deliverables (particularly in work package 6) increase, management of finances and spend profile will become more complex and increased monitoring and support is planned. It will be important to build in appropriate systems to monitor progress at an early stage as financial complexity will increase substantially when the build phase begins at the end of year 5.
- The organisation and delivery of reports and presentations required for effective oversight. In all projects of this type reporting overheads can become onerous if not appropriately managed. The LhARA project has been planned to progress documents through a preparation process where an initial internal collaboration report can be improved and expanded through, first the internal editing processes, then the project oversight committee to emerge as a project deliverable.
- The organisation of regular stakeholder meetings to maintain currency with the latest results in the relevant radiobiological and medical fields. Simultaneously it will be important to communicate the current status and important future developments in the LhARA programme to the prospective user. These meeting will provide an important opportunity to solicit stakeholder feedback on the programme.
- The evaluation of delivery of the programme through active monitoring of the execution of the LhARA project against milestones and the agreed cost profile.
- The tracking of progress and risk by work package, managing effort through monthly progress meetings with each work package management team.

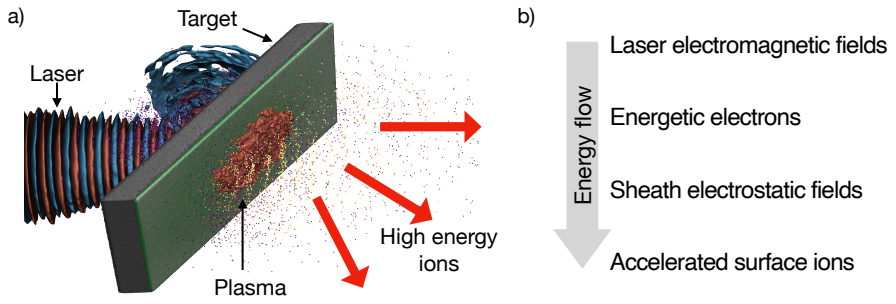

Figure 6: Target Normal Sheath Acceleration Mechanism: a) 3D Particle-in-cell simulation showing the Target Normal Sheath Acceleration mechanism. A high power laser is focused from the left onto a thin foil, forming a plasma and heating electrons to relativistic energies. These electrons form a sheath around the foil, rapidly accelerating surface ions. b) Flow diagram showing the transfer of energy from the laser to the ions.

- The organisation of collaboration meetings on a 4 to 6 monthly schedule to provide cross-collaboration visibility and coordination.
- The recruitment of appropriate patient representatives to advise as the LhARA programme, the LhARA project, and potential treatment regimens evolve.

3.2 Laser-driven proton and ion source (Work Package 2)

Laser driven ion sources are an emerging technology offering ion beams with unique properties [62, 63]. The most widely used technique is known as Target Normal Sheath Acceleration (TNSA) (see figure 6). The intense fields of focused high-power laser beams are sufficient to suppress atomic potentials and ionise a thin dense target. Target electrons are accelerated to relativistic energies in micrometre distances [64] and rapidly leave the target at the rear surface to form a strong electrostatic field which accelerates surface ions to energies of 10 MeV or more with accelerating gradients of order TeV/m, far higher than possible in conventional accelerating cavities [48, 49, 65].

Development of this mechanism towards applications has made significant progress in recent decades and is now known to be a robust and effective technique for use in laser-driven ion sources. Laser-driven ion beams are fundamentally ultra-short at source due to the pulse length of the drive laser. The space-charge limitations of conventional sources is overcome due to co-moving electrons created in the laser-target interaction. This results in a flexible, high flux beam with a low transverse normalised emittance [66].

Our research groups have previously spearheaded research into the underpinning physics of this technology through previous research programmes including A-SAIL (EP/K022415/1) and LIBRA (EP/E035728/1), establishing the UK as a world-leader in this field. It is only recently, however, that high power laser technology has developed to a stage where major challenges in continuous operation of the source have be addressed [67]. Therefore, we are now perfectly poised to apply our considerable expertise in laser driven ion acceleration to building a 10 Hz repetition rate source suitable for radiobiological applications. In addition, we will access UK-based world-class facilities, including the SCAPA laser at the University of Strathclyde and the Cerberus and Zhi laser facilities at Imperial College London, that are ideally suited to performing the work proposed here. An overview of these facilities is shown in figure 7.

The rapid advance in High-Performance-Computing and algorithm design now enables a programmatic approach *in silico* to detailed high fidelity numerical modelling campaigns over the range of experimental conditions of interest. Simulations are crucial in the experimental design phase to select laser and target parameters

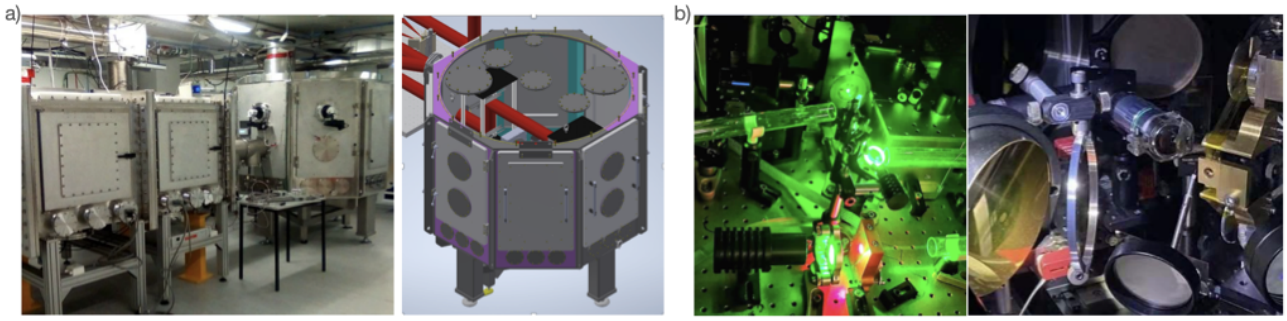

Figure 7: Facilities that will be used to develop the laser generated ion source in WP2: a) The final vacuum chambers for a dedicated laser-solid interaction beamline at SCAPA, at Strathclyde University, and b) front end and typical experimental setup for the Cerberus and Zhi lasers at Imperial College London.

expected to lead to optimum beam quality in terms of charge, energy, energy spread and beam divergence. Simulations, offering a wide range of diagnostics, are also fundamental to support the interpretation of experimental results.

The simulation programme of this work package will be focused on exploring the relevant parameter space and optimising the interaction conditions. This work will include understanding the effect of the laser contrast on target. Our first objective (O1) will be to perform two-dimensional hydrodynamic simulations to model the low-intensity pedestal preceding the main pulse with the solid and liquid targets we will deploy experimentally. We will use laser conditions available at SCAPA. Through this work, we will determine the minimum target thickness required to avoid plasma formation on the target rear side for the expected values of laser contrast. We will also obtain an estimate of the pre-plasma scale-length, which will be generated at the target front side. While the presence of plasma on the target rear side must be avoided to maximise TNSA [68], a pre-plasma in front of the target could aid laser absorption and hot electron generation and ultimately be beneficial for ion acceleration [69, 70]. Hence, these simulations will allow us to infer the most favourable conditions for TNSA to occur. We will use the information provided by the hydrodynamic analysis as input for our multi-dimensional Particle-In-Cell (PIC) simulations. We will model the interaction of the main pulse with pre-formed plasmas in a variety of conditions. In a first phase, this will allow us to identify laser and target parameters, which will enable the generation of 15 MeV proton beams with picoCoulomb charge. In a second phase, through simulations, we will optimise the acceleration of heavier ions. We will proceed by steps, initially exploring a large parameter space with 2D simulations. We will then refine our findings with realistic 3D simulations to provide more accurate estimation of generated beam parameters. These will be used for a quantitative comparison with experiments.

After the initial phase of simulation work, the focus will shift to a series of experiments to measure and optimise the ion source. Our second objective (O2) will be to deliver a comprehensive diagnostic suite for the laser-driven ion source suitable for 10 Hz operation. We will implement a time-of-flight diagnostic to enable rapid spectral reconstruction of proton energies [71]. Reconstruction of heavier ion beams using time-of-flight is challenging due to the mixture of charge states in the beam. Therefore we will commission a Thomson Parabola Spectrometer [52]. This device separates ions by charge-to-mass ratio and energy with co-linear magnetic and electric fields before detection on a scintillator coupled to a high-repetition scientific camera. The spatial properties of the ion beam will be measured by direct irradiation of a filtered scintillator [72, 73]. Our research groups have previously led development in all of these techniques, which are now well established. For LhARA, we will build new optimised versions of these diagnostics configured for high repetition rate and long term operation. Effective monitoring of the drive laser is also key to the control of the ion source. High

quality measurements of the relevant quantities, such as pulse energy, spectrum, pulse length and far-field quality is required for active stabilisation techniques to be applied. Therefore, we will build a full aperture laser diagnostics suite measuring these parameters just before the ion source.

To establish the baseline measurements required for completion of later objectives in this work package, and to benchmark the PIC simulations, our third objective (O3) will be to deliver within the first three years of the programme a seminal experiment on SCAPA with a repetition 1 Hz. These baseline experiments will also enable full commissioning of the diagnostic package developed to deliver O2. We envisage a total of 9-weeks of beam time with the first 2-weeks delivered in the first year of the programme and used to commission and calibrate the diagnostics package and optimise the performance of the SCAPA beamline within the requirements of LhARA, in a single shot operation mode. In the second and third years we will deliver two beam times of 3-weeks and 4-weeks in duration respectively. The first will be focused on testing and the delivery of 1 Hz operation, including the optimisation of the tape-based target-replacement system. The second period of 4-weeks will be used for the baseline data collection and will focus on the comprehensive measurement of key ion-beam metrics such as cut-off energy, conversion efficiency and beam divergence (both for protons and C^{6+} ions). The results of the initial simulation programme will be compared to the measurements obtained and used to inform an updated set of simulations which will support the delivery of future objectives and the design effort in other work packages.

The increase in repetition rate of the laser-driven ion source poses technical challenges related to targetry which need to be addressed for LhARA. Although the current baseline target choice, spooled thin tape, has been proven at lower repetition rates [74, 75], it is known that debris generated during the laser-target interaction will cause increasing issues for future high-repetition rate systems. Therefore, our fourth objective (O4) will be to make experimental measurements of this in LhARA-relevant regimens and apply established mitigation strategies, including magnetic debris capture, buffer gases, and sacrificial pellicles to protect key optics. In parallel, we will continue to develop new low-debris targetry technologies, in particular a liquid sheet, which would solve many of the outstanding issues with tape targets. Our consortium includes researchers from SLAC, CLF and Queen's University Belfast who have already developed and tested a prototype liquid-sheet target [76], which showed generation of protons at higher fluxes, lower divergence and higher energies than tape targets [77]. These are all key parameters for improving the performance of the laser driven source for LhARA. We will continue to develop these liquid targets, improve their stability and demonstrate their use on high repetition rate, 10 Hz, experiments. Regardless of target type, through our studies of high repetition-rate operation we will build on expertise in our consortium to develop active optimisation and stabilisation techniques [78] to ensure a constant and controllable source of ions to the downstream accelerator beamline. This work will use the high repetition rate laser and ion diagnostics developed to deliver O2 to provide fast feedback to the laser and target delivery systems.

Building on the progress made to deliver objectives O1 to O4 our fifth objectiver (O5) will be to complete a conceptual design of the integrated ion source system that combines key components for the generation, characterisation and stabilisation of a laser-driven ion source. This objective will be completed within the final 3-years of the programme and requires 9-weeks of beam time in total. These weeks will enable, for the first time in SCAPA, the testing and iteration of the targetry system developed to deliver O4. As part of this system integration we will also test various feedback and beam optimisation methodologies (e.g. control of the ion beam energy via Bayesian optimisation of the input parameters). Within the collaboration we already have significant experience applying these methodologies both in experiments and in simulation studies. The work to deliver O5 will include testing the fully integrated ion-source system and its diagnostics (with feedback and stabilisation capability). The source at this stage should meet all of the energy, flux, and divergence requirements for capture in the Gabor lens system developed in Work Package 3.

Our final objective (O6) will be, in the final year of the 5-year programme, to demonstrate the continuous

operation of the ion source at 5 Hz, over extended periods. We will initially operate the system at 5 Hz in 10-minute bursts. This will enable a rigorous assessment of debris, activation rates, and the longer term stability of the source to be made. After successful demonstration of the 10-minute operation, a further series of tests with 1-hour continuous operation will then be performed. This would represent a major milestone in the delivery of a continuous source of laser-driven ions and would enable a final concept design for the LhARA ion source to be completed. Although limited to 5 Hz operation by the SCAPA laser, based on measurements of diagnostic readout rates and target replacement time, we will also demonstrate that the integrated ion source system is, as a minimum, capable of 10 Hz operation and therefore compatible with future, higher repetition-rate, laser systems.

Through the programme described above we will demonstrate all the ion-source technology required for the integrated LhARA beamline. The deployment of this ion source in a 10 Hz integrated accelerator will be a landmark demonstration showing the real-life applicability of laser-driven ion sources and will provide the upstream beamline with novel beams that would be impossible to deliver with alternative source technology.

3.3 Proton and ion capture (Work Package 3)

As long ago as 1947, Gabor [79] suggested using the internal electric field of a trapped, non-neutral, electron plasma to focus 100 MeV protons. The proposed device used a known technique [80] to confine the electrons and had a 9 m focal length, which is to be compared to a value of 900 m for the instrument without the plasma. Thus, the plasma electric field reduces the focal length to 1% of that produced by a magnetic field alone, and it is this effect that is to be harnessed in the current work package.

The trapping technique first described by Penning [80], relies upon externally applied magnetic and electric fields to provide, respectively, radial and axial confinement of charged particles. Nowadays, this is typically implemented using the versatile Penning-Malmberg trap, a linear array of electrically biased cylinders arranged along the axis of a uniform magnetic field (see e.g. [81]). As further particles of the same species (such as electrons) are added to the trap, the particles interact and collective behaviour is established: a non-neutral plasma is typically formed [82]. Due to the mutual repulsion of the electrons and the establishment of a space-charge potential, fundamental limits exist for the number of charges (or more specifically their density) that can be stored for the magnetic [83] and electric field strengths used for confinement. While, in theory, such plasmas can be confined indefinitely [84], real-world practicalities such as contaminants and manufacturing defects limit the plasma density (see, e.g., [85]) and the length of time for which it can be trapped without critical parameters, such as its density, changing [86]. However, sophisticated manipulation and cooling techniques (such as those involving the use of rotating electric fields, the so-called "rotating wall", e.g., [87]) have been developed to circumvent many of these issues.

As a non-neutral plasma within a Penning-Malmberg trap produces a significant internal electric field in the radial direction, the trajectory of an ion travelling through this field will be modified. In the case of a trapped electron plasma and a positive ion initially travelling parallel to the aforementioned magnetic field, a radially inward force will redirect the ion towards the symmetry axis of the trap, i.e. the ion is focused and the electron plasma acts as a lens. The focal length, f, of this plasma lens is dependent upon the strength of the radial field (determined by the plasma density, n_e), the kinetic energy of the ion, U, and the length of the plasma, l, (i.e., how long the force acts on the traversing ion) via

$$\frac{1}{f} = \frac{e^2 n_e l}{4\epsilon_0 U}, \tag{1}$$

where e and ϵ_0 are the fundamental electric charge and permittivity of free space, respectively.

Given the common nature of non-neutral plasmas, the establishment of such a lens may be considered routine, but the difficulties become apparent when one considers that the focal lengths of typical, well-confined, plasmas

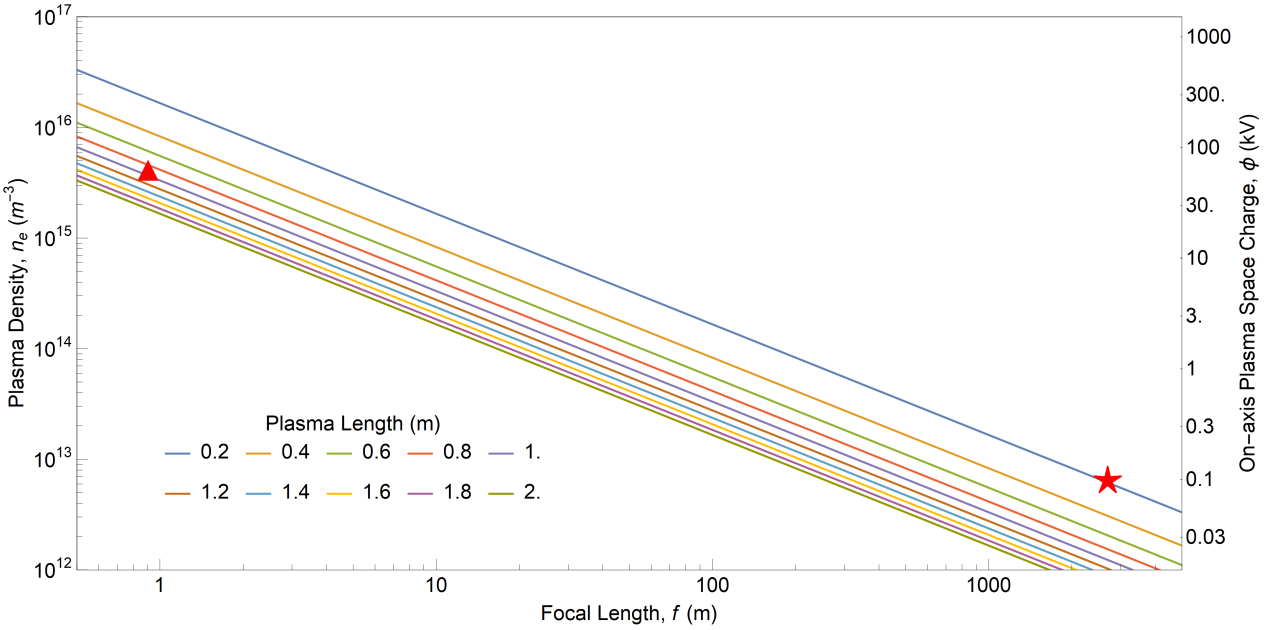

Figure 8: Example focal lengths, f and the corresponding plasma density ,n_e, (and associated space-charge, ϕ) for non-neutral electron plasma of varying lengths, $0.2 \leqslant l \leqslant 2$ m. Indicated is the focal length of a 15 MeV proton traversing current typical plasmas (★), and that expected of the final LhARA facility design (▲).

are currently in the kilometre region, and are produced using magnetic fields of several Tesla, electric fields generated with sub-kilovolt potentials, and with particles occupying $\leqslant 1\%$ of the trap volume. Conversely, from simplified calculation using equation 1, the parameters envisaged for the LhARA facility require metre scale focal lengths from plasma contained by $\leqslant 0.1$ T magnetic fields, 10-100's kilovolt electric potentials, and which occupy large fractions ($> 10\%$) of a trap volume. These represent the simultaneous improvement by several decades of many parameters, with an example scaling illustrated in figure 8.

Due to their high focusing strength, and potential ease of operation, Gabor-type lenses have been implemented for many decades (see e.g. [88, 89]) and have relied upon ionisation of background-gas atoms present within the lens to form weakly-confined quasi-steady-state electron plasmas. Indeed, the most recent experimental efforts (e.g. [90]) continue to use the technique with the support of modern computational capabilities (see e.g. [91, 92]) to model ion beam transport through the lens and understand deleterious plasma phenomena.

While the long-term aim of this work package is to produce a plasma suitable for use within the LhARA facility, it is the ambitious goal of this project to study well-confined plasma with focal lengths of 100's of metres in Phase I (during years 1 and 2) using upgraded existing apparatus and a newly commissioned test bench. In Phase II (during years 3 and 4), the new test bench will be used to study plasma with focal lengths of 10's of metres. In year 5, this advanced, dedicated, apparatus will be transported and interfaced with a suitable ion source to test performance expected from accompanying simulation, and identify any issues prior to finalising a lens design capable of achieving all the requirements of the LhARA facility.

Details of the experimental programme follow:

Phase I (years 1 and 2):

1. An existing positron/electron trapping apparatus at Swansea University will be upgraded to operate at a few hundred volts in order to facilitate the study of plasma at higher density than is currently possible, and compare the results with Particle-In-Cell (PIC) simulations for validation. As these upgrades have a short lead time, study is expected to commence at a very early stage.

2. A standalone test bench capable of manipulating plasma confined by 2 kV potentials will be designed, manufactured, and assembled from scratch, using results from the upgraded system and PIC simulations to guide detailed design decisions.
3. The test bench will be commissioned and electron plasmas established within the apparatus.

Phase II (years 3, 4 and 5):

1. Plasma parameters (radius, space-charge, density, and length) will be incrementally increased towards the expected final design requirement, and the impact of each of these changes on plasma performance and stability will be carefully studied.
2. The plasma environment (confining magnetic field, electric fields, background gas pressure and its constitution) will be systematically studied and the impact of these on the performance and stability of the plasma will be used to guide future beam line design.
3. Plasma manipulation techniques in hitherto unstudied regimes produced within the test bench will be explored in order to improve and tailor aspects of the plasma for improved performance.
4. An ion beam will be directed into the test bench, with the effect of plasma on properties of the ion beam investigated and compared to PIC simulations.

3.4 Real-time dose-deposition profiling (Work Package 4)

The LhARA collaboration has the mission to radically transform the clinical practice of PBT by creating a fully automated, highly flexible system that harnesses the unique properties of laser-driven particle beams. The ambition is that the clinical facility will exploit, for a variety of particle species, ultra-high dose rates and novel spectral (energy/particle)-, spatial (microbeam)- and temporal (FLASH)-fractionation schemes. Moreover, it will integrate soft-tissue imaging and in-situ dose-deposition mapping with real-time treatment planning in an automatic system that triggers the delivery of dose tailored in real time to the individual patient.

Our five-year research objectives are to create the capabilities necessary to deliver a highly flexible infrastructure to allow and accelerate fundamental research into the biological and biochemical impact of proton and ion beams, and to demonstrate in a preclinical context the capability to deliver particle beam therapy using various ion species and exploring timing, dose rate, and dose of the delivered dose fractions. This vision requires the real-time measurement of the dose and its spatial distribution delivered by proton and ion beams. We propose to do this by developing ion-acoustic methodology.

Knowledge of the position of the Bragg peak in relation to anatomy is essential for the automated delivery of PBT to the target tumour and for the sparing of healthy tissue. Furthermore, for preclinical research to provide the radiobiology knowledge needed to take full advantage of novel acceleration techniques, a system is needed to measure the distribution of energy deposited in tissue or biological samples on a pulse-by-pulse basis. Measurement of the deposited dose distribution will be particularly demanding for the low energy (12–15 MeV) beams employed in preclinical radiobiological research where dose varies rapidly on a scale of 100 μm.

The basis of the proton- and ion-acoustic dose measurement technique is similar to that of the emerging technique of photoacoustic tomography [**?**]. Using the ultrasound waves that are emitted when the deposited energy creates a temporally and spatially localised temperature and pressure increase, the Bragg peak (and indeed the whole energy deposition path) can be localised with an accuracy that is submillimetre using clinical ultrasound frequencies, or sub-100μm preclinically. The LhARA collaboration plans to develop *in-vivo* real-time 4D (space and time) proton-acoustic dose localisation and quantitative mapping, for real-time pulse-to-pulse adaptive treatment as the beam is moved around and the absorbed dose varies. In our long-term clinical vision, the ultrasound system used for dose mapping will also employ pre-existing or rapidly developing methods to create simultaneous co-registered multimodal ultrasound images, track tissue motion and register to planning

CT or MRI images. This approach is suitable for organs where acoustic access is possible, including breast, prostate, liver, pancreas, pelvic, head and neck, etc. It is especially applicable to emerging methods of delivering radiotherapy such as mini/micro-beam (narrow spatial dose distribution) and ultra-fast (FLASH) irradiation (short temporal dose deposition) which, in combination with the Bragg-peak energy deposition, generates an acoustic source that can be localised and quantified using passive ultrasound detection and image reconstruction methods currently employed in photoacoustic imaging.

The main challenges that must be overcome to deliver a proton- or ion-acoustic dose mapping system capable of deployment in the clinic, and our proposed solutions to be developed, are:

- The ion-acoustic signals generated by tissue at existing PBT facilities have thus far been extremely weak, requiring a great deal of signal averaging and hence very long acquisition times for their detection. To achieve the maximum acoustic pressure signal, and hence dose sensitivity, an isochoric deposition of the PB energy is necessary, which requires a sufficiently short PB pulse duration. Pulse durations of tens of nanoseconds or less, which have been shown in photoacoustics to result in measurable single-pulse signals, are not achievable with current PBT facilities. Our ion-acoustic dose mapping approach will therefore take advantage of the unique features of laser-hybrid accelerator technology, which will facilitate PBT pulses of 10–40 ns duration. The short bunches delivered by future linac-based PBT facilities may also generate acoustic signals of sufficient strength. We also propose that, eventually, advantage will be taken of massively parallel ultrasound receiver electronics and transducer arrays with tens of thousands of elements, potentially combined with compressive sensing techniques, to record data for dose mapping. The trend toward such development is present in the literature across many areas of medical ultrasound imaging. Uncorrelated noise between array elements will be averaged out, and signal enhanced, implicitly in the image reconstruction. Furthermore, techniques described below for overcoming the bandwidth limitations will enhance the signal-to-noise ratio.
- The frequency content of proton- and ion-acoustic signals varies widely, depending on the spatio-temporal dose distribution, proton energy and direction of acoustic observation, but we will have strong prior knowledge. Knowing the expected beam shape and dose deposition, we will use flexible acoustic detector sub-array configurations and novel acoustic image reconstruction algorithms for dose mapping to take advantage of the natural variation in the frequency content with emitted wave origin and direction. We will tune the frequency responses, sizes, and positions relative to the beam, of individual transducer elements to maximise the overall sensitivity (e.g., the signals from waves emitted in the beam's radial direction may, depending on beam energy and microbeam width, be higher in frequency than along the beam axis). We will also employ the expected shape of the beam and deposited dose, as a prior in the image reconstruction algorithm. This will allow a good dose map to be obtained with less (or noisier) data than would be the case if no knowledge of the initial acoustic pressure distribution existed.
- The ultrasound transducers must permit dose mapping and other imaging without disturbing simultaneous irradiation, in the treatment room without an operator to do the scanning. Our long-term solution will be a flexible ultrasound detector system, based on inter-communicating subarrays with an organ-specific array configuration that provides acoustic data for volumetric image reconstruction as well as PBT access. For specific organs, aspects of existing technology can be used, such as the ring arrays currently used for whole-body photoacoustic imaging of mice or for clinical breast imaging. For abdominal and other organs, novel conformable array configurations will be developed. For preclinical in-vitro radiobiological studies, we will mount up to 512 individual detector elements in a custom housing, such as the surface of a spherical sector (cup). One such 3D array may be used, placed beyond the Bragg peak and looking along the beam axis towards the PBT source. Acoustic coupling to the biological sample may be via a self-contained water stand-offoff (see Figure 8). Alternatively, with the specimen in a water bath, more than one such detector array may be configured flexibly around the beam and sample position

Figure 9: Schematic illustrating coupling of the hemispherical cup to a biological sample.

with mechanics to scan the detector and acquire datasets at different locations for coherent combination in dose-map reconstruction.

- The acoustic properties for which compensation is needed to enable accurately localised and quantitative dose imaging, are patient specific. Speed-of-sound and attenuation imaging are currently being developed for diagnostic imaging. For organs such as the breast, or in a preclinical context, where the target region may be surrounded by an array of acoustic detectors, transmission tomography will be employed. This takes advantage of the outstanding image quality benefits brought about by employing full-wavefield reconstruction methods initially developed for seismology. In the longer term for other target sites, backscatter-based speed of sound and attenuation mapping methods will be employed, where necessary taking advantage of ultrasound contrast microbubbles as beacon signals, to correct for acoustic wave aberrations and attenuation for improving dose map resolution, dose measurement precision and dose accuracy.

To establish laboratory capability for the development of the ion-acoustic technique, we will purchase a Verasonics Vantage Research Ultrasound Platform with Aspectus Legion multichannel preamplifiers to operate with a 512-element array. Personnel from UCL's Photoacoustic Imaging and Biomedical Ultrasound Groups (led by Prof. B. Cox), the Institute of Cancer Research (led by Prof. J. Bamber and Dr. E. Harris), and the Particle Physics Department at STFC RAL (led by Dr. J. Matheson) will exploit the ultrasound laboratory to make the preliminary measurements necessary to develop a proof-of-principle ion-acoustic system. This system will be used to measure the temporal, frequency and spatial characteristics of the ultrasound signals detected from proton beams of various energies from various sources Should probably be more specific here?. The measurements will be compared with predictions from combined Monte Carlo and acoustic wave propagation simulations, develop dose-map reconstruction algorithms and to demonstrate the feasibility of the technique. The data thus generated will be used to design and commission the spherical cup array for the preclinical dose mapping system. The laboratory capability will then be used to develop a complete system that will be used to measure dose profiles at LhARA, the ITRF and/or at other existing facilities. This will lay the foundation for the creation of a transformative technique for measuring the dose profile during in-vitro and in-vivo biological experiments and, eventually, for the real-time measurement of dose delivered to patients in the PBT clinic.

In the first instance, the preclinical dose mapping facility will be used with LhARA as a research tool to help us further the understanding of the radiobiology of PBT and how it is influenced by the proton source parameters. LhARA will have unique pulse parameters and as such will generate unique ion-acoustic signals both in terms of frequency bandwidth and the spatial variation of signal emissions with respect to the proton beam direction.

Details of the workplan are described in Annex A.2.4. In brief, the initial development stages of a real-time ion-acoustic dosimetry system will characterise the acoustic emission signal and use this to build a specification for the sensors (transducers) and their configuration to be used with LhARA. From Monte Carlo simulations (Imperial) and k-WAVE simulations (UCL), we will have the ability to estimate the acoustic emission from current proton sources and from the specifications of LhARA as they evolve during its development. Initially we will require methods to emulate these signals using an optical source (laser), as used in photoacoustic systems (ICR). We will use multiple distributed sensors, which may be single element or multielement (array), that can be easily configured into different geometrical arrangements to test the detection of ion-acoustic signals and how they are attenuated/reflected by candidate biological samples and their holders. The properties of the signal detected at different locations with respect to the beam and the spatial resolution of dose will inform the design of the preclinical ion-acoustic sensor array (the size, frequency response of individual sensors and their positions relative to the beam), which will be used to map the dose distribution generated by LhARA

on a pulse-by-pulse basis. It is anticipated that suitable sensors for LhARA will have to be custom made in collaboration with a sensor manufacturer for optimal sensitivity to the ion-acoustic signal.

The Verasonics Vantage ultrasound research platform is a fully programmable ultrasound scanner that allows control over all transmit and receive parameters. It is used world-wide in research labs to develop novel ultrasound devices and is already used by ICR, who also have code available to control the system and process the raw data that it generates. The system offers unique flexibility in that it can be coupled to a range of different ultrasound sensors, ranging from passive single ultrasound sensors to commercially available multi-channel medical ultrasound probes. The radiofrequency data may be processed by a GPU in the host controller, essential for reconstructing the dose distribution. The Aspectus preamplifiers are required to detect and amplify the weak broadband ion-acoustic emissions, and they are already being used successfully with the Vantage for photoacoustic imaging. Each Vantage provides simultaneous access to 256 channels. Multiple Vantage systems used in combination allow a higher channel count. Given the anticipated small signals we will probably require at least 256 channels to optimise the ion-acoustic technique. A possible solution is a hemi-spherical cup array, as used at ICR for preclinical photoacoustic imaging, which comprises 384 sensors. The prototype system will be easily transported in a car and used at existing proton beam facilities to test the sensors and sensing configuration.

In order to understand the requirements for the ion acoustic dose profiling instrumentation, a complete simulation chain is under development. This uses GEANT4 [ref] code to calculate the interaction of the incident proton beam with water. The resultant energy deposition in space and time is then used as an input to the program k-Wave [ref], which models the propagation of acoustic waves and their interaction with suitable ultrasonic transducers. The complete simulation will allow the design of transducer arrays which are optimised for each particular combination of beam and target characteristics.

The simulation must be verified by and calibrated against measurements. For this verification, a water-filled phantom, known as the SmartPhantom [ref], is under development, which can be transported to suitable proton beam facilities for beam tests. The SmartPhantom is based around a commercially available water phantom, with the addition of an ultrasound transducer array as outlined above. In order to reconstruct the Bragg peak of the incident beam by an independent method, the phantom is equipped with several insertable planes, each equipped with two orthogonal layers of plastic scintillating fibre. Each plane therefore allows measurements of beam profiles in the horizontal and vertical directions and the arrangement of the planes along the beam direction allows localisation of the Bragg peak. Light from the scintillating fibres is transported via clear fibres to photodetectors. The photodetectors will be CMOS cameras in the first instance, although silicon photodiodes or photomultipliers might also be used, depending on signal size and the timing resolution required.

In the early part of the program the SmartPhantom will be used to verify the simulations against real measurements at proton beam facilities. As the program evolves, it will be used, along with further simulations, in the design optimisation of the transducer array for the ion acoustic dose profile measurement.

3.5 Novel, automated end-station development (work Package 5)

To do:

- Editing pass on instrumentation; need to add objectives or deliverables;
- Add text for consultation and automation;
- Distinguish years 1,2 and 3–5.

LhARA has been conceived to serve a definitive programme of *in vitro* and *in vivo* radiation biology. The novel accelerator system will deliver a variety of ion species in a range of spatial, temporal, and spectral fractionation schemes. To realise the full potential of the facility requires that the beam delivered to the bioligical

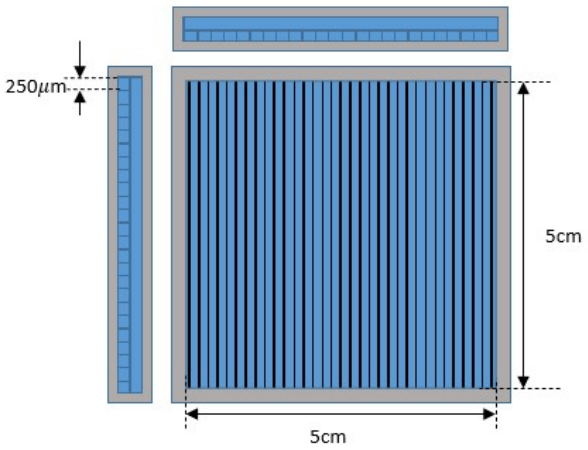

Figure 10: Conceptual layout of a SciWire plane

samples is fully characterised and that sample through put is maximised in both the *in-vitro* and *in-vivo* end stations through appropriate automation. We therefore propose to:

- Develop a full specification for the *in-vitro* and *in-vivo* end stations through a process of peer-group consultation;
- Develop the suit of instrumentation and diagnostics required to characterise the beam delivered to the biological samples; and
- Develop fully automated cell-culture handling systems for the *in-vitro* end stations and appropriately automated systems for the *in-vivo* end station.

3.5.1 Beam-line instrumentation

Characterisation of beam emerging from the vacuum chamber:
SciWire is one proposed instrument and is intended to measure the beam profile in two orthogonal directions, as the beam enters the end stations. SciWire consists of planes, made up of 250 micron plastic scintillating fibres. The conceptual layout of a SciWire plane is shown in figure 10. The scintillation light is transported to suitable photodetectors via lengths of clear fibre. Currently, the use of CMOS cameras to detect the light is under investigation, along with photodiodes and fast amplifiers, for higher speed. The beam profile can be reconstructed from two planes with fibres laid in orthogonal directions, whilst it may be possible to derive the beam energy from the energy loss in consecutive layers. Multiple consecutive layers could provide a destructive measurement of beam energy, for calibration purposes.

Simulations have been carried out of a single plane on the low energy LhARA beam, using GEANT4, which show that the device does not degrade the beam, despite the low energy, figure 11. Further simulations are planned and a prototype will be built for test beam work. The SciWire development may exploit synergies with the SmartPhantom ??CrossRef??, as both make use of scintillating fibre detection.

Emittance measurement of beam delivered to the end station:
The QUASAR Group is a recognised leader in the use of gas jet technology for characterising charged particle beams CITE . The Group has pushed this technology for more than a decade and already optimised it for use with low energy electrons and antiprotons, as well as for the high luminosity upgrade of the Large Hadron Collider (LHC) at CERN CITE. They will now apply their expert knowledge to design a monitor specifically for the challenges found in LhARA.

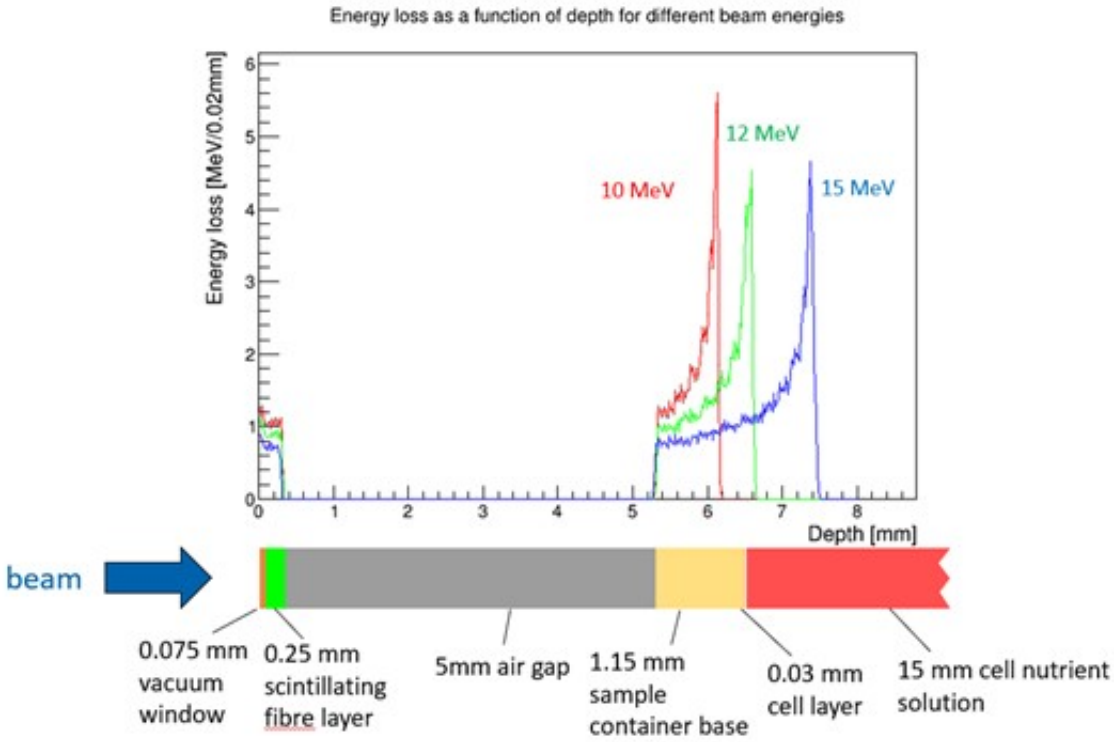

Figure 11: Conceptual layout of a SciWire plane

A schematic of the monitor is presented in figure 12 (left). This system has been tested extensively with a 10 mA, 10 keV electron beam and 3 different working gases: nitrogen, neon and argon. Example results from measurements are shown in figure 12 (right). The monitor is based on fluorescence detection induced in a supersonic gas jet interacting with the ionising primary beam that shall be characterised. One of the advantages of this monitor type is that its characteristics can be tuned according to the requirements of a particular application, including intensity profiling the energetic particles used in a particle beam therapy machine.

The monitor works by generating a supersonic low-density gas jet curtain using a bespoke nozzle-skimmer arrangement, see figure 12 (left) where the beam is travelling into the page. The gas jet crosses the particle beam perpendicularly to the direction of travel of the particle beam and excites the gas molecules. This excitation takes the form of fluorescence, where the light produced can be imaged, or ionisation, where the ions produced can be collected and imaged to generate the beam profile. Both methods have been successfully used by the QUASAR Group for different applications in the past, each having operational challenges and benefits. Identification of the specific mode of operation and an overall optimised design for integration in LhARA will be a deliverable of this project. This monitor will then be used to characterise the beam in a non-invasive way in terms of its position, profile and intensity as well as providing a real time two-dimensional dose map. The monitor will thus be capable of running alongside patient treatment without interfering with the beam. Stability and reproducibility of results will be tested for different working gases. Simulation studies will underpin the experimental campaigns and help to optimise the overall performance of the monitor. The project will capitalise on the existing infrastructure at the Cockcroft Institute which leads to very significant cost reduction.

Studies already conducted:

The Group has carried out extensive studies into gas jet-based monitors for more than a decade and has already developed a first design for a monitor optimised for medical accelerators CITE, shown in figure 13. It has also contributed to studies into the technical challenges for proton beam treatment and in particular new high

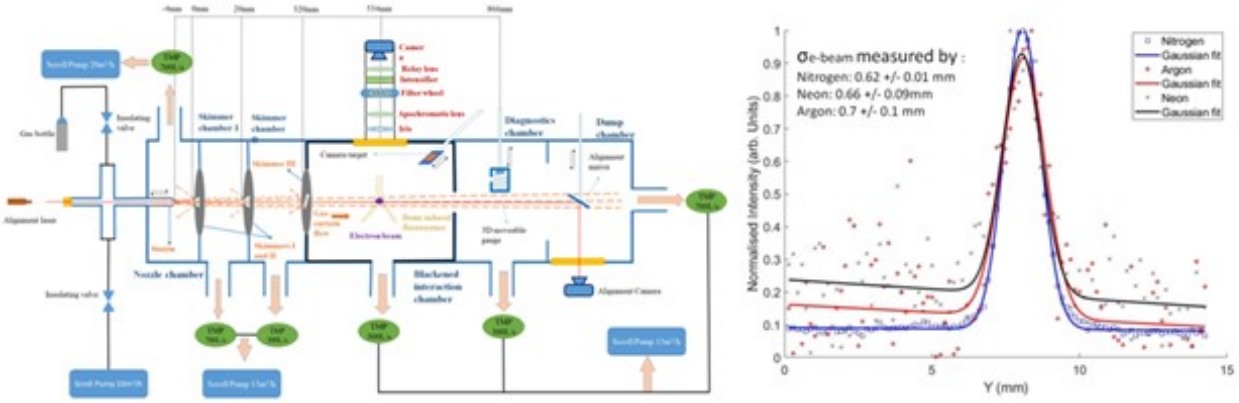

Figure 12: Left – schematic of a gas jet profiler. Right – image of electron beam and three different gases.

dose treatment modalities such as FLASH. This work has demonstrated the unique characteristics and indicated opportunities for simplifying the monitor design for easy integration into a medical accelerator.

The Group has already modified one existing gas jet monitor for measurements at medical accelerators. Figure 14 (left) shows a photo of the original setup at the CI's DITAlab, figure 14 (right) shows a simplified setup optimised for measurements with beam in proton and ion beam therapy centres and this will form the basis of this project.

Novelty and expected improvement over current technologies

Current techniques for dosimetry either provide limited information (one-dimensional dose profile or only total dose value), or are invasive to the treatment beam such as ionisation chambers (ICs) CITE, which can disturb the intended dose profile, require daily calibration, provide low spatial resolution (few mm's, depending upon spacing between electrodes) and suffer from slow response time. A complete knowledge of the beam properties delivered to a patient is essential, so calibration measurements are taken at regular intervals. However, currently there is no method to monitor the beam parameters to a high 2D fidelity during treatment without disturbing the beam. ICs and Faraday cups also require regular maintenance which includes replacing components, followed by calibration to verify their performance, making it time consuming. This is further complicated through the particular pulse structure found at LhARA and the high time resolution required.

Within the project a new online, non-invasive beam monitor that can provide real time beam characterisation and dosimetry with good spatial resolution, requiring no regular maintenance will be developed. The monitor will not affect the particle beam properties, thus allowing measurement of dose and profile to be taken whilst the patient is being treated and giving clinicians a detailed view of the 2D dose map delivered to the patient.

3.6 Facility design and integration (Work Package 6)

The LhARA accelerator system is capable of integrating the laser driven ion source with conventional accelerator systems. This provides a unique capability to perform a broad range of radiobiological experiments with multiple ion species, utilising a flexible dose profile delivery ranging from conventional hadron therapy facilities to the FLASH regime, and exploring novel ideas like microbeams. These ambitious goals can be achieved thanks to advances in development of laser driven source and by developing an innovative capture system utilising Gabor lenses. Gabor lenses allow for a strong focusing simultaneously in both transverse planes necessary to efficiently capture the divergent beam emitted from the laser driven source, while simultaneously being cost efficient and flexible in operation, in particular capable for high repetition rate with fast tunability. Once the successful capture system delivers beam with reduced divergence and moderate size a conventional focusing

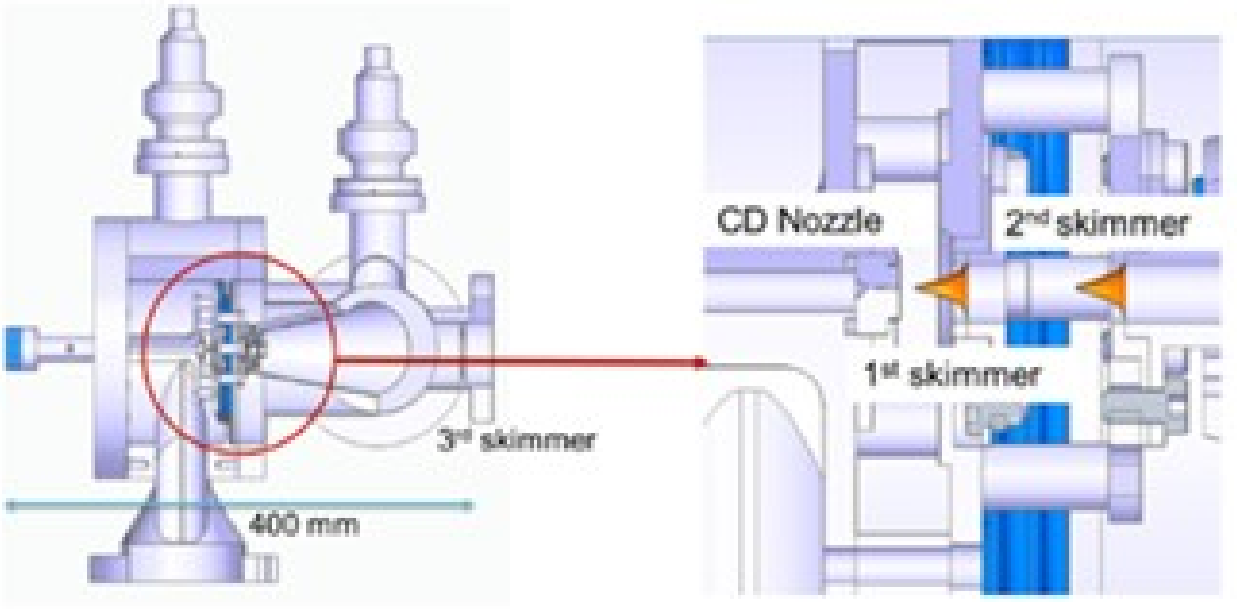

Figure 13: Conceptual compact design of optimised monitor.

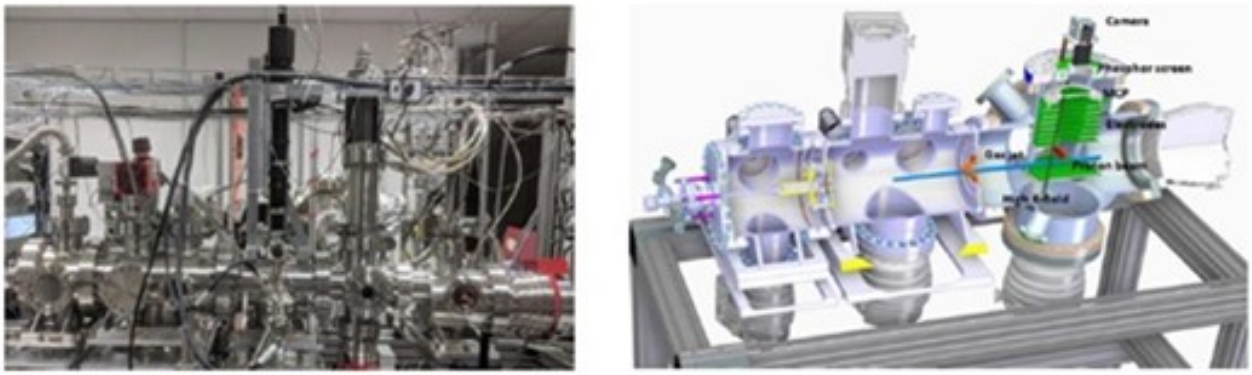

Figure 14: (Left) Existing gas jet system at CI. (Right) Preliminary monitor design for JetDose.

and guiding system can be used, which allows for easy beam matching to the needs of the experiments with respect to the beam size, distribution, etc., and easy and flexible operation.

LhARA aims to deliver the beam to in-vitro station at the Phase I, and in-vitro and in-vivo end stations at the Phase II for broad spectrum of radiobiological experiments with multiple ion species and variety of dose profiles. Although the design of the Gabor lenses is the subject of WP3, this work package - WP6 will develop the mitigation strategy by designing an alternative capture system based on solenoid technology. Although solenoids can fully replace Gabor lenses in the LhARA case, it is foreseen that in its future upgrades aiming at therapy applications the Gabor lenses will be highly beneficial.

A significant design effort for the LhARA facility was already been performed, reviewed, obtained a very positive outcome and published in a pre-CDR report [1, 2]. Nevertheless, a significant amount of work remains to be addressed before the construction of the facility can begin. The first objective (O1 and the associated deliverable D1) of the WP6 in the first two years of the project will be the research towards publishing the Conceptual Design Report (CDR) for the LhARA facility. The lattice design will be further optimised using the updated input from the laser driven source and incorporating new input on the design of the Gabor lenses. The tracking studies incorporating errors will inform the performance of the facility and will dictate the distribution of the correctors. The beam diagnostics along the LhARA beamline, necessary to operate the machine, will be identified including the diagnostics in the FFA post-accelerator. The tracking studies will be also essential to optimise the vacuum chamber parameters, knowledge of which will allow the design the vacuum system for the facility. The radiation protection and shielding requirements will also be studied with initial research starting early for the needs of the CDR document, but will be scaled up significantly in the later stage of the project by subcontracting this topic to a professional company. This study will be necessary to inform the design of the building for the LhARA facility and inform the cost estimate. Mechanical design including the support for accelerator elements, in particular for the vertical arcs for in-vitro stations will be also addressed. The challenging novel FFA-element for the Phase II FFA ring post-accelerator allowing for the variable energy extraction will be designed together with the Magnetic Alloy (MA) RF cavity for acceleration of various type of ions in the ring. The design of the control system will be drawn up and the safety systems for the facility will be specified. RF system requirements, power consumption, etc. will be estimated for the CDR report.

The next goal of the WP6 will be the Technical Design Report (TDR) for the Phase I of LhARA (O2 and the associated deliverable D2), aimed to be submitted at the end of the third year of the project. All the design for the Phase I will need to be updated to contain the necessary details to be ready to start manufacturing. The design of the focusing and bending elements, vacuum chambers, collimation and diagnostic systems will be finalised and the CAD drawings will be generated. The control system will be fully developed together with the personnel safety systems. RF system will be defined and the technical services including the cooling system, ventilation and air conditioning will be fully designed. The radiation protection and shielding solutions for the Phase I will be also fully addressed together with the beam dump. The cable management methodology for the Phase I will be fully developed.

Next, the design of the FFA main magnet for the Phase II will be finalised and the prototype construction will be subcontracted to industry for detailed design and manufacturing. After the construction of the prototype, magnetic measurements will be performed and the tracking studies will be used to validate the design. This is the subject of the next objective (O3 and the associated deliverable D3), which is aimed to be finalised towards the end of the project (after 58 months). On the same timescale the Magnetic Alloy (MA) RF cavity system will be finalised including the construction of the prototype, which will be tested experimentally and fully validated in different modes of operation required for various types of ion species informing the next objective (O4 and the associated deliverable D4).

The final objective of the WP6 work will be the delivery of the TDR for the Phase II of LhARA facility at the end of year five (O5 and the associated deliverable D5). The design of the focusing and bending elements,

including the injection line and high energy beam transport line, injection and extraction systems (kickers and septa), vacuum chamber for the FFA ring and for the transport lines, collimation and diagnostic systems, including the dedicated diagnostics for the ring, will be finalised and the CAD drawings will be generated. The control system will be further developed incorporating the requirements of the Phase II together with the personnel safety system. RF system for the Phase II will be defined and the technical services including the cooling system, ventilation and air conditioning will be fully extended to incorporate the needs of the Phase II. The radiation protection and shielding solutions for the Phase II will be also fully addressed together with the beam dump after the extraction from the FFA. The building design for the entire LhARA facility will be finalised incorporating the input from the radiation study and including solutions allowing for flexible operation of both LhARA phases, providing the space for all end-stations and associated space for radiobiological experimentation. The building design, technology solutions and construction methodology will also address the environmental sustainability solutions to save energy and minimise carbon footprint. The technical rooms and cable management system will be expanded and extended to incorporate the Phase II systems.

The work will be carried out by personnel from Universities by academics and Research Assistants (RA)s, and STFC by engineers and experts, mainly from the Daresbury Laboratory (DL).

4 Summary

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Indicative page count: 1

References

[1] The LhARA consortium, "The Laser-hybrid Accelerator for Radiobiological Applications," Tech. Rep. CCAP-TN-01, The Centre for the Clinical Application of Particles, Imperial College London, 2020. https://ccap.hep.ph.ic.ac.uk/trac/raw-attachment/wiki/Communication/Notes/CCAP-TN-01.pdf.

[2] **LhARA** Collaboration, G. Aymar *et al.*, "The Laser-hybrid Accelerator for Radiobiological Applications," 2006.00493.

[3] A. Lühr, C. von Neubeck, J. Pawelke, A. Seidlitz, C. Peitzsch, S. M. Bentzen, T. Bortfeld, J. Debus, E. Deutsch, J. A. Langendijk, J. S. Loeffler, R. Mohan, M. Scholz, B. S. Sørensen, D. C. Weber, M. Baumann, and M. Krause, " "Radiobiology of Proton Therapy": Results of an international expert workshop," *Radiotherapy and Oncology* (Jul, 2018) 56–67.

[4] J. Bin, K. Allinger, W. Assmann, G. Dollinger, G. A. Drexler, A. A. Friedl, D. Habs, P. Hilz, R. Hoerlein, N. Humble, S. Karsch, K. Khrennikov, D. Kiefer, F. Krausz, W. Ma, D. Michalski, M. Molls, S. Raith, S. Reinhardt, B. Röper, T. E. Schmid, T. Tajima, J. Wenz, O. Zlobinskaya, J. Schreiber, and J. J. Wilkens, "A laser-driven nanosecond proton source for radiobiological studies," *Applied Physics Letters* **101** (2012), no. 24, 243701.

[5] **LhARA** Collaboration, "The LhARA initiative," 2021. https://ccap.hep.ph.ic.ac.uk/trac/raw-attachment/wiki/Research/DesignStudy/2021-10-02-LhARA-Brief-Final.pdf.

[6] "The Laser-hybrid Accelerator for Radiobiological Collaboration institute list." https://ccap.hep.ph.ic.ac.uk/trac/raw-attachment/wiki/Research/DesignStudy/2021-05-14-Institute-list-v8.pdf, May, 2021. Accessed: 2021-12-22.

[7] "The Laser-hybrid Accelerator for Radiobiological Collaboration institute slide." https://ccap.hep.ph.ic.ac.uk/trac/raw-attachment/wiki/Research/DesignStudy/2021-05-11-Institute-slide-v8.pdf, May, 2021. Accessed: 2021-12-22.

[8] "Ion Therapy Research Facility." https://ccap.hep.ph.ic.ac.uk/trac/raw-attachment/wiki/Research/DesignStudy/Proposals/2021/2021-06-15-ITRF-1-page-Final.pdf, June, 2021. Cover page submitted to support the full proposal.

[9] S. Rossi and M. Pullia, "Nuclear Applied Physics and Biophysics at CNAO," in *Int. Biophysics Collaboration meeting*. Rome, 20 February, 2020.

[10] A. Facoetti, B. Vischioni, M. Ciocca, M. Ferrarini, Y. Furusawa, A. Mairani, Y. Matsumoto, A. Mirandola, S. Molinelli, A. Uzawa, F. G. Vilches, and R. Orecchia, "In vivo radiobiological assessment of the new clinical carbon ion beams at CNAO," *Radiation Protection Dosimetry* **166** (04, 2015) 379–382.

[11] T. Inaniwa, "Nuclear Applied Physics and Biophysics at HIMAC," in *Int. Biophysics Collaboration meeting*. Rome, 20 February, 2020.

[12] D. Bettoni, "Nuclear Applied Physics and Biophysics at SPES," in *Int. Biophysics Collaboration meeting*. Rome, 20 February, 2020.

[13] G. de Angelis *et al.*, "The SPES radioactive ion beam project of LNL: status and perspectives," *EPJ Web of Conferences* **107** (2016) 01001.

[14] A. Bugay and E. Nasanova, "Nuclear Applied Physics and Biophysics at NICA," in *Int. Biophysics Collaboration meeting*. Rome, 20 February, 2020.

[15] E. Syresin *et al.*, "Nuclotron New Beam Channels for Applied Researches," in *Proceedings, 8th International Particle Accelerator Conference (IPAC 2017): Copenhagen, Denmark, May 14-19, 2017*, p. TUPVA114. 2017.

[16] G. Battistoni, "Nuclear Applied Physics and Biophysics at TIFPA-INFN," in *Int. Biophysics Collaboration meeting*. Rome, 20 February, 2020.

[17] F. Tommasino, M. Rovituso, E. Bortoli, C. L. Tessa, G. Petringa, S. Lorentini, E. Verroi, Y. Simeonov, U. Weber, P. Cirrone, M. Schwarz, M. Durante, and E. Scifoni, "A new facility for proton radiobiology at the Trento proton therapy centre: Design and implementation," *Physica Medica* **58** (2019) 99 – 106.

[18] L. Giuffrida and D. Margarone, "Nuclear Applied Physics and Biophysics at ELI-Beamlines," in *Int. Biophysics Collaboration meeting*. Rome, 20 February, 2020.

[19] A. S. Ahmad, N. Ormiston-Smith, and P. D. Sasieni, "Trends in the lifetime risk of developing cancer in Great Britain: comparison of risk for those born from 1930 to 1960," *British journal of cancer* **112** (mar, 2015) 943–947.

[20] "Worldwide cancer statistics — Cancer Research UK."

[21] N. R. Datta, M. Samiei, and S. Bodis, "Radiation Therapy Infrastructure and Human Resources in Low- and Middle-Income Countries: Present Status and Projections for 2020," *International Journal of Radiation Oncology*Biology*Physics* **89** (2014), no. 3, 448–457.

[22] "NHS Long Term Plan: Chapter 3: Further progress on care quality and outcomes."

[23] "NHS Commissioning: Proton beam therapy."

[24] "Particle Therapy Co-Operative Group."

[25] "Particle Therapy Co-Operative Group; Statistics."

[26] "Particle Therapy Co-Operative Group; Facilities in operation."

[27] P. Jiang, K. Krockenberger, R. Vonthein, J. Tereszczuk, A. Schreiber, S. Liebau, S. Huttenlocher, D. Imhoff, P. Balermpas, C. Keller, K. Dellas, R. Baumann, C. Rödel, G. Hildebrandt, K. P. Jünemann, A. S. Merseburger, A. Katz, A. Ziegler, O. Blanck, and J. Dunst, "Hypo-fractionated SBRT for localized prostate cancer: a German bi-center single treatment group feasibility trial," *Radiation Oncology (London, England)* **12** (aug, 2017).

[28] P. Montay-Gruel, K. Petersson, M. Jaccard, G. Boivin, J. F. Germond, B. Petit, R. Doenlen, V. Favaudon, F. Bochud, C. Bailat, J. Bourhis, and M. C. Vozenin, "Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100 Gy/s," *Radiotherapy and Oncology* **124** (2017), no. 3,.

[29] Y. Prezado, G. Jouvion, D. Hardy, A. Patriarca, C. Nauraye, J. Bergs, W. González, C. Guardiola, M. Juchaux, D. Labiod, R. Dendale, L. Jourdain, C. Sebrie, and F. Pouzoulet, "Proton minibeam radiation therapy spares normal rat brain: Long-Term Clinical, Radiological and Histopathological Analysis," *Scientific Reports* **7** (2017), no. 1, 14403.

[30] W. González and Y. Prezado, "Spatial fractionation of the dose in heavy ions therapy: An optimization study," *Medical Physics* **45** (jun, 2018) 2620–2627.

[31] S. Bulanov, T. Esirkepov, V. Khoroshkov, A. Kuznetsov, and F. Pegoraro, "Oncological hadrontherapy with laser ion accelerators," *Physics Letters A* **299** (2002), no. 2, 240–247.

[32] E. Fourkal, J. S. Li, M. Ding, T. Tajima, and C. M. Ma, "Particle selection for laser-accelerated proton therapy feasibility study," *Medical Physics* **30** (2003), no. 7, 1660–1670, https://aapm.onlinelibrary.wiley.com/doi/pdf/10.1118/1.1586268.

[33] V. Malka, S. Fritzler, E. Lefebvre, E. d'Humières, R. Ferrand, G. Grillon, C. Albaret, S. Meyroneinc, J.-P. Chambaret, A. Antonetti, and D. Hulin, "Practicability of proton therapy using compact laser systems," *Medical Physics* **31** (2004), no. 6, 1587–1592, https://aapm.onlinelibrary.wiley.com/doi/pdf/10.1118/1.1747751.

[34] S. D. Kraft, C. Richter, K. Zeil, M. Baumann, E. Beyreuther, S. Bock, M. Bussmann, T. E. Cowan, Y. Dammene, W. Enghardt, U. Helbig, L. Karsch, T. Kluge, L. Laschinsky, E. Lessmann, J. Metzkes, D. Naumburger, R. Sauerbrey, M. Schürer, M. Sobiella, J. Woithe, U. Schramm, and J. Pawelke, "Dose–dependent biological damage of tumour cells by laser–accelerated proton beams," *New Journal of Physics* **12** (aug, 2010) 085003.

[35] F. Fiorini, D. Kirby, M. Borghesi, D. Doria, J. C. Jeynes, K. F. Kakolee, S. Kar, S. Kaur, K. J. Kirby, M. J. Merchant, and S. Green, "Dosimetry and spectral analysis of a radiobiological experiment using laser-driven proton beams," *Phys Med Biol* **56** (Nov, 2011) 6969–6982.

[36] D. Doria, K. F. Kakolee, S. Kar, S. K. Litt, F. Fiorini, H. Ahmed, S. Green, J. C. G. Jeynes, J. Kavanagh, D. Kirby, K. J. Kirkby, C. L. Lewis, M. J. Merchant, G. Nersisyan, R. Prasad, K. M. Prise, G. Schettino, M. Zepf, and M. Borghesi, "Biological effectiveness on live cells of laser driven protons at dose rates exceeding 10^9 Gy/s," *AIP Advances* **2** (2012), no. 1, 011209, https://doi.org/10.1063/1.3699063.

[37] K. Zeil, M. Baumann, E. Beyreuther, T. Burris-Mog, T. E. Cowan, W. Enghardt, L. Karsch, S. D. Kraft, L. Laschinsky, J. Metzkes, D. Naumburger, M. Oppelt, C. Richter, R. Sauerbrey, M. Schürer, U. Schramm, and J. Pawelke, "Dose–controlled irradiation of cancer cells with laser-accelerated proton pulses," *Applied Physics B* **110** (2013), no. 4, 437–444.

[38] U. Masood, M. Bussmann, T. E. Cowan, W. Enghardt, L. Karsch, F. Kroll, U. Schramm, and J. Pawelke, "A compact solution for ion beam therapy with laser accelerated protons," *Applied Physics B* **117** (2014), no. 1, 41–52.

[39] O. Zlobinskaya, C. Siebenwirth, C. Greubel, V. Hable, R. Hertenberger, N. Humble, S. Reinhardt, D. Michalski, B. Röper, G. Multhoff, G. Dollinger, J. J. Wilkens, and T. E. Schmid, "The Effects of Ultra–High Dose Rate Proton Irradiation on Growth Delay in the Treatment of Human Tumor Xenografts in Nude Mice," *Radiation Research* **181** (2014), no. 2, 177–183.

[40] "A-SAIL Project." https://www.qub.ac.uk/research-centres/A-SAILProject/.

[41] G. A. P. Cirrone, D. Margarone, M. Maggiore, A. Anzalone, M. Borghesi, S. B. Jia, S. S. Bulanov, S. Bulanov, M. Carpinelli, S. Cavallaro, M. Cutroneo, G. Cuttone, M. Favetta, S. Gammino, O. Klimo, L. Manti, G. Korn, G. L. Malfa, J. Limpouch, A. Musumarra, I. Petrovic, J. Prokupek, J. Psikal, A. Ristic-Fira, M. Renis, F. P. Romano, F. Romano, G. Schettino, F. Schillaci, V. Scuderi, C. Stancampiano, A. Tramontana, S. Ter-Avetisyan, B. Tomasello, L. Torrisi, S. Tudisco, and A. Velyhan, "ELIMED: a new hadron therapy concept based on laser driven ion beams," in *Laser Acceleration of Electrons, Protons, and Ions II; and Medical Applications of Laser-Generated Beams of Particles II; and Harnessing Relativistic Plasma Waves III*, E. Esarey, C. B. Schroeder, W. P. Leemans, K. W. D. Ledingham, and D. A. Jaroszynski, eds., vol. 8779, pp. 216 – 225, International Society for Optics and Photonics. SPIE, 2013.

[42] S. M. Wiggins, M. Boyd, E. Brunetti, N. M. H. Butler, J. S. Feehan, R. J. Gray, B. Hidding, D. G. Ireland, W. Li, A. Maitrallain, G. G. Manahan, P. McKenna, D. O'Donnell, M. Scheck, M. Shahzad, Z.-M. Sheng, R. Spesyvtsev, G. Vieux, D. P. Watts, G. H. Welsh, R. Wilson, N. Zachariou, and D. A. Jaroszynski, "Application programmes at the Scottish Centre for the Application of Plasma-based Accelerators (SCAPA)," in *Relativistic Plasma Waves and Particle Beams as Coherent and Incoherent Radiation Sources III*, D. A. Jaroszynski and M. Hur, eds., vol. 11036, pp. 93 – 103, International Society for Optics and Photonics. SPIE, 2019.

[43] L. Manti, F. Perozziello, M. Borghesi, G. Candiano, P. Chaudhary, G. Cirrone, D. Doria, D. Gwynne, R. Leanza, K. M. Prise, L. Romagnani, F. Romano, V. Scuderi, and A. Tramontana, "The radiobiology of laser-driven particle beams: focus on sub-lethal responses of normal human cells," *Journal of Instrumentation* **12** (mar, 2017) C03084–C03084.

[44] F. Romano, F. Schillaci, G. Cirrone, G. Cuttone, V. Scuderi, L. Allegra, A. Amato, A. Amico, G. Candiano, G. D. Luca, G. Gallo, S. Giordanengo, L. F. Guarachi, G. Korn, G. Larosa, R. Leanza, R. Manna, V. Marchese, F. Marchetto, D. Margarone, G. Milluzzo, G. Petringa, J. Pipek, S. Pulvirenti, D. Rizzo, R. Sacchi, S. Salamone, M. Sedita, and A. Vignati, "The ELIMED transport and dosimetry beamline for laser-driven ion beams," *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment* **829** (2016) 153–158. 2nd European Advanced Accelerator Concepts Workshop – EAAC 2015.

[45] U. Masood, T. E. Cowan, W. Enghardt, K. M. Hofmann, L. Karsch, F. Kroll, U. Schramm, J. J. Wilkens, and J. Pawelke, "A light-weight compact proton gantry design with a novel dose delivery system for broad-energetic laser-accelerated beams," *Physics in Medicine & Biology* **62** (jun, 2017) 5531–5555.

[46] P. Chaudhary, D. Gwynne, D. Doria, L. Romagnani, C. Maiorino, H. Padda, A. Alejo, N. Booth, D. Carroll, S. Kar, P. McKenna, G. Schettino, M. Borghesi, and K. M. Prise, "Effectiveness of laser accelerated ultra high dose rate protons in DNA DSB damage induction under hypoxic conditions," in *44th EPS Conference on Plasma Physics, EPS 2017*, vol. 44F, p. P1.217. European Physical Society (EPS), January, 2017.

[47] D. Margarone, G. A. P. Cirrone, G. Cuttone, A. Amico, L. Andò, M. Borghesi, S. S. Bulanov, S. V. Bulanov, D. Chatain, A. Fajstavr, L. Giuffrida, F. Grepl, S. Kar, J. Krasa, D. Kramer, G. Larosa, R. Leanza, T. Levato, M. Maggiore, L. Manti, G. Milluzzo, B. Odlozilik, V. Olsovcova, J.-P. Perin, J. Pipek, J. Psikal, G. Petringa, J. Ridky, F. Romano, B. Rus, A. Russo, F. Schillaci, V. Scuderi, A. Velyhan, R. Versaci, T. Wiste, M. Zakova, and G. Korn, "ELIMAIA: A Laser–Driven Ion Accelerator for Multidisciplinary Applications," *Quantum Beam Science* **2** (2018), no. 2,.

[48] R. A. Snavely, M. H. Key, S. P. Hatchett, T. E. Cowan, M. Roth, T. W. Phillips, M. A. Stoyer, E. A. Henry, T. C. Sangster, M. S. Singh, S. C. Wilks, A. MacKinnon, A. Offenberger, D. M. Pennington, K. Yasuike, A. B. Langdon, B. F. Lasinski, J. Johnson, M. D. Perry, and E. M. Campbell, "Intense high-energy proton beams from Petawatt-laser irradiation of solids.," *Physical Review Letters* **85** (2000), no. 14, 2945.

[49] S. C. Wilks *et al.*, "Energetic proton generation in ultra-intense laser–solid interactions," *Physics of Plasmas* **8** (2001), no. 2, 542–549.

[50] F. Wagner, O. Deppert, C. Brabetz, P. Fiala, A. Kleinschmidt, P. Poth, V. A. Schanz, A. Tebartz, B. Zielbauer, M. Roth, T. Stöhlker, and V. Bagnoud, "Maximum Proton Energy above 85 MeV from the Relativistic Interaction of Laser Pulses with Micrometer Thick CH_2 Targets," *Phys. Rev. Lett.* **116** (May, 2016) 205002.

[51] A. Higginson, R. J. Gray, M. King, R. J. Dance, S. D. R. Williamson, N. M. H. Butler, R. Wilson, R. Capdessus, C. Armstrong, J. S. Green, S. J. Hawkes, P. Martin, W. Q. Wei, S. R. Mirfayzi, X. H. Yuan, S. Kar, M. Borghesi, R. J. Clarke, D. Neely, and P. McKenna, "Near-100 MeV protons via a laser-driven transparency-enhanced hybrid acceleration scheme," *Nature Communications* **9** (2018), no. 1, 724.

[52] D. C. Carroll, P. Brummitt, D. Neely, F. Lindau, O. Lundh, C. G. Wahlström, and P. McKenna, "A modified Thomson parabola spectrometer for high resolution multi-MeV ion measurements-Application to laser-driven ion acceleration," *Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment* **620** (2010), no. 1, 23–27.

[53] W. J. Ma, I. J. Kim, J. Q. Yu, I. W. Choi, P. K. Singh, H. W. Lee, J. H. Sung, S. K. Lee, C. Lin, Q. Liao, J. G. Zhu, H. Y. Lu, B. Liu, H. Y. Wang, R. F. Xu, X. T. He, J. E. Chen, M. Zepf, J. Schreiber, X. Q. Yan, and C. H. Nam, "Laser Acceleration of Highly Energetic Carbon Ions Using a Double-Layer Target Composed of Slightly Underdense Plasma and Ultrathin Foil," *Phys. Rev. Lett.* **122** (Jan, 2019) 014803.

[54] A. McIlvenny, D. Doria, L. Romagnani, H. Ahmed, N. Booth, E. J. Ditter, O. C. Ettlinger, G. S. Hicks, P. Martin, G. G. Scott, S. D. R. Williamson, A. Macchi, P. McKenna, Z. Najmudin, D. Neely, S. Kar, and M. Borghesi, "Selective Ion Acceleration by Intense Radiation Pressure," *Phys. Rev. Lett.* **127** (Nov, 2021) 194801.

[55] B. M. Hegelich, B. Albright, P. Audebert, A. Blazevic, E. Brambrink, J. Cobble, T. Cowan, J. Fuchs, J. C. Gauthier, C. Gautier, M. Geissel, D. Habs, R. Johnson, S. Karsch, A. Kemp, S. Letzring, M. Roth, U. Schramm, J. Schreiber, K. J. Witte, and J. C. Fernández, "Spectral properties of laser-accelerated mid-Z MeV/u ion beams," *Physics of Plasmas* **12** (2005), no. 5, 056314, https://doi.org/10.1063/1.1915350.

[56] B. M. Hegelich, B. J. Albright, J. Cobble, K. Flippo, S. Letzring, M. Paffett, H. Ruhl, J. Schreiber, R. K. Schulze, and J. C. Fernández, "Laser acceleration of quasi-monoenergetic MeV ion beams," *Nature* **439** (2006), no. 7075, 441–444.

[57] K. Kondo, M. Nishiuchi, H. Sakaki, N. P. Dover, H. F. Lowe, T. Miyahara, Y. Watanabe, T. Ziegler, K. Zeil, U. Schramm, E. J. Ditter, G. S. Hicks, O. C. Ettlinger, Z. Najmudin, H. Kiriyama, M. Kando, and K. Kondo, "High-Intensity Laser-Driven Oxygen Source from CW Laser-Heated Titanium Tape Targets," *Crystals* **10** (2020), no. 9,.

[58] J. Derouillat *et al.*, "Smilei : A collaborative, open-source, multi-purpose particle-in-cell code for plasma simulation," *Computer Physics Communications* **222** (January, 2018) 351–373.

[59] H. Lau, "Beam Tracking Simulations for Stage 1 of the Laser-Hybrid Accelerator for Radiobiological Applications (LhARA)," in *Proc. IPAC'21*, no. 12 in International Particle Accelerator Conference, pp. 2939–2942. JACoW Publishing, Geneva, Switzerland, 08, 2021.

[60] M. J. De Loos and S. B. Van der Geer, "General Particle Tracer: A New 3D Code for Accelerator and Beamline Design,".

[61] W. Shields, A. Kurup, H. Lau, K. Long, and J. Pasternak, "Simulations of the Stage 2 FFA Injection Line of LhARA for Evaluating Beam Transport Performance," in *Proc. IPAC'21*, no. 12 in International Particle Accelerator Conference, pp. 4495–4498. JACoW Publishing, Geneva, Switzerland, 08, 2021.

[62] H. Daido, M. Nishiuchi, and A. S. Pirozhkov, "Review of laser-driven ion sources and their applications," *Reports on Progress in Physics* **75** (2012), no. 5, 056401.

[63] A. Macchi, M. Borghesi, and M. Passoni, "Ion acceleration by superintense laser-plasma interaction," *Reviews of Modern Physics* **85** (2013), no. 2, 751–793.

[64] S. C. Wilks, W. L. Kruer, M. Tabak, and A. B. Langdon, "Absorption of Ultra-Intense Laser Pulses," *Physical Review Letters* **69** (1992), no. 9, 1383–1386.

[65] E. L. Clark, K. Krushelnick, M. Zepf, F. N. Beg, M. Tatarakis, A. Machacek, M. I. K. Santala, I. Watts, P. A. Norreys, and A. E. Dangor, "Energetic heavy-Ion and proton generation from ultraintense laser-plasma interactions with solids," *Physical Review Letters* **85** (2000), no. 8, 1654.

[66] M. Borghesi, A. Mackinnon, D. Campbell, D. Hicks, S. Kar, P. Patel, D. Price, L. Romagnani, A. Schiavi, and O. Willi, "Multi-MeV Proton Source Investigations in Ultraintense Laser-Foil Interactions," *Physical Review Letters* **92** (2004), no. 5, 055003.

[67] C. N. Danson, C. Haefner, J. Bromage, T. Butcher, J. C. F. Chanteloup, E. A. Chowdhury, A. Galvanauskas, L. A. Gizzi, J. Hein, D. I. Hillier, N. W. Hopps, Y. Kato, E. A. Khazanov, R. Kodama, G. Korn, R. Li, Y. Li, J. Limpert, J. Ma, C. H. Nam, D. Neely, D. Papadopoulos, R. R. Penman, L. Qian, J. J. Rocca, A. A. Shaykin, C. W. Siders, C. Spindloe, S. Szatmári, R. M. Trines, J. Zhu, P. Zhu, and J. D. Zuegel, "Petawatt and exawatt class lasers worldwide," *High Power Laser Science and Engineering* **7** (2019), no. June,.

[68] A. Higginson, R. Wilson, J. Goodman, M. King, R. J. Dance, N. M. Butler, C. D. Armstrong, M. Notley, D. C. Carroll, Y. Fang, X. H. Yuan, D. Neely, R. J. Gray, and P. McKenna, "Influence of target-rear-side short scale length density gradients on laser-driven proton acceleration," *Plasma Physics and Controlled Fusion* **63** (2021), no. 114001,.

[69] J. Fuchs, C. A. Cecchetti, M. Borghesi, T. Grismayer, E. d'Humières, P. Antici, S. Atzeni, P. Mora, A. Pipahl, L. Romagnani, A. Schiavi, Y. Sentoku, T. Toncian, P. Audebert, and O. Willi, "Laser-Foil Acceleration of High-Energy Protons in Small-Scale Plasma Gradients," *Physical Review Letters* **99** (2007) 015002.

[70] L. A. Gizzi, E. Boella, L. Labate, F. Baffigi, P. J. Bilbao, F. Brandi, G. Cristoforetti, A. Fazzi, L. Fulgentini, D. Giove, P. Koester, D. Palla, and P. Tomassini, "Enhanced laser-driven proton acceleration via improved fast electron heating in a controlled pre-plasma," *Scientific Reports* **11** (2021) 13728.

[71] D. Margarone, J. Krsa, L. Giuffrida, A. Picciotto, L. Torrisi, T. Nowak, P. Musumeci, A. Velyhan, J. Prokpek, L. Lska, T. Mocek, J. Ullschmied, and B. Rus, "Full characterization of laser-accelerated ion beams using Faraday cup, silicon carbide, and single-crystal diamond detectors," *Journal of Applied Physics* **109** (2011), no. 10,.

[72] J. S. Green, M. Borghesi, C. M. Brenner, D. C. Carroll, N. P. Dover, P. S. Foster, P. Gallegos, S. Green, D. Kirby, K. J. Kirkby, P. McKenna, M. J. Merchant, Z. Najmudin, C. A. J. Palmer, D. Parker, R. Prasad, K. E. Quinn, P. P. Rajeev, M. P. Read, L. Romagnani, J. Schreiber, M. J. V. Streeter, O. Tresca, C.-G. Wahlström, M. Zepf, and D. Neely, "Scintillator-based ion beam profiler for diagnosing laser-accelerated ion beams," *Proc. SPIE* **8079** (2011), no. 807919, 807919.

[73] N. P. Dover, M. Nishiuchi, H. Sakaki, M. A. Alkhimova, A. Y. Faenov, Y. Fukuda, H. Kiriyama, A. Kon, K. Kondo, K. Nishitani, K. Ogura, T. A. Pikuz, A. S. Pirozhkov, A. Sagisaka, M. Kando, and K. Kondo, "Scintillator-based transverse proton beam profiler for laser-plasma ion sources," *Review of Scientific Instruments* **88** (2017), no. 7, 073304.

[74] S. Steinke, J. H. Bin, J. Park, Q. Ji, K. Nakamura, A. J. Gonsalves, S. S. Bulanov, M. Thévenet, C. Toth, J. L. Vay, C. B. Schroeder, C. G. Geddes, E. Esarey, T. Schenkel, and W. P. Leemans, "Acceleration of high charge ion beams with achromatic divergence by petawatt laser pulses," *Physical Review Accelerators and Beams* **23** (2020) 021302.

[75] N. P. Dover, M. Nishiuchi, H. Sakaki, K. Kondo, H. F. Lowe, M. A. Alkhimova, E. J. Ditter, O. C. Ettlinger, A. Y. Faenov, M. Hata, G. S. Hicks, N. Iwata, H. Kiriyama, J. K. Koga, T. Miyahara, Z. Najmudin, T. A. Pikuz, A. S. Pirozhkov, A. Sagisaka, and U. Schramm, "Demonstration of repetitive energetic proton generation by ultra-intense laser interaction with a tape target," *High Energy Density Physics* **37** (2020) 100847.

[76] G. Glenn, C. Crissman, C. B. Curry, D. Deponte, J. Koralek, M. Mo, F. Treffert, S. Glenzer, and M. Gauthier, "Micron-scale ambient-temperature liquid jets for high repetition rate laser-matter interactions," *Bulletin of the American Physical Society* (2021).

[77] C. Palmer. private communication, 2021.

[78] R. J. Shalloo, S. J. Dann, J. N. Gruse, C. I. Underwood, A. F. Antoine, C. Arran, M. Backhouse, C. D. Baird, M. D. Balcazar, N. Bourgeois, J. A. Cardarelli, P. Hatfield, J. Kang, K. Krushelnick, S. P. Mangles, C. D. Murphy, N. Lu, J. Osterhoff, K. Põder, P. P. Rajeev, C. P. Ridgers, S. Rozario, M. P. Selwood, A. J. Shahani, D. R. Symes, A. G. Thomas, C. Thornton, Z. Najmudin, and M. J. Streeter, "Automation and control of laser wakefield accelerators using Bayesian optimization," *Nature Communications* **11** (2020) 6355.

[79] D. Gabor *Nature* **160** (1947) 89.

[80] F. Penning *Physica* **4** (1937) 71.

[81] J. Fajans and C. M. Surko *Physics of Plasmas* **27** (2020) 030601.

[82] R. Davidson, *Physics Of Nonneutral Plasmas*. World Scientific Publishing Company, 2001.

[83] L. Brillouin *Phys. Rev.* **67** (1945) 260.

[84] T. M. O'Neil *The Physics of Fluids* **23** (1980) 2216.

[85] L. Turner *Physics of fluids. B, Plasma physics* **3** (1991) 1355.

[86] J. Notte and J. Fajans *Physics of Plasmas* **1** (1994) 1123.

[87] **ALPHA** Collaboration, M. Ahmadi *et al. Phys. Rev. Lett.* **120** (2018) 025001.

[88] J.A. Palkovic *et al.* tech. rep., 1988. FNAL/C–88/177.

[89] A. Goncharov *Review of Scientific Instruments* **84** (2013) 021101.

[90] R. Pompili *et al. Applied Physics Letters* **110** (2017) 104101.

[91] R. Pompili *et al. Phys. Rev. Accel. Beams* **22** (2019) 121302.

[92] C. Beberweil *et al.* in *Proceedings of IPAC2017, Copenhagen, Denmark*. 2017.

[93] D. Gabor, "A space-charge lens for the focusing of ion beams," *Nature* **160** (1947), no. 4055, 89.

[94] "Project Management Framework." `https://stfc.ukri.org/about-us/how-we-are-governed/policies-standards/project-management-framework/`, April, 2016. Accessed: 2021-10-20.

[95] "The STFC Project Management Framework; Version 5." `https://stfc.ukri.org/files/project-management-framework/`, June, 2017. Accessed: 2021-10-20.

[96] "Pre-publication review of the LhARA pre-CDR." `https://ccap.hep.ph.ic.ac.uk/trac/wiki/Research/DesignStudy/PreCDR/Review`, April, 2020. Accessed: 2020-04-30.

[97] "Ion Therapy Research Facility (ITRF)." Submitted to the Infrastrucvture Advisory Committee of UKRI, June, 2021.

[98] "Technical Notes." `https://ccap.hep.ph.ic.ac.uk/trac/wiki/Communication/Notes`, 2021. Accessed: 2021-10-20.

[99] "The Centre for the Clinical Application of Particles." `https://ccap.hep.ph.ic.ac.uk/trac/wiki`, 2021. Accessed: 2021-10-20.

[100] "CCAP Technical Note git repository." `https://ccap.hep.ph.ic.ac.uk/git/ccap-tn`, 2021. Accessed: 2021-10-20.

A Annex: LhARA preliminary, pre-construction phase project specification

A.1 Introduction

The sections which follow define the 5-year programme necessary to deliver the Preliminary and Pre-construction Phases of the LhARA project to serve the Ion Therapy Research Facility. The principal deliverables are:

1. Conceptual Design Report (CDR) for the facility at the end of the year 2.
2. Technical Design Report (TDR1) for Stage 1, which will provide proton beams with kinetic energy between 12 MeV and 15 Mev to the low energy *in-vitro* end station, at the end of year 3.
3. Technical Design Report (TFD2) for Stage 2, which will provide proton and ion beams to the high energy *in-vitro* and the *in-vivo* end station at the end of year 5.

The preparation of the CDR and both Technical Design Reports will be supported by the R&D programme defined through the work-package definitions which follow and which are summarised in section A.8.3. The overarching goal for the programme defined here is to prepare for the start of the LhARA construction phase by the end of year 5.

The LhARA project is divided into six work packages each managed by a team of 2 or 3 technical experts. The Work Packages are

- WP1: Project management.
- WP2: Laser-driven proton and ion source.
- WP3: Proton and ion capture.
- WP4: Ion-acoustic dose mapping.
- WP5: Novel beam-line instrumentation and end-station development.
- WP6: Design and integration.

The costing presented below has been obtained on the following basis:

- The capital and staff costs have been estimated in calendar year 2021. Following STFC guidelines, an annual inflation rate of 2.5% for equipment and of 3.5% on staff costs has been assumed. The collaboration recognises that the JeS submissions from each of the institutes will need to be submitted against the usual STFC and institutional rules. The staff estimates presented in the tables that follow, therefore, should be regarded as planning estimates.
- For STFC staff, band-average annual costs have been used. For Universities, the 2021 fEC for the staff member in question has been used. A unique identifier is used instead of staff names in order to preserve anonymity. A confidential staff database is being maintained to establish the correspondence between individuals and the unique identifiers.
- VAT (at the rate of 20%) is included in all equipment costs by work package; the total cost of VAT is summarised by work package.
- A working margin of 10% and a contingency of 20% has been added to the capital costs as well as the staff costs. The collaboration recognises that the management of working margin and contingency needs to be agreed with the STFC at the start of the project. Since the project is in its formative stage, the costing for each work package contains a line where resources for particular contingencies are listed explicitly. The risk analysis includes the cost of mitigation for risks that can not be addressed through the working margin and contingency.

Each work package is organised in a number of "tasks". For each work package, the principle objectives of each work package and each task are summarised in the commentary that precedes the resource request.

A.2 Work package details

A.2.1 Work package 1: Project management

Objectives

The Preliminary and Pre-Construction phases of the LhARA Programme will be carried out in the context of the Ion Therapy Research Facility (ITRF) development. A pre-CDR [1], published in Frontiers of Physics [2] for LhARA was prepared using resources provided by an STFC Future Opportunities 2019 award. The pre-CDR identified the key technical risks that needed to be addressed:

- Validation of the simulated laser-generated proton and ion fluxes in test measurements using a representative laser source;
- Validation of the simulated properties of the confined electron gas that is the basis of the Gabor lens and the design and construction of a second prototype;
- Development of real-time, non-destructive dose-profile measurement system based on the acoustic signals generated by the almost rapid deposition of energy in the Bragg peak; and
- Development of fully automated *in-vitro* end station, its instrumentation, and the necessary ion-beam diagnostics.

The LhARA collaboration began to develop the risk management programme by which to address these issues as soon as the pre-CDR was complete. The next steps in this risk management programme forms the basis of work packages 2 to 5. The risk-management programme was developed within the framework of an ongoing "Design and integration" activity. The ongoing programme of design and integration work for the Preliminary and Pre construction phases is defined in the description of work package 6 below.

This work package, "Work package 1: Project management", identifies the resources required to manage the LhARA programme in the Preliminary and Pre-construction phases. Resources are requested to support the Programme Spokes-people and Programme Managers in the execution of the programme. Together the programme-management team has responsibility for:

- Programme management and planning and the development of the LhARA project;
- Reporting to STFC and other funders and stakeholders, including financial reporting and interfacing with oversight bodies;
- Risk management, tracking, and escalation as appropriate;
- The oversight of the maintenance of appropriate technical and scientific documentation, drawing repositories, and technical specifications;
- Stakeholder engagement; and
- Patient and Public engagement.

The Stakeholder Engagement plan described in section A.7 is an important part of the Preliminary and Pre-construction activities. Modest resources for travel and engagement activities are included in table 2 to ensure the success of this activity.

Task objectives and deliverables

The work of the Project Management Team will be organised through the following tasks:

- The development and continuous monitoring of the programme schedule and cost. The evaluation of delivery of the programme through active monitoring of the execution the LhARA programme against milestones and agreed cost profile;

- The organisation and delivery of reports and presentations required for effective STFC and stakeholder oversight;
- The tracking of progress and risk by work package, managing effort through monthly progress meetings with each work package management team;
- The organisation of collaboration meetings on a 4 to 6 monthly schedule to provide cross-collaboration visibility and coordination;
- The organisation of regular stakeholder meetings by which to maintain currency with latest the results in relevant radiobiological and medical fields; to communicate the current status and important developments in the LhARA programme to future user; and to solicit stakeholder feedback on the programme; and
- The recruitment of appropriate patient representatives to advise as the LhARA programme, its specification, and potential treatment regimens evolve.

Resources requested

LhARA is a complex project composed of several interacting work packages the coordination of which will require considerable management effort. Resources are requested to support the LhARA spokespeople and full time programme managers. STFC financial staff assistance at 0.2FTE is requested to support the project management team. Funds are requested to support travel and subsistence costs for two patient representatives. Resources to support STFC Oversight Committee activities also been identified.

Travel and subsistence are requested to allow three collaboration meetings to be held per year. The collaboration meetings have been and will continue to be important to drive the programme forward and monitor progress. Project office consumables are requested, this resource will cover incidental expenses for the project office, both Spokespersons and the WP1 work package managers. A modest travel budget is requested; with work packages managed in 4 different cities, and experimental projects planned in all of these locations as well as at the national laboratories and elsewhere it is important that the programme spokespersons and the programme managers have the resources to make visits as required. Travel should also be expected for Stakeholder and patient-engagement meetings. This request has been increased as the programme enters years 4 and 5 to reflect the increased workload as the programme moves towards completion of the pre-construction phase. A a modest annual budget is requested for public engagement and outreach.

Gantt chart and principle milestones

Risk register

The principal technical risks in the LhARA project relate to the components that enable the facility's unique performance characteristics: the laser particle source in combination with the ion capture system. These risks are managed through rigorous theoretical analysis and simulation coupled with an extensive experimental investigation led by an expert teams (work packages 2 and 3). The unique LhARA beam properties lead to a unique set of challenges in the ion acoustic dose mapping project (work package 4). Simulation software is capable of addressing the issues raised and guiding the purchase of suitable hardware. LhARA has access to the principal authors of that software. Project management risks post mitigation are dominated by those occasioned by funding and staff retention. LhARA has adopted a system where each work package has co-leads, mitigating this risk.

An extract of the LhARA Top Level risk register is shown in table 2.

Table 1: LhARA WP1 costing

PROJECT:	**LhARA**
Issue Date:	**01/11/2021**
Manager:	**J. Parsons & C. Whyte**
Start Date:	**2022**
End Date:	**2027**

Cost Profile

Staff	2022/23 Fraction	2022/23 £k	2023/24 Fraction	2023/24 £k	2024/25 Fraction	2024/25 £k	2025/26 Fraction	2025/26 £k	2026/27 Fraction	2026/27 £k	Total Fraction	Total £k
Project office support												
Imperial Physics												
IC-Phys-Support-1	1	100.00	1	100.00	1	100.00	1	100.00	1	100.00	5	500.00
Strathclyde Physics												
Strathclyde-Phys-Stf-1	1	100.00	1	100.00	1	100.00	1	100.00	1	100.00	5	500.00
STFC-PPD												
STFC-Finance-Support	0.2	20.00	0.2	20.00	0.2	20.00	0.2	20.00	0.2	20.00	1	100.00
Cost of risk mitigation, staff (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
Staff total:	2.2	**220.00**	2.2	**220.00**	2.2	**220.00**	2.2	**220.00**	2.2	**220.00**	11	**1100.00**
Non-staff		**£k**		**£k**		**£k**		**£k**		**£k**		**£k**
Project office support												
Collaboration meetings - 3 per year		15.00		15.00		15.00		15.00		15.00		75.00
Equipment total:		**15.00**		**15.00**		**15.00**		**15.00**		**15.00**		**75.00**
Inflation (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
PPI, engagement, and outreach		10.00		10.00		10.00		10.00		10.00		50.00
Patient representative and other seconded advisor expenses		6.00		6.00		6.00		6.00		6.00		30.00
Review-committee expenses		5.00		5.00		5.00		5.00		5.00		25.00
Consumables		10.00		10.00		10.00		10.00		10.00		50.00
Travel		15.00		15.00		15.00		20.00		20.00		85.00
Cost of risk mitigation, equipment (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
Working margin:		23.50		23.50		23.50		23.50		23.50		117.50
Contingency, equipment:		3.00		3.00		3.00		3.00		3.00		15.00
Contingency, CG staff:		0.00		0.00		0.00		0.00		0.00		330.00
Contingency, all staff:		66.00		66.00		66.00		66.00		66.00		0.00
Total:		**373.50**		**373.50**		**373.50**		**378.50**		**378.50**		**1877.50**

Table 2: LhARA Top level risk register showing only risks scoring 5 or more post mitigation

,

	Number	Name	Description	Likelihood	Impact	Score	Mitigation	Mitigated Likelihood	Mitigated Impact	Mitigated score	Comments	Significant Dates	Retirement date
	1	Stakeholder engagement	Insufficient stakeholder engagement leading to a deterioration in relationships that impact on the project success.	3	5	15	Develop a multidiscipline stakeholder engagement plan for the project. Include relevant radiobiology, medical and patient representation in core project management	3	3	9			
	3	Performance specification parameters	Inadequate ion beam parameters specification to meet the Physics and Biolology requirements for the facility.	3	5	15	The project consortium consists of all the multidiscipline experts to understand the required parameters.	2	4	8			
	5	Resources	Insufficient resources secured to deliver the project aims, project scope, quality or specifications to the required timescale.	5	4	20	Request adequate resources based on experience of delivering similar multidiciple facilities with comparable technical complexity, address key callenges in the Conceptual Design Report (CDR) to those identified in the pre - CDR phase.	4	4	16			
	9	Key specialist staff	Availability of key specialist staff critical to delivering the project.	4	5	20	Identify potential single point failure risks, apply cover and succession planning where appropriate.	2	5	10			
	10	Safety, Health & Enviroment	SHE related issues arising during the project.	3	5	15	Construct facility at appropriately resourced site, enforce comprehensive SHE policy to STFC standards or better. Establish and communicate codes of practice. Procure appropriately experienced staff in Radiation Test Facility management, skills to include risk assessment, method statements, permit to work systems and RTF operational systems and methodology.	1	5	5			
	14	Particle source and capture	Integration of source and Lens requires compromises which impact on final performance	3	5	15	Early and continuing engagement with WPM teams for WP2&3	2	4	8			
	15	Dose	Photo-acoustic signal cannot provide required fidelity	2	5	10	Use expertise in modelling of interaction to guide optimisation of detection hardware frequencies. Exploit options offered by parallel arrays of detectors.	2	4	8			

A.2.2 Work package 2: Laser-driven proton and ion source

Objectives

The overarching objective for Work package 2 is to deliver a design for a stable laser-driven high-flux proton and ion source capable operating at 10 Hz together with the instrumentation necessary for its characterisation. The source will be optimised to maximise coupling efficiency with the capture system designed in WP3. To achieve the overarching goal, the work has been divided into two principal themes:

1. Source demonstration and characterisation with existing technology; and
2. Development of underpinning technology towards stable and sustainable 10 Hz operation.

The work within the two themes will be carried out through 6 distinct tasks, each designed to deliver a particular objective (objectives O1–O6, defined below).

Six UK groups (STFC CLF, Imperial, Lancaster, Queen's, and Strathclyde, & STFC Scientific Computing Department) and one overseas group (Stanford/SLAC) will contribute to the work. The links between these groups are shown in figure 15. The "Work package 2 consortium" includes the principal UK University groups with expertise in the experimental and numerical development of laser driven proton and ion sources. These University groups have forged a collaboration with the STFC Central Laser Facility (CLF) and brought in key expertise from SLAC to achieve Work-package objectives. Tests will be carried out as appropriate at the facilities listed in table 3.

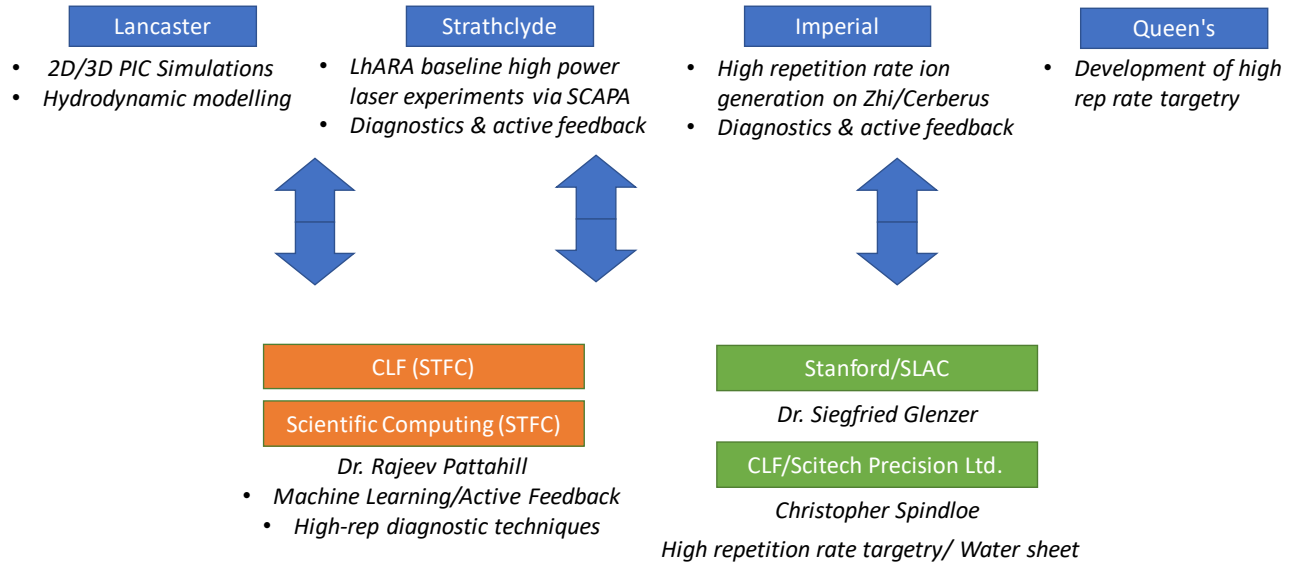


Figure 15: Principal contributors to the execution of work package 2 and the relationships between them.

Task objectives and deliverables

The objectives are defined for each of the two themes are defined below.

Theme 1: Source demonstration & characterisation with established technology

O1: Perform Full 3D PIC +hydro baseline simulations using optimised LhARA baseline conditions:

Table 3: Facilities at which test experiments will be carried out in the execution of work package 2.

Facility	SCAPA (Strath)	Zhi (ICL)	Cerberus (ICL)
Max. laser energy (J)	10	0.2	0.1 / 20
Pulse length (fs)	30	40	450
Rep. rate (Hz)	5	>10	10 / .001
Est. H+ energies (MeV)	> 15	> 2	> 1 / > 10
Associated MS	2, 3, 5, 6	2, 4, 5	4, 5

1. Programme of hydrodynamics and particle in cell simulations in 2D and 3D to identify key laser plasma requirements to generate 15 MeV protons;
2. Conduct an extended programme of simulations to optimise conditions for ion production.

O2: Deliver a diagnostic platform for proton and heavy ion beam characterisation:

1. Design and test 10 Hz ion diagnostics packages:
   - Thomson parabola spectrometer with appropriate spectral resolution/time-of-flight spectroscopy system;
   - Proton and ion sensitive 2D scintillator imager diagnostic.
2. Implement a comprehensive laser diagnostics package at 10 Hz to monitor drive fluctuations and its impact on ion source stability.

O3: Perform baseline experiment for proton and carbon beams at 1 Hz using optimised conditions on SCAPA laser;

1. Produce and measure proton and carbon beams on SCAPA at 1 Hz using PIC defined optimal conditions;
2. Use results to benchmark PIC simulation output to help define future design concepts.

Theme 2: Development of Underpinning Beamline Technology

O4: Complete conceptual design of sustainable repetitive target system:

1. Perform feasibility study of advanced targetry concepts (e.g. thin liquid sheet) by deployment on high repetition laser system and PIC modelling;
2. Experimental measurements of debris and activation and application of mitigation strategies at 10 Hz;
3. Development of active stabilisation techniques of laser, target and ultimately ion source properties at 10 Hz.

O5: Completed conceptual design of integrated ion source system:

1. Complete design and testing of a combined laser and source diagnostic platform including active feedback for source stabilisation at 1 Hz for 15 MeV protons and 10 Hz at 1 MeV protons;

Table 4: Resources required to execute work package 2.

Laser-driven proton and ion source
Work package number 2

PROJECT:	**LhARA**
Issue Date:	**01/11/2021**
Manager:	**E. Boella, N. Dover, R. Gray**
Start Date:	**2022**
End Date:	**2027**

Cost Profile

Staff	**2022/23**		**2023/24**		**2024/25**		**2025/26**		**2026/27**		**Total**	
	Fraction	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**
Task 1												
Strathclyde Physics												
Strathclyde-Phys-PDRA-1	1	100.00	1	100.00	1	100.00	1	100.00	1	100.00	5	500.00
Strathclyde-Phys-RF-Eng-1	0.5	50.00	0.5	50.00	0.5	50.00	0.5	50.00	0.5	50.00	2.5	250.00
Strathclyde-Phys-Tech-1	0.1	10.00	0.1	10.00	0.1	10.00	0.1	10.00	0.1	10.00	0.5	50.00
Strathclyde-Phys-PG-1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Imperial Physics												
IC-Phys-PDRA-1	1	100.00	1	100.00	1	100.00	1	100.00	1	100.00	5	500.00
IC-Phys-RF-Eng-1	0.5	50.00	0.5	50.00	0.5	50.00	0.5	50.00	0.5	50.00	2.5	250.00
IC-Phys-Tech-1	0.1	10.00	0.1	10.00	0.1	10.00	0.1	10.00	0.1	10.00	0.5	50.00
IC-Phys-PG-1	0.25	25.00	0.25	25.00	0.25	25.00	0.25	25.00	0.25	25.00	1.25	125.00
Lancaster												
Lanc-Phys-Stf-1	0.25	25.00	0.25	25.00	0.25	25.00	0.25	25.00	0.25	25.00	1.25	125.00
Lanc-Phys-PDRA-1	1	100.00	1	100.00	1	100.00	1	100.00	1	100.00	5	500.00
Lanc-Phys-PG-1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Queens												
Qns-Phys-Stf-1	0.05	5.00	0.05	5.00	0.05	5.00	0.05	5.00	0.05	5.00	0.25	25.00
Qns-Phys-PG-1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Cost of risk mitigation, staff (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
Staff total:	4.75	**475.00**	4.75	**475.00**	4.75	**475.00**	4.75	**475.00**	4.75	**475.00**	**23.75**	**2375.00**
Non-staff		**£k**		**£k**		**£k**		**£k**		**£k**		**£k**
Task 1												
F/4 Parabola		40.00		0.00		0.00		0.00		0.00		40.00
Storage/ Analysis Cluster		30.00		0.00		0.00		0.00		0.00		30.00
Custom Ion TOF spectrometer		20.00		0.00		0.00		0.00		0.00		20.00
Custom Ion TP spectrometer		50.00		0.00		0.00		0.00		0.00		50.00
Custom Proton/Ion imager		30.00		0.00		0.00		0.00		0.00		30.00
Laser Diagnostic Platform		150.00		0.00		0.00		0.00		0.00		150.00
Advaced Target Characterisation		50.00		0.00		0.00		0.00		0.00		50.00
Advaced Target Platform		100.00		0.00		0.00		0.00		0.00		100.00
Equipment total:		**470.00**		**0.00**		**0.00**		**0.00**		**0.00**		**470.00**
Inflation (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
SCAPA Access		40.00		80.00		120.00		120.00		120.00		480.00
Imperial Access		40.00		40.00		30.00		20.00		20.00		150.00
Birmingham Accelerator		2.00		2.00		2.00		2.00		2.00		10.00
Simulation/HPC time		20.00		20.00		20.00		20.00		20.00		100.00
Consumables		20.00		20.00		20.00		20.00		20.00		100.00
Travel		20.00		20.00		20.00		20.00		20.00		100.00
Cost of risk mitigation, equipment (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
Working margin:		94.50		47.50		47.50		47.50		47.50		284.50
Contingency, equipment:		94.00		0.00		0.00		0.00		0.00		94.00
Contingency, CG staff:		0.00		0.00		0.00		0.00		0.00		712.50
Contingency, all staff:		142.50		142.50		142.50		142.50		142.50		0.00
Total:		**1418.00**		**847.00**		**877.00**		**867.00**		**867.00**		**4876.00**

2. PIC simulation driven ML optimisation/stabilisation studies targeting high repetition rate and long run time
3. Complete design and testing of source with integrated capture capability at 1 Hz.

O6: Demonstration of full specification continuous operation of ion source:

1. Demonstrate stable source at 5 Hz (and 10 Hz capable) within beam capture specifications and sustainable debris/activation rates in burst mode over 10 minutes and in continuous mode for 1 hour;
2. Produce a final concept design/cost/setup including targets, laser, diagnostics etc.

Resources requested

The resources required to execute work package 2 are summarised in table 4. The costs are broken down as follows.

Directly Incurred Staffing:

- Management and supervision for the research will be provided by academics at Queen's University Belfast and Lancaster University and research fellows at Imperial College London and University of Strathclyde.

- One PDRA and PhD student at Lancaster University will be dedicated to the required numerical modelling. One PDRA and PhD student and part-funded technician at Strathclyde will focus on implementation of LhARA equivalent laser driven ion source experiments on the SCAPA laser system.
- A PhD student at Queen's and a PhD student, PDRA and part-funded technician at Imperial will focus on the investigation of high repetition rate techniques and advanced targetry using the Zhi and Cerberus high power laser facilities at Imperial.

Equipment:

- An off-axis parabolic mirror for use on SCAPA (£40k) which will be suitable for long term high-repetition use.
- Comprehensive laser diagnostic suites for both SCAPA, Zhi and Cerberus laser systems, essential for active source stabilisation (total £150k).
- A targetry characterisation system for existing tape target systems to enable high-repetition rate operations (£50k)
- A water sheet target amenable to sustainable high-repetition rate operation (£100k).
- A diagnostic system for measuring the ion beams generated from the laser source, including a time-of-flight spectroscopy system (£20k), a Thomson Parabola Spectrometer suitable for measuring different ion species (£50k), and a spatial beam imaging system (£30k).
- High volume, rapid access data acquisition and storage systems at Strathclyde and Imperial (total £30k).

Facilities Usage:

- 24 weeks SCAPA access (£20k p/w) spread over 5 years (total £480k) to complete major experimental testing working in O3, O5 and O6.
- 75 weeks between the Zhi and Cerberus lasers at Imperial (£2k p/w) (total £150k) to complete experimental work in O4.
- Calibration activities at Birmingham cyclotron (10 days, £1k per diem) to support design and development work in O2.

Consumable items:

- (£50k p/y) include single-use detectors, filters, optics and optomechanics and targets (total £250k).

Travel:

- Travel funding (£20k p/y) is requested to facilitate travel to experiments, including inviting our collaborators at SLAC National Laboratory to attend experiments at Strathclyde/Imperial, as well as travel to relevant domestic and international conferences for staff funded by the grant.

Cost of risk mitigation:

- Resource estimates for the cost of mitigating risks included over the course of the project have been made including risks associated with lack of access to simulation resources and laser facilities (total £160k).

Gantt chart and principle milestones

The planned schedule for work package 2 is given in the Gantt chart in figure 16.

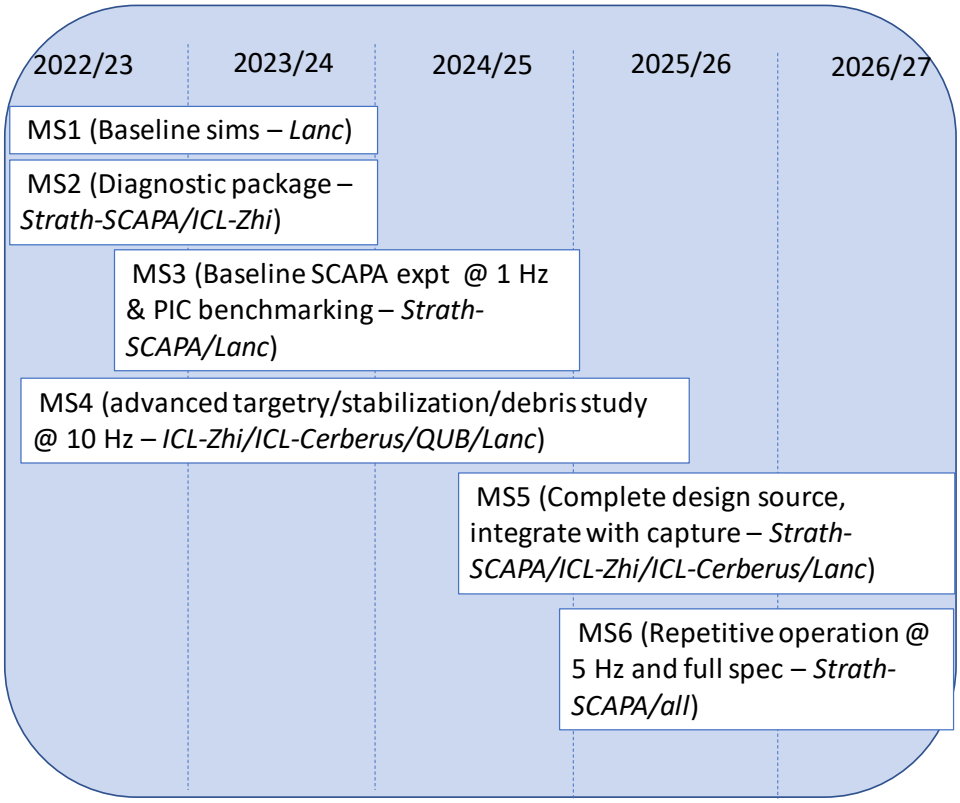


Figure 16: (Placeholder) Gantt chart for WP2

Risk register

The risks associated with work package 2 have been carefully evaluated and mitigation strategies developed, as shown in table 5. The risks are related to three overall issues: access to laser test sources HPC resources, the ability to deliver the required ion flux, and the ability to provide an ion-source design that meets the LhARA requirements.

An inability to secure laser beamtime or technical issues with the laser during beamtime would significantly hamper progress on the technical demonstrations of objectives 2-6. To mitigate these risks, resources have been included to pay access fees by which to purchase beam time directly. We have also developed a work programme including three different laser facilities (SCAPA, Zhi, Cerberus). Although each facility provides different beam parameters, many of the objectives can be achieved at multiple facilities, providing redundancy in case of laser failure. Additional risk comes from lack of high performance computing access for numerical simulations, and we have mitigated this by including the resources required to pay for access.

The second main area of risk involves the source output. In order to supply the downstream beamline the laser driven source needs to deliver the beam energy and proton and ion flux into the required solid angle. Numerical simulations indicate this is possible using the laser specification given in the pre-conceptual design report [1, 2]. There is a risk that the actual experimental performance is not as good as predicted by simulations and therefore we will test this at the earliest opportunity using the SCAPA laser system. This will provide time to adjust the laser conditions, test experimentally the required laser specifications for the LhARA design and, if needed, investigate techniques to maximise the particle flux in the required energy band. There is also significant risk that the stability of the source is not sufficient for the desired LhARA applications. This is linked to the stability of the drive laser and targetry system. The focus will therefore be on the development of

Number	Name	Description	Likelihood	Impact	Score	mitigation	Mitigated Impact	Mitigated score
1	PM - Unable to secure laser beamtime	SCAPA schedule does not allow for beamtime access	2	4	8	Pay for beamtime access/ Perform scaled experiments at other laser systems (e.g. Imperial)	3	6
2	Laser - Technical issues with laser prevent access	SCAPA/Imperial laser has technical issues that cause delays	3	4	12	Use different laser facility for similar experiments/ pay for beamtime access	3	9
3	Simulations - Insufficient HPC resource	Simulations take long or are more costly than planned	1	3	3	Included mitigation costs to pay for access to the Hartree HPC system	0	0
4	Source output - Energy	Unable to deliver sufficient beam energy from source	2	4	8	Early testing regime. Adjust laser cond	2	4
5	Source output - Intensity	Unable to deliver sufficient beam intensity.	3	3	9	Early testing regime. Multiple shot treatment	2	6
6	Source output - divergence	Unable to capture sufficient particles in beam due to un/mis understood source dynamics	3	3	9	Early testing regime. Close engagement with WP3	2	6
7	Source output - particle type	C6 / other ion yield low	4	3	12	Investigate experimental techniques to increase yield (i.e target cleaning)	2	8
8	Source output - stability is too low	Source parameters are unstable shot-to-shot	4	4	16	Apply active stabilisation techniques	2	8
9	Source design - Target debris	Target debris for optimal source is too high for long term operation	2	4	8	Reduce target thickness, capture as much debris as possible	2	4
10	Source design - activation	Unsustainable activation of materials surrounding interaction	2	4	8	Change design to minimise potential for activated materials around interaction point	2	4
11	Source design - vacuum	Targetry unable to perform in vacuum required by capture system	2	4	8	Design differential pumping system capable of maintaining adequate vacuum levels	2	4

Table 5: LhARA WP2 risk register.

active stabilisation and optimisation techniques to ensure consistent beam delivery.

The final area of risk involves technical issues with the design of the source. This includes the production of target debris which can coat fragile optics in the target vacuum chamber, activation of the materials surrounding the target, and vacuum quality issues for coupling into the beam capture system. These risks will all be addressed by careful and methodical studies, and optimisation of the target and vacuum design to minimise issues, as detailed in the risk register.

A.2.3 Work package 3: Proton and ion capture

The overarching objective for Work Package 3 is to deliver a second prototype of the electrostatic, Gabor [93], lens that will provide low-cost, cylindrically symmetric, strong focusing in the LhARA proton and ion beamline [1, 2]. A plasma of electrons contained within a so-called Penning-Malmberg trap, which uses a combination of electric and magnetic fields to achieve confinement of the charge in three dimensions, will be used to provide the electric field required to focus the positive ion beam. The large aperture and short focal length make it the ideal device to capture and focus the proton and ion flux generated from the pulsed-laser source.

The five-year programme has been developed in two phases: the initial two-year programme of measurement and simulation is designed to provide the understanding and tools required to design a lens capable of meeting the LhARA specifications; the programme in years three to five builds on this programme to create the second Gabor lens prototype.

Objectives

Two-year programme:

1. To perform experiments using an upgraded electron trapping apparatus based at Swansea by which to test and validate numerical simulations of the plasma dynamics simulations=, thereby developing the confidence necessary to exploit the simulations in the design of a second lens prototype; and
2. The design and construction of a Gabor lens test bench based upon state-of-the art plasma techniques and diagnostics. The first iteration of the test bench will be capable of operation at trapping voltages of up to 2 kV.

Five-year programme:

1. To design, build and test a second Gabor lens prototype. The programme will include the consideration of plasma loading, stabilisation and reproducibility. The required apparatus and the design parameters of a Gabor lens that meets the LhARA specification will be identified. This will require the development of a lens with a focal length of approximately 1 m, corresponding to trapping voltages of approximately 20 kV.

Task objectives and deliverables

Methodology: We will use guidance from validated Particle-in-Cell (PIC) simulations of plasma properties and behaviour. The programme will chart unexplored regions of trapped plasma density and length, such that the PIC data will be an invaluable predictive guide. Of particular importance is the need to understand and control plasma instabilities.

Two-year programme:

- Exploitation of an existing and slightly upgraded apparatus at Swansea University to make measurements on trapped electron plasmas. This programme will involve the installation of a medium voltage (up to a few hundred volts) trap in the existing apparatus to allow results from the PIC code to be validated with measurements. The validated PIC model will be employed to simulate plasma manipulations and instabilities which will offer important extensions to current PIC capabilities. This new trap will also allow us to test hardware and control for the 2 kV device.

- Concurrently, a high voltage (up to 2 kV) plasma apparatus will be designed, manufactured and assembled. This will be a new, stand-alone device intended to be a test bench and prototype for the LhARA Gabor lens. This constitutes a considerable piece of work, as the creation of high space charge, stable plasmas requires careful consideration of loading and diagnostic capabilities, as well as the configuration of the trapping electrodes and the uniformity requirements of the magnetic field.

5-year programme:

- Detailed studies of high voltage (10–20 kV) plasma apparatus as a Gabor lens prototype, establishing conditions for the creation of a reproducible and stable plasma.

- Interface, if possible, of the high-voltage device with a test source apparatus.

- Finalise design parameters for a Gabor lens capable of meeting the LhARA specifications. It is envisaged that plasmas at densities around $5 \times 10^{15}\,\mathrm{m}^{-3}$, with lengths and radii of the order of 1 m and 3 cm respectively will be confined within electrodes of 10 cm radius, biased at up to 50 kV and that a suitably large magnet with better than 0.1% field uniformity will be required.

Resources requested

Proton and ion capture
Work package number 3

PROJECT:	**LhARA**
Issue Date:	**01/11/2021**
Manager:	**M. Charlton & W. Bertsche**
Start Date:	**2022**
End Date:	**2027**

Cost Profile

Staff	**2022/23**		**2023/24**		**2024/25**		**2025/26**		**2026/27**		**Total**	
	Fraction	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**
All												
Manchester Physics												
Man-Phys-PDRA-1	1	100.00	1	100.00	1	100.00	1	100.00	1	100.00	5	500.00
Man-Phys-Stf-1	0.2	20.00	0.2	20.00	0.2	20.00	0.2	20.00	0.2	20.00	1	100.00
Swansea Physics												
Swns-Phys-PDRA-1	1	100.00	1	100.00	1	100.00	1	100.00	1	100.00	5	500.00
Swns-Phys-Stf-1	0.3	30.00	0.3	30.00	0.3	30.00	0.3	30.00	0.3	30.00	1.5	150.00
Swns-Phys-PG-1	1	100.00	1	100.00	1	100.00	0.5	50.00	0	0.00	3.5	350.00
Swns-Phys-PG-2	0	0.00	0.5	50.00	1	100.00	1	100.00	1	100.00	3.5	350.00
Swan-Phys-Tech-1	0.5	50.00	0.5	50.00	0.5	50.00	0.5	50.00	0.5	50.00	2.5	250.00
Swan-Phys-Tech-2	1	100.00	1	100.00	0	0.00	0	0.00	0	0.00	2	200.00
Berkeley												
Consultant	0.04	4.00	0.04	4.00	0.04	4.00	0.04	4.00	0.04	4.00	0.2	20.00
Task 1 - Preliminary Measurements												
Task 2 - Gabor testbench												
Cost of risk mitigation, staff (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
Staff total:	5.04	**504.00**	**5.54**	**554.00**	**5.04**	**504.00**	**4.54**	**454.00**	**4.04**	**404.00**	**24.2**	**2420.00**
Non-staff		**£k**		**£k**		**£k**		**£k**		**£k**		**£k**
All												
Task 1 - Preliminary Measurements												
Vacuum Generation		23.00		0.00		0.00		0.00		0.00		23.00
Vacuum Hardware		2.50		0.00		0.00		0.00		0.00		2.50
Trap/Expt. Hardware		16.50		0.00		0.00		0.00		0.00		16.50
Diagnostics		54.50		0.00		0.00		0.00		0.00		54.50
Control		28.00		0.00		0.00		0.00		0.00		28.00
Magnet(s)		10.00		0.00		0.00		0.00		0.00		10.00
Misc.		1.00		1.00		1.00		1.00		1.00		5.00
Task 2 - Gabor testbench												
Vacuum Generation		80.20		0.00		0.00		0.00		0.00		80.20
Vacuum hardware		40.46		0.00		0.00		0.00		0.00		40.46
Trap/Expt. Hardware		33.00		0.00		0.00		0.00		0.00		33.00
Diagnostics		41.50		0.00		10.00		10.00		0.00		61.50
Control		158.00		0.00		0.00		0.00		0.00		158.00
Magnet(s)		135.00		0.00		0.00		0.00		0.00		135.00
Misc.		1.00		1.00		1.00		1.00		1.00		5.00
Equipment total:		**624.66**		**2.00**		**12.00**		**12.00**		**2.00**		**652.66**
Inflation (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
PPI, engagement, outreach		2.00		2.00		2.00		2.00		2.00		10.00
Consumables		186.00		13.00		13.50		18.00		14.50		245.00
Travel		32.00		32.00		32.00		32.00		42.00		170.00
Cost of risk mitigation, equipment (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
Working margin:		112.87		55.60		51.60		46.60		40.60		307.27
Contingency, equipment:		124.93		0.40		2.40		2.40		0.40		130.53
Contingency, CG staff:		0.00		0.00		0.00		0.00		0.00		726.00
Contingency, all staff:		151.20		166.20		151.20		136.20		121.20		0.00
Total:		**1737.66**		**825.20**		**768.70**		**703.20**		**626.70**		**4661.46**

Staff:

Swansea We have requested a 30% PI contribution. This is necessary to effect the hands-on involvement of a senior scientist. In addition, a full PDRA position is requested to undertake both the demanding experimental runs with the existing/upgraded apparatus, and the design and construction of the 2 kV testbench. In this, aid will be provided by 2 PhD students, with start dates slightly offset to ensure continuity within the laboratory over the 5 year programme.

Since the apparatus development and construction will largely take place at Swansea, 1.5 FTE technical assistance is requested in the initial phase, decreasing to 0.5 FTE in the later phase–mainly to provide electrical and mechanical workshop, design, repair and maintenance assistance. Highly specialised manufacturing is expected to be outsourced.

Manchester

Again, 20% PI time is requested to promote the involvement of a senior scientist with the PIC simulations, design of apparatus (e.g., appropriate magnet uniformity), and interpretation of experimental results. The main body of the computational work will be undertaken by the PDRA. Its scope is sufficiently ambitious and wide-ranging to require skills beyond the postgraduate level.

Non-staff:

Task 1

This involves upgrades to existing apparatus at Swansea to include: replacement of vacuum hardware (such as pumps); new and updated charged particle trapping apparatus (such as power supplies, and the manufacture

and assembly of the medium voltage apparatus); diagnostics, including a replacement multi-channel plate/CCD imaging system and a purpose-built solenoid to study field uniformity conditions.

Milestones of task 1:

- The generation and confinement for several seconds of a medium voltage electron plasma;
- The study of deleterious effects (such as lifetime and expansion rates) for a range of plasma and environmental parameters to inform hardware decisions of task 2.

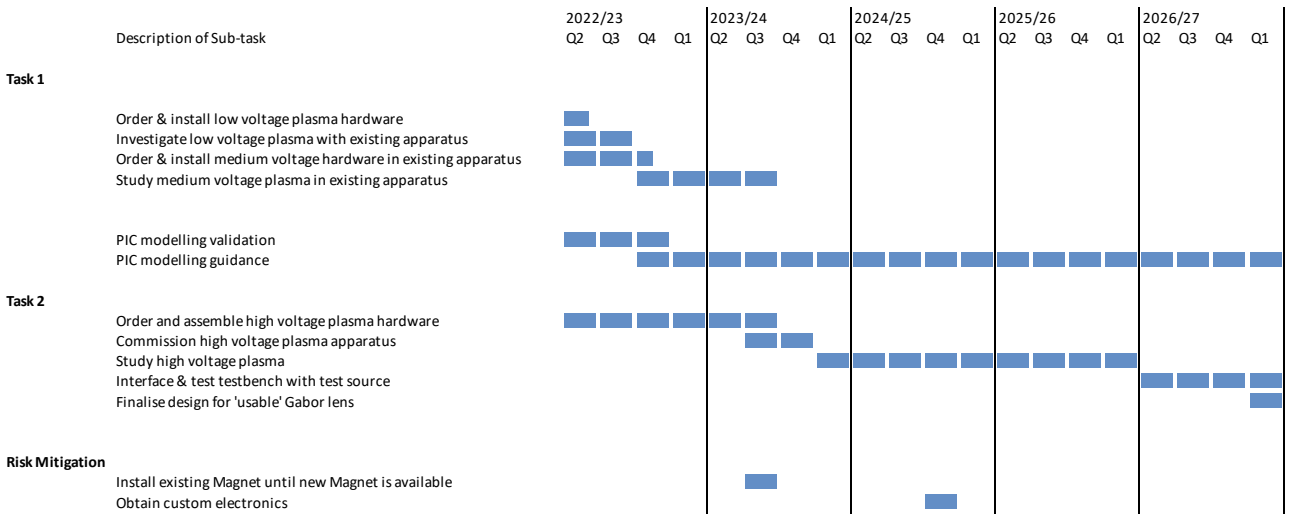
Task 2

This is the major hardware deliverable of Work Package 3. The apparatus will be developed in its entirety from scratch, so all the vacuum and trap hardware needs to be purchased and/or machined, and dedicated diagnostics and control systems have to be incorporated. A new 0.1 T solenoid is required. This device will have a field uniformity in the region of 0.1% over a large (to be specified, but of the order of 1 m long, and 5 cm radius) volume, with a wide enough bore to house a vacuum chamber incorporating trapping electrodes (to be specified from task 1 milestones).

Milestones of task 2:

- The generation and confinement for several seconds of a high voltage plasma;
- The quantification of deleterious effects (such as lifetime and expansion rates) for an extended range of plasma and environmental parameters;
- To attempt the transport and interface of the apparatus to a test ion source to confirm PIC models;
- To develop a computationally verified design specification for a lens, with 1 m focal length, utilising protons delivered from the ion source.

Gantt chart and principle milestones



Risk register

Blank	Number	Name	Description	Likelihood	Impact	Score	Mitigation	Mitigated Impact	Mitigated score	Comments	Significant Dates	Retirement date
			Note: The risks identified below are specific to the Gabor 5 year preliminary and testbench measurements, NOT the final Gabor lens **Note: Mitigated score is product of Likelihood & Mitigated impact**									
		Plasma lifetime	A short lifetime might adversely effect the ability to suitably study the plasma	3	4	12	Careful design and study to increase lifetime. Multiple causes can be identified:					
		Plasma Density	A low density will result in too long a focal length (& beamline)	4	4	16	Careful design and study to ensure a suitable density can be reached:					
			Pressure	3	4	12	Monitoring the source pressures (& constituents) and independently studying the effect on the plasma	2	6	Baffles, pumping restrictions, pumps, getters, etc. can be implemented to reduce background pressure within the testbench when the nature of the source pressure issue is understood. Worst case scenario will likely result in a reduced plasma confinement time, and associated duty cycles. These will provide invaluable information for the final Gabor/beamline design	Yr 5	Yr 5
			Secondary electrons	3	4	12	Band pass filter	2	6	In addition to the ions, two populations of electrons are expected from the source. Both are expected to have different characteristics & potentially destabilise the Gabor plasma ExB-like filtering to allow transmission only of the ions from the source into the Gabor plasma is a likely mitigation. Details will develop as the ion source is characterised.	Yr 5	Yr 5
			Solenoid fringe field affecting source	3	2	6	Effect of B-field on the source, and extent of fringe field can be measured. Source / solenoid can be shielded.	1	3	Space limitations may make mitigation complicated, and shielding may introduce deleterious B-field asymmetries. There would be costs & delays associated with B-field shielding.	Yr 5	Yr 5
			WP2 test source unavailable	1	3	3	Utilise beamport at a 3rd-party facility	2	1	Although beam parameters will likely be different at a 3rd-party facility, the Gabor lens testbench can be tested and results compared to simulations.	Yr 5	Yr 5

Risk: Achievement of desired plasma properties

Mitigation: We envisage a gradual build-up in complexity and technical demand from current state-of-the-art, through intermediate stages to the final LhARA lens design. The main issues are addressed in detail in the risk register.

Risk: Delivery delays:

Mitigation: Utilising existing and off-the-shelf components in the first instance is expected to reduce the impact of delivery delays. The gradual increase in complexity, identification of associated scaling laws, and discussions with community-based colleagues is expected to mitigate modest supply-chain issues.

Risk: Source interface issues:

Mitigation: With regular two-way discussions, potential interfaces issues (such as high pressures, high divergence, or co-propagating electrons) can be identified, and appropriate design changes made, at early stages. Should no LhARA-based ion test source be available, beam time at external 3rd-party facilities can be used to verify performance against simulations.

A.2.4 Work package 4: Ion-acoustic dose mapping

Objectives

The overarching objective for Work package 4 over the five years of the programme defined here is to deliver an ion-acoustic system capable of recording shot-by-shot the dose profile delivered in LhARA Stage 1. The system will be capable of development to allow the dose profile to be measured shot-by-shot in the *in vivo* measurements that will be made in LhARA Stage 2. Further, the development of the systems required for LhARA will be carried out with a view to their deployment at other facilities for radiobiology and with the aim of developing a system capable of clinical deployment.

To achieve the overarching goal, the work has been divided into two principal themes:

1. The design construction, and operation of a proof-of-principle system in years 1 and 2; and
2. The development of a device capable of serving in the fully automated Stage 1 *in vitro* end station.

The work within the two themes will be carried out through 8 distinct tasks, each designed to deliver a particular objective (objectives O1–O8, defined below).

The work of Work Package 4 will be led by expert personnel from four UK groups, each with particular responsibilities. The Institute of Cancer Research (ICR) is expert in acoustic-signal measurement and acoustic sensor deployment and will take primary responsibility for the design of the ion-acoustic signal detection. The STFC Particle Physics Group is expert in detector construction, readout, and data management and will take responsibility for the construction of a sintillating-fibre dose-measurement device that will be used to validate the proof-of-principle and *in vitro* ion-acoustic systems. The Imperial HEP Group is expert in simulation and analysis and will provide the Geant4-based simulation of the proof-of-principle and *in vitro* ion-acoustic systems and the beams with which they will be illuminated. The simulation will be used to optimise the designs and to interpret the results of test-beam exposures. The UCL Bioengineering Group is expert in the simulation and reconstruction of acoustic waves generated by the deposition of energy in tissue and will take responsibility for developing modes of the response of the proof-of-principle, *in vitro* and *in vivo* systems.

Task objectives and deliverables

Task objectives and deliverables

The objectives are defined for each of the two themes are defined below.

Theme 1: Proof of principle demonstration

O1: Development of Geant4 simulation of the forward model:

1. Development of the forward simulation consisting of a simulation in Geant4 of the beam impinging on an instrumented water phantom (the SmartPhantom) and the deposition of energy resolved in four dimensions (three space and one time);
2. Exploitation of the forward simulation to optimise the performance of the SmartPhantom and to provide the power-density spectrum required as input to the acoustic model.

O2: Development of k-wave forward acoustic model:

1. Development of a k-wave-based simulation of the acoustic wave generated by by the energy deposited by the beam. The simulation will be used to quantify the magnitude of the pressure wave and to estimate the expected acoustic-sensor response;
2. Exploitation of the forward acoustic model to optimise the specifications for the acoustic-sensor array.

O3: Development of inverse dose-map reconstruction software:

1. Development of direct ion-acoustic reconstruction software capable of handling a range of sensor-array configurations;
2. Development of iterative ion-acoustic reconstruction exploiting spatio-temporal and angular-frequency priors derived from O1;
3. Implementation of the most appropriate ion-acoustic reconstruction algorithms on the Varisonics acoustic readout and signal-processing system.

O4: Assembly of apparatus for validation of models and approach:

1. Assessment and choice of most suitable acoustic sensors for the proof-of-principle system and initial consideration of sensor-specification for LhARA Stage 1 system;
2. Characterisation and test of acoustic sensors in the laboratory using a laser source with parameters that approximate the beam to be used in the proof-of-principle beam test;

3. Design, build, test and commission SmartPhantom and acoustic-sensor system to validate its performance prior to beam test.

O5: Forward-model validation experiments:

1. Measurement of ion-acoustic signal as a function of dose, position, and a variety of beam parameters. The forward model developed in O1 will be exploited to evaluate the available test-beam facilities. The results will inform negotiations with the beam providers to ensure that appropriate beam parameters can be delivered;

2. Comparison of the reconstructed ion-acoustic dose profiles with the measurements made using the scintillating-fibre detector and with the predictions of the forward models developed in O1 and O2.

Theme 2: Development of ion-acoustic system for LhARA Stage 1

O6: Design and specification of ion-acoustic dosimeters for use in *in vitro* radiobiological studies in LhARA Stage 1:

1. Specify and order sensor array, assemble the system, initial received-signal testing using alternative emission sources;

2. Experimentally evaluate algorithms to reconstruct dose maps using alternative emission sources;

3. Design, construct and test the sensor array in a reconfigured SmartPhantom;

4. Integrate ion-acoustic rig with high-throughput radiobiology experimental system;

5. Integrate ion-acoustic dosimeter and smart phantom for comparison measurements.

O7: Acoustically compatible biological sample holders for high-throughput radiobiological studies;

1. 8.1 Consult with biologists, identify and evaluate materials, design and execute demonstrator experiments, discuss findings;

2. Construct, characterise and test single and multiple units;

3. Systems for multi-well/chamber read out of biological effects;

4. Systems for two-dimensional dose pattern and spatial biology read out;

5. System for three-dimensional dose pattern and spatial biology read out;

6. Design and construct high throughput system dosimeters for use in *in vitro* radiobiological studies in LhARA Stage 1.

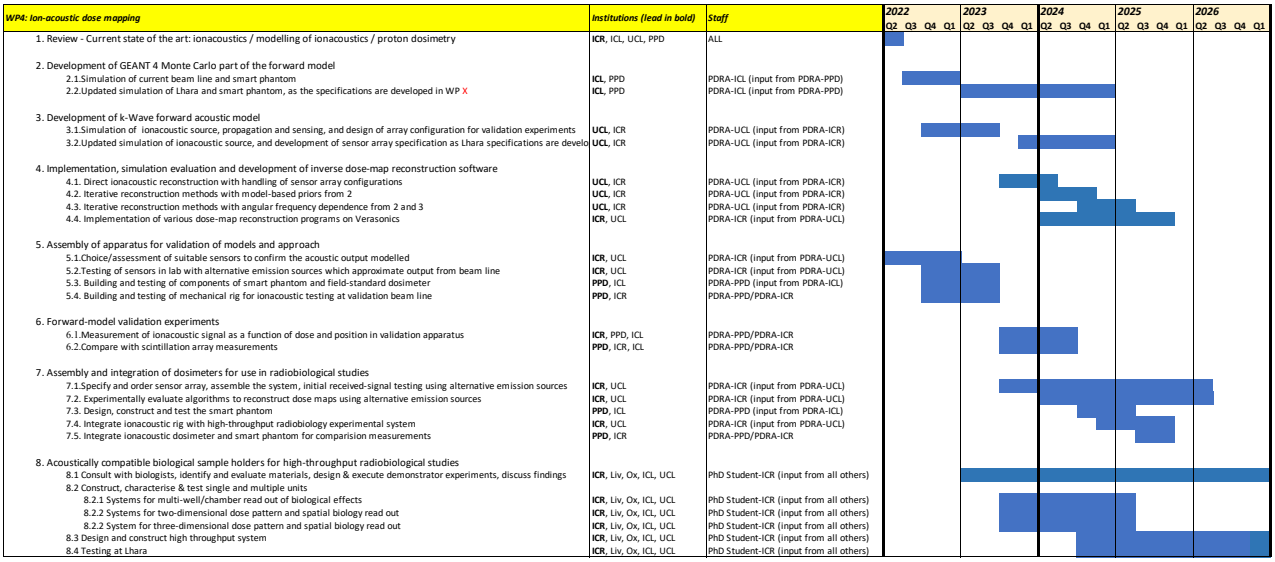


Figure 17: (Placeholder) Gantt chart for WP4

Resources requested

Ion-acoustic imaging
Work package number 4

PROJECT:	**LhARA**
Issue Date:	**01/11/2021**
Manager:	**J. Bamber, E. Harris, J. Matheson**
Start Date:	**2022**
End Date:	**2027**

Cost Profile

Staff	2022/23		2023/24		2024/25		2025/26		2026/27		Total	
	Fraction	£k	Fraction	£k	Fraction	£k	Fraction	£k	Fraction	£k	Fraction	£k
Final design and procurement												
ICR												
ICR Staff 1	0.1	10.00	0.1	10.00	0.1	10.00	0.1	10.00	0.1	10.00	0.5	50.00
ICR Staff 2	0.1	10.00	0.1	10.00	0.1	10.00	0.1	10.00	0.1	10.00	0.5	50.00
ICR Staff/PhD	0	0.00	0.5	50.00	1	100.00	1	100.00	1	100.00	3.5	350.00
UCL Biomedical Engineering												
UCL Staff1	0.25	25.00	0.25	25.00	0.25	25.00	0.25	25.00	0.25	25.00	1.25	125.00
UCL PDRA	0.5	50.00	0.5	50.00	0.5	50.00	0.5	50.00	0.5	50.00	2.5	250.00
UCL PhD	0.5	50.00	1	100.00	1	100.00	1	100.00	0	0.00	3.5	350.00
STFC-PPD												
STFC staff	0.25	25.00	0.25	25.00	0.5	50.00	0.5	50.00	0.5	50.00	2	200.00
Cost of risk mitigation, staff (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
Staff total:	1.7	**170.00**	2.7	**270.00**	3.45	**345.00**	3.45	**345.00**	2.45	**245.00**	13.75	**1375.00**
Non-staff		**£k**		**£k**		**£k**		**£k**		**£k**		**£k**
Final design and procurement												
Work package management		1.50		1.50		2.50		2.50		2.50		10.50
Vantage 256		5.00		5.00		120.00		5.00		5.00		140.00
Equipment total:		**6.50**		**6.50**		**122.50**		**7.50**		**7.50**		**150.50**
Inflation (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
PPI, engagement, and outreach		2.00		2.00		2.00		2.00		2.00		10.00
Consumables		15.00		15.00		30.00		30.00		30.00		120.00
Travel		3.00		3.00		3.00		3.00		3.00		15.00
Cost of risk mitigation, equipment (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
Working margin:		17.65		27.65		46.75		35.25		25.25		152.55
Contingency, equipment:		1.30		1.30		24.50		1.50		1.50		30.10
Contingency, CG staff:		0.00		0.00		0.00		0.00		0.00		412.50
Contingency, all staff:		51.00		81.00		103.50		103.50		73.50		0.00
Total:		**266.45**		**406.45**		**677.25**		**527.75**		**387.75**		**2265.65**

Gantt chart and principle milestones

The planned schedule for Work package 4 is given in the Gantt chart in figure 17.

Risk register

A.2.5 Work package 5: Novel end-station development

Lead authors: R. McLauchlan, T. Price, C.P. Welsch

Objectives

The principle objective for this work package, "Work package 5 (WP5): Novel end-station development", is to produce a feasible design for the beam diagnostics and dosimetry alongside instrumentation for the novel in-vitro and in-vivo end-station. Alternative technologies to work package 4 will be explored to develop a robust solution capable of delivering a novel end-station unlike anything currently available.

Task objectives and deliverables

A series of tasks and deliverables has been established in order to design and construct end-stations capable of allowing world leading science to be conducted at LhARA. The end-stations will be delivered at the end of a 60 month programme with deliverables and limitations identified at 24 months, and an R&D programme to overcome these obstacles by the end of the programme as detailed below.

- O1: Technology developed and tested which capable of monitoring LhARA beams on a pulse-by-pulse basis in real time with a plan for integration into the accelerator feedback

  D1: Assess current beam monitoring technology and identify the required R&D for Lhara beams [24 months]

  D2: Undertake required R&D on technologies identified in D1 and integrate with beam delivery system [60 months]

- O2: Demonstrate experiments using the end-stations including cell irradiations, cell imaging and dose monitoring from WP4

  D1: Design automated cell dish handling system and required environmental system [24 months]

  D2: Engage with cellular imaging community to assess the room and end-station requirements [24 months]

  D3: Construct beam delivery room including end-station and cellular imaging capabilities [60 months]

- O2: Identify/Develop a facility capable of delivering LhARA-like beams for R&D purposes

  D1: develop a vertical beamline at the University of Birmingham MC40 cyclotron to allow irradiation of samples horizontally [24 months]

  Develop a beam delivery system capable of mimicing LhARA time profiles [60 months]

- O4: Develop the layout of LhARA beam delivery system with Beam Position Monitors, magnets, and dosimetry apparatus locations identified and technology developed [60 months]

Resources requested

Novel instrumentation and endstation development
Work package number 5

PROJECT:	**LhARA**
Issue Date:	**01/11/2021**
Manager:	**R. McLauchlan, T. Price, C. Welsch**
Start Date:	**2022**
End Date:	**2027**

Cost Profile

Staff	**2022/23**		**2023/24**		**2024/25**		**2025/26**		**2026/27**		**Total**	
	Fraction	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**
Final design and procurement												
BHM Physics												
BHM-Phys-Stf-1	0.25	25.00	0.25	25.00	0.5	50.00	0.5	50.00	0.5	50.00	2	200.00
BHM-Phys-PDRA	0.1	10.00	0.1	10.00	1	100.00	1	100.00	1	100.00	3.2	320.00
BHM-Phys-PhD	0	0.00	0.5	50.00	1	100.00	1	100.00	1	100.00	3.5	350.00
IC NHS HC Trust												
IC-NHS-HC-Trst-Stf-1	0.25	25.00	0.25	25.00	0.5	50.00	0.5	50.00	0.5	50.00	2	200.00
Liverpool Physics												
Liv-Phys-PDRA	0.1	10.00	0.55	55.00	1	100.00	1	100.00	1	100.00	3.65	365.00
Liv-Phys-PhD	0	0.00	0.5	50.00	1	100.00	1	100.00	1	100.00	3.5	350.00
Cost of risk mitigation, staff (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
Staff total:	0.7	**70.00**	**2.15**	**215.00**	**5**	**500.00**	**5**	**500.00**	**5**	**500.00**	**17.85**	**1785.00**
Non-staff		**£k**		**£k**		**£k**		**£k**		**£k**		**£k**
Final design and procurement												
2D Detector		0.00		0.00		600.00		20.00		20.00		640.00
Equipment total:		**0.00**		**0.00**		**600.00**		**20.00**		**20.00**		**640.00**
Inflation (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
Consumables		7.00		7.00		22.00		22.00		22.00		80.00
Travel		3.00		3.00		3.00		3.00		3.00		15.00
Cost of risk mitigation, equipment (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
Working margin:		7.00		21.50		110.00		52.00		52.00		242.50
Contingency, equipment:		0.00		0.00		120.00		4.00		4.00		128.00
Contingency, CG staff:		0.00		0.00		0.00		0.00		0.00		535.50
Contingency, all staff:		21.00		64.50		150.00		150.00		150.00		0.00
Total:		**108.00**		**311.00**		**1505.00**		**751.00**		**751.00**		**3426.00**

Gantt chart and principle milestones

Risk register

A.2.6 Work package 6: Design and integration

Lead authors: N. Bliss, J. Pasternak

Objectives

The principle objective for this work package, ”Work package 6 (WP6): Design and integration ”, is to prepare feasible design for the LhARA facility, which will integrate the laser driven ion source followed by an innovative capture system utilising Gabor lenses with accelerator system fully exploiting its advantages of the flexible dose capability, delivering the beam to in-vitro station at the Phase I, and in-vitro and in-vivo end stations at the Phase II for broad spectrum of radiobiological experiments. Although the design of the Gabor lenses is the subject of WP3, WP6 will develop the mitigating strategy by designing alternative capture system based on solenoids. WP6 will explore the radiation protection and shielding requirements, which will inform the design of the building for the LhARA facility. Mechanical design including the support for accelerator elements, in particular for the vertical arcs for in-vitro stations will be addressed. The challenging novel FFA-element for the Phase II allowing for the variable energy extraction will be designed and the prototype construction will be subcontracted to industry for manufacturing. The Magnetic Alloy (MA) RF cavity system for Phase II ring post-accelerator will be designed and its prototype constructed. Work of WP6 will also include the design of the vacuum system, controls, electrical and RF engineering, beam diagnostics, technical services including environmental sustainability solutions and the safety system design.

The work of WP6 will inform the Conceptual Design Report (CDR) for the LhARA facility followed be the Technical Design Reports (TDRs), firstly for the Stage 1 and later for the Stage II.

The work will carried by the personnel from Universities and STFC, mainly from the Daresbury Laboratory (DL) as shown in the resource table 6.

Task objectives and deliverables

Objectives (Os) and associated Deliverables (Ds) for the WP6 are listed below:

- **O1:** Conceptual design of the LhARA facility, accelerator systems and its integration with the source and the end stations;
  D1: CDR for the LhARA facility (24 months).
- **O2:** Technical design of LhARA accelerator systems for Stage I and its integration with the source and the end station;
  D2: TDR for the LhARA accelerator systems for Stage I (36 months).
- **O3:** Design, construction and validation of the FFA magnet prototype for LhARA Phase II post-accelerator;
  D3: Technical report on the design and performance of the FFA main magnet prototype (58 months).
- **O4:** Design, construction and validation of the MA RF cavity prototype for LhARA Phase II post-accelerator;
  D4: Technical report on the design and performance of the MA RF cavity prototype (58 months).
- **O5:** Technical design of accelerator systems for Stage II and its integration with the source and the end stations;
  D5: TDR for the LhARA accelerator systems for Stage II (60 months).

Resources requested

The resources requested for the work package 6 are shown in table 6.

Gantt chart and principle milestones

The schedule for work package 6 is shown in table 7 as a Gantt chart. The schedule extends beyond the five years to illustrate the schedule for the potential construction project of the LhARA facility.

Risk register

Risk register for work package 6 is shown in table 8.

Table 6: LhARA WP6 resources request.

Design and intergration
Work package number 6

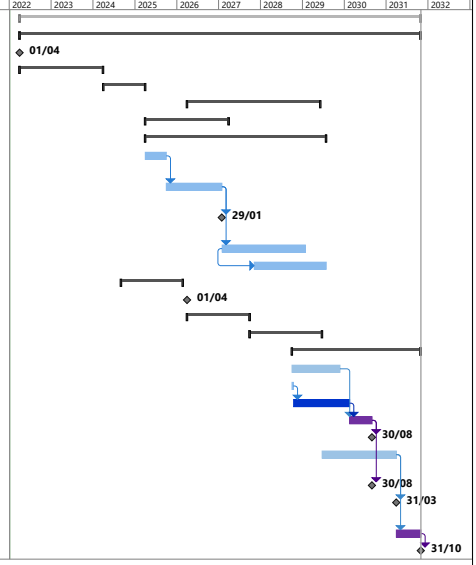
PROJECT:	**LhARA**
Issue Date:	**01/11/2021**
Manager:	**N. Bliss & J. Pasternak**
Start Date:	**2022**
End Date:	**2027**

Cost Profile

Staff	**2022/23**		**2023/24**		**2024/25**		**2025/26**		**2026/27**		**Total**	
	Fraction	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**
Final design and procurement												
Imperial Physics												
IC-Phys-Stf-1	0.1	10.00	0.1	10.00	0.1	10.00	0.1	10.00	0.1	10.00	0.5	50.00
IC-Phys-PDRA-2	1	100.00	1	100.00	1	100.00	1	100.00	1	100.00	5	500.00
IC-Phys-PDRA-3	1	100.00	1	100.00	1	100.00	1	100.00	1	100.00	5	500.00
RHUL Physics												
RHUL-Phys-PDRA-1	1	100.00	1	100.00	1	100.00	1	100.00	1	100.00	5	500.00
STFC-TD												
Mech	0.5	50.00	0.8	80.00	1	100.00	1.2	120.00	1.2	120.00	4.7	470.00
Elec	0	0.00	0.6	60.00	0.9	90.00	1.1	110.00	1.1	110.00	3.7	370.00
Controls	0	0.00	0.5	50.00	0.5	50.00	0.5	50.00	0.5	50.00	2	200.00
Tech Serv	0	0.00	0.4	40.00	0.5	50.00	0.5	50.00	0.5	50.00	1.9	190.00
Vacuum	0	0.00	0.2	20.00	0.3	30.00	0.1	10.00	0.1	10.00	0.7	70.00
Radiation	0	0.00	0.6	60.00	0.4	40.00	0	0.00	0	0.00	1	100.00
Cost of risk mitigation, staff (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
Staff total:	3.6	**360.00**	6.2	**620.00**	6.7	**670.00**	6.5	**650.00**	6.5	**650.00**	29.5	**2950.00**
Non-staff		**£k**		**£k**		**£k**		**£k**		**£k**		**£k**
Final design and procurement												
Widget		10.00		10.00		10.00		10.00		10.00		50.00
Equipment total:		**10.00**		**10.00**		**10.00**		**10.00**		**10.00**		**50.00**
Inflation (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
Consumables		3.00		3.00		3.00		3.00		3.00		15.00
Travel		5.00		5.00		10.00		10.00		10.00		40.00
Cost of risk mitigation, equipment (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
Working margin:		37.00		63.00		68.00		66.00		66.00		300.00
Contingency, equipment:		2.00		2.00		2.00		2.00		2.00		10.00
Contingency, CG staff:		0.00		0.00		0.00		0.00		0.00		885.00
Contingency, all staff:		108.00		186.00		201.00		195.00		195.00		0.00
Total:		**525.00**		**889.00**		**964.00**		**936.00**		**936.00**		**4250.00**

Table 7: LhARA WP6 schedule.

ID	Task Mode	WBS	Task Name	Duration	Start	Finish
0		0	**LhARA WP6 schedule**	**2501 days**	**Fri 01/04/22**	**Fri 31/10/31**
1		1	**LhARA**	**2501 days**	**Fri 01/04/22**	**Fri 31/10/31**
2		1.1	**Project Start**	**0 days**	**Fri 01/04/22**	**Fri 01/04/22**
3		1.2	**Conceptual Design Report (CDR) - 2 years**	**521 days**	**Fri 01/04/22**	**Fri 29/03/24**
13		1.3	**Stage 1 Technical Design Report (TDR) - 1 year**	**261 days**	**Mon 01/04/24**	**Mon 31/03/25**
20		1.4	**Stage 1 Procurement & testing**	**831 days**	**Wed 01/04/26**	**Wed 06/06/29**
25		1.5	**Stage 2 Technical Design - 2 years**	**522 days**	**Tue 01/04/25**	**Wed 31/03/27**
35		1.6	**STAGE 2 Procurement & Testing**	**1129 days**	**Tue 01/04/25**	**Fri 27/07/29**
36		1.6.1	Tender & award contract for FFA main magnet & MA Cavity prototypes	131 days	Tue 01/04/25	Tue 30/09/25
37		1.6.2	FFA main magnet & MA Cavity prototypes construction, test and finalise technical report	348 days	Wed 01/10/25	Fri 29/01/27
38		1.6.3	**FFA main magnet & MA Cavity prototypes technical report complete**	**0 days**	**Fri 29/01/27**	**Fri 29/01/27**
39		1.6.4	Stage 2 Equipment Procurement	520 days	Mon 01/02/27	Fri 26/01/29
40		1.6.5	Stage 2 Offline Assemby & Testing	450 days	Mon 08/11/27	Fri 27/07/29
41		1.7	**Building Specifiation & Architect Design**	**386 days**	**Mon 02/09/24**	**Mon 23/02/26**
44		1.8	**Construction project funded**	**0 days**	**Wed 01/04/26**	**Wed 01/04/26**
45		1.9	**Building Construction**	**392 days**	**Wed 01/04/26**	**Thu 30/09/27**
49		1.10	**Radiation Shielding & Technical Services**	**450 days**	**Fri 01/10/27**	**Thu 21/06/29**
54		1.11	**Equipment Installation in Building & Commissioning with Beams**	**805 days**	**Mon 02/10/28**	**Fri 31/10/31**
55		1.11.1	Stage 1 Equipment installation & testing in building	300 days	Mon 02/10/28	Fri 23/11/29
56		1.11.2	Install Laser	10 days	Mon 02/10/28	Fri 13/10/28
57		1.11.3	**Laser, target & capture testing**	**350 days**	**Mon 16/10/28**	**Fri 15/02/30**
58		1.11.4	**Stage 1 Commissioning with beam**	**140 days**	**Mon 18/02/30**	**Fri 30/08/30**
59		1.11.5	**Start stage 1 scientific programme**	**0 days**	**Fri 30/08/30**	**Fri 30/08/30**
60		1.11.6	Stage 2 Equipment installation, PS system and testing in building	462 days	Fri 22/06/29	Mon 31/03/31
61		1.11.7	**Stage 1 Commissioning with Beam complete**	**0 days**	**Fri 30/08/30**	**Fri 30/08/30**
62		1.11.8	**Construction Project complete, ready to start Stage 2 Commissioning with Beams**	**0 days**	**Mon 31/03/31**	**Mon 31/03/31**
63		1.11.9	**Stage 2 Commissioning with beam**	**154 days**	**Tue 01/04/31**	**Fri 31/10/31**
64		1.11.10	**Start stage 2 scientific programme**	0 days	Fri 31/10/31	Fri 31/10/31



Project: LhARA WP6 schedule
Date: Thu 06/01/22

Task | Split | Milestone | Summary
Project Summary | Inactive Task | Inactive Milestone | Inactive Summary
Manual Task | Duration-only | Manual Summary Rollup | Manual Summary
Start-only | Finish-only | External Tasks | External Milestone
Deadline | Progress | Manual Progress

Page 1

Table 8: LhARA WP6 risk register.

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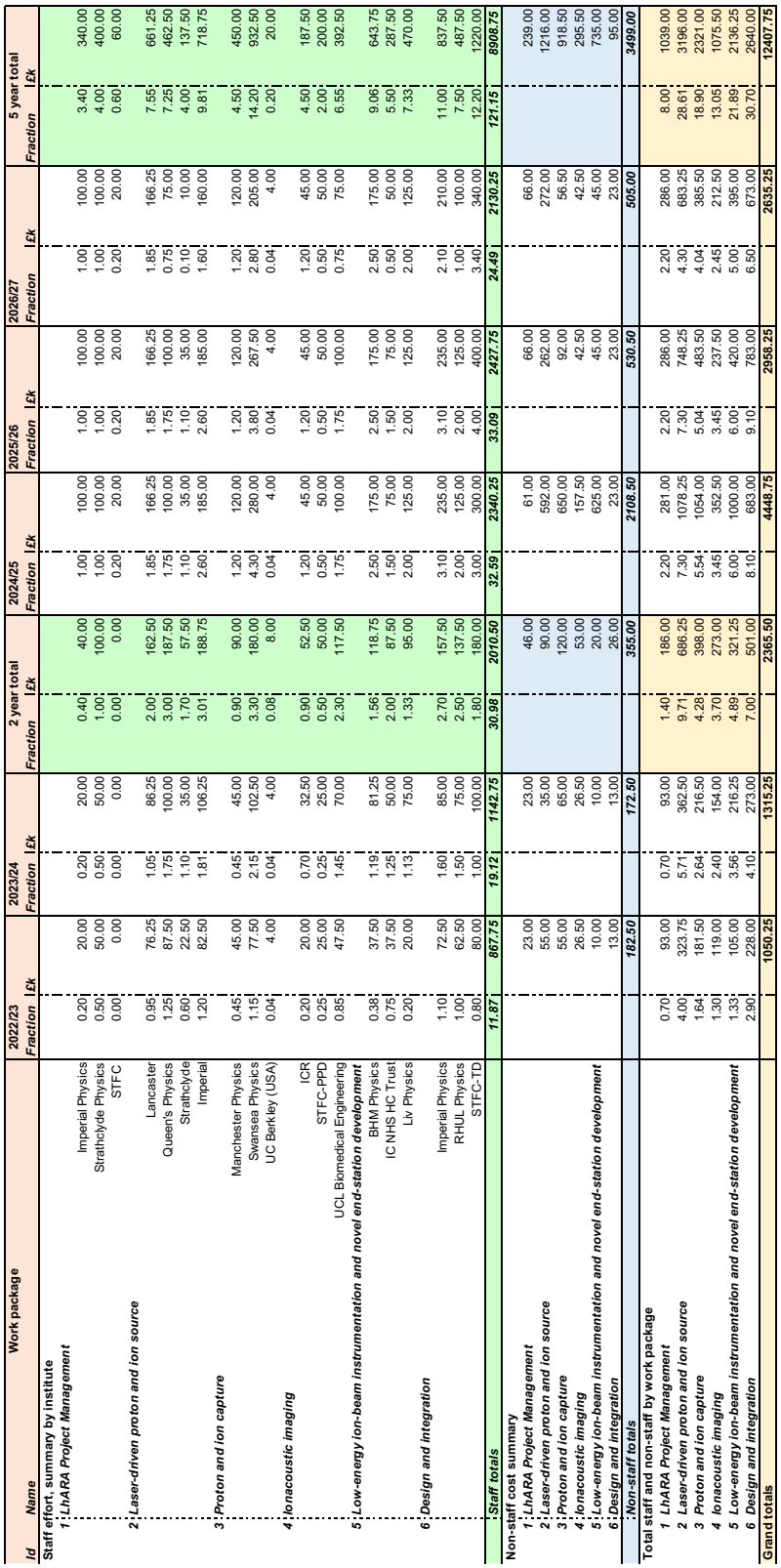
Number	Name	Description	Likelihood	Impact	Score	Mitigation	Mitigated Likelihood	Mitigated Impact	Mitigated score
1	Fixed Field Accelerator (FFA) Performance.	FFA does not deliver parameters in performance specification.	3	5	15	Continue R&D on the critical item that is the FFA spiral magnet. Construct a prototype before production of 10 magnets.	1	5	5
2	Gabor lens performance	Gabor lens does not deliver parameters in performance specification.	4	5	20	Continue a R&D plan that involves the construction of a prototype Gabor lens and have a back up plan available that uses solenoid magnets in the place of Gabor lens.	2	5	10
3	MA Cavity construction	Insufficient availablility of Magnet Alloy (MA) Cavity suppliers.	5	4	20	Design and construct MA cavity in-house based on reference devices construsted by CERN, J-PARC & KURNS institutes. Component parts manufactured by industry.	5	1	5
4	Injection and extraction magnets	Insufficient availablility of injection and extraction magnets suppliers.	3	4	12	Design and construct of injection and extraction magnets by STFC national laboratorie expertise. Component parts manufactured by industry.	3	2	6
5	Facility infrastructure	Facility infrastructure is not fit for purpose.	4	4	16	Include facility infrastructure design during the Conceputal Design Report (CDR) stage to provide a fit for purpose design that will inform the project cost and schedule.	1	4	4
6	Radiation protection	Radiation bulk shielding thickness, labyrinths and services penetrations are inadequate to meet specification.	4	5	20	Conduct radiation protection assessment during the CDR phase of the project to satisfy safety legislation and identify construction method to inform cost and schedule.	1	5	5

A.3 Overview of preliminary, pre-construction phase project costs

Need to add comments on: basis of costing, inflation, working margin and contingency, match to Preliminary and Pre-construction phases . . .



Id	Name	Work package	2022/23 Fraction	2022/23 £k	2023/24 Fraction	2023/24 £k	2 year total Fraction	2 year total £k	2024/25 Fraction	2024/25 £k	2025/26 Fraction	2025/26 £k	2026/27 Fraction	2026/27 £k	5 year total Fraction	5 year total £k
Staff effort, summary by institute																
1	*LhARA Project Management*															
		Imperial Physics	0.20	20.00	0.20	20.00	0.40	40.00	1.00	100.00	1.00	100.00	1.00	100.00	3.40	340.00
		Strathclyde Physics	0.50	50.00	0.50	50.00	1.00	100.00	1.00	100.00	1.00	100.00	1.00	100.00	4.00	400.00
		STFC	0.00	0.00	0.00	0.00	0.00	0.00	0.20	20.00	0.20	20.00	0.20	20.00	0.60	60.00
2	*Laser-driven proton and ion source*															
		Lancaster	0.95	76.25	1.05	86.25	2.00	162.50	1.85	166.25	1.85	166.25	1.85	166.25	7.55	661.25
		Queen's Physics	1.25	87.50	1.75	100.00	3.00	187.50	1.75	100.00	1.75	100.00	0.75	75.00	7.25	462.50
		Strathclyde	0.60	22.50	1.10	35.00	1.70	57.50	1.10	35.00	1.10	35.00	0.10	10.00	4.00	137.50
		Imperial	1.20	82.50	1.81	106.25	3.01	188.75	2.60	185.00	2.60	185.00	1.60	160.00	9.81	718.75
3	*Proton and ion capture*															
		Manchester Physics	0.45	45.00	0.45	45.00	0.90	90.00	1.20	120.00	1.20	120.00	1.20	120.00	4.50	450.00
		Swansea Physics	1.15	77.50	2.15	102.50	3.30	180.00	4.30	280.00	3.80	267.50	2.80	205.00	14.20	932.50
		UC Berkley (USA)	0.04	4.00	0.04	4.00	0.08	8.00	0.04	4.00	0.04	4.00	0.04	4.00	0.20	20.00
4	*Ionacoustic imaging*															
		ICR	0.20	20.00	0.70	32.50	0.90	52.50	1.20	45.00	1.20	45.00	1.20	45.00	4.50	187.50
		STFC-PPD	0.25	25.00	0.25	25.00	0.50	50.00	0.50	50.00	0.50	50.00	0.50	50.00	2.00	200.00
		UCL Biomedical Engineering	0.85	47.50	1.45	70.00	2.30	117.50	1.75	100.00	1.75	100.00	0.75	75.00	6.55	392.50
5	*Low-energy ion-beam instrumentation and novel end-station development*															
		BHM Physics	0.38	37.50	1.19	81.25	1.56	118.75	2.50	175.00	2.50	175.00	2.50	175.00	9.06	643.75
		IC NHS HC Trust	0.75	37.50	1.25	50.00	2.00	87.50	1.50	75.00	1.50	75.00	0.50	50.00	5.50	287.50
		Liv Physics	0.20	20.00	1.13	75.00	1.33	95.00	2.00	125.00	2.00	125.00	2.00	125.00	7.33	470.00
6	*Design and integration*															
		Imperial Physics	1.10	72.50	1.60	85.00	2.70	157.50	3.10	235.00	3.10	235.00	2.10	210.00	11.00	837.50
		RHUL Physics	1.00	62.50	1.50	75.00	2.50	137.50	2.00	125.00	2.00	125.00	1.00	100.00	7.50	487.50
		STFC-TD	0.80	80.00	1.00	100.00	1.80	180.00	3.00	300.00	4.00	400.00	3.40	340.00	12.20	1220.00
	Staff totals		***11.87***	***867.75***	***19.12***	***1142.75***	***30.98***	***2010.50***	***32.59***	***2340.25***	***33.09***	***2427.75***	***24.49***	***2130.25***	***121.15***	***8908.75***
Non-staff cost summary																
1	*LhARA Project Management*			23.00		23.00		46.00		61.00		66.00		66.00		239.00
2	*Laser-driven proton and ion source*			55.00		35.00		90.00		592.00		262.00		272.00		1216.00
3	*Proton and ion capture*			55.00		65.00		120.00		650.00		92.00		56.50		918.50
4	*Ionacoustic imaging*			26.50		26.50		53.00		157.50		42.50		42.50		295.50
5	*Low-energy ion-beam instrumentation and novel end-station development*			10.00		10.00		20.00		625.00		45.00		45.00		735.00
6	*Design and integration*			13.00		13.00		26.00		23.00		23.00		23.00		95.00
	Non-staff totals			***182.50***		***172.50***		***355.00***		***2108.50***		***530.50***		***505.00***		***3499.00***
Total staff and non-staff by work package																
1	*LhARA Project Management*		0.70	93.00	0.70	93.00	1.40	186.00	2.20	281.00	2.20	286.00	2.20	286.00	8.00	1039.00
2	*Laser-driven proton and ion source*		4.00	323.75	5.71	362.50	9.71	686.25	7.30	1078.25	7.30	748.25	4.30	683.25	28.61	3196.00
3	*Proton and ion capture*		1.64	181.50	2.64	216.50	4.28	398.00	5.54	1054.00	5.04	483.50	4.04	385.50	18.90	2321.00
4	*Ionacoustic imaging*		1.30	119.00	2.40	154.00	3.70	273.00	3.45	352.50	3.45	237.50	2.45	212.50	13.05	1075.50
5	*Low-energy ion-beam instrumentation and novel end-station development*		1.33	105.00	3.56	216.25	4.89	321.25	6.00	1000.00	6.00	420.00	5.00	395.00	21.89	2136.25
6	*Design and integration*		2.90	228.00	4.10	273.00	7.00	501.00	8.10	683.00	9.10	783.00	6.50	673.00	30.70	2640.00
Grand totals				1050.25		1315.25		2365.50		4448.75		2958.25		2635.25		12407.75

A.4 Staff effort

Because individuals have been removed from tables which only shows totals, need some narative about what is in the table basis of costing etc. Also WWW link to full table.

Staff	2022/23		2023/24		2024/25		2025/26		2026/26		Total	
	Fraction	£k	Fraction	£k	Fraction	£k	Fraction	£k	Fraction	£k	Fraction	£k
BHM Physics												
Total	0.35	35.00	0.85	47.50	2.50	175.00	2.50	175.00	2.50	175.00	8.70	607.50
IC NHS HC Trust												
Total	0.75	37.50	1.25	50.00	1.50	75.00	1.50	75.00	0.50	50.00	5.50	287.50
ICR												
Total	0.20	20.00	0.70	32.50	1.20	45.00	1.20	45.00	1.20	45.00	4.50	187.50
Imperial Physics												
Total	4.95	476.25	4.95	476.25	4.95	476.25	4.95	476.25	4.95	476.25	24.75	2381.25
Lancaster Physics												
Total	1.25	125.00	1.25	125.00	1.25	125.00	1.25	125.00	1.25	125.00	6.25	625.00
Liverpool Physics												
Total	0.10	10.00	1.05	67.50	2.00	125.00	2.00	125.00	2.00	125.00	7.15	452.50
Manchester Physics												
Total	1.20	120.00	1.20	120.00	1.20	120.00	1.20	120.00	1.20	120.00	6.00	600.00
Queen's Physics												
Total	0.05	5.00	0.05	5.00	0.05	5.00	0.05	5.00	0.05	5.00	0.25	25.00
RHUL Physics												
Total	1.00	100.00	1.00	100.00	1.00	100.00	1.00	100.00	1.00	100.00	5.00	500.00
Strathclyde Physics												
Total	2.60	260.00	2.60	260.00	2.60	260.00	2.60	260.00	2.60	260.00	13.00	1300.00
STFC-PPD												
Total	0.45	45.00	0.45	45.00	0.70	70.00	0.70	70.00	0.70	70.00	3.00	300.00
STFC-TD												
Total	0.50	50.00	3.10	310.00	3.60	360.00	3.40	340.00	3.40	340.00	14.00	1400.00
Swansea Physics												
Total	3.80	305.00	4.30	317.50	3.80	230.00	3.30	217.50	2.80	205.00	18.00	1275.00
UC Berkeley (USA)												
Total	0.04	4.00	0.04	4.00	0.04	4.00	0.04	4.00	0.04	4.00	0.20	20.00
UCL Biomedical Engineering												
Total	1.25	87.50	1.75	100.00	1.75	100.00	1.75	100.00	0.75	75.00	7.25	462.50
Grand total	*18.49*	*1680.25*	*24.54*	*2060.25*	*28.14*	*2270.25*	*27.44*	*2237.75*	*24.94*	*2175.25*	*123.55*	*10423.75*

A.5 Schedule and milestones

Lead authors: K. Long, C. Whyte: digested from WP schedules.

A.6 Risk

Lead authors: K. Long, C. Whyte: digested from WP risks

A.7 Stakeholder outreach and engagement plans

Through the LhARA programme the collaboration seeks to establish an entirely new technique for the automated delivery of personalised, precision, multi-ion PBT. The present proposal is a step on the way and will bring together novel technologies, each developed for, or demonstrated in, unrelated fields. This programme carries significant technical risk. The high-risk approach is justified by the high level of reward and will place the UK at the forefront of the PBT field, establish UK industry as a key player in the delivery of novel clinical equipment, and allow significantly enhanced access to state-of-the-art PBT across the UK.

In addition to the long-term transformation of clinical practice in PBT, the importance the programme derives from the breadth of impact it will generate:

Clinical: incremental deployment of automated on-the-couch patient-imaging and patient-positioning systems and development of fast, optimised treatment-planning software. Definitive *in vitro* and *in vivo* biological measurements that will be used to enhance the accuracy of treatment planning software in the short, medium, and long term.

Technological: Prototypes of novel accelerator technologies, novel real-time "proton-acoustic" dose-deposition imaging; automated robotic systems that can be developed for clinical application, optimised image-processing and treatment-planning systems, and a simulation of the full clinical facility to be used to optimise its efficacy and to inform its development, construction, and operation. Exploitation of the biological facility and incremental development of the novel technologies.

Industrial: The R&D prototypes and components of the PoP system will be developed and produced in partnership with the industrial members of the collaboration. Active involvement in the R&D and PoP activities will position UK industry to take a leading role in the implementation phase.

Scientific: Direct scientific impact will be generated in the fields of laser-driven acceleration, imaging, instrumentation, diagnostic-technology, and software-system development during the initial R&D phase. Scientific impact in the field of biology will be delivered during the PoP phase. Key technologies developed and proved in operation can be spun-out to accelerator-based infrastructure for science and innovation. Execution of the proposed programme will maintain and enhance the UK's internationally recognised position of leadership in the provision of intense, pulsed ion beams.

Over the Preliminary Activity in years 1 and 2 we propose to engage with each of the key stakeholder groups to build on the engagement and outreach work that the collaboration has done to date. We propose to engage with the peer groups in the biomedical and natural sciences through peer-reviewed publications, presentations at conferences, seminars, and by organising national and international workshops on the biomedical science that LhARA will deliver, the plasma and accelerator science that underpins the LhARA facility, and the development of the technologies that underpins its success.

The long-term, transformative nature of the LhARA initiative calls for a sustained Patient and Public Involvement (PPI) programme. The collaboration takes this aspect of its work very seriously; two PPI representatives attend the LhARA meetings and sit on the Institute Board. We propose a staged build up of patient and public involvement the emphasis of which will change as the project evolves. The modest resources requested in Work package 1 to support the PPI activity will be used to support meetings and other activities. Initial discussion has led the identification of the following involvement themes:

Patient involvement:

- The discussion of the benefits of techniques that will provide precise, targeted radiotherapy which efficiently kills cancer cells while avoiding significant radiation damage to healthy tissue. Research in this area is presently focused on ultra-high dose-rate "FLASH" radiotherapy (RT) and the delivery of non-uniform dose distributions in mini- and micro-beam RF. The flexibility of the LhARA system will allow these effects to be studied as well as more advances temporal, spatial, and ion-species fractionation schemes.
- The discussion of use of automation and feedback to increase patient throughput to allow PBT to be delivered to more patients at less cost and in less time.
- The exploration of the use of the unique flexibility of the laser-hybrid approach in terms of the develop of new strategies and therapies in difficult to treat, rare, or tumours that were previously not responsive to RT.
- Discussion of the enhancements in treatment that can be derived from the biological insights gained through the execution of the LhARA programme over the next 5–10 years. These will include FLASH, MBRT, RT in combination with immunotherapy, and other cancer-treatment regimens. The potential for insights into dormancy and the biology of late effects will also be addressed.
- Discussion of the importance of supporting treatment developments in rare cancers, difficult to treat tumours, and where side effects need to be reduced.

Public involvement:

- Discussion of the need to enhance the education and training within and across all disciplines, including clinical practitioners and scientists. The development of a cohort of scientists and clinicians with the multidisciplinary expertise required to realise the full potential of the unique flexibility provided by the laser-hybrid technique.
- Discussion of the mechanisms by which the unique opportunity provided by LhARA will allow the UK to maintain and enhance its international reputation for scientific excellent and leadership.
- Discussion of the case for sustained UK investment in big biomedical science initiatives and the degree to which the impact of the uniquely flexible facility justifies the substantial technical risk that execution of the project implies.

To inform these discussions we propose to engage with social scientists and health economists to:

- Build an operational model for a fully automated laser-hybrid system of the type that will be prototyped in LhARA. This model will be used to identify critical aspects of the LhARA R&D programme and to estimate the possible gains in terms of patient throughput and quality adjusted life years (QALYs) or equivalent.
- Using the model outlined above the operational costs of the future clinical laser-hybrid facility will be evaluated in order to establish the health-economics benefits of the LhARA initiative. This assessment will include consideration of the possibility that reduction in long-term side effects will yield substantial economic benefit.
- Quantify the benefit to be derived from the creation of a lasting infrastructure for experimental work on a wide range of ions and energies; unique in the world which is destined to have huge scientific output and provide a step change in our understanding of radiation cell damage.

Communication strategy

To ensure maximum stakeholder and patient/public involvement, we will need ultimately need a communications and engagement manager. Reaching out to wider stakeholders such as the international community, Business Schools with their involvement in financial models and health economist, and higher education policy to promote physical sciences will be important. Clinical involvement of the NIH BRC network and cancer charities will widen the patient engagement. This is seen as a 4 nation project and links with MPs and their constituents particularly around R&D and jobs will be key.

A.8 Management plan

A.8.1 Programme organisation

The multidisciplinary LhARA collaboration's mission [5] is to harness the disruptive potential of laser-driven proton and ion sources to create a ground-breaking biomedical research facility [1, 2]. The collaboration's ambition is that the technologies demonstrated in LhARA will be transformative in the automated delivery of personalised, precision, multi-Ion Beam Therapy (IBT).

The LhARA programme encompasses the:

- Execution of the LhARA project by which the Laser-hybrid Accelerator for Radiobiological Applications will be realised;
- Development of a cutting-edge radiobiology research programme in which the novel techniques developed by the collaboration play an ever increasing role and which culminates in the exploitation of the uniquely flexible LhARA facility; and

Figure 18: The LhARA collaboration organisational chart. The organisation structure has been defined by the collaboration to deliver the LhARA programme. The functions of the Institute Board and Executive Board are described in the text. The LhARA project is defined in the context of the overarching programme, see **??**.

- Generation of clinical and other impact through incremental deployment of the novel techniques and technologies developed by the collaboration.

The organisation of the LhARA collaboration has been modelled on that of a large, successful particle-physics collaboration that, in partnership with a host laboratory or institute, delivers a complex scientific infrastructure. Successful execution of the LhARA programme will generate substantial societal and economic impact. Therefore, the organisational structure includes representation from key stakeholder groups beyond the direct scientific and technology-development communities. The collaboration places great importance on maintaining the multidisciplinarity of the programme. The essential nature of the life science/natural science partnership is therefore manifest at all levels.

The organisational structure of the LhARA collaboration is shown in figure 18 and has the following key Boards, roles and resonsibilities:

The Institute Board represents the interests of the institutes, industrial partners, and patient groups that make up the collaboration (see figure 19 and Annex B). Each collaborating institute and stakeholder group is represented on the Institute Board. All positions of responsibility within the collaboration are approved by the Institute Board. The collaboration's spokespeople and programme managers attend the Institute Board.

The Institute Board (IB) is co-chaired by a life-scientist and natural scientist chosen from among the IB membership. The inaugural chairs of the IB have responsibility for drafting the collaboration's constitution. Once agreed, the IB will reviews and amend the organisational structure of the collaboration from time to time as the programme evolves.

The Institute Board reviews and approves the technical options and distribution of responsibilities among the participating institutes proposed by the LhARA Executive Board. It ratifies major strategic and technical decisions and supports the collaboration management team in the preparation of reports, funding

proposals, and other documentation required to drive the programme forward.

Figure 19: Graphical representation of the institutes that make up the LhARA collaboration. The list of collaborating institutes is reproduced in Annex B.

The Executive Board provides the management of the LhARA collaboration and is responsible for governance of the delivery of the programme, performing both an oversight and top-level management function. The Executive Board (EB) will have the authority to make cost, scope and schedule decisions. The membership of the board will consist of collaboration co-spokespeople, the IB co-chairs and the collaboration programme managers. Other expertise may be co-opted as required. The programme managers will deliver status reports on progress, finance, risks and issues at the EB. The board will meet approximately every 2–4 weeks or as required. It has overall responsibility for managing the LhARA initiative. It EB represents the collaboration in its relations with outside bodies. The EB is chaired by the LhARA spokespeople.

The key roles in the LhARA programme management team are:

Institute Board co-chairs: The LhARA Institute Board has two co-chairs. The co-chairs are chosen from the Institute Board membership such that their expertise and experience cover the natural and biomedical science and technology development aspects of the collaboration's programme.

The present co-chairs are:

- Yolanda Prezado, Institut Curie, Paris;
- Timothy Greenshaw, Liverpool.

Spokespeople: The LhARA collaboration has two Spokespeople who jointly lead the collaboration. The spokespeople are chosen such that their expertise and experience cover the natural and biomedical science and technology development aspects of the collaboration's programme.

The present spokespeople are:

- Amato Giacca, Oxford Institute of Radiation Oncology;
- Kenneth Long, Imperial College London and STFC.

Programme managers: The LhARA collaboration has two programme managers who are jointly responsible for coordinating all technical, financial, and programme-planning activities. The programme managers

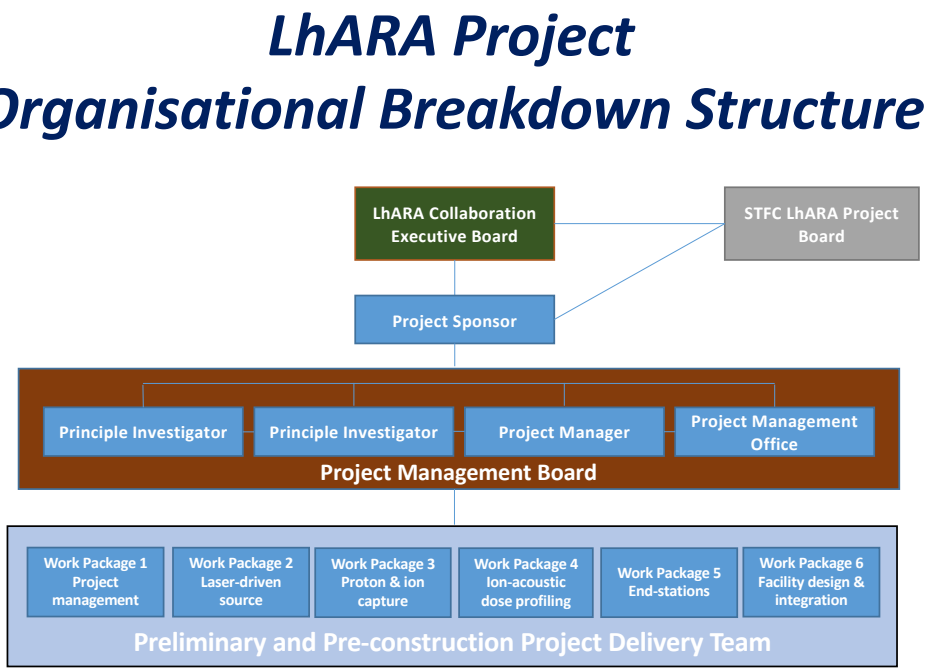


Figure 20: The organisational chart for the LhARA project. The functions of the Project Management Board are described in the text. The key roles within the project structure are indicated. The preliminary phase project is executed through six work packages, as indicated in the figure. The work content of each work package is defined in section A.2.1 to A.2.6.

are chosen such that their expertise and experience cover the natural and biomedical aspects of the collaborations programme.

The present project managers are:

- Jason Parsons, University of Liverpool;
- Colin Whyte, University of Strathclyde.

Programme administrator: The LhARA collaboration's programme administrator assists the LhARA programme management team in the execution of their functions.

The present programme administrator is:

- Dionysia Kordopati, Imperial College London

A.8.2 Project organisation

The scope of the LhARA project is to deliver the Laser-hybrid Accelerator for Radiobiological Applications. The present proposal is being prepared in the context of the dvelopment of the Ion Therapy Research Facility (ITRF) and defines the programme and resources required during the Preliminary and Pre-construction phases.

The organisation of the LhARA project will be carried out in accordance with the STFC Project Management Handbook [94, 95] in partnership by the STFC Daresbury and Rutherford Appleton Laboratories and the LhARA collaboration.

The organisational structure of the LhARA project is shown in figure 20 and has the following key Boards, roles and resonsibilities:

The Project Management Board oversees all aspects of the facility design, schedule development, project planning and execution, cost estimation, software development, and computing matters. It serves as an advi-

sory body for the Executive Board and Project Sponsor.

The PMB will be chaired by the project manager and include the principle investigator, work package leaders and Project Management Office representatives that collectively manage all aspects of the project management of the LhARA project. The project management plan (PMP) will include all the plans and reference all the key project-management documentation required to deliver the project successfully; including specifications, scope, finance, resources, schedule, objectives and deliverables, risk management, stakeholder plan, procurement plan, quality assurance management, benefits realisation and impact plan, safety health and environment plan. The PMB will meet monthly. Focussed specific technical and planning meeting will meet more regularly with progress reported at the monthly project group meetings by work package managers.

The LhARA project has been underway for several years and produced a pre Conceptual Design Report [1, 2]. Further definition is proposed by developing the Conceptual Design Report followed by the Implementation phase of the project. During the implementation phase the LhARA project will baseline the project and adopt strict project management methodology including the management of:

- Stakeholders;
- Planning;
- Scope;
- Quality;
- Finance and Cost;
- Resources;
- Schedule;
- Change control;
- Risk and value-engineering issues;
- Procurement;
- Health, safety and environment;
- Off line assembly and testing;
- Installation and testing; and
- Commissioning with beams.

During the LhARA project's lifecycle decision gates will review and confirm the continued viability of the work. Design review will be implemented during the concept and definition phases of the project. Gates will also be implemented at the end of each phase of work. The review focussing on; what has been achieved, what are the key requirements for the next phase, what are the key decisions to be made, and is the business case still viable; i.e. can the desired benefits be achieved for an acceptable level of cost and risk?

The Project Management Office (PMO) provides project management administration support to the LhARA project and collaboration. The PMO will standardise the project-related management processes in support of the project manager, principle investigator and project delivery team.

Roles in the project management team have been defined to ensure appropriate expertise is broght to bear on the executio of the work package. The key roles in the LhARA management team are:

Project sponsor: who will champion the project, and provide the essential links between the LhARA collaboration, STFC Project Board and the project management team. The sponsor is the owner of the business case and develops the business case throughout the project lifecycle. There will be a close relationship between the sponsor and the project manager to ensure that the business case remains viable. That it continues to deliver the project deliverables and benefits. The sponsor will chair the Project Board (or Oversight Committee). The sponsor will represent the LhARA User Facility interests and requirements,

agree the project management plan with the project manager and ensure that the project is actively managed and meets its vision and objectives.

The Principle Investigator: will lead the science team requirements and deliverables for the LhARA project and be responsible for the scientific success of the LhARA project.

The present Principle Investigator is:

- Kenneth Long; Imperial College London/STFC.

The Project Scientist: is responsible for ensuring that the specifications for the LhARA beam delivered to the endstations, the beamline instrumentation, the diagnostics and endstation capability remains aligned with the scientific requirements of the LhARA user community. team requirements and deliverables and be responsible for the scientific success of the project.

The present Project Scientist is:

- Kenneth Long; Imperial College London/STFC.

Project manager: is accountable to the project sponsor. Together they will maintain a continuous dialogue with the laboratory, the collaboration and the work package managers to ensure a common understanding of the; 1work, cost, risk, schedule and deliverables. The role and responsibilities of the project manager is well understood and clearly defined in the STFC Project Management Framework [94, 95].

The present Project Manager is:

- Colin Whyte, University of Strathclyde.

Project manager: The Project Manager will be accountable to the project sponsor. Together they will maintain a continuous dialogue with the laboratory, the collaboration and the work package managers to ensure a common understanding of the; 1work, cost, risk, schedule and deliverables. The role and responsibilities of the project manager is well understood and clearly defined in the STFC Project Management Framework [94, 95].

The present project manager is:

- Colin Whyte, University of Strathclyde.

Project administrator: The LhARA collaboration's project administrator assists the LhARA management team in the execution of their functions.

The present project administrator is:

- Dionysia Kordopati, Imperial College London

The LhARA collaboration recognises the importance of independent scrutiny of its activity. Therefore, the collaboration has established the principle of formal reviews of its programme by independent experts of international standing. The first such review [96] was held before publication of the pre-CDR [1] for the facility. A committee is being established to review the Preliminary and Pre-construction Phase programmes proposed here. The recommendations of the review committee will be considered in the completion of the present proposal and the review committee's report will be made public.

A.8.3 Project specification

The R&D programme necessary to deliver a full Conceptual Design Report (CDR) for LhARA was first presented in the pre-CDR [1]. This proposal builds on the pre-CDR and is designed to establish the conditions for the technical-design phase of the LhARA project to begin. The five-year programme defined above and summarised in the sections which follow will significantly improve the definition of the project, remove uncertainties, mitigate risks and deliver the principal milestone defined in the proposal for an Ion Therapy Research Facility (ITRF) [97] submitted to the UKRI Infrastructure Advisory Committee on the 15^{th} June 2021, namely the completion of a full CDR for the facility at the end of the two-year Preliminary Phase. The present proposal also defines the work that must be carried out in the subsequent three-year Pre-construction Phase. An overview

of the schedule for the development of the LhARA initiative in the Preliminary and Pre-construction Phases is shown in figure 21.

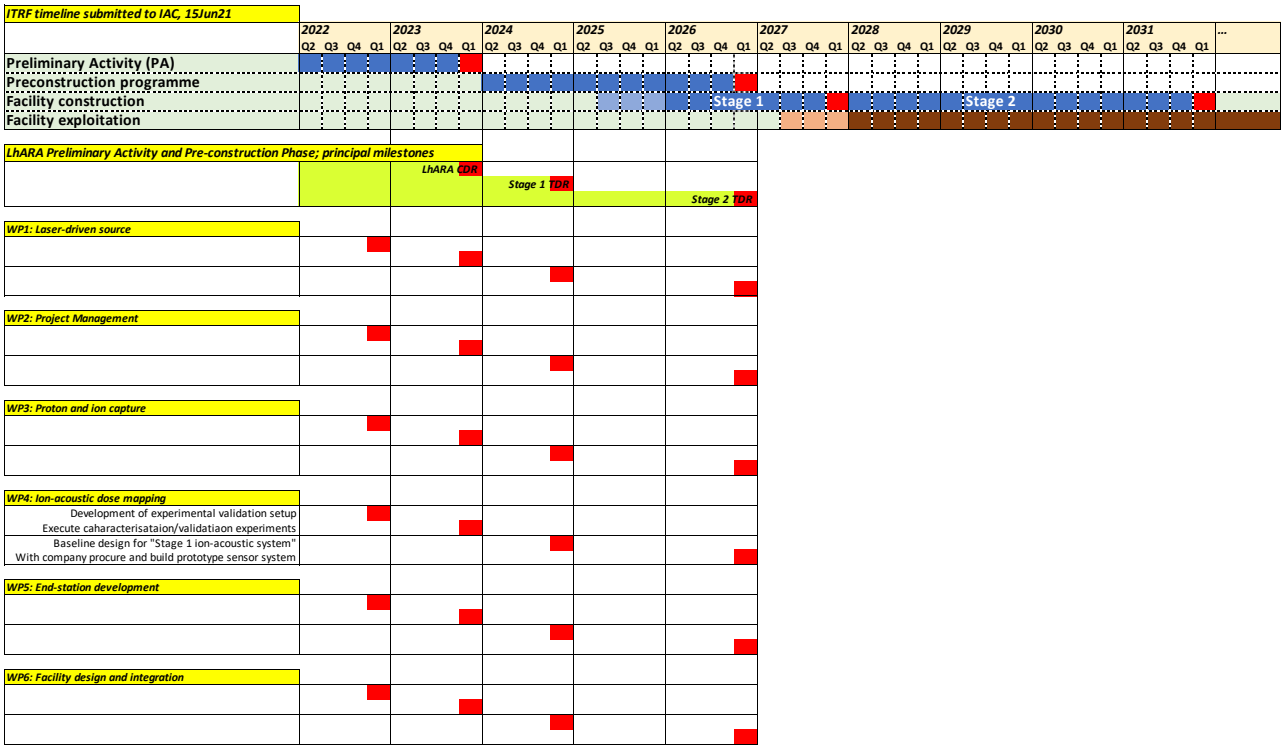


Figure 21: Waterfall chart showing the principal milestones that define the project proposed herein. The block entitled "ITRF timeline submitted to IAC, 15Jun21" shows the timeline for the development of the ITRF submitted to the UKRI's Infrastructure Advisory Committee. The block entitled "LhARA Preliminary Activity and Pre-construction Phase; principal milestones" shows the principal milestones of the LhARA Preliminary Activity and Pre-construction Phase proposed here. The subsequent blocks present the principle milestones that serve to specify each of the work packages.

The specification of the Preliminary and Pre-construction Phase programmes has been split into two streams:

Facility design and integration encompasses the preparation of full conceptual and technical designs for all aspects of the LhARA facility. The implementation of LhARA has been conceived in two Stages:

- *Stage 1*: Proton beam to the low-energy *in-vitro* end station; and
- *Stage 2*: Proton and ion beams to the high-energy *in-vitro* and the *in-vivo* end station.

Risk management encompasses the R&D programme necessary to address the principal risks attendant on the implementation of LhARA.

An overview of the project schedule is presented in figure 21. The Preliminary Phase is assumed to take place over the first two years of the project while the Pre-construction Phase is assumed to take place over years three to five. The principal deliverables that define the project are:

Preliminary Phase:

- *Facility design and integration*:
  1. Full conceptual design for LhARA Stage 1 and LhARA Stage 2 (work package 6).
- *Risk management*:
  2. Characterisation of the proton phase space produced by the laser-driven source and the comparison of the measured spectra to simulation (work package 2);

3. Detailed design of the second Gabor lens prototype based on the study of non-neutral plasma dynamics and benchmarked simulation (work package 3);
4. Proof-of-principle demonstration of Bragg peak localisation using acoustic signals (work package 4); and
5. Specification of end-station diagnostics and instrumentation (work package 5).

Pre-construction Phase:

- *Facility design and integration*:
  6. Technical Design Report for Stage 1 at the end of year three (work package 6); and
  7. Technical Design Report for Stage 2 at the end of year five (work package 6).
- *Risk management*:
  8. Complete design and initial characterisation of laser-driven proton and ion source (work package 2);
  9. Detailed design and initial characterisation of plasma lens (work package 3);
  10. Design and initial characterisation of acoustic dose-profile measurement system for the Stage 1 low-energy *in-vitro* end station (work package 4); and
  11. Initial evaluation of *in-vitro* end-station diagnostics and instrumentation (work package 5); and
  12. Specification and design of high throughput automated sample-handing system for Stage 1 low-energy *in-vitro* end station (work package 5).

A.8.4 Safety, health and environment (SHE) Plan

The LhARA collaboration has adopted a "safety-first" culture. The project team will deliver the SHE management plan for the project in collaboration with the SHE representatives of each institute and the project delivery teams throughout all phases in the project lifecycle.

Safety management at the definition stage of the project will include:

- Radiation Shielding (IRR17) estimated thicknesses, material selection and construction methods;
- Personnel safety system compliance with IRR17 and Accelerator Code of Practice in accordance with IEC61508; Adopting current best practise for accelerator access control and key exchange systems, that will shielded areas to be searched prior to operation of the laser and accelerator system;
- Local Exhaust Ventilation requirements–Extract/Exhaust systems (COSHH 2002).;
- HAZoP Process outline for systems integration; and
- Emergency Lighting, Fire Alarm and Fire suppression systems.

The person responsible for managing the technical work will be responsible for producing the risk assessment and method statement (RAMS) for each task with risks in conjunction with the staff performing the work. Contractors will provide RAMS prior to work conducted that will be approved by the construction site manager, who oversees and coordinates all the multidiscipline construction work. All work on the construction site will be conducted under a permit to work system.

It is the responsibility of the LhARA management team (Project Office and Project Group) to support the Work Package managers in this task and to ensure that it is done. The Project Group is responsible for ensuring that special issues such as radiation, the presence of magnetic fields, etc. are widely discussed and addressed and that a full safety analysis is performed.

A Project Safety Manager will be appointed to take responsibility for delivering a coherent safety case for LhARA and submitting it at appropriate times for review by STFC and/or other relevant institutions. The Project Management Group will commission independent safety reviews as appropriate where the perceived risks are considered high or to meet the eventual goal of obtaining permission to operate. The Project Group

will be responsible for defining, carrying out, and documenting appropriate component- and system-level acceptance tests.

Final permission to operate the stages and sub stages of the facility under construction will be based on a Safety Readiness Reviews with checks and sign-off sheets by the technical leads of each discipline. Documentary evidence of adherence of the agreed safety procedures and methods, evidence of materials certification, and engineering calculations will also be required. The operation of LhARA will be based on best practise of similar complex laser-accelerator complex's managed by STFC radiation test facility processes, procedures, roles and responsibilities.

The projects influence on the environment will be a key consideration through the project lifecycle. Minimising energy consumption and energy losses will be essential. Design, technology choices and construction techniques of the building, its technical services and accelerator systems to reduce the projects carbon footprint will be crucial. Design for mitigating decommissioning impact and cost on the environment will be established during the planning stages of the project to reduce the use of raw materials and enable the re-use of the building, shielding materials and generic components.

A.8.5 Work breakdown structure

Top level, refer to Gantt charts, say needs to be refined in first 2 years, anticipate growth in yrs 3-5.

A.8.6 Critical path

A.8.7 Project schedule and milestones

Including key review/decision points

Cull from Gantt charts.

A.8.8 Risk management plan

The Project delivery team is required to keep the Project Office apprised of potential risks, their consequences and the development of appropriate contingency plans. The Project Manager and Work Package Managers s will report regularly on the evolution of the project risk register to the Project Management Office. Where appropriate costs will be assigned to the risk-mitigation strategies and recorded in the risk register. "Trigger levels" will be set in the risk register so that potential problems are highlighted and reported to the Project Management Office in a timely manner. Risk Management will be a standing agenda item at the Project Delivery Team Committee, Project Board and Steering Group meetings. Risks will be identified, captured, have mitigation controls implemented to reduce the risk likelihood or impact (or both), and recorded and monitored by a Risk Register process. Risks that become an issue will be captured in an Issue Log to be monitored and resolved.

A risk analysis at the Work Package level has been performed by the Work Package managers. Project risks and the principal risks identified in the work-package analysis have been presented above. The list will be updated in preparation for each Institute Board meeting; significant changes will be presented by the Project Managers in their report to the Institute Board.

A.8.9 Quality assurance plan

Quality assurance will be delivered as described in the projects Quality Assurance Management Plan (QAMP) that will be written during the definition phase of the project.

To assure the success of the project, the integration of quality will be critical throughout the project lifecycle. The QAMP will set the management arrangements for people, processes and tools to provide the structure for assuring that LhARA requirements will be met and the risks of not meeting requirements minimised. The QAMP will be reviewed and updated throughout the lifecycle of the project. The QAMP will include the following sections:

- Project Quality Policy, Purpose and related documents;
- Quality Management Roles and Responsibilities;
- Deliverables;
- Communication;
- Configuration Management and Change Control;
- Procurement Management and Assurance;
- Product Identification and Traceability;
- Document and Data Management;
- Software Assurance;
- Component Handling, Storage and Transportation;
- Transfer of Ownership;
- Design Reviews;
- Product Acceptance;
- Manufacturing Inspection Plans;
- Non-Conformance Management;
- Measurement and Analysis; and
- Continuous Improvement.

The Quality assurance management plan is based on the project-management methodology presented in [94, 95]. The following tools will be used:

- The evaluation through simulation of the design performance of components of the LhARA system;
- The benchmarking of the simulations against published data, measurements on model systems, and the characterisation of appropriate prototypes;
- The documentation of designs and their evaluation at appropriate intervals in Technical Notes held in the document repository described below; and
- Independent verification of engineering drawings, engineering calculations and documentation through both internal and independent design reviews.

The initial Work Breakdown Structure (WBS) has been developed and is summarised above. Of particular concern is the issue of integration; there are three levels at which particular attention to the interfaces and system integration will be given:

- The interfaces between adjacent modules;
- The internal interfaces in a module where the responsibilities are shared between different institutes; and
- The interfaces required at the time of installation and the overall integration of with the environment.

The WBS is overseen by the Project Managers and reviewed by the Project Group which includes the managers of the "Design and integration" work package (WP6). One of the managers of WP6 is and will continue to be an experienced expert in accelerator-system integration. This individual will take the lead in discussions leading to the identification, specification, and documentation of system interfaces within the Project Group.

The various bodies that form the formal LhARA management structure use action lists to initiate and track issues of design, interface, installation, and integration. Changes to the project specification, cost and schedule are also considered by the Project Group and in turn by the Project Office. A change control mechanism will be established as the project enters the Pre-Construction Phase.

A.8.10 Document control plan

Project documentation, including engineering drawings and specification documents, is collected in the "Technical Note" repository [98] that is maintained as part of the CCAP wiki [99]. The documentation source files (WORD, LaTeX, figures, spreadsheets etc.) are stored in a GIT repository [100]. The GIT repository is used to maintain a detailed version history of the individual documents.

Documents are organised by category and labelled with the date, subject and revision numbers. Technical Note numbers are issued by the Project Managers and review of the content of the notes is provided by the Project Group and Project Office.

A.8.11 Staffing strategy

A.8.12 Consideration of diversity issues

A.8.13 Procurement plan

LhARA is a collaborative project, with devolved responsibilities for procurement. The overall procurement plan is established by discussion within the collaboration; the Project Office is responsible for proposing strategy. Collaborating institutions along with the appropriate funding agencies will develop their own procurement plan. The responsibility for the procurement of the parts of the LhARA system is to be established by MoU between STFC and the individual collaborating institutes against this plan.

A.8.14 Supplier market

The significant components, both novel and off-the-shelf will be required during the Pre-construction Phase. These will be obtained through competitive tender based on a design specification worked-out in the Preliminary or Pre-construction Phases. As part of the Quality assurance management (section A.8.9), the documentation of specifications, designs, and the design evaluation will be subjected to independent technical review prior to the initiation of the tender process.

A.8.15 Impact plan and benefits realisation

The LhARA collaboration seeks to establish an entirely new technique for the automated delivery of personalised, precision, multi-ion PBT. To achieve this novel technologies, each developed for, or demonstrated in, unrelated fields will be brought together in a single system. This LhARA programme carries significant technical risk. The high-risk approach is justified by the high level of reward and will place the UK at the forefront of the PBT field, establish UK industry as a key player in the delivery of novel clinical equipment, and allow significantly enhanced access to state-of-the-art IBT across the UK.

In addition to the long-term transformation of clinical practice in IBT, the programme has the potential to generate a substantial breadth of impact in the R&D and pre-construction phases:

Clinical: incremental deployment of automated on-the-couch patient-imaging and patient-positioning systems and development of fast, optimised treatment-planning software. Definitive in vitro and in vivo biological measurements that will be used to enhance the accuracy of treatment planning software in the short, medium, and long term.

Technological: Prototypes of novel accelerator technologies, novel real-time "proton-acoustic" dose-deposition imaging; automated robotic systems that can be developed for clinical application, optimised image-processing and treatment-planning systems, and a simulation of the full clinical facility to be used to optimise its efficacy and to inform its development, construction, and operation. Exploitation of the biological facility and incremental development of the novel technologies.

Industrial: The R&D prototypes and components of the various proof-of-principle (PoP) systems will be developed and produced in partnership with the industrial members of the collaboration. Active involvement in the R&D, PoP, pre-construction, and construction activities will position UK industry to take a leading role in the implementation phase.

Scientific: Direct scientific impact will be generated in the fields of laser-driven acceleration, imaging, instrumentation, diagnostic-technology, and software-system development during the initial R&D phase. Scientific impact in the field of biology will be delivered during the PoP phase. Key technologies developed and proved in operation can be spun-out to accelerator-based infrastructure for science and innovation. Execution of the proposed programme will maintain and enhance the UK's internationally recognised position of leadership in the provision of intense, pulsed ion beams.

This proposal includes a robust Stakeholder development plan (see section A.7. The early engagement with all stakeholder groups will allow opportunities to deliver impact to be exploited as the project evolves. The development of proposals to spin-out elements of the LhARA technology-development programme to benefit patients through the incremental enhancement of clinical IBT facilities the collaboration will expand its intellectual impact and attract additional investment into its core programme. Regular stakeholder consultation will inform the development of the R&D programme and the impact-generation activities of the collaboration.

Through the stakeholder-engagement activities a benefits-realisation plan will be developed during the Preliminary Phase and implemented during the Pre-construction and subsequent construction phases. Maximising the potential for the LhARA initiative to generate impact at all stages of its development is a high priority for the collaboration.

A.8.16 Evaluation strategy

The evaluation of the designs for the various components and sub-systems will be through careful and systematic evaluation of simulations, comparison of the results of simulation with measurements made on appropriately specified prototypes, and beam tests. The technical evaluation that ensures that components meet their specification will be through design review prior to production and the implementation of QA and QC procedures documented and agreed prior to the production and receipt of the item. The evaluation will be carried out through specialist sub-group meetings, collaboration meetings and, where appropriate, the simulations, measurements, and conclusions drawn will be subjected to external expert review.

The progress of the project will be carried out using the appropriate project management tools to the standard defined in [95]. The tools will include Gantt and slip charts, milestone tracking, the routine review of the project and work package risk registers, and wherever possible earned-value analysis. Appropriate risk escalation and contingency management processes will be agreed with the funding agencies at the start of the Preliminary and Pre-constriction phases.

A.8.17 Monitoring and reporting

The LhARA collaboration meets by video every fortnight to review the status of the initiative in general. In addition to status reports from the Work Package managers particular scientific or technical contributions are regularly made. Both the Project Office and Project Group meet fortnightly; the individual meetings taking place on alternate weeks. Details of the development of the project, the evolution of cost, schedule, and risk are addressed in the Project Group meetings, the Project Office providing oversight and taking responsibility for organising formal technical and scientific reviews.

In addition to the regular fortnightly meetings, the collaboration has begun to establish a pattern of plenary, in person meetings. The objective will be for a plenary, in person, collaboration meeting to take place at least three times a year. The transition to a regular in-person meeting pattern will depend on the collaboration's success in attracting resources and the development of the Covid-19 pandemic.