The Laser-hybrid Accelerator for Radiobiological Applications

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

The LhARA collaboration

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Executive summary

The LhARA collaboration's long-term vision [1] is to 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. Such a facility will be capable of delivering 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. The automated, laser-hybrid system will integrate patient, soft-tissue and dose-deposition imaging with real-time treatment planning to trigger the delivery of dose tailored to the individual patient in real time. The automated, triggerable system we propose has the potential to remove the requirement for a large gantry, thereby reducing the size and therefore the cost, of a clinical IBT facility and to follow movement of patient and tissue, thereby increasing patient throughput and reducing the cost of IBT per patient.

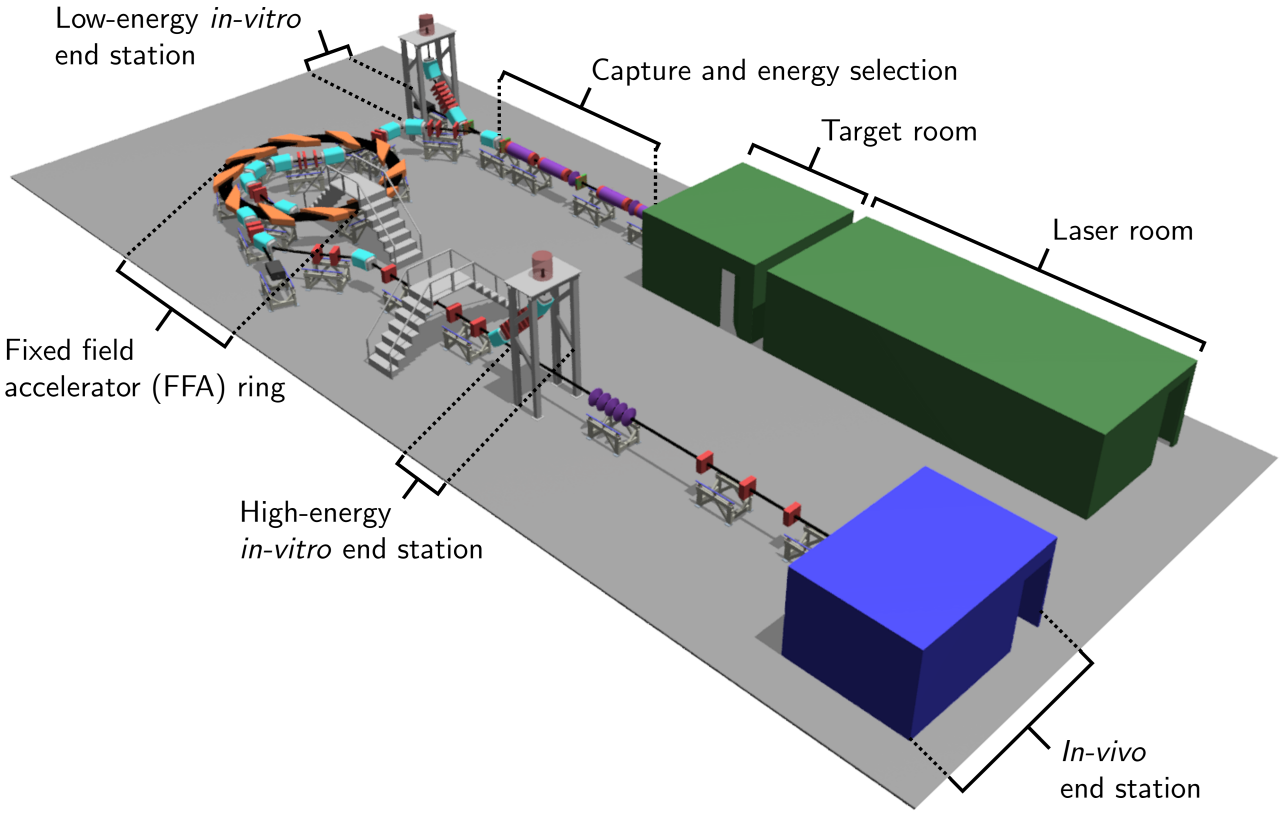


Figure 1: LhARA—the Laser-hybrid Accelerator for Radiobiological Applications. Two separate shielded areas are planned to accommodate the laser and target system. After the 'Capture and energy selection' section of the beamline, the beam is directed either to the vertical *in-vitro* end station or injected into the fixed-field alternating-gradient (FFA) ring. After post-acceleration, the beam is extracted from the FFA and directed either to the high-energy *in-vitro* end station or to the *in-vivo* end station.

We propose to develop LhARA [2, 3], the Laser-hybrid Accelerator for Radiobiological Applications, to serve the "Ion Therapy Research Facility" (ITRF) [4]. LhARA 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 [5]. The LhARA collaboration's concept, shown in figure 1 is to exploit a laser to create 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

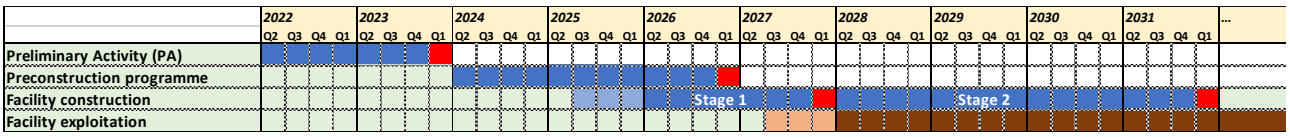
allows protons and ions to be captured at energies significantly above the capture energies of conventional facilities, elegantly circumventing the current space-charge limit on the instantaneous dose rate that can be delivered [6]. The plasma (Gabor) lenses provide the same focusing strength as high-field solenoids at a fraction of the cost. Post-acceleration using a fixed field alternating gradient accelerator (FFA) preserves the unique flexibility in the time, energy, and spatial structure of the beam afforded by the laser-driven source.

The multi-disciplinary LhARA collaboration [7, 8] consists of clinical oncologists, medical, particle, plasma, laser, ultrasound, and optical physicists, accelerator, computer, and instrumentation scientists, radiobiologists, industrialists, and patient representatives. 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) [4]. 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 ... 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 LhARA to serve the ITRF defined in the proposal is shown in table 1.

Table 1: Timeline for the development of LhARA to serve the Ion Therapy Research Facility presented in the proposal to the UKRI Infrastructure Advisory Committee [4].



We propose that LhARA be developed to serve the ITRF in two stages [2, 3]. In Stage 1, 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 2, 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 of 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 short pulse over a tiny area—to be preserved and exploited to deliver radiobiological investigations in completely new regimens.

The collaboration will build on its present industrial links to ensure appropriate industrial engagement from the outset. Such engagement is essential if the technology-development programme is to yield practical, cost-effective solutions. As the LhARA build-phase becomes established, the collaboration's will continue to work with its industrial partners to develop a laser-hybrid system capable of clinical deployment. This approach will ensure timely development of industrial capability and provide the opportunity for UK industry to take pole position in the delivery of the IBT systems of the future.

With this proposal, we seek the resources to deliver the Preliminary Activity and Preconstruction Phase of the programme necessary for LhARA to serve the ITRF. Over the first two years the Preliminary Phase will:

- Deliver the Conceptual Design Report for LhARA to serve the Ion Therapy Research Facility;

- Demonstrate the feasibility of the laser-driven creation of the requisite proton and ion flux through measurement and simulation;
- Create the detailed specification of a second Gabor-lens prototype through a programme of experiment, simulation, and design;
- Experimentally prove the principle of ion-acoustic dose-profile measurement; and
- Create a detailed specification for the *in-vitro* and *in-vivo* end stations through peer-group consultation, design and simulation.

The Preconstruction Phase will be carried out over years three to five and will deliver Technical Design Reports for LhARA Stage 1 in year 3 and LhARA Stage 2 in year 5. The programme of technical-risk mitigation will continue and will culminate in the production of complete designs for a proton and ion production target and capture system capable of 10 Hz operation, the detailed design of the Stage 2 FFA, and the beam-line and end-station instrumentation necessary to provide fast feedback and control to the accelerator components.

The proposed five-year programme will lay the foundations for the establishment of an entirely new technique for delivery of proton and ion beams for science and innovation. Serving the ITRF, LhARA will be a unique, compact, research infrastructure delivering ions from protons to carbon at energies sufficient for both *in-vitro* and *in-vivo* studies. Fundamentally new biological mechanisms in radiation treatment and immune response which underpin the clinical efficacy of future proton- and ion-beam therapy will be elucidated. Exploitation of LhARA at the ITRF will promote the disruptive accelerator, diagnostic, imaging, and computing technologies required radically to transform clinical practice.

Lay summary

The LhARA collaboration's mission is to revolutionise ion-beam radiotherapy (IBT). The ambition is to greatly improve the accuracy and effectiveness of IBT in destroying cancer cells while minimising the risk of damage to healthy tissue. Integral to the vision is the development of the novel instrumentation and diagnostics required to automate the treatment facility. Such automation is essential to increase throughput. As a crucial first step towards its goals the collaboration proposes the construction and exploitation of a research facility that will exploit emerging new laser-plasma accelerator technology to deliver beams of protons and ions onto biological materials to study their cancer-killing properties. This will prove the principle of the new technologies and allow the best space and time structures of the beams to be evaluated.

The clinical need is clear. In the UK it is anticipated that 1 in 2 people will develop cancer and 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. Radiotherapy is used in treatments of 50% of cancer patients and results in 40% of cancer cures, second only to surgery. The UK currently sits at the bottom of the league of cancer survival for high income countries and the UK Government has recently announced that it wants a War on Cancer and is committed to increasing cancer cures. For many years, radiotherapy using beams of high energy X-rays has been the main way of delivering radiotherapy. This has proved to be very effective for many types of cancer although there is a risk of damage to non-cancerous tissues. Recently, proton-beam-based radiotherapy has been used. In the UK, the NHS has brought into action two proton-beam machines, one in Manchester and one in London. Many more proton-beam therapy centres are in operation in other countries. There is a clinical need for increased UK coverage and to reduce the cost per patient while improving the effectiveness of the therapy and reducing its side effects.

Exciting recent results indicate that short pulses of ions and protons confined in very narrow beams have excellent therapeutic effect while significantly reducing damage to healthy tissue. This is new science which needs to be researched and tested thoroughly to enable the next step of designing and manufacturing a new class of radiotherapy machines for clinical use to be taken. The new class of machine has the potential to reduce a course of radiotherapy to period of days rather than weeks and to enable more patients to be treated.

The LhARA collaboration of accomplished physicists, engineers, medical scientists and clinicians from several universities and research institutes will bring together their expertise and experience to build and operate this world-leading research facility. This would lead both to significant advances in our understanding of cancer biology as well as the establishment of technology to greatly improve cancer treatments to the benefit of patients all around the world at a reduced cost per patient. Specific tasks include the development of the laser-driven production of the required fluxes of protons and ions, the production of beams and their focussing using electron plasma lenses (Gabor lenses), the acceleration of the beams using a fixed-field alternating-gradient accelerator and beam guidance onto laboratories for biological experiments where the research into radiobiology will be carried out.

LhARA will be a UK investment which, serving the Ion Therapy Research Facility, will attract scientists from around the world, create jobs in engineering, construction, science and technology (lasers, electron-plasma lenses, accelerator physics, ion-acoustic imaging, robotics, chemistry, and biology), it will develop increased international collaboration including with CERN in Switzerland, and the National Institute of Radiological Sciences in Japan, with the potential to attract crucial inward and external industrial funding. This would facilitate the production of new machines for clinical use to be sold throughout the world.

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1 Motivation

In the UK, 1 in 2 people will develop cancer [9]. Globally, the present incidence of 17 million new cases per year is predicted to increase to 27.5 million new cases per year by 2040 [10]. Radiotherapy (RT) is used in approximately 50% of cancer patients and is already involved in 40% of cancer cures [11]. The NHS long-term plan [12] to increase the rate of diagnosis of cancer in the early, curative stage, implies an increasing need for optimal therapeutic interventions, including RT.

While photons are used most frequently to deliver external-beam RT, there is an 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 ions come to rest. This allows dose to be conformed to the tumour while sparing proximal healthy tissue and organs at risk. The benefits of IBT are widely recognised. The NHS has invested £250M in proton-beam therapy facilities in Manchester and London [23], and the Particle Therapy Co-Operative Group (PTCOG) [13, 14] currently lists 102 proton therapy facilities and 13 carbon-ion-therapy facilities [15] worldwide. These facilities are located predominantly in high-income countries [15]. Nearly 70% of cancer patients in low-and-middle-income countries globally do not have access to RT [11].

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 is limited by the need to minimise damage to healthy tissue. The use of novel beams with strikingly different characteristics has led to exciting evidence of enhanced therapeutic benefit, particularly using radiation at a very high dose per fraction [16] or very high dose rates ($>$ 40 Gy/s, "FLASH") [17], and also "mini-beam" radiotherapy (MBRT) [18, 19]. 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 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 [2, 3]. 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; a laser-driven source is required.

1.1 Scientific case

Radotherapy using X-rays is one of the most effective cancer treatments, particularly for solid tumours including those of the head, neck and brain. After reaching a peak at a depth of around 1 cm, the dose delivered using X-rays falls approximately exponentially with depth, meaning that there is a limit on the maximum dose that can be delivered to the tumour without delivering an unacceptably large dose to adjacent, healthy, tissue. For a given treatment beam-entry point, tumours that lie deep within the patient will receive a dose significantly lower than that delivered to the healthy tissues through which the beam passes on its way to the treatment site. X-rays that pass through the tumour will also deliver a dose to the tissues that lie behind. Dose delivered to

healthy tissues can cause the death of healthy cells and lead to adverse treatment side-effects. Furthermore, the maximum X-ray dose that can be delivered is limited by the presence of sensitive organs such as the brain and spinal cord. This situation is particularly acute in infants for whom dose to healthy tissue, sensitive organs, and bone can lead to developmental issues and a higher probability of secondary malignancies later in life.

Proton- and ion-beam therapy (IBT) has the potential to overcome some of the fundamental limitations of RT delivered using X-rays [20]. The physics of the interaction between ionising radiation and tissue determines the radiobiological effect. Energy loss through ionisation is the dominant mechanism at the beam energies relevant to IBT. The energy lost per unit distance travelled, the linear energy transfer (LET), increases as the protons or ions slow down. At low velocity, the rate of increase in LET is extremely rapid. This generates a 'Bragg peak' in the energy deposited at the maximum range of the beam just as the protons or ions come to rest. In contrast to photons, this characteristic allows the dose delivered to healthy tissue behind the target tumour (i.e., beyond the Bragg peak) to be reduced to zero for protons, and almost to zero for carbon ions. Scanning the Bragg peak over the tumour volume allows the dose to the tumour to be increased while, in comparison to X-ray RT, sparing tissues in front of the tumour. Careful choice of treatment fields allows dose to sensitive organs to be reduced significantly compared to an equivalent treatment with photons, thereby improving patient outcomes.

The Particle Therapy Co-Operative Group (PTCOG) [13] currently lists proton therapy facilities and 13 carbon ion therapy facilities [15] worldwide. These facilities are located predominantly in high-income countries [15]. Low- and middle-income countries (LMIC) are relatively poorly served. Indeed, nearly 70% of cancer patients globally do not have access to RT [21]. Novel RT techniques incorporated in facilities that are robust, automated, efficient, and cost-effective are therefore required to deliver the necessary scale-up in provision. This presents both a challenge and an opportunity; developing the necessary techniques and scaling up RT provision will require significant investment but will also create new markets, drive economic growth through the development of new skills and technologies and deliver impact through improvements in health and well-being.

The case for a systematic study of the radiobiology of proton and ion beams

The nature of the particle-tissue interaction in IBT allows the dose to be controlled precisely and closely conformed to the tumour volume. However, there are still significant biological uncertainties in the impact of ionising radiation, including ion beams, on living tissue. The efficacy of proton and ion beams is characterised by their relative biological effectiveness (RBE) in comparison to reference photon beams. The treatment-planning software that is in use in the clinic today assumes an RBE value for protons of 1.1 [22]. This means that a lower dose of protons is needed to produce the same therapeutic effect that would be obtained using X-rays. However, a number of studies have shown that there can be significant variation in RBE, largely due to the rapid rise in LET at and around the Bragg peak [23–25]. Indeed, RBE values from 1.1 to over 3 have been derived from *in-vitro* clonogenic-survival assay data following proton irradiation of cultured cell lines derived from different tumours [26–28]. This is comparable to RBE values of $\sim$ 3 that are accepted for high-LET carbon-ion irradiation, although higher values have been reported [29]. RBE uncertainties for carbon and other ion species are at least as large as they are for protons.

The RBE depends strongly on many physical factors, including particle energy, dose and dose rate but also biological factors, such as the level of oxygenation (hypoxia), tissue type and the inherent radiosensitivity of the tumour cells [26]. Uncertainties in RBE can lead to an incorrect estimation of the dose required to effectively treat a particular tumour. An overestimation of the required dose can lead to significant damage to healthy tissues and organs at risk.

RT causes cell death by inducing irreparable damage to the DNA. Hence, differences in RBE can be reflected by the different spectrum of DNA damage induced within tumour cells. Larger RBE values, corresponding to higher LET, generally cause increases in the frequency and complexity of DNA damage, particularly DNA

double-strand breaks (DSB) and complex DNA damage (CDD) where multiple DNA lesions are induced in close proximity [30, 31]. These DNA lesions are a major contributor to radiation-induced cell death as they represent a significant barrier to the cellular DNA-repair machinery. Furthermore, the specific nature of the DNA damage induced by ions determines the principal repair pathways employed to stimulate DNA repair; base excision repair is employed in response to DNA base damage and single strand breaks (SSBs), while non-homologous end-joining and homologous recombination is employed in response to DSBs [30]. The pathways used to repair CDD are less clear, and very much depends on the ion species and the LET. For example, recent work has shown a dependence on SSB repair pathways following relatively high-LET protons [32].

In addition to the efficiency of DNA damage repair pathways, the biological factors that produce large variations in the RBE of specific tumours include the intrinsic radiosensitivity of the tissue, the degree of hypoxia, the tissue growth and repopulation characteristics, and the associated tumour micro-environment. Consequently, there is significant uncertainty in the precise radiobiological mechanisms that arise and how these mechanisms are affected by IBT. A more detailed and precise understanding is required for optimal patient-treatment strategies to be devised. Detailed systematic studies of the biophysical effects of the interaction of protons and ions, under different physical conditions, with different tumour tissue types will provide important information on RBE variation and could enable enhanced treatment-planning algorithms to be devised. In addition, studies examining the impact of combination therapies with IBT (e.g. targeting the DNA damage response, hypoxia signalling mechanisms and also the tumour micro-environment) are currently sparse; performing these studies will provide input vital to the development of future personalised patient-therapy strategies using IBT.

The case for novel beams for radiobiology

IBT delivery to date has been restricted to a small number of beam characteristics. In a typical clinical treatment regimen, the therapeutic dose is provided in a series of daily sessions over a period of several weeks. In each session, a single "fraction" of $\sim$2 Gy is delivered at a rate of ~ 5 Gy/min, distributed uniformly over the of the tumour. Recent reports provide exciting evidence of therapeutic benefits when the radiation is delivered at ultra-high dose rates (> 40 Gy/s) "FLASH" RT [33, 34]. These studies indicate significantly reduced lung fibrosis in mice, skin toxicity in mini-pigs, and reduced side-effects in cats with nasal squamous-cell carcinoma. Furthermore, the first patient with a T-cell cutaneous lymphoma was successfully treated with FLASH RT using a linear accelerator [35]. Varian has indicated that dose rates greater than 40 Gy/s are useful for FLASH irradiation [36], while IBA have indicated that the FLASH phenomenon is observed at dose rates above 33 Gy/s [37]. An increasing number of *in-vitro* and *in-vivo* studies are now being performed utilising the combination of FLASH with proton beam therapy [38].

In addition to FLASH, therapeutic benefit has been demonstrated through the use of multiple mini-beams, each with diameter of less than 1 mm, distributed over a grid with inter-beam spacing of ~ 3 mm [18]. Even so, there is still significant uncertainty regarding the thresholds and the radiobiological mechanisms by which therapeutic benefit is generated following FLASH and mini-beam radiotherapy, which require extensive further study both *in-vitro* and in appropriate *in-vivo* models.

LhARA is designed to be a highly flexible source delivering a variety of ion species over the range of temporal, spectral, and spatial beam structures required to elucidate the mechanisms by which the biological response to ionising radiation is determined by the characteristics of the beam, including FLASH and mini-beam effects. These comprehensive studies are not currently possible at clinical IBT facilities. The LhARA facility will provide greater accessibility to stable ion beams, enable different temporal fractionation schemes, and deliver reliable and reproducible biological data with fewer constraints than is possible at current clinical centres. The availability of several ion beams (from protons to heavier ions) within the same facility will provide further flexibility and the ability to perform direct radiobiological comparisons of the effect of different charged particles. Furthermore, LhARA will enable exhaustive evaluations of RBE using more complex end-points

(e.g. angiogenesis and inflammation) in addition to routine cell survival measurements. The ability to evaluate charged particles in conjunction with other therapies (immunotherapy and chemotherapy), and to perform *in-vivo* experiments with the appropriate animal models is a huge advantage given the current lack of evidence in these areas. LhARA, therefore, has the potential to provide the radiobiological data that can drive a significant change in current clinical practice.

The performance of the LhARA facility has been evaluated through source-to-end-station simulations [2, 3]. These simulations show that instantaneous particle rates on the order of 10^9 particles per shot can be achieved, corresponding to average dose rates up to $\gtrsim 120$ Gy/s for protons and $\gtrsim 700$ Gy/s for carbon ions. These estimates are based on the baseline specifications for LhARA [2, 3].

Laser-hybrid beams for radiobiology and clinical application

High-power lasers have been proposed as an alternative to conventional proton and carbon-ion facilities for RT [39–41]. The capability of laser-driven ion beams to generate protons and high-LET carbon ions at FLASH dose rates is a significant step forward for the provision of local tumour control whilst sparing normal tissue. High-power lasers have also been proposed as the basis of electron-, proton-, and ion-beams for radiobiology [42–47]. A number of laboratories [48] are engaged in or planning radiobiology research with laser-driven protons. More recent projects (e.g. A-SAIL [49], ELI [50] and SCAPA [51]) will also investigate radiobiological effects using laser-driven ion beams. These studies will also address various technological issues [52–56]. Pioneering research platforms based on petawatt lasers (e.g. BELLA [57], Draco [58]) have recently started to serve pilot studies on *in-vitro* cell cultures [57] and small-animal models [59].

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), preserving the unique flexibility in the time, energy, 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 tens 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. Laser-driven ion sources create beams that are highly divergent and have a large energy spread, and an intensity that can vary by up to 40% pulse-to-pulse [60]. These issues are addressed in the conceptual design through the use of plasma lenses to provide strong focusing and to allow energy selection. In addition, sophisticated instrumentation will be used in a fast feedback-and-control system to ensure that the dose delivered is both accurate and reproducible. This approach will allow multiple ion species, from proton to carbon, to be produced from a single laser by varying the target foil properties and particle-capture optics.

The LhARA consortium's vision is that LhARA will prove the principle 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 IBT to be delivered in completely new regimes.

1.2 Technological advancement

While the development of the technologies necessary to realise LhARA will be focused on the delivery, control and measurement of beams for radiobiological studies, the anticipated advances will also have impact beyond the areas directly addressed by the LhARA project. These start with a large range of possible applications

of multi-MeV ion beams. LhARA will employ a commercially available 100 TW class laser, providing the required stability, pulse lengths and repetition rate, and couple this with a target system that allows generation of protons and a range of heavier ions. LhARA will develop targets which produce the needed ions with high efficiency and reliability. As might be expected, such source systems are ideal for use in conventional ion accelerators, where repetition rates of at least 1 Hz, pulse lengths less than the revolution time for ions in a synchrotron, high intensity, and the flexibility to produce a wide variety of ions are required [61]. Further applications include the production of short-lived isotopes for medical diagnostics using positron-emission tomography, in particular Tc^{99} [62], the use of protons as probes for measuring electromagnetic fields in plasmas [63], implantation of ions in the fabrication of semiconductor devices and in materials science research, and even ion-beam welding of nano-scale structures [64].

Another innovative feature of the LhARA beam line is the use of Gabor lenses [65] to capture the beam produced by the laser target. Producing lenses with the required properties, including the necessary stability, is perhaps the most challenging technical development the LhARA collaboration faces, but the benefits of a plasma-lens-based system are significant. For example, simulations suggest that the beam energy spread can be reduced by a factor of about three compared to that achievable using conventional systems [66], whilst simultaneously significantly reducing mass, size, and cost. Again, these developments will have impact beyond the LhARA project. For example, the focusing strength plasma lenses offer has led to active research programmes on their use in high-energy electron-positron linear colliders at CERN [67, 68] and SLAC [69].

Following production in the laser target at an energy of about 15 MeV, LhARA will accelerate its proton beam to an energy of about 125 MeV, providing a penetration depth of about 10 cm in tissue and allowing *in-vivo* experiments. The technology proposed here is a fixed-field alternating-gradient accelerator (FFA). The fixed magnetic field in an FFA allows for rapid acceleration of particle beams, in as few as ten turns, as there is no need to ramp up the current in the coils of the magnets, with their attendant large inductance. The price paid for this is that variable radio-frequency cavities are generally required. This rapid acceleration capability has contributed to a vast increase in the list of applications for which FFAs are now proposed. These include accelerator based neutron sources (e.g. the ISIS neutron and muon source upgrade), the neutrino factory, accelerator driven sub-critical reactors and the eRHIC injector. LhARA will both extend the UK's contribution to this effort, which includes the first demonstration of acceleration in a non-scaling FFA [70], and profit from the work of the international community carrying out research on these devices.

The gamut of innovations LhARA will provide does not end with the development of a novel particle accelerator. In order to realise the long-term goal of providing high-quality and low-cost ion therapy for all, a suite of diagnostic tools must be developed and incorporated into the control system of the LhARA accelerator. Some of these tools are used to determine the state of the particle beams non-destructively, allowing verification and steering of the accelerator's performance. For example, the proposed gas curtain monitor [71] will exploit fluorescence generated in a high velocity, low density gas jet crossing the ion beam to measure both the beam's position and its intensity. Again, LhARA will contribute to the development of this technology, particularly for medical applications, and will benefit from research done in other fields which are seeking to apply the same technique, such as monitoring the proton beams in the Large Hadron Collider at CERN.

Direct measurement of the dose delivered to the patient, and the precise location of that dose, is provided through the ion-acoustic system under development for LhARA. The energy deposited by the ion beam causes extremely rapid and localised heating of the tissue, and hence the generation of sound waves. Ion-acoustic imaging exploits this signal, through externally placed ultrasound sensors, to localise and quantify the energy deposition. Early measurements have demonstrated the potential of this concept [72]. Particularly as progress is made towards the use of FLASH therapy, an excellent understanding of such techniques becomes crucial to ensure the correct dose is delivered to the patient in the right place. As such, ion-acoustic measurements will be of use to a wide range of proton and ion therapy centres. They may also find application in areas such as

materials testing.

Though not the focus of the current proposal, in order to realise the goal of providing the best possible radiotherapy at the lowest possible cost, in the longer term, LhARA will bring together all the components of its research programme with a state-of-the art control system. This will allow shot-by-shot steering of the dose delivered to the patient, using information on the patient's breathing, heart rate, physical position, the location of any organs at risk and of the treatment area, and the dose delivered. Developing this challenging system will require exploitation of current experience in clinical software, but also the investigation of artificial intelligence-based control systems, such as autonomous driving technology, with the attendant problems of verifying the safety and reliability of the system. Such methods have been a recent focus of research in UK universities, which have seen the establishment of doctoral training centres dedicated to data science.

To summarise, the LhARA project will develop a range of techniques for producing, capturing and accelerating proton and ion beams, to provide a uniquely flexible facility for radiobiology research and, ultimately, radiotherapy. The accelerator developments will profit from current expertise in accelerator science in the UK and internationally, but also advance capabilities in areas ranging from high energy physics to semiconductor fabrication. Furthermore, LhARA developments in beam monitoring and dose deposition measurement techniques will enable detailed understanding of the performance of the LhARA accelerator during operation resulting in unprecedented precision regarding the location and magnitude of the dose it delivers. Again, these developments will benefit not only LhARA, but also all radiotherapy centres at which they can be applied.

1.3 Impact

Radiotherapy is currently needed in 40% of cancer cures either alone or in combination with surgery or systemic therapy. It is also needed for prolonging survival in metastatic disease either by ablating oligometastatic ($< \times 5$ metastases) disease or by stimulating the body's own immune response to allow immunotherapy to be more effective. Since it was first used (as radium in the 1930s), the more we have studied and understood the biology of the effect of radiation, the more we have been able to harness its power in the clinic. Examples of the translation of increased biological understanding to the enhancement treatment include the understanding of the effect of oxygen tension on radiation damage and the optimisation of dose fractionation to enhance the therapeutic ratio. Technical advances have allowed precise radiotherapy, such as IBT, to spare normal tissue and allow greater dose and smaller fractions. Now, it is clear that off-target effects on the vasculature and immune system will allow the next step-change in improving the effectiveness of radiation.

LhARA will be able to provide an international research facility for such experimentation by delivering a flexible range of charged particles at different energies to investigate *in-vitro* and *in-vivo* effects in appropriate tumour models, as well as examining combinatorial therapies. These investigations will provide fundamental new biological knowledge, insights and understanding of the impact of IBT. Improvements in radiation-induced cell killing and the enhancement of systemic effects at reduced normal-tissue toxicity will ensure increasing cure rates and allow the treatment and cure of radio-resistant cancers which to date it has not been been amenable to RT. Advancement of the understanding of radiation biology is also likely to lead to prolonged survival in metastatic disease.

The LhARA collaboration is committed to maximising the impact of the initiative throughout its life-cycle. During the Preliminary Activity, Preconstruction, and Construction phases, impact will be generated, for example, through advancement of capability in laser-driven ion sources, ion-beam capture, dosimetry, the design, simulation, and engineering of advanced accelerator technologies as well as in biological science. The Preconstruction and Construction phases will ensure job and wealth creation and a focus on scientific collaboration across the four nations of the UK, scientific training opportunities and inward scientific pull from international scientists keen to carry out their high-impact science at the facility.

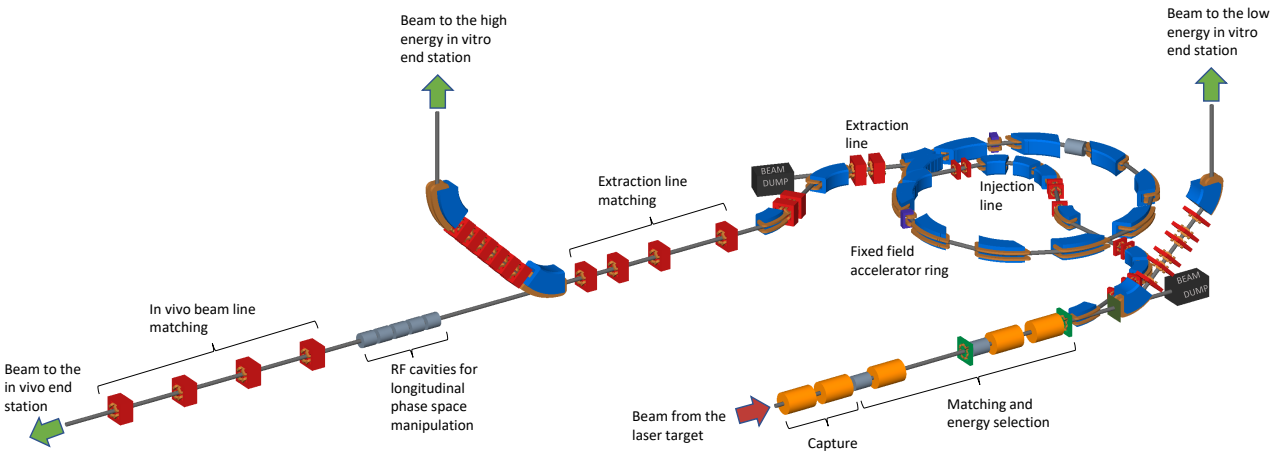

Figure 2: Schematic diagram of the LhARA beam lines. The particle flux from the laser-driven source is shown by the red arrow. The 'Capture' section is followed by the 'Matching and energy selection' section. The beam is then directed either into the 90° bend that takes it to the low-energy *in-vitro* 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.

Future clinical facilities based on the LhARA methodology will provide cost-effective cancer care, be sustainable and ensure the UK restores its scientific and technical position internationally in this area, creating inward investment. The four-nation approach to the science will be in line with the Government's levelling-up agenda and is a priority for scientific and technological development and the enhancement of industrial capability. The UK is one of the few places internationally which can boast a proud track record in multidisciplinary science and which can deliver at the highest level.

2 LhARA; the Laser-hybrid Accelerator for Radiobiological Application

2.1 Overview

The LhARA facility, shown schematically in figure 2, 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

The protons and ions for LhARA will be produced through target normal sheath acceleration (TNSA) [73, 74] which occurs when a high power pulsed laser strikes a thin foil target. The thickness of the target foil is

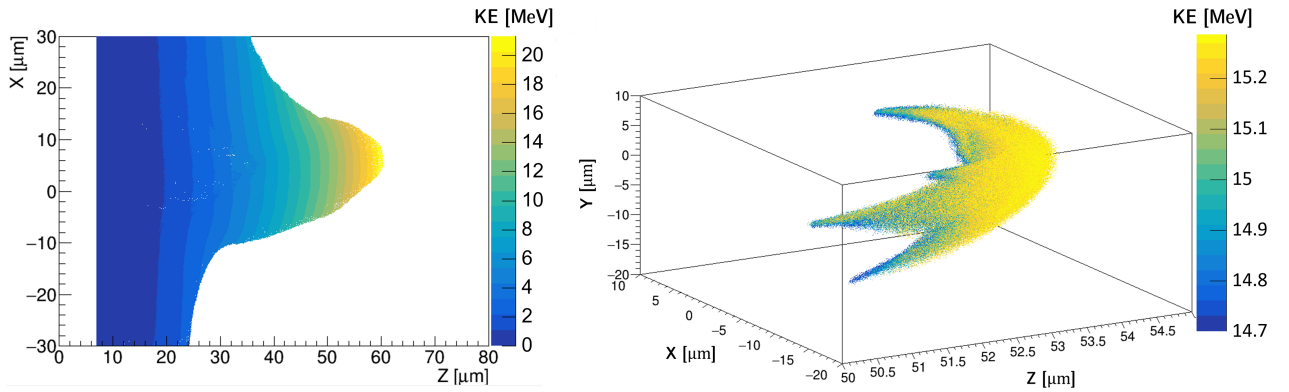

Figure 3: Left: Proton macro-particles at the final time-step of 1 ps of the 2D simulation of the TNSA interaction between the laser and the target. Right: 3D sampled proton beam generated from the 2D simulation on the left. Only protons with a kinetic energy of 15 MeV $\pm$ 2% are shown as these particles will be accepted by the energy-selection section of the LhARA beam line. Colours in both plots correspond to the kinetic energy.

typically in the range 0.1 µm to a few tens of microns. 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 gradients $\gtrsim 10$ 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 [75] or hybrid schemes [76].

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 [77]. 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 accelerate carbon ions selectively [78, 79]. 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 [80, 81]. Proof-of-principle experiments aimed at the generation of oxygen ions have been carried out using the same technique of controlling and removing contaminants from targets that can be used at high repetition rates [82].

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 J in < 25 fs pulses, at a 10 Hz repetition rate with shot contrast $> 10^{10} : 1$. The laser will serve a tape target system or an alternative advanced target system developed and optimised as outlined in subsection 3.2.

Simulations of the TNSA interaction have been carried out to estimate the typical bunch profile and proton-energy spectrum. The 2D simulations, performed using the particle-in-cell (PIC) code SMILEI [83], modelled a focused laser pulse incident on a thin plastic film at a 45° angle [84, 85]. A large spread of proton kinetic energies 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 [84, 85]. Figure 3 shows a typical spatial distribution of the protons generated through TNSA in a 2D PIC simulation. The result of the sampling procedure by which a 3D proton beam is generated is also shown.

To capture the beam, we propose to use a series of plasma (Gabor) lenses developed as outlined in section 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 [86]. The lens consists of a trapped non-neutral electron plasma that creates a radially focusing force in both transverse planes simultaneously. The strong focusing in both transverse planes is necessary to efficiently capture the divergent beam emitted from the laser driven source. Furthermore, the lens is cost efficient and flexible in operation and, in particular, suitable at a high repetition rate with fast tunability. The magnetic field required to confine the plasma is significantly lower than that of a conventional solenoid with the same focusing strength by a factor that is proportional to the square root of the mass of the particles entering the lens. Thus, the Gabor lens is even more advantageous for focusing heavier ions such as 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 two dipoles and six 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 [87] and GPT (General Particle Tracer) [88], which includes the modelling of space-charge forces. The co-propagating electron cloud is assumed to neutralise the space charge for a short distance after the laser target. In this region the proton propagation is simulated without space-charge. Subsequently, space-charge effects are included 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 focusing strengths of the plasma lenses can counteract any space-charge induced emittance growth.

For Stage 2 operation, the focusing strengths of the Gabor lenses 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, ten quadrupoles, six 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 [89] despite the use of modified Gabor lens settings. Focusing to a smaller spot size in the matching section compared to the nominal Stage 1 configuration is susceptible to further space-charge forces. Whilst the beam transport performance is adversely impacted, it is anticipated that further optimisation efforts will resolve such issues.

The Stage 2 FFA ring is comprised of ten 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 needed to accommodate the injection and extraction systems. Simulations show that the ring's 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 the next lattice cell. 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 at a voltage of up to 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 allow the provision of a wide spectrum of beam conditions to the *in-vitro* and *in-vivo* end stations, as well as to accommodate uncertainties in the beam distribution originating from the Stage 1 beam transport and space-charge effects during acceleration in the FFA ring. The first section 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 the flexibility needed to produce a range of beam sizes of over three orders of magnitude. Beam transport simulations showed that the optics and geometric acceptance of the extraction line are similar for beams of 40 and 127 MeV.

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 can be provided using 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 the installation of diagnostic devices. A subsequent section contains four quadrupoles to perform final focusing adjustments prior to delivery to the end station. A further straight section is reserved for magnets used in spot scanning. 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. Providion of a parallel sub-mm beam is still under study since the production of such a beam may be susceptible to space-charge effects at the lowest energies.

The dose deliverable by LhARA was estimated 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. The simulation showed that the low-energy *in-vitro* end station received 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 facility was first discussed in the Pre-CDR [2]. 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, the Gabor-lens proton- and ion-capture system, the ion-acoustic dose-mapping system, and the need to develop full designs for the novel end stations with the associated instrumentation. The need for detailed simulation of the facility that includes appropriate consideration of space-charge effects was recognised. 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 (ITRF) in the UK [4]. The ITRF proposal identified a two-year Preliminary Phase followed by a three-year Preconstruction 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 Preconstruction Phases is shown in figure 4 (reproduced from figure 18 in the annex to this

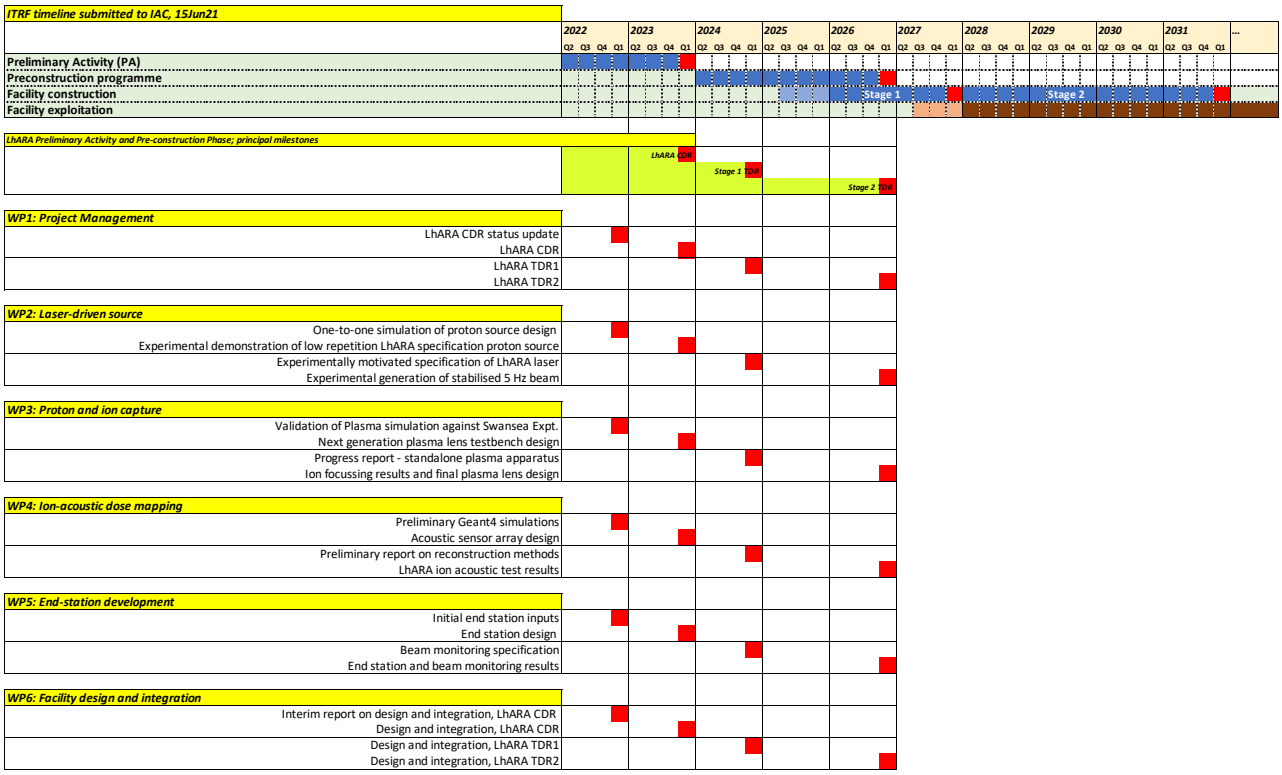

Figure 4: Waterfall chart showing the principal milestones that define the project proposed herein. The block entitled "ITRF time-line submitted to IAC, 15Jun21" shows the time-line for the development of the ITRF submitted to the UKRI's Infrastructure Advisory Committee. The block entitled "LhARA Preliminary 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 principal milestones that serve to specify each of the work packages.

proposal).

2.4 Timeline for the LhARA initiative

Once the physical beam production, ion type and energy have been optimised, an additional work steam will focus on the design and development of a clinical machine. This work will grow in importance during the Preconstruction phase once the TDR for LhARA Stage 1 has been completed (years 4–7). The collaboration will work with commercial partners. Currently, we are working with Leo Cancer Care who are a UK company specialising in innovative, cost-effective, upright particle therapy. Our aim will be to initiate the manufacture a commercial product at low cost for sale worldwide (years 8–10). The testing of the clinical machine will go through the usual rigorous development process to be ready for market. Once fully functional, clinical studies will be developed in collaboration with our clinical UK NHS partners to deliver therapy (years 10–12).

The UK has an excellent track record for delivering international-level clinical research in radiotherapy. Currently, this is done through the CRUK centres of excellence in radiation research in conjunction with the NCRI Clinical and Translational Radiotherapy Research Working Group (CTRad). It is likely clinical research with radiobiological feedback will continue to develop the technology over the subsequent years.

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 beam properties in test measurements using a representative laser source;
- Validation of the simulated properties of the confined electron plasma 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 A fully automated *in-vitro* end station, its instrumentation, and the necessary ion-beam diagnostics.

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 presently 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 Executive Board. The organisational breakdown structure for the LhARA Programme presented in annex A.8.1 foresees a third programme manager who will take responsibilty for "Impact; clinical and industrial". This position will be filled as the LhARA Project enters the pre-construction phase.

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 and scientific documentation and drawing repositories to accurately record the project activities and results;
- Stakeholder engagement; and
- Patient and Public Involvement (PPI) and outreach.

The work of the project management team will be driven by the LhARA Project Manager supported by the administrator. 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 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 in which an initial internal collaboration report is improved and expanded through an internal editing activity followed by presentation to the appropriate project oversight committee subsequently to emerge as a project deliverable.
- The organisation of regular stakeholder meetings to keep up-to-date with the latest results in the relevant radiobiological and medical fields. Simultaneously, the current status and important future developments in the LhARA programme will be communicated to the prospective users. These meetings 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.
- 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 [60, 90]. The most widely used technique is known as Target Normal Sheath Acceleration (TNSA) (see figure 5). 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 [91] and rapidly leave the target at the rear surface to form a strong electrostatic field which accelerates surface ions to energies of tens of MeV or more with accelerating gradients of order TV/m, far higher than possible in conventional accelerating cavities [73, 74, 92].

Development of this mechanism towards applications has made significant progress in recent years. It 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 ($< 1\,\mathrm{ps}$) at source, due to the pulse-length of the drive laser. The space-charge limitation of conventional sources is overcome due to the high initial ion energies ($\gg 1\,\mathrm{MeV/u}$) and inherent co-moving electron cloud created in the laser-target interaction. This results in a flexible, on-demand high flux beam with a low transverse normalised emittance [93]. Typically, the accelerated ions originate from a thin ($\sim 1\,\mathrm{nm}$) layer of hydrocarbon contaminants on the target surface, resulting predominantly in the acceleration of protons alongside carbon and oxygen. Applying established contaminant removal techniques allows for acceleration of the ions in the target bulk material rather than the contaminant layer [94, 95]. This provides a relatively simple way of generating high energy ions of different species, increasing the flexibility of the source.

Research groups which are members of the LhARA collaboration 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 challenges related to continuous operation of the source have been addressed [96]. Therefore, we are now perfectly poised to apply

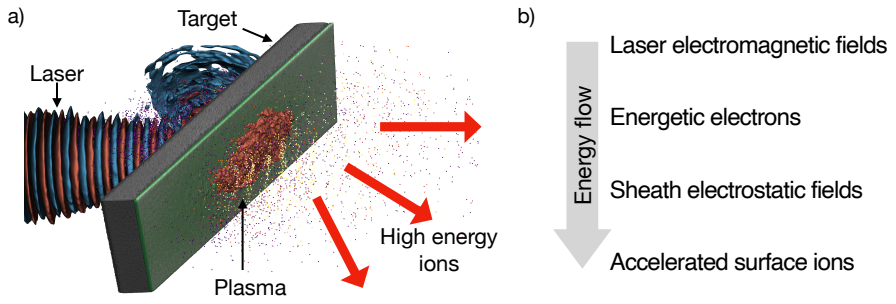

Figure 5: Target Normal Sheath Acceleration mechanism: a) 3D Particle-In-Cell simulation showing the Target Normal Sheath Acceleration mechanism. A high power laser is focused from the left onto a thin foil, forming a plasma and heating electrons to relativistic energies. These electrons form a sheath on the surfaces of the foil, rapidly accelerating surface ions. b) Flow diagram showing the transfer of energy from the laser to the ions.

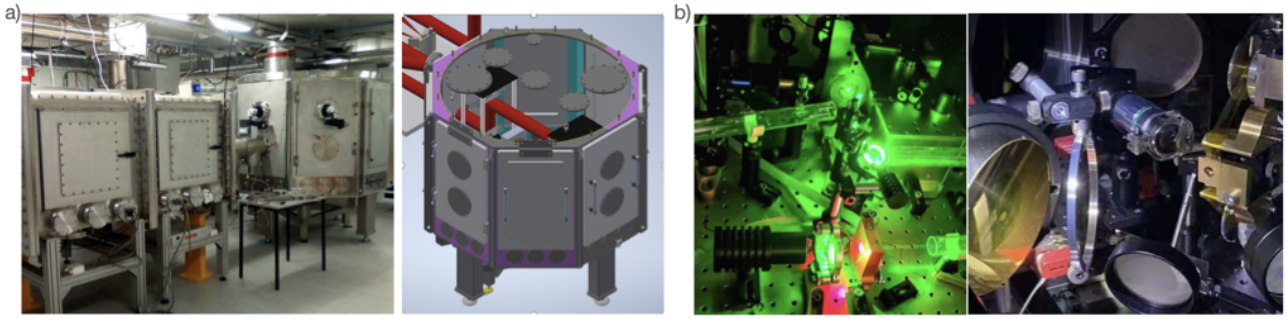

Figure 6: Facilities that will be used to develop the laser generated ion source in WP2: a) The final vacuum chambers for a dedicated laser-solid interaction beamline at SCAPA, at Strathclyde University, and b) front end and typical experimental setup for the Cerberus and Zhi lasers at Imperial College London.

our considerable expertise in laser-driven ion acceleration to designing a dedicated 10 Hz repetition rate source tailored for use in a beamline for radiobiological applications. 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 (figure 6) which, due to their $>$ 1 Hz repetition rate, are ideally suited to demonstrating the concept. This will lead to a final specification of the laser-driven ion source for the LhARA beamline.

Rapid advances in High Performance Computing and algorithm design now make possible 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 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.

Therefore, the first objective (O1) for this Work Package is to apply state-of-the-art simulation techniques to investigate and predict ion source performance using the SCAPA laser facility, which has similar pulse specifications to the proposed LhARA ion source. The simulation programme will focus on exploring the relevant parameter space and optimising the interaction conditions. This work will include understanding the effect of the laser contrast on target. After convergence testing and benchmarking to determine the computational requirements of the simulation, we will begin by performing two-dimensional hydrodynamic simulations to model the low-intensity pedestal preceding the main pulse with the 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 pre-plasma formation on the rear side of the target for the expected values of laser contrast. We will also obtain an estimate of the preplasma scale-length, which will be generated at the target front side. While the presence of preplasma on the rear side of the target must be avoided to maximise the ion energies achieved by TNSA [97], a preplasma in front of the target could aid laser absorption and hot electron generation and ultimately be beneficial for ion acceleration [98, 99]. 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 to 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 pico-Coulomb charge per bunch. In a second phase, through simulations, we will optimise the acceleration of heavier ions. We will proceed in 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.

Alongside 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) is to deliver a comprehensive diagnostic suite for the laser-driven ion source suitable for 10 Hz-rate operation. Initially, we will deliver a conceptual design for the ion diagnostics, before building and testing suitable diagnostics for the first stage of experiments. We will implement a time-of-flight diagnostic to enable rapid spectral reconstruction of proton energies [100]. Diagnosing 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 [77]. This device separates ions by charge-to-mass ratio and energy using co-linear magnetic and electric fields before detection using 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 [101, 102]. Our research groups have previously led development in all of these techniques, which are now well established. For LhARA, following the conceptual design and initial experiments, 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 laser diagnostics suite including a full beam aperture diagnostic to measure the beam spatial profile and a low dispersion diagnostic line to measure the beam temporal profile.

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) is to deliver within the first three years of the programme a seminal experiment campaign on SCAPA with a repetition rate of 1 Hz. These baseline experiments will also enable full commissioning of the diagnostic package developed to deliver O2. We envisage a total of 10-weeks of beam time with the first week delivered in the first year of the programme and used to commission and calibrate the diagnostics package and to optimise the SCAPA beamline to meet the LhARA requirements, in single-shot operation mode. In the second and third years we will deliver two beam times of 3-weeks and 6-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. This will enable parametric optimisation of the laser driven proton source, and measurements of beam metrics such as cut-off energy, conversion efficiency and beam divergence. The second period will be used for the baseline data collection and will focus on the comprehensive measurement and optimisation of heavy ions, and in particular C^{6+}. Throughout these experiments, results will be compared with and used to benchmark simulations. This will 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 will be addressed to deliver our fourth objective (O4). Although the current baseline target choice of spooled thin tape has been proven at lower repetition rates [103, 104], it is important to test it at the LhARA baseline 10 Hz and address any issues that arise. We will investigate the stability of ion generation from the source and how it is affected by target and laser fluctuations. We will start testing target contaminant removal strategies to facilitate acceleration of ions other than protons. It is also known that debris generated during the laser-target interaction will cause increasing issues for future high-repetition rate systems. We will make experimental measurements of this in LhARA-relevant regimes and apply established mitigation strategies, including magnetic debris capture, buffer gases, and sacrificial pellicles to protect key optics. We will also develop new low-debris targetry technologies, in particular a liquid sheet, which would solve many of the outstanding issues with tape targets. Our collaboration includes researchers from SLAC, CLF and Queen's University Belfast who have already developed and tested a prototype liquid-sheet target [105], which showed generation of protons at higher fluxes, lower divergence and higher energies than tape targets [106]. 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 [107] 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 objective (O5) is 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 and stabilisation techniques developed in O4. As part of the 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. The final stage of O5 is to do a preliminary demonstration of the integration of the source and capture system at the SCAPA beamline.

Our final objective (O6) is, 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 be performed. This would represent a major milestone in the delivery of a continuous source of laser-driven ions and would enable a final conceptual 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. In Phase I (years 1–2) we will determine key source parameters and conduct the first in a series of baseline simulations and experiments, aided by the development of a dedicated ion beam diagnostic system. In Phase II (years 3–5) we will demonstrate an operational and actively stabilised 5 Hz ion source, with capability to extend to 10 Hz, which meets the requirements for long term operations and beam

capture.

3.3 Proton and ion capture (Work Package 3)

As long ago as 1947, Gabor [65] 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 [108] to confine the electrons. The electron plasma produced a lens with a focal length of 9 m, which is to be compared to a focal length 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 charged particle trapping technique, first described by Penning [108], 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. [109]). 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 [110]. Due to the mutual repulsion of the electrons and the establishment of a so-called space-charge electrical potential, fundamental limits exist for the number of charges (or more specifically their density) that can be stored for the magnetic [111] and electric field strengths used for confinement. While, in theory, such plasmas can be confined indefinitely [112], real-world practicalities such as contaminants and manufacturing defects limit the plasma density (see, e.g. [113]) and the length of time for which it can be trapped without changes in the critical parameters, such as its density [114]. However, sophisticated manipulation and cooling techniques (such as those involving the use of rotating electric fields, the so-called "rotating wall", e.g. [115]) have been developed to circumvent many of these issues.

The non-neutral plasma within a Penning-Malmberg trap produces a significant internal electric field in the radial direction. The trajectory of a positive ion passing through this field will be modified. A positive ion of charge Ze (where e the fundamental electric charge and Z a positive integer) travelling parallel to the magnetic field will experience a radial force directed towards the symmetry axis of the trap. The trapped electron plasma will therefore focus the ion beam and act 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

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

where ϵ_0 is the permittivity of free space.

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 are currently in the kilometre region, and are produced using magnetic fields of several T, with electric fields generated by sub-kilovolt potentials, and with particles occupying $\leqslant 1\%$ of the trap volume. Conversely, from a 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 kV electric potentials, and which occupy large fractions ($> 10\%$) of the trap volume. These represent the simultaneous improvement by several decades of many parameters, with as illustrated in figure 7.

Due to their high focusing strength and potential ease of operation, Gabor-type lenses have been experimented upon for many decades (see e.g. [116, 117]) 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. [118]) continue to use this technique with the support of modern computational capabilities (see e.g. [119, 120]) to model ion beam transport through the lens and understand deleterious plasma

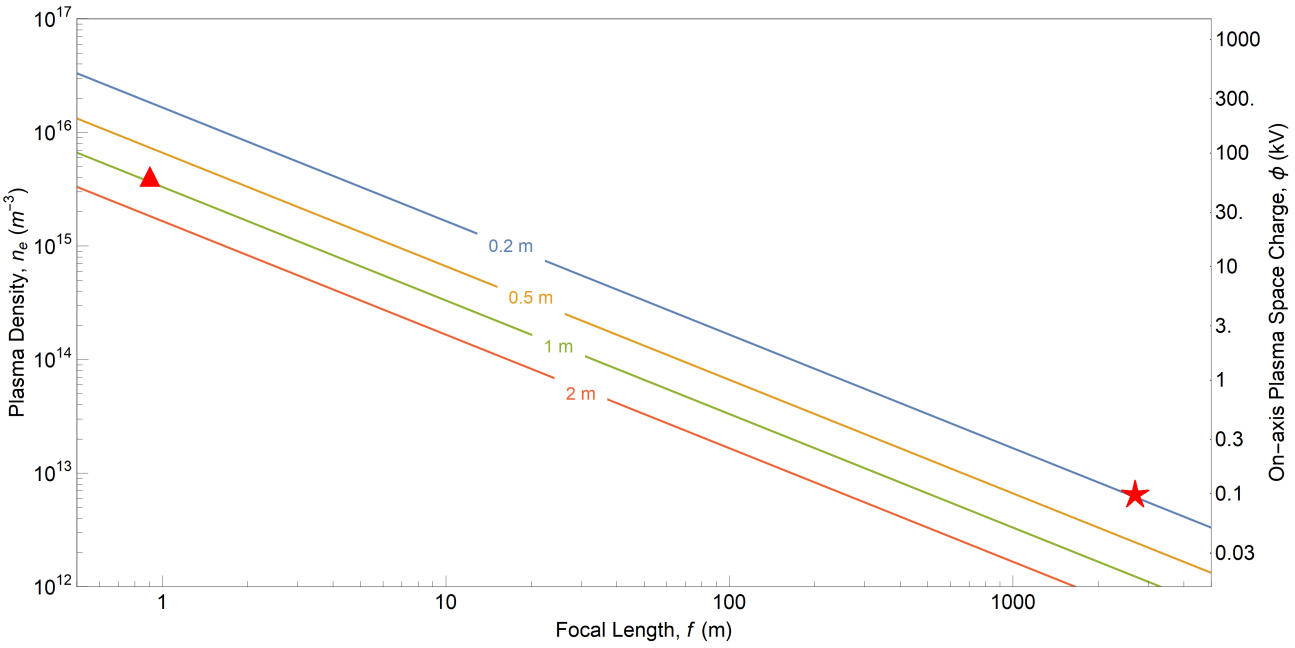

Figure 7: Example focal lengths, f, and the corresponding plasma density, n_e (and associated space-charge, ϕ), for non-neutral electron plasmas of varying lengths (indicated by the text on the respective curves), $0.2 \leqslant l \leqslant 2$ m. Indicated are the focal lengths for a 15 MeV proton traversing current typical plasmas (★), and that expected of the final LhARA facility design (▲).

phenomena. In part, due to these issues, a sufficiently stable Gabor lens suitable for routine use has yet to be achieved.

While the long-term aim of this Work Package is to produce a plasma suitable for use within the LhARA facility, this package will direct its Phase I (years 1 and 2) experimental efforts to the study of non-neutral plasmas with long storage times and radii large compared to the confining apparatus. While literature provides some guidance on the behaviour of non-neutral plasmas for several parameters (e.g. B-field, or density), the "fill-factor" seems to be the least studied and furthest from that anticipated for a final design (typically only $< 1\%$ of that required). These studies will take place within modestly modified pre-existing apparatus at Swansea University, with the experimental results from this apparatus, and associated computational modelling, providing direction for the design of a new test bench (the primary outcome of Phase I). In Phase II (during years 3, 4 and 5) a new test bench will be commissioned and will be used to study plasma with focal lengths of tens of metres. It is hoped that the results from Phase I will enable a more compact design to emerge for this test bench. In year 5, this advanced, dedicated apparatus will be transported to teh SCAPA facility and interfaced with a suitable ion source to test its performance. The results will be used to validate simulations of the response to 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 in order to facilitate the study of plasmas at higher densities, and with larger radii, than is currently possible. These plasmas will be compared with Particle-In-Cell (PIC) simulations for code validation. As these upgrades have a short lead time, the study is expected to commence at a very early stage. It is expected plasmas

with radii up to 80% of the electrode radius will be investigated.
2. A standalone test bench capable of manipulating plasmas confined by 2 kV potentials will be designed, and suppliers sought for the most complex components, using results from the upgraded system and PIC simulations to guide detailed design decisions.

Phase II (years 3, 4 and 5):

1. A standalone test bench will be constructed from scratch and fully commissioned. Plasmas will be studied within the test bench with parameters incrementally increased towards the expected final design requirement (radius up to 50% of the electrodes, space-charge up to 2 kV, density up to $10^{15}\,\mathrm{m}^{-3}$, and length up to 1 m), see figure 7, and the impact of each of these changes on plasma performance and stability/lifetime 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 beamline design.
3. Plasma manipulation techniques in hitherto unstudied regimes produced within the test bench will be explored in order to improve and tailor the plasma properties for improved performance.
4. An ion beam will be directed into the test bench so that the effect of the plasma on the properties of the ion beam can be 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 (minibeam)- 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 the 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 radiobiological 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 $100\,\mu\mathrm{m}$.

The basis of the proton- and ion-acoustic dose measurement technique is similar to that of the emerging technique of photoacoustic tomography [121]. 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 sub-millimetre using clinical ultrasound frequencies, or sub-$100\,\mu\mathrm{m}$ preclinically. The LhARA collaboration plans to develop *in-vivo* real-time 4D (space and time) ion-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. 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 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 beam energy is necessary, which requires a sufficiently short beam 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 the signal enhanced, implicitly in the image reconstruction. Furthermore, the 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 sub-arrays 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 or hemispherical 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

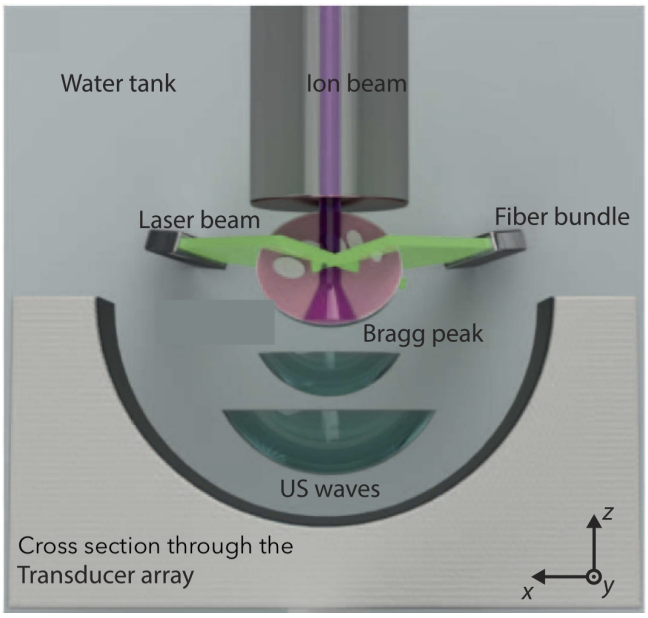

Figure 8: Schematic illustrating coupling of the hemispherical cup to a biological sample with integrated kaser for photo-acoustic imaging of the sample (adapted from [122]).

sample may be via a self-contained water stand-off (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 with mechanics to scan the detector and acquire data sets 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, back-scatter-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 pre-amplifiers 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 (ICR, 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. The measurements will be compared with predictions from combined Monte Carlo and acoustic wave propagation simulations and will be used to 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 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 work plan 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 multi-element (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 [123] 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 radio frequency data may be processed by a GPU in the host controller, essential for reconstructing the dose distribution. The Aspectus pre-amplifiers 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 [124] 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 [125], 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 [85], 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 photo-detectors. The photo-detectors will be CMOS cameras in the first instance, although silicon photo-diodes or photo-multipliers might also be used, depending on signal size and the timing resolution required.

In the early part of the programme the SmartPhantom will be used to verify the simulations against measurements at proton beam facilities. As the programme 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)

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. Realisation of the full potential of the facility requires that the beam delivered to the biological samples is fully characterised and that sample throughput is maximised in both the *in-vitro* and *in-vivo* end stations through appropriate automation. The MC40 cyclotron at the University of Birmingham will allow for the instrumentation proposed here to be tested in a proton beam up to ultra-high dose rates of kiloGray per second at proton energies matching those of the early LhARA phases. These measurements are essential to ensure that the end stations developed are capable of delivering the scientific goals of the project. 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 specification for the suite 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 End station development

The requirements, specifications, and design of the *in-vitro* and *in-vivo* end stations for LhARA will be established through national and international consultation with the radiobiology, radiotherapy and other relevant end-user communities. This process of consultation will begin immediately and continue throughout the Preliminary Activity to ensure that the end-station designs presented in the CDR are fit-for-purpose and future-proof. The consultation process will continue through the pre-construction period. Experts from the end-user communities will be invited to serve on technical and scientific review boards throughout the project life cycle.

The LhARA accelerator facility has been conceived to deliver a wide variety of ion species in almost arbitrary time, spatial, and spectral structures. The end station must be designed to maximise the science that can be performed at the facility. This requires the implementation of a fully automated system capable of extended, high throughput operation without operator intervention. In turn, this requires a programmable system which selects a particular sample from appropriate storage and exposes it to a beam with pre-selected properties selected from across the full range of beams that LhARA can deliver.

Each irradiation must be precisely controlled and reproducible. Instrumentation in the end station is therefore required to measure in real time the properties of the dose delivered to the sample to ensure that the desired irradiation was carried out. The end-station-control system must record and process the delivered dose and

provide feedback that ensures that the desired irradiation is delivered. LhARA will operate with a maximum repetition rate of 10 Hz, therefore the control system is required to make decisions and influence the accelerator-control settings in less than a tenth of a second.

It is essential that the novel, bespoke techniques developed to exploit the unique beams that LhARA will provide are tested to ensure that the end-stations are ready to deliver science as soon as the first LhARA beam is commissioned. Therefore, use will be made of the MC40 cyclotron [126] at the University of Birmingham and other appropriate infrastructures to de-risk the end-station development by verifying the performance of components and systems at an early stage. The MC40 cyclotron is capable of delivering proton and helium beams at the low energies that will be delivered at LhARA Stage 1 and with a fluence far in excess of current clinical facilities. The tools needed for the MC40 cyclotron to deliver low-energy ion beams for such experiments will be developed during the 24-month Preliminary Activity so that initial studies of component performance can be carried out in preliminary radiation biology experiments during the Preconstruction Phase.

Priority features for the *in-vitro* and *in-vivo* end stations

While the specification for the end stations will be developed through the peer-group consultation process outlined above, it is possible to identify a number of priority features. These are outlined below for the *in-vitro* and *in-vivo* end stations:

Automated cell handling

To enable high throughput, reproducible irradiations of cell samples, a robotic system to move samples from appropriate storage into the beam and then transporting these away from the beam for subsequent storage or analysis will be developed. The robotics and housing will be flexible in accommodating cells grown in different formats (e.g. dishes, flasks and multi-well plates), but will also ensure rapid turnover of samples in order to optimise the numbers of irradiations/experiments performed with the beam.

Controlled atmosphere

The atmosphere, particularly in the *in-vitro* end stations, will be designed to be variably controlled to enable flexibility in different irradiation conditions. Key parameters include temperature, humidity, and CO_2/O_2 levels (thus enabling studies into hypoxia-induced effects). It is expected that the end station for this will be detachable from the beam lines, enabling a switch between controlled and uncontrolled environments where required.

Acoustic imaging

Careful consideration of the end-station designs will be made to ensure the real-time dosimetry via acoustic imaging being developed as part of Work Package 4 are optimally integrated. A particular consideration is to devise a setup that maximises the acoustic signal and dose sensitivity proximal to the cells/tissues being irradiated, without interfering with the sample irradiation or subsequent processing.

Cellular imaging

The novel beam structures and the ability of LhARA to vary them offers a unique ability to image the changes within cells/tissues during and post-irradiation. Similar to the end-station development, we will engage and consult with the radiobiology/radiotherapy community to ensure the delivery of the required equipment for cellular imaging is available within the treatment room, and that these devices will be compatible with the end-station design. A particular consideration is the potential development of microscopy facilities for live cell imaging (e.g. visualisation of cells or molecular markers in real-time post-irradiation) versus facilities that can be utilised for fixed cells/tissues.

***In-vivo* irradiations**

An end station for *in-vivo* (small animal model) irradiations will be developed that uses the high energy beam line. The animals will need to be placed in temperature controlled holder tubes to ensure correct

positioning in front of the beam. An image guided system to ensure a high degree of precision and accuracy in irradiating the target will also be required. Similar to the *in-vitro* end stations, the specifications and design of the *in-vivo* end station will be developed following the consultation period with experts in the field.

The user beam lines at the MC40 cyclotron will require a number of minor modifications to serve the LhARA end-station de-risking programme. These modifications include:

- Thinned entrance windows to allow the passage of low-energy ion beams;
- Revision of the location and material composition of beam-energy degraders and collimators used in the delivery of low-energy proton and carbon-ion beams; and
- Integration of movable stages designed to support the LhARA test equipment on the MC40 user beam lines.

Designs for the necessary modifications will be developed during the Preliminary Activity so that experiments to serve the end-station risk-mitigation programme can begin in the Preconstruction Phase.

3.5.2 Beam-line instrumentation

The peer-group consultation through which the requirements and specifications of the *in-vitro* and *in-vivo* end stations are defined will yield a set of requirements for the beam-line instrumentation. In advance of this consultation it is possible to anticipate that it will be necessary to measure the beam energy, emittance, and phase-space envelope as well as the dose profile. The instrumentation must be capable of characterising the intense, short (10–40 ns) pulses delivered at repetition rates of up to 10 Hz by the LhARA accelerator facility. Furthermore, the instrumentation is required to characterise proton and ion beams of low energy (12–15 MeV proton beams at Stage 1, and ion beams with energies up to $\sim$ 34 MeV/u at Stage 2). The characterisation of such low energy beams presents particular challenges, since the ionisation energy loss is large and strongly dependent on energy.

During the two-year Preliminary Activity the specifications for the suite of instrumentation will be defined as part of the peer-group consultation exercise by which the end-station specification will be derived. In parallel, designs for the emerging technological choices for the instrumentation will be developed taking into account the constraints imposed by integration with the LhARA facility. The necessary prototype development-and-test programmes will also be defined. Where possible, initial prototypes will be developed and tested during the Preliminary Activity.

A key pursuit during the Preliminary Activity will be the development of the specification and design of the fast feedback-and-control system together with a detailed plan for its implementation. Full automation of *in-vitro* sample handling and appropriate automation of the *in-vivo* end station requires that the instrumentation is fully integrated with the control system. Full exploitation of the flexibility of the LhARA beam will require the use of modern high-throughput and high-performance computing techniques.

The specifications for the instrumentation suite will be defined in the CDR for the facility delivered over the two-year Preliminary Activity. As the project enters the Preconstruction Phase, the emphasis of the Work Package will turn to the execution of the prototype development and test programme required to ensure that the beam-line instrumentation end-station diagnostic systems are ready to be implemented and commissioned so that they are available as soon as beams are delivered to the Stage 1 end station.

Key elements of the beam-line instrumentation

While the specification for the beam-line instrumentation will be developed through the process outlined above, it is possible to identify a number of key elements. These are outlined below:

Characterisation of beam emerging from the vacuum chamber

A scintillating-fibre detector (SciWire) integrated with the beam-exit window is one instrument proposed to characterise the beam emerging from the beam vacuum chamber. SciWire consists of planes, made up of 250 µm scintillating fibres (see figure 9). The scintillation light is transported to suitable photo-detectors via lengths of clear fibre. Currently, the use of low-cost CMOS cameras to detect the light is under investigation. If the CMOS-camera based system is shown not to be capable of 10 Hz operation, proven techniques that exploit photodiodes and fast amplifiers will be used. Two planes with fibres laid in orthogonal directions will yield the two-dimensional beam profile. Multiple consecutive layers could provide a destructive measurement of beam energy for calibration purposes as proposed for residual range measurements in proton Computed Tomography [127]. Simulations using GEANT4 [124] have been carried out of a single plane in the low energy LhARA beam. The simulations show that the device does not degrade the beam at 15MeV, see figure 10. Further simulations are planned for thinner fibres and a prototype will be built for test beam work.

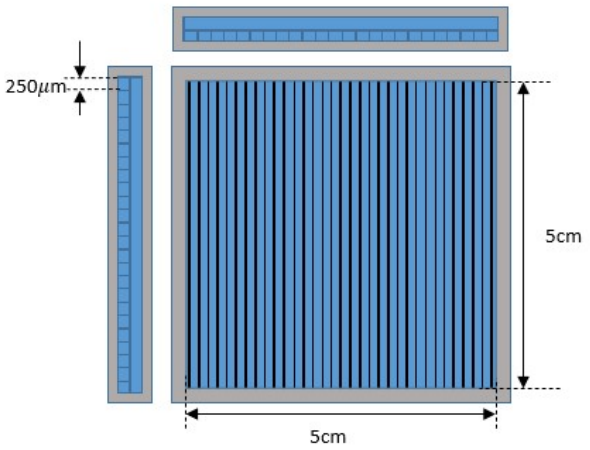

Figure 9: Conceptual layout of a SciWire plane

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 [128]. The technology is optimised for use with low-energy electrons and anti-protons as well as for the high luminosity upgrade of the Large Hadron Collider (LHC) at CERN [129]. The system shown schematically in figure 11 (left) has been tested extensively with a 10 mA, 10 keV electron beam and three different working gases: nitrogen, neon and argon. Sample results from beam exposures are shown in figure 11 (right).

The monitor works by generating a supersonic, low-density gas jet curtain using a bespoke nozzle-skimmer arrangement, see figure 11 (left), where the beam is travelling into the page. The gas jet crosses the 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 the project. 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.

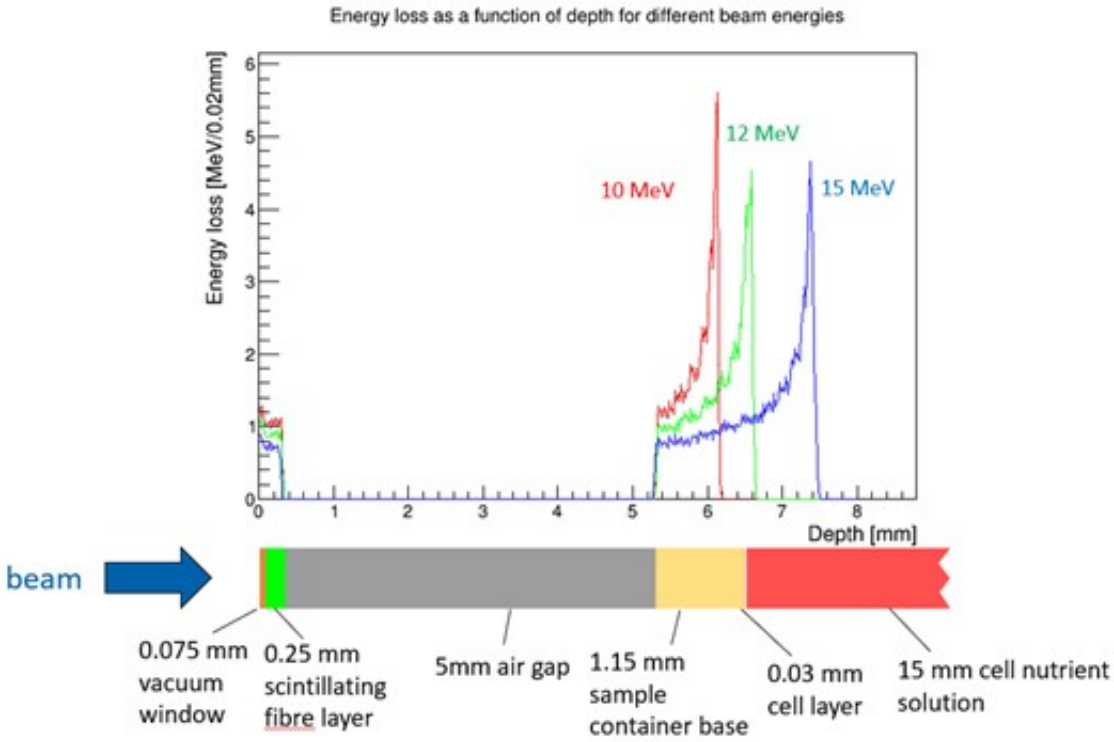

Figure 10: Simulation of the energy deposited in cell-culture vessel for beams entering the low-energy *in-vitro* end station.

The QUASAR 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 [130]. It has also contributed to studies of the technical challenges for proton beam treatment and in particular new high dose treatment modalities such as FLASH. This work has demonstrated the unique characteristics of the monitors and indicated opportunities for simplifying the monitor design for easy integration into a medical accelerator. This will form the basis of this project.

Current techniques for dosimetry typically provide limited information (one-dimensional dose profile or only total dose value), are invasive to the treatment beam, which can disturb the intended dose profile provide low spatial resolution, and suffer from slow response times. A complete knowledge of the beam properties delivered to a patient is essential, so calibration measurements must be taken at regular intervals. Currently there is no method to monitor the beam parameters to high fidelity in 2D during treatment without disturbing the beam. Ionisation Chambers and Faraday cups require regular maintenance which includes replacing components, followed by calibration to verify their performance, which is time consuming. The use of current technologies is further complicated by the particular pulse structure found at LhARA, where the instantaneous dose rates will cause severe saturation effects in ionisation chambers.

The existing gas profiler will be exposed to LhARA-like beams to evaluate its performance and its limitations in the Preliminary Activity. By the end of the Preconstruction Phase, 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 measurements 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.

In addition to the technologies highlighted above, we will engage with the beam monitoring, detector development, and dosimetry communities to offer access to the MC40 cyclotron at the University of

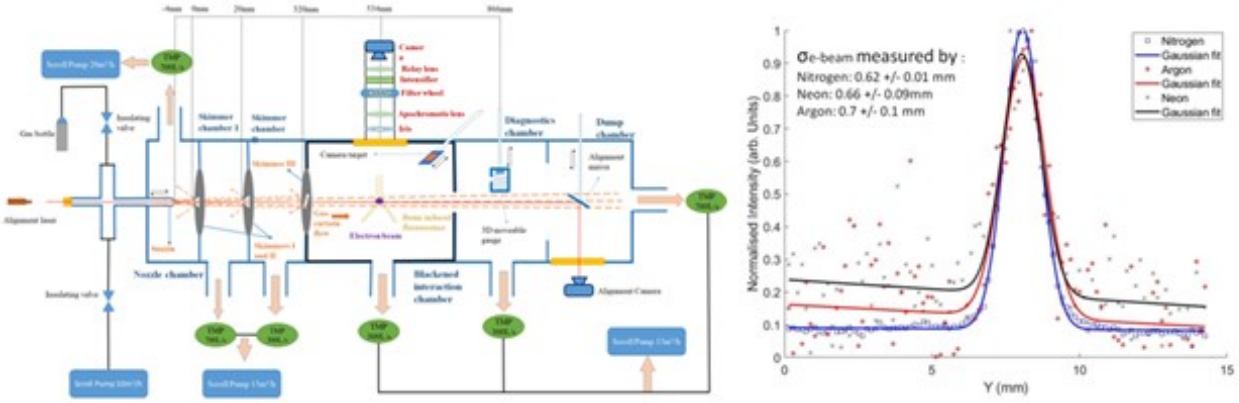

Figure 11: Left – schematic of a gas jet profiler. Right – image of electron beam and three different gases.

Birmingham to allow R&D for further developments. We anticipate engagement from High Energy Physics, Nuclear Physics, and other accelerator communities for this Work Package.

3.5.3 Dosimetry verification

The high flux, high repetition rate characteristics of the beams delivered by LhARA require the development of new technologies to allow spatially resolved dosimetry in 2 and 3 dimensions that can deliver results in real time. Through consultation with the National Physical Laboratory (NPL), three potential standard dosimetric techniques have been identified which are dose rate, time, and particle-species independent and could therefore be used to verify the performance of the novel technologies developed throughout this project. It is foreseen that a combination of these standards will be required to characterise fully the beams and novel detectors. Brief descriptions of these techniques follow:

Radiochromic films

A standard dosimetric tool used in radiotherapy are radiochromic films. When exposed to radiation, the dose induces a change in colour of the film which is then imaged on a flat bed scanner to measure the dose profile. Films have high spatial resolution and can be used for a variety of particle species. Correction factors can be applied for very high LET particles such as those at the distal edge of a proton Bragg peak. However, the film response changes with time after irradiation and therefore the films must be developed at a prescribed time after exposure. The dose may then be calculated. Different films provide optimal responses for specific dose ranges. The appropriate films for use to cross-calibrate novel instrumentation developed for LhARA will be identified during the Preliminary Activity.

Alanine pellets

Alanine pellets are another standard dosimetric tool. When radiation is incident upon an alanine pellet a chemical reaction occurs. The reaction products can be measured to provide a measurement of total dose. Alanine has shown excellent performance over a range or particle species, doses, dose rates, and its response is time independent. NPL offers a service for the calculation of the dose delivered to pellets. Using this service, alanine pellets can be used to verify the measurements made using novel dosimeters. Currently, the thinnest pellet available is 0.5 mm thick. At low proton and ion energies there will be an LET gradient across the pellet. Correction factors that account for this variation will be derived using test exposures and Monte Carlo studies during the project.

Primary and secondary standard calorimeters

NPL have developed a collection of graphite calorimeters for measuring absolute dose during radiother-

apy. These calorimeters include devices optimised for intensity modulated radiation therapy (IMRT), small fields, and hadron therapy. The graphite calorimeters have been shown to yield results independent of dose rate and particle species provided a uniform irradiation of the calorimeter core is possible. Due to their finite sizes, graphite calorimeterrs will be considered for LhARA Stage 2.

3.6 Facility design and integration (Work Package 6)

The LhARA accelerator system requires the integration of the laser-driven ion source with both novel and conventional accelerator systems. The integrated system will provide unique capability to perform a broad range of radiobiological experiments with multiple ion species, delivering flexible dose profiles ranging from those available at conventional hadron-therapy facilities to novel mini- and micro-beams at dose rates up to and significantly beyond the FLASH regime. These ambitious goals can be achieved thanks to advances in the development of laser-driven proton and ion sources and the exploitation of an innovative capture system that uses Gabor lenses. Gabor lenses provide the simultaneous strong focusing in both transverse planes necessary to capture the divergent beam emitted from the laser driven source efficiently, while simultaneously being cost effective and flexible in operation. In particular, they can be tuned rapidly in keeping with the requirements of LhARA's 10 Hz repetition rate. The capture system delivers beam with reduced divergence and moderate size allowing a conventional focusing and guiding system to be used to match the beam size, kinematic distributions, etc., to the needs of the experiments. The beam transport system also delivers the beam to the fixed-field alternating gradient (FFA) accelerator.

The LhARA beams will serve an *in-vitro* end station at the Stage 1 and *in-vitro* and *in-vivo* end stations at the Stage 2. The design of the Gabor lenses is the subject of Work Package 3, however, to mitigate risks in the realisation of the Gabor lens, this work package will develop the mitigation strategy by designing the solenoids required to construct an alternative capture system. The alternative capture system will also include a Wien filter to select particle species. While conventional solenoids can provide the focusing strength required to replace Gabor lenses in the case of LhARA, the extension of the laser-hybrid technique to deliver proton and ion beams for clinical use would require high-field solenoids. The demonstration in operation of the cost-effective, compact, cylindrically-symmetric strong focusing provided by the Gabor lens will be highly beneficial to the development of clinical capability based on the laser-hybrid approach.

A significant design effort for the LhARA facility has already been performed and published in a pre-CDR [2, 3]. This design was reviewed by an international panel [131] and the outcome of the review was a very positive evaluation [131]. Nevertheless, a significant amount of work remains to be done before the construction of the facility can begin. The first objective (O1) of WP6 over the two-year Preliminary Activity will be the R&D required to develop the full Conceptual Design Report (CDR) for the LhARA facility. The lattice design will be further optimised using updated input from studies of the laser-driven source and incorporating new input on the design of the Gabor lenses. Tracking studies, incorporating errors, will inform the evaluation of the performance of the facility and will dictate the distribution of the correctors. The beam diagnostics along the LhARA beam line necessary to operate the machine, will be identified. The analysis will include consideration of the diagnostics required in the FFA. Tracking studies will also be essential for the optimisation of the vacuum chamber parameters, knowledge of which will allow the vacuum system for the facility to be designed. The radiation protection, shielding and beam-dump requirements will also be studied with initial research starting early to ensure the needs of the CDR document are met. Radiation-protection studies will be scaled up significantly in the later stages of the project by subcontracting this topic to a specialist company. The radiation-protection study will be necessary to inform the design of the building for the LhARA facility and to inform the cost estimation. Mechanical design, including the supports for accelerator elements, in particular for the vertical arcs serving the *in-vitro* stations, will also be addressed. The challenging, novel FFA-

element for the Stage 2 post-accelerator that allows variable-energy extraction will be designed together with the magnetic-alloy (MA) RF cavity for acceleration of various types of ions in the ring. The design principles of the control system and the safety systems for the facility will be specified. RF system requirements, power consumption, etc. will be estimated for the CDR. A preliminary building concept for the ITRF housing the LhARA accelerator facility is shown in figure 12. The overall layout will continue to be developed throughout the Preliminary Activity and Preconstruction Phase.

The second objective (O2) of WP6 will be the delivery of the Technical Design Report (TDR) for Stage 1 of LhARA, scheduled for completion at the end of the third year of the project. All the design specifications for Stage 1 will need to be updated to contain the details necessary for manufacturing to start. The design of the focusing and bending elements, vacuum chambers, collimation and diagnostic systems will be finalised and CAD drawings will be generated. The control system will be fully developed together with the personnel safety systems. The 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 Stage 1 will also be fully addressed together with the beam dump. The cable management methodology for Stage 1 will be fully developed.

Following the completion of the TDR for Stage 1, the design of the FFA main magnet for Stage 2 will be finalised and prototype construction will be subcontracted to industry. After the construction of the prototype, magnetic measurements will be performed and tracking studies will be used to validate the design. This objective (O4) is scheduled to be be achieved towards the end of the project (after 58 months). On the same timescale, the design of the MA-cavity system will be finalised. The programme will include the construction of a prototype, which will be tested experimentally and fully validated in the different modes of operation required for the various types of ion species (objective O5).

The final objective of WP6 will be the delivery of the TDR for Stage 2 of LhARA facility at the end of Preconstruction Phase (O3). 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 Stage 2 together with the personnel safety system. The RF system for the Stage 2 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 Stage 2. The radiation protection and shielding solutions for Stage 2 will be fully addressed together with the beam dump after 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 Stage 1 and Stage 2, and providing the space for all end stations and radiobiological experiments. The building design, technology solutions and construction methodology will also address the environmental sustainability, minimising energy usage and optimising the facility's carbon footprint. The technical rooms and cable management system will be expande to incorporate the Stage 2 systems.

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

4 Summary

The programme proposed here will lay the foundations for the establishment of an entirely new technique for delivery of proton and ion beams for science and innovation. Serving the Ion Therapy Research Facility, the Laser-hybrid Accelerator for Radiobiological Applications will be a unique, compact, research infrastructure delivering ions from protons to carbon at energies sufficient for both *in-vitro* and *in-vivo* studies. Fundamentally

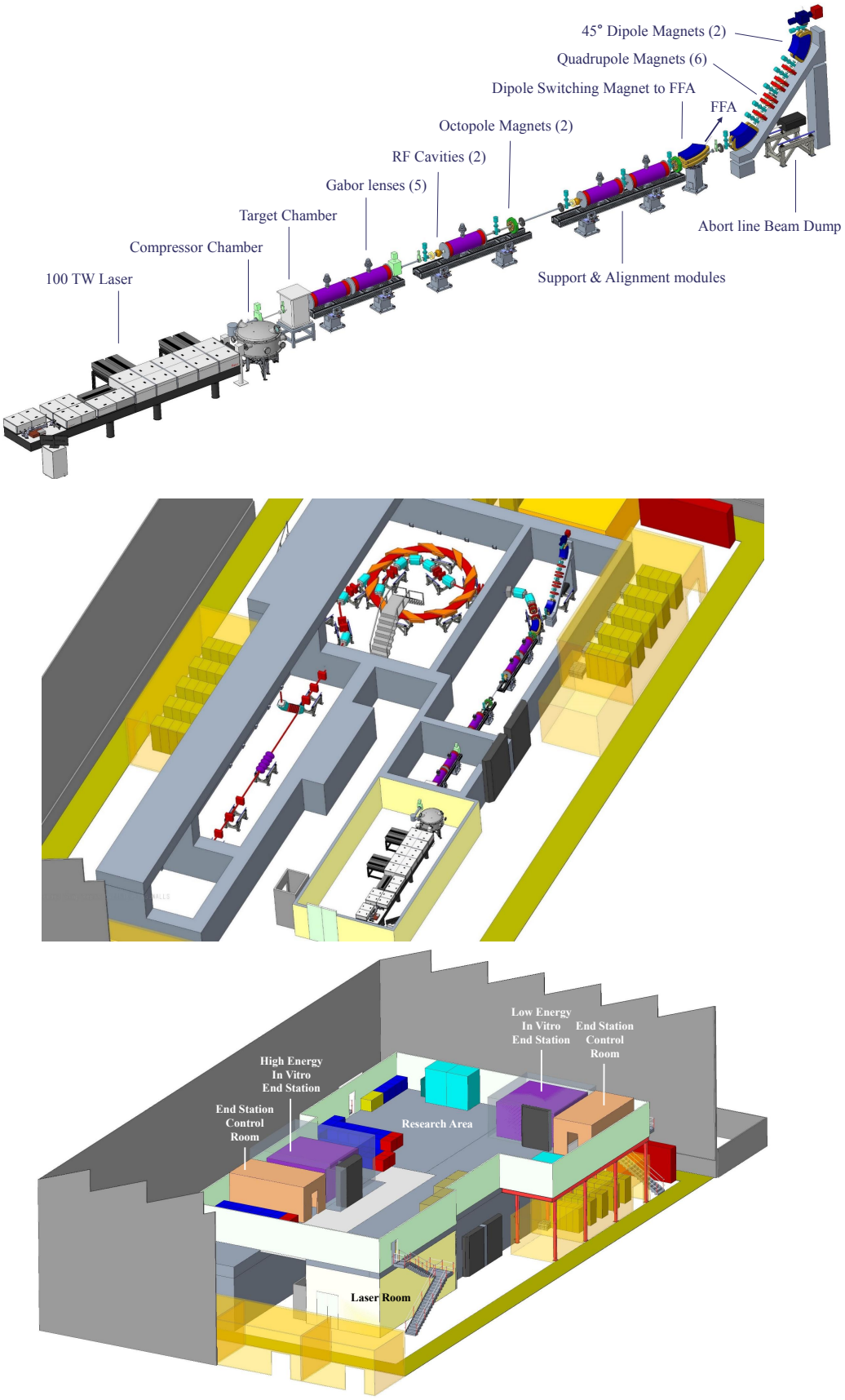

Figure 12: Top panel: Schematic layout of the Stage 1 beam line. The principal components from the laser to the beam-line elements that deliver the beam to the low-energy *in-vitro* end station are indicated. Central panel: Cut-away concept of the full LhARA accelerator complex. Initial sitings for services are indicated. Bottom panel: Building concept for the LhARA facility showin the *in-vitro* laboratories and services provided on the first floor.

new biological mechanisms in radiation treatment and immune response that underpin the clinical efficacy of future proton- and ion-beam therapy will be elucidated. Exploitation of LhARA at the ITRF will promote the disruptive accelerator, diagnostic, imaging, and computing technologies required to radically transform clinical practice.

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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 Preconstruction Phases of the LhARA project to serve the Ion Therapy Research Facility (ITRF). 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.

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". The ITRF proposal requested the resources for a two-year Preliminary Phase activity designed to deliver the conceptual design report for the facility and identified the need for a subsequent three-year Preconstruction Phase. The five-year programme defined here has been constructed to map onto the Preliminary Activity and Preconstruction Phase defined in the ITRF proposal. The collaboration is optimistic that resources will become available following the UKRI IAC review. Initial indications are that the resources available to fund the Preliminary Activity will not be sufficient to support the first two years of the programme defined below. Once the ITRF allocation is known a document defining the scope of the LhARA contribution to the ITRF Preliminary Activity will be produced and agreed with the ITRF management. The search for the resources necessary to deliver the full programme defined below has already begun.

The LhARA project is divided into six Work Packages each managed by a team of 2 or 3 technical experts. The LhARA Work Packages (WPs) are:

- WP1: Project management;
- WP2: Laser-driven proton and ion source;
- WP3: Proton and ion capture;
- WP4: Ion-acoustic dose mapping;
- WP5: Novel automated end-station development; and
- 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 2022. No inflation is added for the Preliminary Phase (years 1 and 2). From year 3, 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 cost estimates presented in the tables that follow, therefore, should be regarded as planning estimates.
- The staff cost estimate has been made on the assumption that all staff cost £100k per staff year. The collaboration recognises that for STFC staff, band-average annual costs should be used and that for University staff the full economic cost (fEC) of each staff member must be used. To ensure anonymity, a costing tool has been set up in which unique identifiers are used instead of staff names. A confidential

staff database has been created to establish the correspondence between individuals and the unique identifiers. The collaboration is actively negotiating budget allocations with the STFC ITRF management. The staff data base will be populated with the correct staff costs when these negotiations converge.

- 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 below.
- No working margin or contingency is included for the Preliminary Phase activity (years 1 and 2). From year 3, a working margin of 10% and a contingency of 20% have been added to the equipment costs and 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 Preconstruction Phase project (year 3). Since the project is in its formative stage, the costing for some Work Packages identify resources for particular contingencies. 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". Milestone reports at appropriate points are used to record important results and stimulate discussion and analysis within the broader collaboration at progress, collaboration, and oversight meetings. The milestone reports will form the building blocks from which the project deliverables are constructed. For each Work Package, the principal objectives of each task and the Work Package as a whole 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 Activity and Preconstruction Phase of the LhARA Project will be carried out in the context of the development of the Ion Therapy Research Facility (ITRF). A pre-CDR [2] for LhARA, published in Frontiers of Physics, Medical Physics and Imaging [3], was prepared using resources provided by an STFC Future Opportunities 2019 award. The pre-CDR identified the key technical risks that need 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 a real-time, non-destructive dose-profile measurement system based on the acoustic signals generated by the rapid deposition of energy in the Bragg peak; and
- Development of the specification and design of the *in-vitro* and *in-vivo* end stations, their instrumentation, and the necessary ion-beam diagnostics. The design of the *in-vitro* end station will be fully automated to maximise throughput.
- Design and integration of the LhARA facility including beam transport system and novel FFA. Specifications for the controls, electrical and RF engineering, beam diagnostics, technical services and safety system design sufficient to support costing.

The LhARA collaboration began to develop the risk management project by which to address these issues as soon as the pre-CDR had been completed. The next steps in this risk management project forms the basis of Work Packages 2 to 5. This project was developed within the framework of the ongoing "Design and integration" activity defined in Work Package 6.

Work Package 1: Project management is required to manage the LhARA project in the Preliminary and Preconstruction phases. Resources are requested to support the LhARA Project Manager and project management

office in the execution of the project. Together the project-management team has responsibility for:

- Project management and the 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 Involvement (PPI).

The Stakeholder Engagement plan presented in section A.7 is an important part of the Preliminary Activity and Preconstruction Phase. Modest resources to support for travel and the engagement activities are requested.

Task objectives and deliverables

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

Task 1. The development and continuous monitoring of the project schedule and cost. The evaluation of the delivery of the project through active monitoring of the execution of the LhARA project against milestones and the agreed cost profile;

Task 2. The organisation and delivery of reports and presentations required for effective STFC and stakeholder oversight;

Task 3. The tracking of progress and risk by Work Package, managing effort through monthly progress meetings with each Work Package management team;

Task 4. The organisation of collaboration meetings on a 4 to 6 monthly schedule to provide cross-collaboration visibility and coordination;

Task 5. The organisation of regular stakeholder meetings to maintain currency with the latest results in relevant radiobiological and medical fields; to communicate the current status and important developments in the LhARA project to future users; and to solicit stakeholder feedback on the project; and

Task 6. The recruitment of appropriate patient representatives to advise as the LhARA project, its specification, and potential treatment regimens evolve.

Project progress for each task will be recorded in deliverable reports spaced at 6 month intervals throughout the project. The project management team will draw input as required from the relevant work packages to inform the deliverable reports with each work package tasked with an agreed set of milestone reports the timing of which are dovetailed into the project deliverables. The project deliverables are:

Preliminary Activity:

1. Early progress review CDR
2. Interim progress review CDR
3. Pre-CDR Review
4. CDR

Preconstruction Phase:

5. Pre-TDR review
6. TDR1
7. Early progress review TDR2
8. Interim progress review TDR2
9. Pre-TDR2 review
10. TDR2

Table 2: Resources required to execute Work Package 1.

LhARA Work Package 1: Project Management	J. Parsons, C. Whyte										16/05/2022	
Staff	**Year 1**		**Year 2**		**Year 3**		**Year 4**		**Year 5**		**Total**	
	Fraction	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**
Project office support												
Imperial Physics												
IC-Phys-Support-1	0.2	20.00	0.2	20.00	1	100.00	1	100.00	1	100.00	3.4	340.00
Strathclyde Physics												
Strathclyde-Phys-Stf-1	0.5	50.00	0.5	50.00	1	100.00	1	100.00	1	100.00	4	400.00
STFC-PPD												
STFC-Finance-Support	0	0.00	0	0.00	0.2	20.00	0.2	20.00	0.2	20.00	0.6	60.00
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**	0.7	**70.00**	2.2	**220.00**	2.2	**220.00**	2.2	**220.00**	8	**800.00**
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		12.21		18.55		25.05		55.80
PPI, engagement, and outreach		1.00		1.00		10.00		10.00		10.00		32.00
Patient representative and other seconded advisor expenses		2.00		2.00		6.00		6.00		6.00		22.00
Review-committee expenses		4.00		4.00		5.00		5.00		5.00		23.00
Consumables		0.00		0.00		10.00		10.00		10.00		30.00
Travel		4.00		4.00		15.00		20.00		20.00		63.00
Cost of risk mitigation, equipment (not yet implemented):		0.00		0.00		0.00		0.00		0.00		0.00
Working margin:		0.00		0.00		23.50		23.50		23.50		70.50
Contingency, equipment:		0.00		0.00		3.00		3.00		3.00		9.00
Contingency, CG staff:		0.00		0.00		0.00		0.00		0.00		132.00
Contingency, all staff:		0.00		0.00		44.00		44.00		44.00		132.00
Total:		**96.00**		**96.00**		**363.71**		**375.05**		**381.55**		**1312.30**

Resources requested

The resources requested to support Work Package 1: Project Management are summarised in table 2. 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 Project Manager. STFC financial staff assistance at 0.2 FTE is requested to support the project management team from year 3. Funds are requested to support travel and subsistence costs for two patient representatives. Resources to support STFC Oversight Committee activities have 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 project forward and to monitor progress.

Initially the travel budget requested has been confined to fit within the funding envelope. With Work Packages managed in 4 different cities, and experimental projects planned in all of these locations as well as at the national laboratories, the project will require care to fit travel demand within the budget. Travel should also be expected for stakeholder and patient-engagement meetings. The travel request increases substantially at the end of year 2 and again as the project enters years 4 and 5 to reflect the increased workload as the project moves towards completion of the Preconstruction Phase. A modest annual budget is requested for public engagement and outreach.

Gantt chart and principal milestones

The LhARA project has been planned in two sections to match the Preliminary Activity and Preconstruction Phase defined in the ITRF proposal. The inital Preliminary Activity supporting two years of work just sufficient to deliver the Conceptual Design Report (CDR). The following period of three years requiring funding at a higher level required to allow Technical Design Reports (TDRs) for LhARA Stages 1 and 2 to be delivered and to allow the technical-risk mitigation programme to continue. To monitor and document progress throughout the project, WP1 will produce and deliver milestone reports on a six monthly schedule. The CDR will document progress towards de-risking and address the major scientific questions. It will include a more robust costing of the full facility with the necessary expert input to support that costing. The completion of the CDR will therefore

mark a transition in the project to the higher per annum spend and the higher laboratory-staff commitment required to begin the Preconstruction Phase. At the 2 year point, monitoring of the project spend will require STFC Finance Department input to track and account for STFC staff input, this is included in the project plan.

The initial 2 year project has been planned to align with STFC project management best practise and deliver the required inputs to STFC monitoring. The collaboration anticipates that an oversight committee will be constituted to monitor and advise on progress two times per year. The oversight committee meetings will not only assess technical progress but will also interface with PPI, patient representative and seek stakeholder input. The LhARA project management has planned funds at a low level to facilitate these functions.

An extract of the LhARA Gantt chart highlighting the deliverables and other activities coordinated through WP1 is shown in table 3. Efficient use of resources to deliver STFC project management inputs is essential. The LhARA project management has planned a regular series of meetings with the individual work package managers and has identified a single contact point within each work package to which urgent communication can be addressed. These meetings not only allow tracking of progress against objectives but also provide the rigour behind monthly updates provided for the STFC Project Risk Committee. All meetings have been timetabled to allow reporting inputs to cascade through the management systems. Weekly progress meeting will feed the monthly Risk Committee meetings which will in turn feed into the collaboration meetings and, eventually, the Oversight Committee meetings. It is the intention that this structure should minimise repetition in paperwork preparation. LhARA's major deliverable in the Preliminary Activity, the CDR, will capture all of these inputs.

Risk register

The principal technical risks in the LhARA project relate to the components that enable the facility's unique performance characteristics: the laser-driven 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 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 guides the purchase of suitable hardware. LhARA has access to the principal authors of that software as well as a team expert in the application of ultrasonic detectors and arrays of detectors including the reconstruction of source characteristics from multiple detector signals. The LhARA facility end station specification also carries risk in that the capture of end user requirements may lead to irreconcilable demands, these can be mitigated using a modular design of end station. Project management risks post mitigation are dominated by those occasioned by funding and staff retention. LhARA has adopted a system in which each Work Package has co-leads, mitigating this risk. An extract of the LhARA Top Level risk register is shown in table 4.

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 to characterise the particle flux produced. The source will be optimised to maximise the collection efficiency of 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

Table 3: Extract of the LhARA Gantt chart showing the timeline of the work coordinated through Work Package 1. The timetable for the project deliverables is also shown.

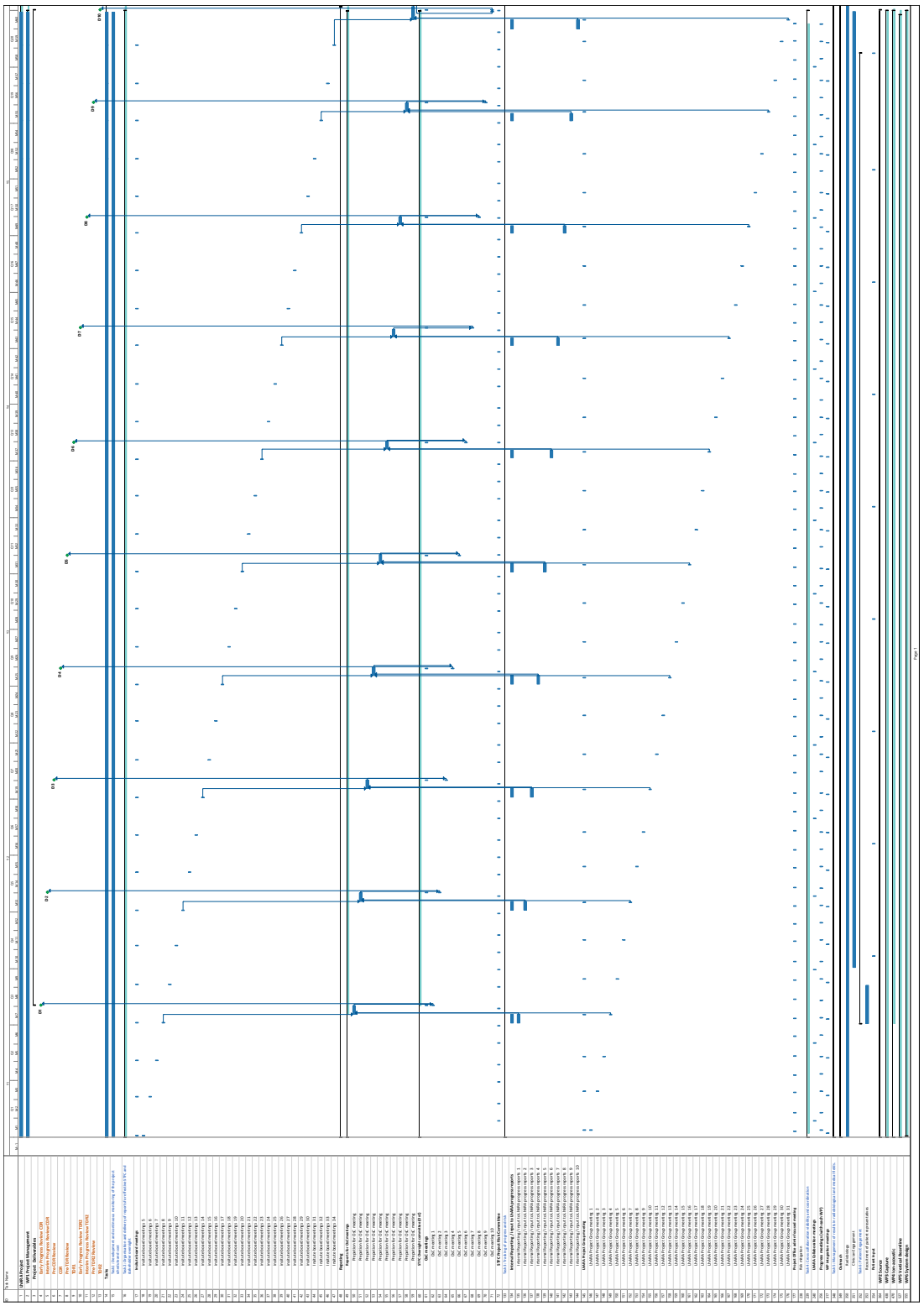

Table 4: LhARA Top level risk register showing only risks scoring 5 or more post mitigation.

	Number	WP Number	Name	Description	Likelihood	Impact	Score	Mitigation	Mitigated Likelihood	Mitigated Impact	Mitigated score
WP1	1	1.5	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 multidicipline facilities with comparable technical complexity. Use pre - CDR outputs to inform work towards Conceptual Design Report (CDR).	4	4	16
WP1	2	1.3	Performance specification parameters	Inadequate ion beam parameters specification to meet the Physics and Biology requirements for the facility.	3	5	15	The project consortium consists of all the multidiscipline experts to understand the required parameters.	2	5	10
All	3	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
WP2	4	2.7	Source output	Unable to deliver desired beam.	4	3	12	Investigate experimental techniques to increase yield	4	2	8
WP2	5	2.1	Source design - activation	Unsustainable activation of materials surrounding interaction	2	4	8	Change design to minimise potential for activated materials around interaction point	2	2	4
WP3	6	3.3	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:	4	3	12
WP4	7	4.1	Low acoustic signal	Insufficient acoustic signal to noise ratio (SNR) (i.e., low amplitude acoustic emission)	3	5	15	Frequency optimisation, prefocused large array, averaging over multiple pulses, adaptive reconstruction with priors and optimisation of frequency with element location. Adaptively trade dose-map resolution for SNR	3	3	9
WP6	8	6.2	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
WP5	9	5.1	End Station Specification	End station specification does not provide sufficient detail or is unable to accommodate conflicting requirements	5	5	25	Early involvement of multiple sources of user input. Modular end-station design.	1	5	5
WP4	10	4.5	Beam Line access	Lack of access to validation beam line	5	3	15	Several possible sources	3	3	9

2. Development of the underpinning technology necessary to deliver 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, and the STFC Scientific Computing Department) and one overseas group (Stanford/SLAC) will contribute to the work. The links between these groups are shown in figure 13. 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 deliver the Work Package objectives. Tests will be carried out as appropriate at the facilities listed in table 5.

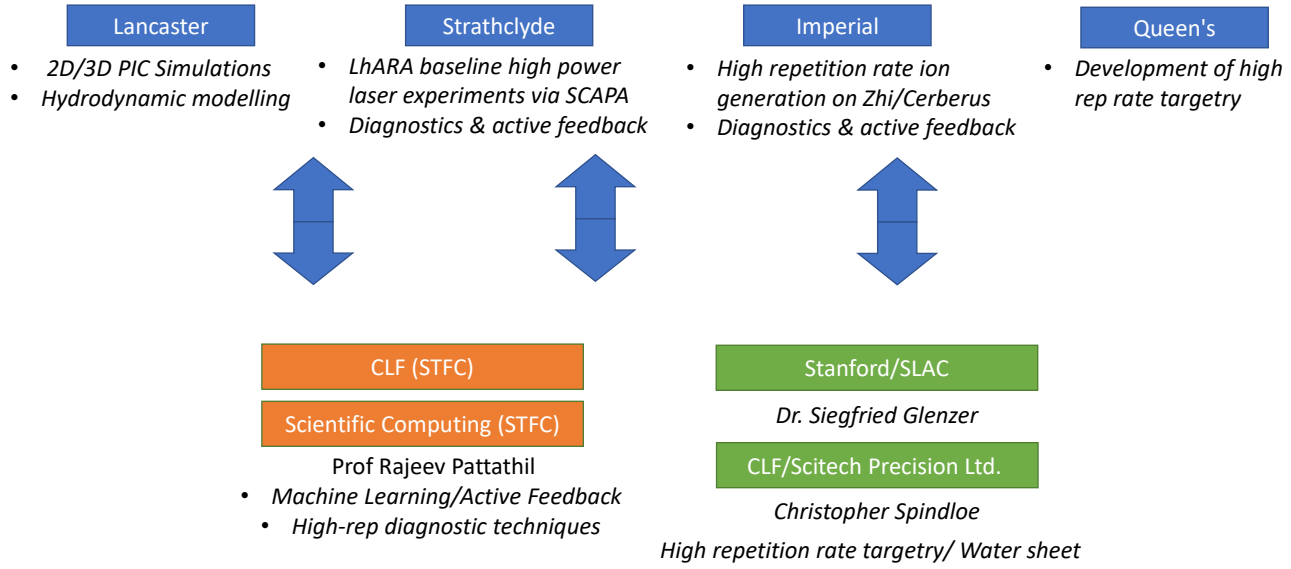

Figure 13: Principal contributors to the execution of Work Package 2 and the relationships between them.

Table 5: 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

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:

1. Programme of hydrodynamics and PIC 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 proton and heavier 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 capable of 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 the SCAPA laser;

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

Theme 2: Development of Underpinning Beam line Technology

O4: Complete conceptual design of target system capable of sustained and stabilised 10 Hz operation:

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

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;
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 14. The costs are broken down as follows.

Figure 14: Resources required to execute Work Package 2.

LhARA WP2: Laser-driven proton and ion source	E. Boella, N. Dover, R. Gray											26/05/2022
	Year 1		Year 2		Year 3		Year 4		Year 5		Total	
Staff	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**
All												
Strathclyde Physics												
Strathclyde-Phys-PDRA-1	0.5	50.00	0.5	50.00	1	100.00	2	200.00	2	200.00	6	600.00
Strathclyde-Phys-Stf-1	0.1	10.00	0.1	10.00	0.5	50.00	0.5	50.00	0.5	50.00	1.7	170.00
Strathclyde-Phys-Tech-1					0.2	20.00	0.2	20.00	0.1	10.00	0.5	50.00
Strathclyde-Phys-PG-1					0.5	12.50	1	25.00	2	50.00	3.5	87.50
Imperial Physics												
IC-Phys-PDRA-1	0.25	25.00	0.5	50.00	1.5	150.00	1.5	150.00	1	100.00	4.75	475.00
IC-Phys-Stf-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					0.2	20.00	0.2	20.00	0.1	10.00	0.5	50.00
IC-Phys-PG-1					0.5	12.50	1	25.00	2	50.00	3.5	87.50
Lancaster Physics												
Lanc-Phys-Stf-1	0.05	5.00	0.05	5.00	0.15	15.00	0.15	15.00	0.1	10.00	0.5	50.00
Lanc-Phys-PDRA-1	0.5	50.00	0.5	50.00	2	200.00	2	200.00	1	100.00	6	600.00
Lanc-Phys-PG-1					1	25.00	1	25.00	1	25.00	3	75.00
Queen's Physics												
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			0.5	87.50							0.5	87.50
Cost of risk mitigation, staff (not yet implemented):												
Staff total:	1.95	**195.00**	**2.7**	**307.50**	**8.1**	**660.00**	**10.1**	**785.00**	**10.35**	**660.00**	**33.2**	**2607.50**
Non-staff		**£k**		**£k**		**£k**		**£k**		**£k**		**£k**
All												
F/4 Parabola						40.00						40.00
Storage/ Analysis Cluster								30.00				30.00
Custom Ion TOF spectrometer						20.00						20.00
Custom Ion TP spectrometer						50.00						50.00
Custom Proton/Ion imager						30.00						30.00
Laser Diagnostic/Control Platform						20.00		65.00		65.00		150.00
Advaced Target Characterisation						25.00		50.00		25.00		100.00
Advanced Target Platform						25.00		50.00		25.00		100.00
Equipment total:						**210.00**		**195.00**		**115.00**		**520.00**
Inflation:						48.37		81.56		85.48		215.41
SCAPA Access		20.00		60.00		120.00		140.00		140.00		480.00
Imperial Access		25.00		25.00		40.00		30.00		30.00		150.00
Birmingham Accelerator						4.00		4.00		2.00		10.00
Costs for domestic travel to beamtime at Strathclyde/Imperial		8.00		16.00		11.00		13.00		13.00		61.00
Costs for inviting overseas collaborators (SLAC) to beamtime at Strathclyde						3.00		6.00		6.00		15.00
Consumables		35.00		35.00		60.00		60.00		60.00		250.00
Travel		2.00		4.00		6.00		6.00		6.00		24.00
Cost of risk mitigation, equipment (not yet implemented):												
Working margin:						87.00		98.00		77.50		262.50
Contingency, equipment:						42.00		39.00		23.00		104.00
Contingency, CG staff:												421.00
Contingency, all staff:						132.00		157.00		132.00		421.00
Total:		**285.00**		**447.50**		**1423.37**		**1614.56**		**1349.98**		**5120.41**

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.
- Six years FTE at the PDRA level at Lancaster University will be dedicated to the required numerical modelling. A PhD student will be recruited into the programme at the end of year 2.
- Six years FTE at the PDRA level and one 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, 4.75 years FTE at the PDRA level and a 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 control contaminants and enable high-repetition rate operations (£100k).
- 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 tests required to deliver O3, O5 and O6.
- 75 weeks between the Zhi and Cerberus lasers at Imperial (£2k p/w) (total £150k) to complete experimental work required to deliver O2, O4 and O5.
- Calibration activities at Birmingham cyclotron (10 days, £1k *per diem*) to support design and development work required to deliver O2.

Consumable items:

- £250k to defray routine laboratory costs include single-use detectors, filters, optics and optomechanics and targets.

Travel:

- Travel, and non-staff funding required to defray facility access costs, (£100k total. An average £20k per year) 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 associated with lack of access to simulation resources and laser facilities, requiring paid access to infrastructure (total £160k).
- Unforeseen experimental equipment requirements are also included to mitigate risk (total £100k).
- Further staff funding (total 1.25 FTE) is included to mitigate risk of insufficient staff effort to complete critical deliverables.
- Further details of justification of costs for risk mitigation is included in the risk analysis presented below.

Gantt chart and principal milestones

The planned schedule for work package 2 is given in the Gantt chart in table 6.

Table 6: Gantt chart for WP2.

Risk register

The risks associated with WP2 have been carefully evaluated and mitigation strategies developed, as shown in table 7. The risks are related to three overall issues: access to infrastructure (laser test sources, HPC resources), the ability to deliver the required beam parameters, and the ability to provide an ion-source design that meets the technical LhARA requirements.

An inability to secure laser beam time or technical issues with the laser during beam time 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 beam line 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 [2, 3]. 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 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 [65], lens that will provide low-cost, cylindrically symmetric, strong focusing in the LhARA proton and ion beamline [2, 3]. 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 will be executed 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

Preliminary Activity (initial two-year) programme:

Table 7: LhARA WP2 risk register.

Blank	Number	Name	Description	Likelihood	Impact	Score	mitigation	Mitigated Likelihood	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)	2	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	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	1	0	0
	4	Source output - Energy	Unable to deliver sufficient beam energy from source	2	4	8	Early testing regime. Adjust laser cond	2	2	4
	5	Source output - Intensity	Unable to deliver sufficient beam intensity.	3	3	9	Early testing regime. Multiple shot treatment	3	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	3	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)	4	2	8
	8	Source output - stability is too low	Source parameters are unstable shot-to-shot	4	4	16	Apply active stabilisation techniques	4	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	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	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	2	4

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, thereby developing the confidence necessary to exploit the simulations in the design of a second lens prototype; and
2. The design of a second Gabor lens test bench based upon state-of-the art plasma techniques and diagnostics. This iteration of the test bench will be capable of operation at trapping voltages of up to 2 kV.

Preconstruction Phase (additional three-year) programme:

1. To 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.

Preliminary Activity:

- Exploitation of an existing and slightly upgraded apparatus at Swansea University to make measurements on trapped electron plasmas. This programme will involve loading plasmas which occupy a large fraction of the trapping volume 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.
- Concurrently, a high voltage (up to 2 kV) plasma apparatus will be designed. This will be a new, standalone 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.

Preconstruction Phase (additional three-year) programme:

- Detailed studies of high voltage (2 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

The resource request for Work Package 3 is presented in table 8.

Table 8: Resources required to execute Work Package 3.

LhARA WP3 Proton and ion capture	C. Baker, W. Bertsche										17/05/2022	
	Year 1		Year 2		Year 3		Year 4		Year 5		Total	
Staff	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	3	300.00
Man-Phys-Stf-1	0.1	10.00	0.1	10.00	0.2	20.00	0.2	20.00	0.2	20.00	0.8	80.00
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-PDRA-2					1	100.00	1	100.00	1	100.00	3	300.00
Swns-Phys-Stf-1	0.1	10.00	0.1	10.00	0.3	30.00	0.3	30.00	0.3	30.00	1.1	110.00
Swns-Phys-PG-1					1	25.00	1	25.00	1.5	37.50	3.5	87.50
Swns-Phys-PG-2					1	25.00	1	25.00	1.5	37.50	3.5	87.50
Swan-Phys-Tech-1					1	100.00	1	100.00	0.5	50.00	2.5	250.00
Swan-Phys-Tech-2					1	100.00	1	100.00	0.5	50.00	2.5	250.00
UC Berkley (USA)												
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
Phase I												
Phase II												
Cost of risk mitigation, staff (not yet implemented):												
Staff total:	1.24	**124.00**	**1.24**	**124.00**	**7.54**	**604.00**	**7.54**	**604.00**	**7.54**	**529.00**	**25.1**	**1985.00**
Non-staff		**£k**		**£k**		**£k**		**£k**		**£k**		**£k**
All												
Preliminary activity												
Vacuum Generation		23.00										23.00
Vacuum Hardware		1.00										1.00
Trap/Expt. Hardware		9.50										9.50
Diagnostics		10.00										10.00
Control		5.00		3.00								8.00
Magnet(s)												
Misc.		1.00		1.00								2.00
Preconstruction Phase												
Vacuum Generation						88.10				18.00		106.10
Vacuum Hardware						41.86				2.00		43.86
Trap/Expt. Hardware						35.50		8.60				44.10
Diagnostics						22.00		67.50				89.50
Control						145.00		78.00		31.00		254.00
Magnet(s)						185.00						185.00
Misc.						3.00		3.00		3.00		9.00
Equipment total:		**49.50**		**4.00**		**520.46**		**157.10**		**54.00**		**785.06**
Inflation:						67.65		63.52		62.88		194.05
PPI, engagement, outreach		2.00		2.00		2.00		2.00		2.00		10.00
Consumables		12.50		16.00		98.50		99.00		110.50		336.50
Travel		5.00		10.00		32.00		32.00		47.00		126.00
Cost of risk mitigation, equipment (not yet implemented):												
Working margin:						112.45		76.11		58.30		246.86
Contingency, equipment:						104.09		31.42		10.80		146.31
Contingency, CG staff:												347.40
Contingency, all staff:						120.80		120.80		105.80		347.40
Total:		**193.00**		**156.00**		**1661.95**		**1185.95**		**980.28**		**4177.18**

Staff:

Preliminary Activity

Swansea

At Swansea, we have requested a 10% 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 test bench. Support will be requested externally for a PhD student.

Manchester

Again, 10% PI time is requested to promote the involvement of a senior scientist with the PIC simulations, design of the testbench apparatus, and interpretation of experimental results. A PhD student will also be requested externally to provide aid.

UC Berkley (USA)

Support is requested to promote the limited involvement of senior scientists with advice regarding the PIC simulations, design of the test bench apparatus, and interpretation of experimental results.

Preconstruction Phase

Swansea

We request a 30% PI contribution. This is necessary to extend the hands-on involvement of a senior scientist. We request two full PDRAs to continue the experimental programme with the existing apparatus, to engage with suppliers, construct and commission the 2 kV testbench, and to perform the demanding experimental campaign

using the new apparatus. We also request support for two PhD students.

Since the apparatus development and construction will largely take place at Swansea, two full-time technical assistants are initially requested—mainly to provide assembly, mechanical workshop, and design assistance. Highly specialised manufacturing is expected to be outsourced. Later, we request 1 FTE of technical effort to provide repair and maintenance assistance, and to facilitate transport of the testbench.

Manchester

We request 20% PI time to further promote the involvement of a senior scientist with the PIC simulations, use of the testbench apparatus, and interpretation of experimental results. The main body of the computational work will be undertaken by a PDRA. The scope of work is sufficiently ambitious and wide-ranging to require skills beyond the postgraduate-student level.

UC Berkley (USA)

Resources to allow the continued, limited, support of senior scientists is requested for advice regarding the PIC simulations, use of the test bench apparatus, and interpretation of experimental results.

Non-staff:

Preliminary Activity

This involves upgrades and modest modification to existing apparatus at Swansea to include: replacement vacuum hardware (such as pumps); new and updated charged particle trapping apparatus (such as power supplies, and electrodes); and diagnostics, including a replacement multi-channel plate/CCD imaging system.

Milestone summary for the Preliminary Activity:

- The generation and confinement for several seconds of a large volume 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 the Preconstruction Phase; and
- The complete design of apparatus to be purchased, assembled, commissioned, and used in the Preconstruction Phase.

Preconstruction Phase

This major hardware deliverable of Work Package 3 will be constructed in the Preconstruction Phase. 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 Preliminary Activity milestones).

Milestone summary for the Preconstruction Phase:

- The generation and confinement for several seconds of a high voltage (2 kV) 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.

The detailed milestone table for Work Package 3 is presented in table 9.

Table 9: Detailed milestone table for Work Package 3.

Period End (Year)	**Milestone**
0.5	1. Finish modifying the Swansea apparatus and trap electron plasmas. 2. Implement PIC software on High Performance Computing (HPC) system and model basic plasmas.
1	1. Perform lifetime studies of small plasma in the modified Swansea system. 2. Compare the behaviour of standard plasmas with results from the PIC code. 3. Numerically study the plasmas being experimentally produced. 4. Produce design parameters for the standalone testbench.
1.5	1. Study the lifetime of large radius plasmas in the modified Swansea apparatus. 2. Numerically duplicate experimental conditions, and study plasmas beyond those experimentally produced. 3. Refine the standalone testbench design based upon experimental results. 4. Identify all off-the-shelf components and potential suppliers.
2	1. Continue to study plasmas in the modified Swansea apparatus. Specifically, manipulation techniques (e.g., attempt to improve lifetime with "Rotating Wall" confinement studies), and environmental conditions (e.g., background gas pressures) as the apparatus allows. 2. Continue to numerically simulate experimental conditions, and study plasmas beyond those experimentally produced. 3. Finalise the testbench design. 4. Identify all custom-manufactured components and potential suppliers.
2.5	1. Place orders for testbench components 2. Begin assembly of the testbech apparatus. 3. Begin writing software to control the hardware. 4. Continue to numerically simulate the experimental conditions and the plasmas to be studied using the standalone testbench.
3	1. Continue assembly of the standalone testbench, and commission the apparatus.
3.5-4.5	The prioritisation of the plasma parameters to be studied will be guided by the experimental results. But e.g.,: 1. Study parameter X to confirm or advanced the scaling of behaviours from previous observations/ literature, and study its impact on the lifetime of high density plasmas. Where X = plasma size (up to 50% of electrode volume), magnetic field magnitude (vary $50\% - 100\%$), background pressure (vary from background to 10^{-3} mbar). 2. Continue to numerically confirm experimental observations, and study plasmas beyond those being experimentally produced.
5	1. Interface standalone workbench with a suitable ion source, and pass ions into plasmas. 2. Numerically simulate ion beam transport through plasmas. 3. Finalise the design of the apparatus needed for the LhARA beamline.

Gantt chart and principal milestones

The Gantt chart for Work Package 3 is presented in table 10.

Risk register

The top level risks of the Work Package 3 programme are presented in table 11.

The actions planned to mitigate the principal risks are:

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 year 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 7 distinct tasks, each designed to deliver a particular objective (objectives O1–O7, 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 scintillating-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

Table 10: Gantt chart for Work Package 3.

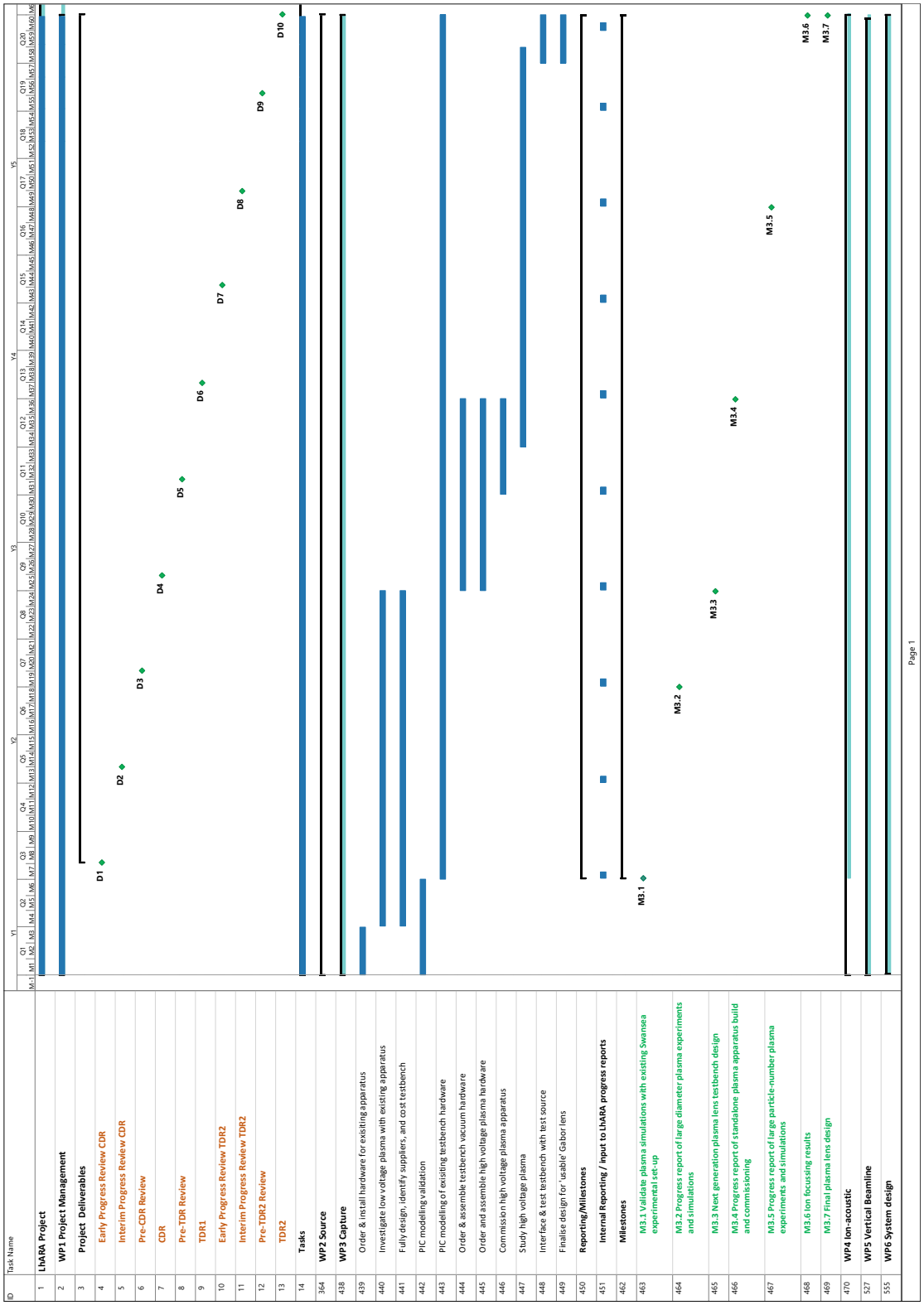

Table 11: Extract from the Work Package 3 risk register.

Blank	Number	Name	Description	Likelihood	Impact	Score	Mitigation	Mitigated Likelihood	Mitigated Impact	Mitigated score	Comments
	1	Plasma initialisation	Slow load / long stabilisation time	3	3	9	Design / Purchase improved electron source	3	1	3	Interplay between various experimental components prevents this being known for sure a priori
	2	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:	3	3	9	Multiple causes- Background gas pressure; Radial confinement; Plasma length dependance. Mitigation by good experimental technique; rotating wall/active control.
	3	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:	4	3	12	Multiple causes. The crux of the problem in this WP. Amenable to known solutions but these solutions are not proven to reach the required densities and in some cases (very high B field) are not atrractive.
	4	Acceptance	An insufficiently large plasma radius to focus all the ion beam	3	3	9	Increase electrode radius	3	2	6	Increasing the electrode radius to accommodate a larger plasma radius maintains a plasma to wall radius ratio <<1, a well studied parameter regime. Although initial designs will have large radii electrodes, these can be increased further, perhaps with vacuum system & confining solenoid redesign. As initial plans intend to use exisiting solenoids (at Swansea & Strathclyde), the electrode radius is limited. There will be significant additional costs and time delays associated with such an upgrade, if necessary.
	5	Delivery delays	Delays in sourcing / receiving equipment	3	3	9	Appropriate personnel to source off-the-shelf equipment / engage with suppliers. Use pre-existing magnet for testing	3	2	6	Although bespoke apparatus might be available commercially, it can often be time consuming to source a suitable supplier (considering competency, cost, & leadtime). Use existing infrastructure in extremis Some advanced equipment may need to be designed & produced specifically to match the experimental conditions. Ensuring appropriate personnel are able to engage with suppliers will mitigate this.
	6	Equipment failure	Due to the nature of the project, equipment will likely operate at limits to achieve final goals	2	4	8	Appropriately over spec. / design wherever possible. Ensure suitable warranties are provided. Don't operate at 100% until all 'easier' parameter space has been completed	2	2	4	Realistically this mitigation reduces the likelihood of failure as much as impact of a failure. Such mitigation comes at a small increase to the initial financial cost. Alternatively, alternative/redundant apparatus can be obtained and stored. This leads to a significantly higher initial cost, although per item cost savings are likely. Relying on repair or replacement by external supplier/contractor adds significant delays, and often results in comparable costs.
	7	Source-capture Interface - 'high' vacuum pressure in source	Pressure in source region is expected to be relatively poor compared to vacuum in capture section	3	4	12	Monitoring the source pressures (& constituents) and independently studying the effect on the plasma	3	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
	8	Source-capture Interface -secondary electrons from source impact capture	Secondary electrons will be produced by source - these can be expected to affect the capture plasma source.	3	4	12	Band pass filter	3	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.
	9	Source-capture Interface -Solenoid fringe field affecting sourcee	Solenoid fringe field affects source	3	2	6	Effect of B-field on the source, and extent of fringe field can be measured. Source / solenoid can be shielded.	3	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.
	10	Source-capture Interface -WP2 test source unavailable	WP2 test source unavailable at required time	1	3	3	Utilise beamport at a 3rd-party facility	1	1	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.

and to interpret the results of test-beam exposures. The UCL Department of Medical Physics and Biomedical Engineering 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

The objectives 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 Verasonics 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 an acoustic sensor 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. 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.

Resources requested

The resources required to execute Work Package 4 is presented in table 12.

Table 12: Resources required to execute Work Package 4.

LhARA WP4: Ion acoustic dose-profile measrement	**J. Bamber, E. Harris, J. Matheson**											**30/05/2022**
	Year 1		**Year 2**		**Year 3**		**Year 4**		**Year 5**		**Total**	
Staff	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**
All												
ICR, Radiotherapy and Imaging												
ICR Staff 1	0.03	3.00	0.07	7.00	0.07	7.00	0.07	7.00	0.07	7.00	0.31	31.00
ICR Staff 2	0.03	3.00	0.07	7.00	0.07	7.00	0.07	7.00	0.07	7.00	0.31	31.00
ICR PDRA			1	100.00	1	100.00	1	100.00	1	100.00	4	400.00
ICR PhD					1	25.00	1	25.00	1.5	37.50	3.5	87.50
UCL, Biomedical Engineering												
UCL Staff 1	0.03	3.00	0.15	15.00	0.15	15.00	0.15	15.00	0.15	15.00	0.63	63.00
UCL PDRA(shared ICL)			1	100.00	1	100.00	1	100.00	1	100.00	4	400.00
STFC-PPD												
STFC-PPD Staff 1 (Matheson)	0.03	3.00	0.05	5.00	0.15	15.00	0.15	15.00	0.5	50.00	0.88	88.00
STFC-PPD PDRA					1	100.00	1	100.00	1	100.00	3	300.00
Cost of risk mitigation, staff (not yet implemented):												
Staff total:	0.12	**12.00**	**2.34**	**234.00**	**4.44**	**369.00**	**4.44**	**369.00**	**5.29**	**416.50**	**16.63**	**1400.50**
Non-staff		**£k**		**£k**		**£k**		**£k**		**£k**		**£k**
All												
Verasonics Vantage 256						120.00						120.00
Verasonics 256-1024 multiplexer						10.00						10.00
Aspectus LEGION AMP pre-amplifier, 256 channel						10.00						10.00
Broadband single element sensor (e.g., passive cavitation detector)				3.00								3.00
Broadband single channel receiver (e.g., LeCoeur)				2.00								2.00
Bespoke 1024 element acoustic sensor array						15.00						15.00
Technician time for mechanical rig/alternative source studies				10.00								10.00
Any computing kit/software for UCL and ICL?				10.00								10.00
Hardware for smartphantom assembly		9.00				35.00		5.00		5.00		54.00
Technician time for smartphantom construction						*19.80*		*19.80*				*39.60*
Beam time		1.50		3.50		5.00		5.00		5.00		20.00
Equipment total:		**10.50**		**28.50**		**214.80**		**29.80**		**10.00**		**293.60**
Inflation:						33.98		31.61		44.71		110.31
PPI, engagement and Outreach				2.00		2.00		2.00		2.00		8.00
Consumables				24.00		38.60		38.60		38.60		139.80
Travel		11.60		11.60		14.40		14.40		14.40		66.40
Cost of risk mitigation, equipment (not yet implemented):												
Working margin:						58.38		39.88		42.65		140.91
Contingency, equipment:						42.96		5.96		2.00		50.92
Contingency, CG staff:												230.90
Contingency, all staff:						73.80		73.80		83.30		230.90
Total:		**34.10**		**300.10**		**847.92**		**605.05**		**654.16**		**2441.34**

Gantt chart and principal milestones

The planned schedule for Work package 4 is given in the Gantt chart in table 13.

Risk register

The principal risks extracted from the Work Package 4 risk register are presented in table 14.

Table 13: Gantt chart for WP4.

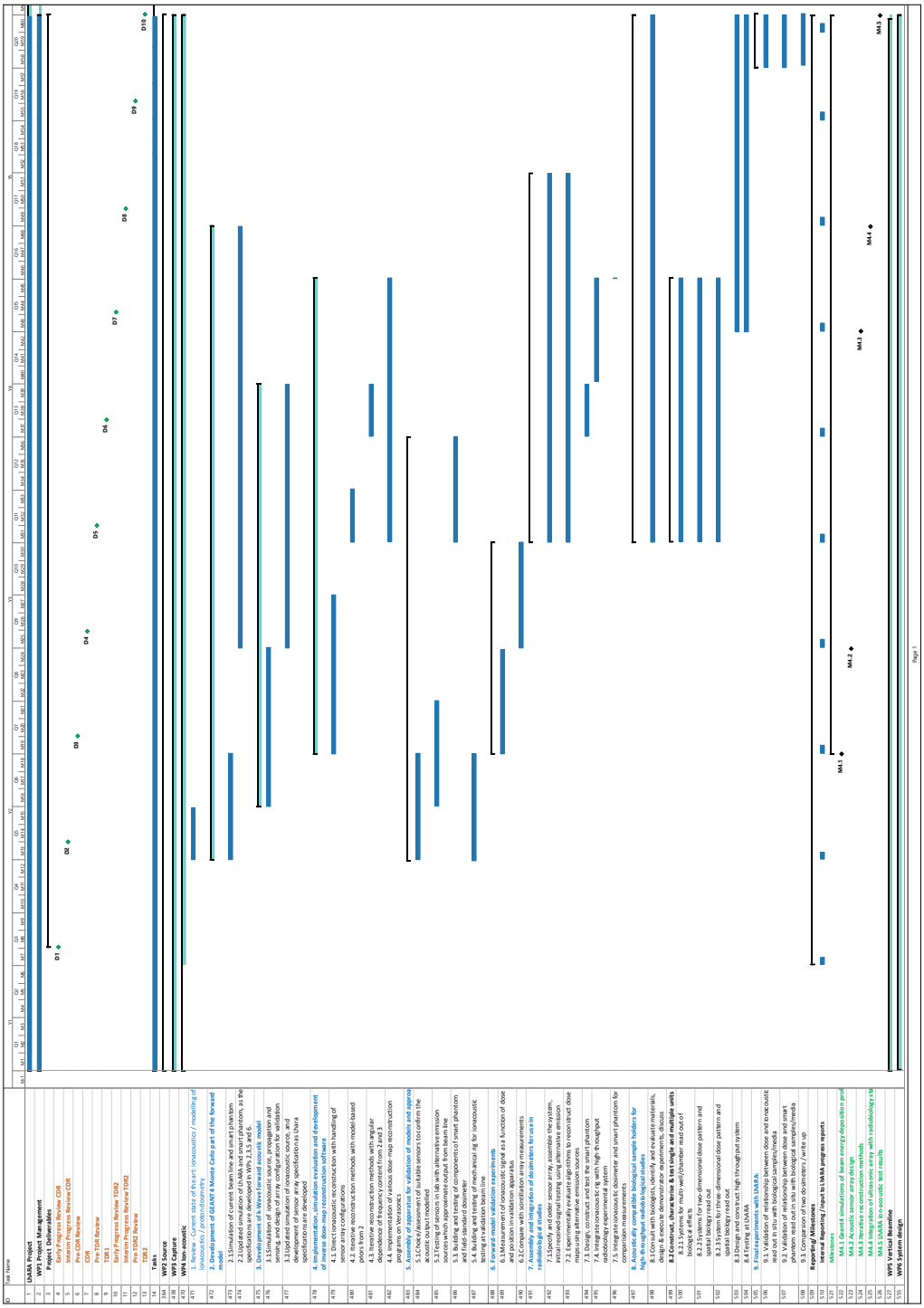

Table 14: Principal risks extracted from the Work Package 4 risk register.

	Number	WP Number	Name	Description	Likelihood	Impact	Score	Mitigation	Mitigated Likelihood	Mitigated Impact	Mitigated score
WP1	1	1.5	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 multidicipline facilities with comparable technical complexity. Use pre - CDR outputs to inform work towards Conceptual Design Report (CDR).	4	4	16
WP1	2	1.3	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	5	10
All	3	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
WP2	4	2.7	Source output	Unable to deliver desired beam.	4	3	12	Investigate experimental techniques to increase yield	4	2	8
WP2	5	2.1	Source design-activation	Unsustainable activation of materials surrounding interaction	2	4	8	Change design to minimise potential for activated materials around interaction point	2	2	4
WP3	6	3.3	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:	4	3	12
WP4	7	4.1	Low acoustic signal	Insufficient acoustic signal to noise ratio (SNR) (i.e., low amplitude acoustic emission)	3	5	15	Frequency optimisation, prefocused large array, averaging over multiple pulses, adaptive reconstruction with priors and optimisation of frequency with element location. Adaptively trade dose-map resolution for SNR	3	3	9
WP6	8	6.2	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
WP5	9	5.1	End Station Specification	End station specification does not provide sufficient detail or is unable to accommodate conflicting requirements	5	5	25	Early involvement of multiple sources of user input. Modular end-station design.	1	5	5
WP4	10	4.5	Beam Line access	Lack of access to validation beam line	5	3	15	Several possible sources	3	3	9

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

Objectives

The principal objective for this work package, "Work package 5 (WP5): Novel end-station development", is to produce the detailed specifications and designs for the *in-vitro* and *in-vivo* end stations and the associated dosimetry along with the beam diagnostics necessary to characterise the beam delivered to the end stations. Alternative technologies to the ion-acoustic technique under development in Work Package 4 will be explored to ensure the beam delivered to the biological sample is fully characterised. The end-station specification will be developed through peer-group consultation. Careful consideration will be given to appropriate automation and feedback to the accelerator so that an advanced, robust, and optimised solution is identified with capabilities in terms of precision beam delivery, environment control, and sample throughput that is unlike anything that is currently available.

Task objectives and deliverables

The objectives (O1 to O4 below) will be delivered through a series of tasks—each being designed to provide a particular milestone (M1 to M7 below). The end-station specifications 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: Experimental demonstration of cell irradiation in end station, including cell imaging and dose monitoring from WP4:
  - M1: Design LhARA automated cell dish handling and environmental system [24 months]
  - M2: Report on end-station user-community consultation. Engage with cellular imaging community to assess end-station space and supporting infrastructure requirements [24 months]
  - M3: End station component testing at Birmingham. De-risk key end station components though experimental measurements at Birmingham. Energy selection and collimation for low energy proton beams as well as end-station windows will be studied [24 months]
  - M4: Construct beam delivery room including end-station and cellular imaging capabilities [60 months]
- O2: 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:
  - M5: Specification of LhARA beam monitoring technology. Assess current beam monitoring technology and identify the required R&D for LhARA beams [24 months]
  - M6: Report on delivery of LhARA beam monitoring system. Undertake required R&D on technologies identified in M5 and integrate with beam delivery system [60 months]
- O3: Develop a facility capable of delivering ultra high dose rates for R&D purposes
  - M7: kGy/s tests at Birmingham [24 months]
- O4: Finalise the layout of LhARA beam delivery system with Beam Position Monitors, magnets, and dosimetry apparatus locations identified and technology developed [60 months]

Resources requested

The resources requested to deliver Work Package 5 are presented in table 15. In the first 24 months we request 20% of Dr Price's and Dr McLauchlan's time to lead the Work Package. In addition, we require a PDRA

Table 15: Resources requested to execute Work Package 5.

.

LhARA WP5: Novel end station development	R. McLauchlan, T. Price, C. Welsch										17/05/2022	
	Year 1		Year 2		Year 3		Year 4		Year 5		Total	
Staff	Fraction	£k	Fraction	£k	Fraction	£k	Fraction	£k	Fraction	£k	Fraction	£k
All												
BHM Physics												
BHM-Phys-Stf-1	0.2	20.00	0.2	20.00	0.5	50.00	0.5	50.00	0.5	50.00	1.9	190.00
BHM-Phys-PDRA					1	100.00	1	100.00	1	100.00	3	300.00
BHM-Tech	1	100.00	1	100.00	1	100.00	1	100.00	1	100.00	5	500.00
IC NHS HC Trust												
IC-NHS-HC-Trst-Stf-1	0.2	20.00	0.2	20.00	0.5	50.00	0.5	50.00	0.5	50.00	1.9	190.00
IC-NHS-HC-Trst-PhD-1					1	25.00	1	25.00	1.5	37.50	3.5	87.50
Liverpool Physics												
Liv-Phys-PDRA	0.5	50.00	0.5	50.00	1	100.00	1	100.00	1	100.00	4	400.00
Liv-Phys-PhD					1	25.00	1	25.00	1.5	37.50	3.5	87.50
Cost of risk mitigation, staff (not yet implemented):												
Staff total:	1.9	**190.00**	1.9	**190.00**	6	**450.00**	6	**450.00**	7	**475.00**	**22.8**	**1755.00**
Non-staff		**£k**		**£k**		**£k**		**£k**		**£k**		**£k**
All												
Equipment total:												
Inflation:						22.78		34.60		49.31		106.69
User consultation meetings		5.00		5.00		2.50		2.50		2.50		17.50
Consumables		10.00		10.00								20.00
Travel		4.00		4.00		5.00		5.00		5.00		23.00
Cost of risk mitigation, equipment (not yet implemented):												
Working margin:						45.00		45.00		47.50		137.50
Contingency, equipment:												
Contingency, CG staff:												275.00
Contingency, all staff:						90.00		90.00		95.00		275.00
Total:		**209.00**		**209.00**		**615.28**		**627.10**		**674.31**		**2334.69**

funded at 0.5 FTE with matched funding from University of Liverpool, and £15k consumables to develop the beam monitoring technologies identified in WP5. Beamline developments, integration, end-station component testing, and machine operation for beam-monitoring technologies at the University of Birmingham will be conducted by a technician at 1.0 FTE for two years. The technician will be supported by Dr Price and the rest of the cyclotron team including Dr Carl Wheldon and Prof. Tzany Wheldon at 0.05 FTE in kind contribution. We request £10k to allow the organisation of three consultation meetings on the end-station requirements over the 24 months to specify user requirements and £20k to allow initial designs and tests to be conducted on end-station and beamline components. Access for users to the cyclotron will be at the discounted research rate of £1.2k/day and we include 24 days of access at a total of £28.8k. The cyclotron facility will contribute one in kind day for each two days funded on the project up to a maximum of 12 in kind days.

Gantt chart and principal milestones

The planned schedule for Work Package 5 is given in the Gantt chart in table 16.

Risk register

The principal risks extracted from the Work Package 5 risk register are presented in table 17.

A.2.6 Work package 6: Design and integration

Objectives

The principal objective for this work package, ”Work package 6 (WP6): Design and integration” is to prepare the conceptual and technical designs for the LhARA facility. The design of the Gabor lenses is the subject of WP3. To mitigate the risk that the Gabor-lens solution will not be completed in time, WP6 will develop an

Table 16: Gantt chart for WP5.

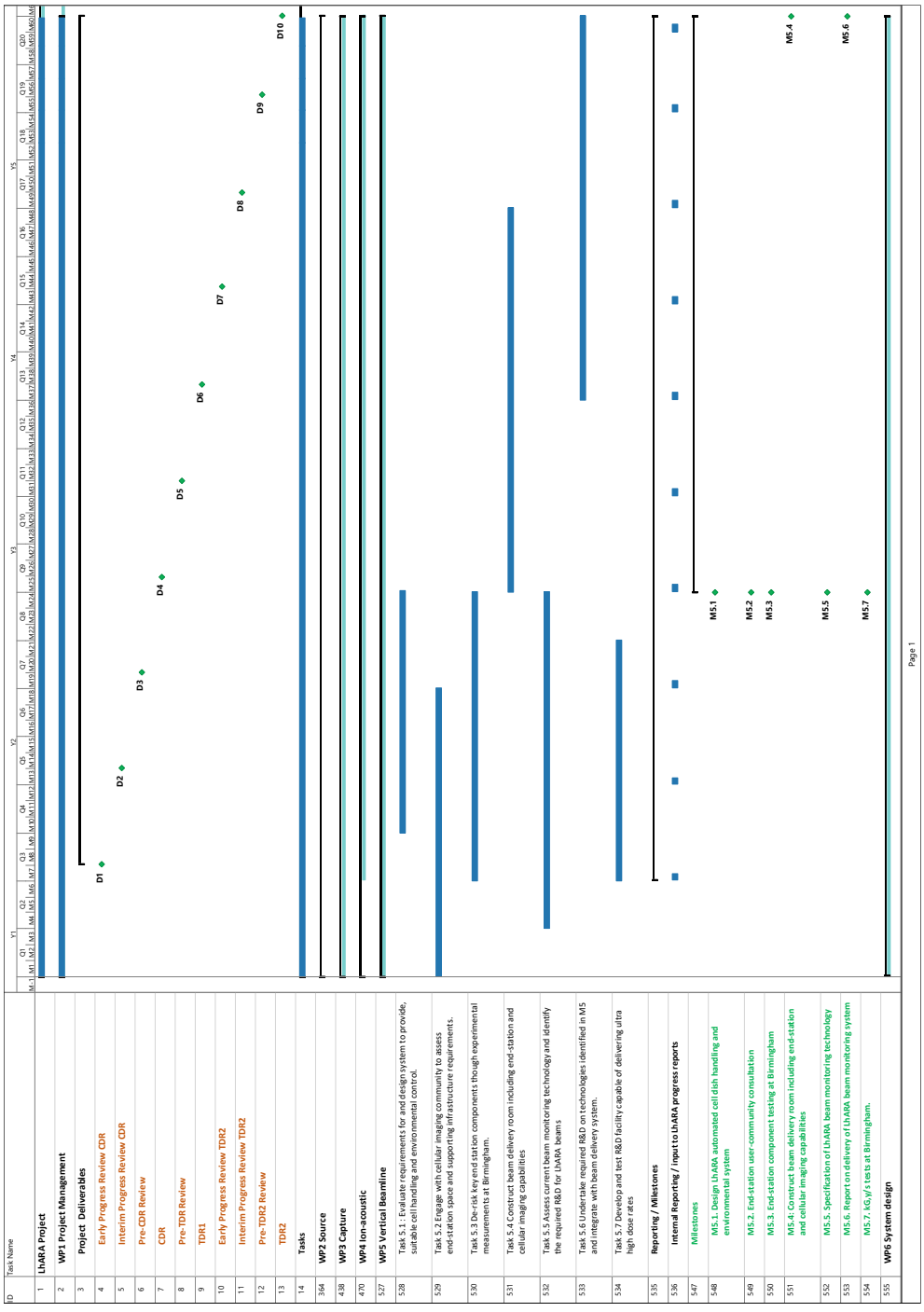

Table 17: Principal risks extracted from the Work Package 5 risk register.

Blank	Number	Name	Description	Likelihood	Impact	Score	Mitigation	Mitigated Likelihood	Mitigated Impact	Mitigated score	Comments	Significant Dates	Retirement date
	1	End Station Specification	End station specification does not provide sufficient detail or is unable to accommodate conflicting requirements	5	5	25	Early involvement of multiple sources of user input. Modular end-station design.	1	5	5			
	2	Beam instrumentation	Beam instrumentation specification and delivery delays	3	3	9	Progress montoring and effort supplementation from LhARA project expertise	2	3	6			

alternative solution based on solenoid magnets. The alternative solution will include an electromagnetic Wien filter for ion-species selection.

WP6 will evaluate the radiation protection and shielding requirements to 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 for the Stage 2, which will allow variable energy extraction will be designed and the construction of a prototype magnet will be subcontracted to industry. The Magnetic Alloy (MA) RF cavity system for the FFA will be designed and a prototype will be constructed.

WP6 will also encompass the design of the vacuum system as well as specification of the controls, electrical and RF engineering, beam diagnostics, technical services and the safety system design. The design of the facility will pay close attention to environmental sustainability.

The work of WP6 will inform the completion of the Conceptual Design Report (CDR) for the LhARA facility by the end of year 2. Technical Design Reports (TDRs) for Stage 1 and Stage 2 will follow in year 3 and 5, respectively. The work will be carried by the personnel from Universities and STFC, mainly from the Daresbury Laboratory (DL), as shown in the resource table 18.

Task objectives and deliverables

Objectives (Os) and milestones (Ms) for WP6 and associated WP1 Deliverables (Ds) are listed below:

- **O1:** Conceptual design of the LhARA facility, accelerator systems and its integration with the source and the end stations;
    1. Lattice optimisation, aperture estimation, parameter list and schematic diagram update
    2. Preliminary design of collimators
    3. Preliminary design of the MA RF cavity
    4. Preliminary design of the FFA magnet
    5. Error study and estimation of corrector positions
    6. Preliminary design of the RF system
    7. Preliminary design of the mitigating solenoid
    8. Preliminary design of the bulk shielding, beam dump and radioprotection requirements
    9. Preliminary design of the arc magnets
    10. Preliminary design of the diagnostic system
    11. Preliminary design of the control and feedback systems
    12. Mechanical design of accelerator system and integration
    13. Preliminary design of the building and infrastructure requirements
    14. Preliminary design of the vacuum system
    15. Preliminary design of the mechanical supports including the vertical arc
    16. Estimation of the power consumption and cooling requirements
    17. Finalise the Conceptual Design (all systems)
    18. Write CDR towards LhARA CDR (12 months)

    M6.1: Final review of R&D work towards LhARA CDR (18 months)

    D4: CDR for the LhARA facility (24 months)
- **O2:** Technical design of LhARA accelerator systems for Stage 1 and its integration with the source and the end station;
    19. Design of the vacuum system for Stage 1
    20. Design of collimators for Stage 1
    21. Design of the shielding, beam dump and radioprotection system (by the specialised company)

22. Design of the RF system for Stage 1
23. Design of the mitigating solenoid
24. Design of the arc magnets for Stage 1
25. Design of the diagnostic system for Stage 1
26. Design of the control and feedback systems for Stage 1
27. Design of the mechanical support for the vertical arc
28. Design of the power supplies and cooling systems, including cabling definitions
29. Design of the personnel protection system
30. Finalise Technical Design (all systems) and write TDR for Stage 1

M6.2: Early review of R&D work towards LhARA Stage 1 TDR (30 months)

D6: TDR for the LhARA accelerator systems for Stage 1 (36 months).

- **O3:** Technical design of accelerator systems for Stage 2 and its integration with the source and the end stations;

31. Design of collimators for Stage 2
32. Design of shielding, beam dump and radioprotection system (by the specialised company) for Stage 2
33. Design of magnets for the injection line, injection system, extraction line, extraction system and the vertical arc for Stage 2
34. Design of the diagnostic system for Stage 2
35. Design of the control and feedback systems for Stage 2
36. Design of the power supplies and cooling systems, including cabling definitions
37. Extension of design of the personnel protection system for Stage 2
38. Building specification and design
39. Design of the RF system for Stage 2
40. Design of the vacuum system for Stage 2

M6.3: Final review of R&D work towards LhARA Stage 2 TDR (54 months)

- **O4:** Design, construction and validation of the FFA magnet prototype for LhARA Stage 2 post-accelerator;

41. Design of the FFA magnet prototype
42. Tender and award for construction of the FFA magnet prototype
43. Construction of the FFA magnet prototype (by specialised company)
44. Tests and magnetic measurements of the FFA magnet prototype

M6.4: Technical report on the design and performance of the FFA main magnet prototype (58 months).

- **O5:** Design, construction and validation of the MA RF cavity prototype for LhARA Stage 2 post-accelerator;

45. Design of the MA RF cavity prototype
46. Construction of the MA RF cavity prototype
47. Tests and measurements of the MA RF cavity prototype

M6.5: Technical report on the design and performance of the MA RF cavity prototype (58 months).

48. Finalise Technical Design for Stage 2 (all systems)
49. Write TDR for Stage 2

D10: TDR for the LhARA accelerator systems for Stage 2 (60 months).

Resources requested

The resources requested for the work package 6 are shown in table 18.

Table 18: LhARA WP6 resources request.

LhARA WP6 Design and integration	N. Bliss, J. Pasternak											17/05/2022
	Year 1		Year 2		Year 3		Year 4		Year 5		Total	
Staff	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**	**Fraction**	**£k**
CDR and conceptual design development												
Imperial Physics												
Imp Staff 1	0.1	10	0.1	10	0.1	10	0.1	10	0.1	10	0.5	50
Imp PDRA1	0.5	50	0.5	50	1	100	1	100	1	100	4	400
Imp PDRA2					1	100	1	100	1	100	3	300
Imp PG1			0.5	87.5							0.5	87.5
RF eng.					0.3	30	0.6	60	0.6	60	1.5	150
Diagnostics expert					0.3	30	0.5	50	0.5	50	1.3	130
RHUL Physics												
RHUL PDRA1	0.5	50	0.5	50	1	100	1	100	1	100	4	400
RHUL PG1			0.5	87.5							0.5	87.5
CDR and technical design studies												
STFC Technical												
STFC WP management	0.2	20	0.25	25	0.25	25	0.25	25	0.25	25	1.2	120
Mechanical engineering design specification	0.5	50	0.8	80	1	100	1.2	120	1.2	120	4.7	470
Electrical engineering design specification	0.05	5	0.55	55	0.9	90	1.1	110	1.1	110	3.7	370
Controls specification	0.05	5	0.25	25	0.35	35	0.65	65	0.7	70	2	200
Technical services specification			0.4	40	0.5	50	0.5	50	0.5	50	1.9	190
Vacuum specification			0.2	20	0.5	50	0.3	30	0.3	30	1.3	130
Radiation Protection Advisor	0.03	2.75	0.08	7.5	0.1	10	0.1	10	0.1	10	0.4	40.25
Cost of risk mitigation, staff (not yet implemented):												
Staff total:	1.9275	**192.75**	**4.625**	**537.5**	**7.3**	**730**	**8.3**	**830**	**8.35**	**835**	**30.5025**	**3125.25**
Non-staff		**£k**		**£k**		**£k**		**£k**		**£k**		**£k**
CDR and conceptual design development												
FFA magnet prototype								50.00		50.00		100.00
FFA MA Cavity prototype						50.00		75.00		75.00		200.00
Software		2.50		2.50		2.50		2.50		2.50		12.50
CDR and technical design studies												
Radiation Protection Study (specialist company)						45.00		45.00				90.00
Equipment total:		**2.50**		**2.50**		**97.50**		**172.50**		**127.50**		**402.50**
Inflation:						43.90		82.57		105.49		231.97
Work package management (meetings)moved WP1												
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):												
Working margin:						82.75		100.25		96.25		279.25
Contingency, equipment:						19.50		34.50		25.50		79.50
Contingency, CG staff:												479.00
Contingency, all staff:						146.00		166.00		167.00		479.00
Total:		**203.25**		**548.00**		**1132.65**		**1398.82**		**1369.74**		**4652.47**

Gantt chart and principal milestones

The schedule for work package 6 is shown in table 19 as a Gantt chart.

Risk register

Risk register for work package 6 is shown in table 20.

Table 19: LhARA WP6 schedule.

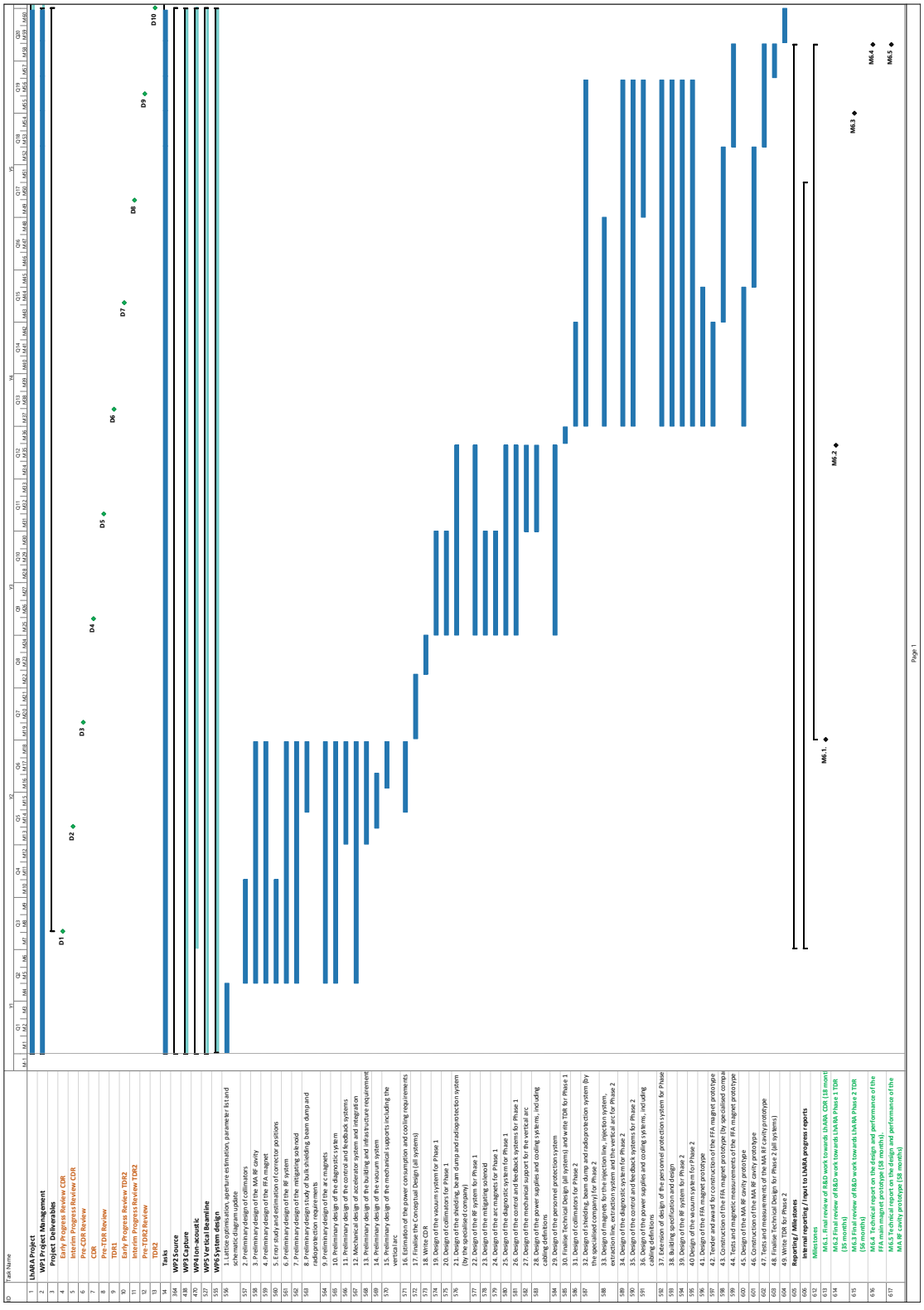

Table 20: LhARA WP6 risk register.

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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	Delay or technical difficulties in construction of Magnet Alloy (MA) cavity	5	4	20	Establish close collaboration with CERN, J-PARC & KURNS institutes, where similar systems have been constructed and are in operation. Component parts manufactured by industry.	5	1	5
4	Injection and extraction magnets	Insufficient availability 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 leglislation and identify construction method to inform cost and schedule.	1	5	5

A.3 Overview of Preliminary Activity and Preconstruction Phase project costs

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

- The capital and staff costs have been estimated in calendar year 2022. From year 3, 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 and university staff an annual cost of £100k has been used. Each staff member or role has been asigned a unique identifier is 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 below.
- From year 3, 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 Preconstruction Phase project (year 3). 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.

Table 21: Overview of project cost.

Id	Name	Work package	Year 1		Year 2		2 year total		Year 3		Year 4		Year 5		5 year total	
			Fraction	£k	Fraction	£k	Fraction	£k	Fraction	£k	Fraction	£k	Fraction	£k	Fraction	£k
Staff effort, summary by institute																
1	*LhARA Project Management*															
		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
		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
		STFC-PPD							0.20	20.00	0.20	20.00	0.20	20.00	0.60	60.00
2	*Laser-driven proton and ion source*															
		Strathclyde Physics	0.60	60.00	0.60	60.00	1.20	120.00	2.20	182.50	3.70	295.00	4.60	310.00	11.70	907.50
		Imperial Physics	0.75	75.00	1.00	100.00	1.75	175.00	2.70	232.50	3.20	245.00	3.60	210.00	11.25	862.50
		Lancaster Physics	0.55	55.00	0.55	55.00	1.10	110.00	3.15	240.00	3.15	240.00	2.10	135.00	9.50	725.00
		Queen's Physics	0.05	5.00	0.55	92.50	0.60	97.50	0.05	5.00	0.05	5.00	0.05	5.00	0.75	112.50
3	*Proton and ion capture*															
		Swansea Physics	1.10	110.00	1.10	110.00	2.20	220.00	6.30	480.00	6.30	480.00	6.30	405.00	21.10	1585.00
		Manchester Physics	0.10	10.00	0.10	10.00	0.20	20.00	1.20	120.00	1.20	120.00	1.20	120.00	3.80	380.00
		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, Radiotherapy and Imaging	0.06	6.00	1.14	114.00	1.20	120.00	2.14	139.00	2.14	139.00	2.64	151.50	8.12	549.50
		STFC-PPD	0.03	3.00	0.05	5.00	0.08	8.00	1.15	115.00	1.15	115.00	1.50	150.00	3.88	388.00
		UCL, Biomedical Engineering	0.03	3.00	1.15	115.00	1.18	118.00	1.15	115.00	1.15	115.00	1.15	115.00	4.63	463.00
5	*Novel end station development*															
		BHM Physics	1.20	120.00	1.20	120.00	2.40	240.00	2.50	250.00	2.50	250.00	2.50	250.00	9.90	990.00
		IC NHS HC Trust	0.20	20.00	0.20	20.00	0.40	40.00	1.50	75.00	1.50	75.00	2.00	87.50	5.40	277.50
		Liverpool Physics	0.50	50.00	0.50	50.00	1.00	100.00	2.00	125.00	2.00	125.00	2.50	137.50	7.50	487.50
6	*Design and integration*															
		Imperial Physics	0.60	60.00	1.10	147.50	1.70	207.50	2.70	270.00	3.20	320.00	3.20	320.00	10.80	1117.50
		RHUL Physics	0.50	50.00	1.00	137.50	1.50	187.50	1.00	100.00	1.00	100.00	1.00	100.00	4.50	487.50
		STFC Technical	0.83	82.75	2.53	252.50	3.35	335.25	3.60	360.00	4.10	410.00	4.15	415.00	15.20	1520.25
	Staff totals		***7.84***	***783.75***	***13.50***	***1463.00***	***21.34***	***2246.75***	***35.58***	***3033.00***	***38.58***	***3258.00***	***40.73***	***3135.50***	***136.23***	***11673.25***
Non-staff cost summary																
1	*LhARA Project Management*			26.00		26.00		52.00		131.50		136.50		136.50		456.50
2	*Laser-driven proton and ion source*			90.00		140.00		230.00		715.00		748.00		604.50		2297.50
3	*Proton and ion capture*			69.00		32.00		101.00		990.30		518.43		388.40		1998.13
4	*Ionacoustic Imaging*			22.10		66.10		88.20		444.94		204.44		192.95		930.53
5	*Novel end station development*			19.00		19.00		38.00		142.50		142.50		150.00		473.00
6	*Design and integration*			10.50		10.50		21.00		358.75		486.25		429.25		1295.25
	Non-staff totals			***236.60***		***293.60***		***530.20***		***2782.99***		***2236.12***		***1901.60***		***7450.91***
Total staff and non-staff by work package																
1	*LhARA Project Management*		0.70	96.00	0.70	96.00	1.40	192.00	2.20	363.71	2.20	375.05	2.20	381.55	8.00	1312.30
2	*Laser-driven proton and ion source*		1.95	285.00	2.70	447.50	4.65	732.50	8.10	1423.37	10.10	1614.56	10.35	1349.98	33.20	5120.41
3	*Proton and ion capture*		1.24	193.00	1.24	156.00	2.48	349.00	7.54	1661.95	7.54	1185.95	7.54	980.28	25.10	4177.18
4	*Ionacoustic Imaging*		0.12	34.10	2.34	300.10	2.46	334.20	4.44	847.92	4.44	605.05	5.29	654.16	16.63	2441.34
5	*Novel end station development*		1.90	209.00	1.90	209.00	3.80	418.00	6.00	615.28	6.00	627.10	7.00	674.31	22.80	2334.69
6	*Design and integration*		1.93	203.25	4.63	548.00	6.55	751.25	7.30	1132.65	8.30	1398.82	8.35	1369.74	30.50	4652.47
Grand totals				**1020.35**		**1756.60**		**2776.95**		**5815.99**		**5494.12**		**5037.10**		**15711.61**

A.4 Staff effort

Table 22 presents a list by institute and task of the effort required to execute the programme defined above.

Table 22: Overview of staff effort and cost.

Staff	Year 1 Fraction	£k	Year 2 Fraction	£k	Year 3 Fraction	£k	Year 4 Fraction	£k	Year 5 Fraction	£k	Total Fraction	£k
BHM Physics												
BHM-Phys-PDRA												
LhARA: Novel end station development	0.00	0.00	0.00	0.00	1.00	100.00	1.00	100.00	1.00	100.00	3.00	300.00
BHM-Phys-Stf-1												
LhARA: Novel end station development	0.20	20.00	0.20	20.00	0.50	50.00	0.50	50.00	0.50	50.00	1.90	190.00
BHM-Tech												
LhARA: Novel end station development	1.00	100.00	1.00	100.00	1.00	100.00	1.00	100.00	1.00	100.00	5.00	500.00
Total	**1.20**	**120.00**	**1.20**	**120.00**	**2.50**	**250.00**	**2.50**	**250.00**	**2.50**	**250.00**	**9.90**	**990.00**
IC NHS HC Trust												
IC-NHS-HC-Trst-PhD-1												
LhARA: Novel end station development	0.00	0.00	0.00	0.00	1.00	25.00	1.00	25.00	1.50	37.50	3.50	87.50
IC-NHS-HC-Trst-Stf-1												
LhARA: Novel end station development	0.20	20.00	0.20	20.00	0.50	50.00	0.50	50.00	0.50	50.00	1.90	190.00
Total	**0.20**	**20.00**	**0.20**	**20.00**	**1.50**	**75.00**	**1.50**	**75.00**	**2.00**	**87.50**	**5.40**	**277.50**
ICR, Radiotherapy and Imaging												
ICR PDRA												
LhARA: ionacoustic Imaging	0.00	0.00	1.00	100.00	1.00	100.00	1.00	100.00	1.00	100.00	4.00	400.00
ICR PhD												
LhARA: ionacoustic Imaging	0.00	0.00	0.00	0.00	1.00	25.00	1.00	25.00	1.50	37.50	3.50	87.50
ICR Staff 1												
LhARA: ionacoustic Imaging	0.03	3.00	0.07	7.00	0.07	7.00	0.07	7.00	0.07	7.00	0.31	31.00
ICR Staff 2												
LhARA: ionacoustic Imaging	0.03	3.00	0.07	7.00	0.07	7.00	0.07	7.00	0.07	7.00	0.31	31.00
Total	**0.06**	**6.00**	**1.14**	**114.00**	**2.14**	**139.00**	**2.14**	**139.00**	**2.64**	**151.50**	**8.12**	**549.50**
Imperial Physics												
Diagnostics expert												
LhARA: Design and integration	0.00	0.00	0.00	0.00	0.30	30.00	0.50	50.00	0.50	50.00	1.30	130.00
IC-Phys-PDRA-1												
LhARA: Laser-driven proton and ion source	0.25	25.00	0.50	50.00	1.50	150.00	1.50	150.00	1.00	100.00	4.75	475.00
IC-Phys-PG-1												
LhARA: Laser-driven proton and ion source	0.00	0.00	0.00	0.00	0.50	12.50	1.00	25.00	2.00	50.00	3.50	87.50
IC-Phys-Stf-1												
LhARA: Laser-driven proton and ion source	0.50	50.00	0.50	50.00	0.50	50.00	0.50	50.00	0.50	50.00	2.50	250.00
IC-Phys-Support-1												
LhARA: LhARA Project Management	0.20	20.00	0.20	20.00	1.00	100.00	1.00	100.00	1.00	100.00	3.40	340.00
IC-Phys-Tech-1												
LhARA: Laser-driven proton and ion source	0.00	0.00	0.00	0.00	0.20	20.00	0.20	20.00	0.10	10.00	0.50	50.00
Imp PDRA1												
LhARA: Design and integration	0.50	50.00	0.50	50.00	1.00	100.00	1.00	100.00	1.00	100.00	4.00	400.00
Imp PDRA2												
LhARA: Design and integration	0.00	0.00	0.00	0.00	1.00	100.00	1.00	100.00	1.00	100.00	3.00	300.00
Imp PG1												
LhARA: Design and integration	0.00	0.00	0.50	87.50	0.00	0.00	0.00	0.00	0.00	0.00	0.50	87.50
Imp Staff 1												
LhARA: Design and integration	0.10	10.00	0.10	10.00	0.10	10.00	0.10	10.00	0.10	10.00	0.50	50.00
RF eng.												
LhARA: Design and integration	0.00	0.00	0.00	0.00	0.30	30.00	0.60	60.00	0.60	60.00	1.50	150.00
Total	**1.55**	**155.00**	**2.30**	**267.50**	**6.40**	**602.50**	**7.40**	**665.00**	**7.80**	**630.00**	**25.45**	**2320.00**
Lancaster Physics												
Lanc-Phys-PDRA-1												
LhARA: Laser-driven proton and ion source	0.50	50.00	0.50	50.00	2.00	200.00	2.00	200.00	1.00	100.00	6.00	600.00
Lanc-Phys-PG-1												
LhARA: Laser-driven proton and ion source	0.00	0.00	0.00	0.00	1.00	25.00	1.00	25.00	1.00	25.00	3.00	75.00
Lanc-Phys-Stf-1												
LhARA: Laser-driven proton and ion source	**0.05**	**5.00**	**0.05**	**5.00**	**0.15**	**15.00**	**0.15**	**15.00**	**0.10**	**10.00**	**0.50**	**50.00**
Total	**0.55**	**55.00**	**0.55**	**55.00**	**3.15**	**240.00**	**3.15**	**240.00**	**2.10**	**135.00**	**9.50**	**725.00**
Liverpool Physics												
Liv-Phys-PDRA												
LhARA: Novel end station development	0.50	50.00	0.50	50.00	1.00	100.00	1.00	100.00	1.00	100.00	4.00	400.00
Liv-Phys-PhD												
LhARA: Novel end station development	0.00	0.00	0.00	0.00	1.00	25.00	1.00	25.00	1.50	37.50	3.50	87.50
Total	**0.50**	**50.00**	**0.50**	**50.00**	**2.00**	**125.00**	**2.00**	**125.00**	**2.50**	**137.50**	**7.50**	**487.50**
Manchester Physics												
Man-Phys-PDRA-1												
LhARA: Proton and ion capture	0.00	0.00	0.00	0.00	1.00	100.00	1.00	100.00	1.00	100.00	3.00	300.00
Man-Phys-Stf-1												
LhARA: Proton and ion capture	0.10	10.00	0.10	10.00	0.20	20.00	0.20	20.00	0.20	20.00	0.80	80.00
Total	**0.10**	**10.00**	**0.10**	**10.00**	**1.20**	**120.00**	**1.20**	**120.00**	**1.20**	**120.00**	**3.80**	**380.00**
Queen's Physics												
Qns-Phys-PG-1												
LhARA: Laser-driven proton and ion source	0.00	0.00	0.50	87.50	0.00	0.00	0.00	0.00	0.00	0.00	0.50	87.50
Qns-Phys-Stf-1												
LhARA: Laser-driven proton and ion source	0.05	5.00	0.05	5.00	0.05	5.00	0.05	5.00	0.05	5.00	0.25	25.00
Total	**0.05**	**5.00**	**0.55**	**92.50**	**0.05**	**5.00**	**0.05**	**5.00**	**0.05**	**5.00**	**0.75**	**112.50**
RHUL Physics												
RHUL PDRA1												
LhARA: Design and integration	0.50	50.00	0.50	50.00	1.00	100.00	1.00	100.00	1.00	100.00	4.00	400.00
RHUL PG1												
LhARA: Design and integration	0.00	0.00	0.50	87.50	0.00	0.00	0.00	0.00	0.00	0.00	0.50	87.50
Total	**0.50**	**50.00**	**1.00**	**137.50**	**1.00**	**100.00**	**1.00**	**100.00**	**1.00**	**100.00**	**4.50**	**487.50**
STFC Technical												
Controls specification												
LhARA: Design and integration	0.05	5.00	0.25	25.00	0.35	35.00	0.65	65.00	0.70	70.00	2.00	200.00
Electrical engineering design specification												
LhARA: Design and integration	0.05	5.00	0.55	55.00	0.90	90.00	1.10	110.00	1.10	110.00	3.70	370.00
Mechanical engineering design specification												
LhARA: Design and integration	0.50	50.00	0.80	80.00	1.00	100.00	1.20	120.00	1.20	120.00	4.70	470.00
Radiation Protection Advisor												
LhARA: Design and integration	0.03	2.75	0.08	7.50	0.10	10.00	0.10	10.00	0.10	10.00	0.40	40.25
STFC WP management												
LhARA: Design and integration	0.20	20.00	0.25	25.00	0.25	25.00	0.25	25.00	0.25	25.00	1.20	120.00
Technical services specification												
LhARA: Design and integration	0.00	0.00	0.40	40.00	0.50	50.00	0.50	50.00	0.50	50.00	1.90	190.00
Vacuum specification												
LhARA: Design and integration	0.00	0.00	0.20	20.00	0.50	50.00	0.30	30.00	0.30	30.00	1.30	130.00
Total	**0.83**	**82.75**	**2.53**	**252.50**	**3.60**	**360.00**	**4.10**	**410.00**	**4.15**	**415.00**	**15.20**	**1520.25**
STFC-PPD												
STFC-Finance-Support												
LhARA: LhARA Project Management	0.00	0.00	0.00	0.00	0.20	20.00	0.20	20.00	0.20	20.00	0.60	60.00
STFC-PPD PDRA												
LhARA: ionacoustic Imaging	0.00	0.00	0.00	0.00	1.00	100.00	1.00	100.00	1.00	100.00	3.00	300.00
STFC-PPD Staff 1 (Matheson)												
LhARA: ionacoustic Imaging	0.03	3.00	0.05	5.00	0.15	15.00	0.15	15.00	0.50	50.00	0.88	88.00
Total	**0.03**	**3.00**	**0.05**	**5.00**	**1.35**	**135.00**	**1.35**	**135.00**	**1.70**	**170.00**	**4.48**	**448.00**
Strathclyde Physics												
Strathclyde-Phys-PDRA-1												
LhARA: Laser-driven proton and ion source	0.50	50.00	0.50	50.00	1.00	100.00	2.00	200.00	2.00	200.00	6.00	600.00
Strathclyde-Phys-PG-1												
LhARA: Laser-driven proton and ion source	0.00	0.00	0.00	0.00	0.50	12.50	1.00	25.00	2.00	50.00	3.50	87.50
Strathclyde-Phys-Stf-1												
LhARA: LhARA Project Management Laser-driven proton and ion source	0.60	60.00	0.60	60.00	1.50	150.00	1.50	150.00	1.50	150.00	5.70	570.00
Strathclyde-Phys-Tech-1												
LhARA: Laser-driven proton and ion source	0.00	0.00	0.00	0.00	0.20	20.00	0.20	20.00	0.10	10.00	0.50	50.00
Total	**1.10**	**110.00**	**1.10**	**110.00**	**3.20**	**282.50**	**4.70**	**395.00**	**5.60**	**410.00**	**15.70**	**1307.50**
Swansea Physics												
Swan-Phys-Tech-1												
LhARA: Proton and ion capture	0.00	0.00	0.00	0.00	1.00	100.00	1.00	100.00	0.50	50.00	2.50	250.00
Swan-Phys-Tech-2												
LhARA: Proton and ion capture	0.00	0.00	0.00	0.00	1.00	100.00	1.00	100.00	0.50	50.00	2.50	250.00
Swns-Phys-PDRA-1												
LhARA: Proton and ion capture	1.00	100.00	1.00	100.00	1.00	100.00	1.00	100.00	1.00	100.00	5.00	500.00
Swns-Phys-PDRA-2												
LhARA: Proton and ion capture	0.00	0.00	0.00	0.00	1.00	100.00	1.00	100.00	1.00	100.00	3.00	300.00
Swns-Phys-PG-1												
LhARA: Proton and ion capture	0.00	0.00	0.00	0.00	1.00	25.00	1.00	25.00	1.50	37.50	3.50	87.50
Swns-Phys-PG-2												
LhARA: Proton and ion capture	0.00	0.00	0.00	0.00	1.00	25.00	1.00	25.00	1.50	37.50	3.50	87.50
Swns-Phys-Stf-1												
LhARA: Proton and ion capture	0.10	10.00	0.10	10.00	0.30	30.00	0.30	30.00	0.30	30.00	1.10	110.00
Total	**1.10**	**110.00**	**1.10**	**110.00**	**6.30**	**480.00**	**6.30**	**480.00**	**6.30**	**405.00**	**21.10**	**1585.00**
UC Berkley (USA)												
Consultant												
LhARA: Proton and ion capture	0.04	4.00	0.04	4.00	0.04	4.00	0.04	4.00	0.04	4.00	0.20	20.00
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												
UCL PDRA(shared ICL)												
LhARA: ionacoustic Imaging	0.00	0.00	1.00	100.00	1.00	100.00	1.00	100.00	1.00	100.00	4.00	400.00
UCL Staff 1												
LhARA: ionacoustic Imaging	0.03	3.00	0.15	15.00	0.15	15.00	0.15	15.00	0.15	15.00	0.63	63.00
Total	**0.03**	**3.00**	**1.15**	**115.00**	**1.15**	**115.00**	**1.15**	**115.00**	**1.15**	**115.00**	**4.63**	**463.00**
Grand total	***7.84***	***783.75***	***13.50***	***1463.00***	***35.58***	***3033.00***	***38.58***	***3258.00***	***40.73***	***3135.50***	***136.23***	***11673.25***

A.5 Deliverables and milestones

The LhARA Prelminary Activity and Preconstruction Phase projects are scheduled over five years. The budget for the two-year Preliminary Activity was developed to provide the LhARA contributions to the key deliverables defined in the ITRF proposal to the UKRI IAC, principally the CDR for the facility. Resources for the subsequent, three-year, Preconstruction Phase need to be revised during the Preliminary Activity and will be dependant on progress and will require further independent review.

LhARA project reviews with external oversight will take place every six months. Progress will be recorded at each review in a deliverable report. These deliverable reports will roll up all milestones delivered in that period as well as reporting overall project progress. At the 18 month review, funding options for years three to five will be presented and evaluated. A plan will be agreed and appropriate actions assigned to ensure a smooth transition.

Milestone reports have been inserted in the schedule by the expert work package managers. Some dates have been adjusted to allow appropriate reporting of progress within the structure of the project. Where possible, milestones are scheduled to arrive in good time to provide the justification for continued project funding. Milestone reports will be issued by the LhARA project and will be subject to internal review before issue. Work package 1: *Project Management* "owns" all Project deliverables and hence has no Milestones.

Deliverables

Work Package 1. Project management: Deliverables

- D1 Early progress review CDR M6
- D2 Interim progress review CDR M12
- D3 Pre-CDR Review M18
- D4 CDR M24
- D5 Pre-TDR review M30
- D6 TDR1 M36
- D7 Early progress review TDR2 M42
- D8 Interim progress review TDR2 M48
- D9 Pre-TDR2 review M54
- D10 TDR2 M60

Milestones

Work package 2: Laser-driven proton and ion source

- M2.1: Prediction of optimised proton source parameters for 100+ TW laser systems based on hydrodynamic and kinetic simulations M12
- M2.2: First SCAPA ion source simulations and experiment completed M18
- M2.3: Report detailing optimisation of proton and ion generation on SCAPA, leading to LhARA laser specification M30
- M2.4: Demonstration of 10 Hz operation of advanced targetry platform at ICL M48
- M2.5: Demonstration of stabilised 5 Hz beam generation on SCAPA M60

Work package 3: Proton and ion capture

- M3.1: Validate plasma simulations with existing Swansea experimental set-up M6
- M3.2: Progress report of large diameter plasma experiments and simulations M18

- M3.3: Next generation plasma lens testbench design M24
- M3.4: Progress report of standalone plasma apparatus build and commissioning M36
- M3.5: Progress report of large particle-number plasma experiments and simulations M48
- M3.6: Ion focussing results M60
- M3.7: Final plasma lens design M60

Work package 4: Ion-acoustic dose mapping

- M4.1: Geant4 simulations of beam energy deposition profile M18
- M4.2: Acoustic sensor array design M24
- M4.3: Iterative reconstruction methods M42
- M4.4: Integration: ultra-sonic array with radiobiology station M48
- M4.5: LhARA ion-acoustic test results M60

Work package 5: Novel end-station development

- M5.1: Design LhARA automated cell dish handling and environmental system M24
- M5.2: Report on delivery of LhARA beam monitoring system M60
- M5.3: Report on end-station user-community consultation M24
- M5.4: End station component testing at Birmingham M24
- M5.5: Specification of LhARA beam monitoring technology M24
- M5.6: Report on delivery of LhARA beam monitoring system M60
- M5.7: kGy/s tests at Birmingham M24

Work package 6: Design and integration

- M6.1: Final review of R&D work towards LhARA CDR M18
- M6.2: Final review of R&D work towards LhARA Phase 1 TDR M35
- M6.3: Final review of R&D work towards LhARA Phase 2 TDR M54
- M6.4: Technical report on FFA main magnet prototype M58.
- M6.5: Technical report on MA RF cavity prototype M58.

A.6 Risk

Risk in the LhARA project is assessed in each work package by the Work Package Managers. Two factors enter the calculation of the risk score: the likelihood that the risk will occur and the degree of impact to the project should the risk occur. The criteria and scoring is outlined in table 23. The overall score is the product of the two factors.

The risk register for the LhARA project provides pages for each work package. The work-package risks are directly managed by the Work Package Managers. Culled from the work package risk assessment is a register of "Top Level Risks" which are actively tracked by the project management team. The date on which a risk will be retired is recorded, but the cost of mitigation are yet to be determined. Updates to the work-package risk registers will be required monthly, one week before the overall project update is due. In addition, Work Package Managers are charged with informing the Project Management Team of any likely or actual change in risk level within their work package at the time of a significant change. The Project Management Team assess the risk register returns monthly, moving those with significant project impact into the top level risk register and demoting those for which the score has substantially reduced.

The top level risk register for the LhARA project is shown in table 24. Risk 1 is generic to most large research projects in that the funding request must be tailored not only to the objectives of the project but also to the realistically available funding. To a degree this risk has already been realised in that the full research content of this document will not be funded from a single source, a significant and self consistent subset of the research

Table 23: LhARA risk scoring.

Probability scoring criteria: Likelihood of Risk Occuring

Qualitative Description	Definition/Criteria
Very unlikely	<20%
Unlikely	20%-40%
Moderate	40%-60%
Likely	60%-80%
Very likely	>80%

Impact scoring criteria: What effect would the risk have if it did occur

Use quantitative criteria where possible eg. % of budget for cost, weeks/months delay for schedule.

Qualitative Description	Definition			
	Estimated impact if the risk does occur to:			
	Cost	Schedule	Quality	Reputation
Very low	<1% over budget	Cannot deliver activity to plan, no significant impact to schedule.	Minimal or no consequence to quality of output.	Short term damage to project reputation.
Low	1-5% over budget	Cannot deliver task to plan, no impact on interim milestone.	Minor reduction to quality, can be tolerated with little/no impact to customer.	Medium term damage to project reputation.
Moderate	5-10% over budget	Cannot meet an interim milestone, no impact to customer milestone.	Significant quality reduction, complicates customer acceptance.	Long term damage to project reputation.
High	10-20% over budget	No float remaining for key/customer milestone.	Quality of final output reduced, does not meet customer expectation.	Long term national damage to project & consortium reputation.
Very high	>20% over budget	Cannot meet a key/customer milestone.	Quality of final output severely reduced, falls significantly short of customer expectation.	Long term international damage to project & consortium reputation.

will be funded by from the resources awarded by the UKRI IAC to support the ITRF. Mitigation measures that are in place include seeking additional funds from other sources, several possible sources have already been identified. Risk 3 is also generic. Talented university staff often find opportunities which take them away from their current work. Similarly, STFC TD staff are greatly in demand with opportunities across many interesting, important projects with the added complication that staff recruitment and retention at the national labs is a well recognised problem of long standing. The remaining risks can be divided into two groups; those dominated by technical challenges, amenable to mitigation through quality research and problem solving—risks 2, 4, 5, 6 and 7 fall into this category—and those which are best mitigated through appropriate project management—risks 8 and 9 being good examples. Risk 8 is currently showing green, post mitigation, as considerable resource has been provided to advance the infrastructure parts of the facility design and bolster the credibility of the costing component of the CDR.

Table 24: LhARA Top Level Risk Register

	Number	WP Number	Name	Description	Likelihood	Impact	Score	Mitigation	Mitigated Likelihood	Mitigated Impact	Mitigated score
WP1	1	1.5	Resources	Insufficient resources secured to deliver the project.	5	4	20	Pursue additional sources of funds.	4	4	16
WP1	2	1.3	Performance specification parameters	Inadequate ion beam parameters to meet the Physics and Biolology requirements.	3	5	15	The project consortium includes the required experts to improve performance and adapt requirements to maximise convergence of capability and need.	2	5	10
All	3	9	Key specialist staff	Availability of key specialist staff critical to project.	4	5	20	Identify potential single point failure risks, apply cover and succession planning where appropriate.	2	5	10
WP2	4	2.7	Source output	Unable to deliver desired beam.	3	4	12	Investigate experimental techniques to increase yield	2	2	4
WP2	5	2.1	Laser Access	Laser schedule does not allow sufficient access.	3	4	12	Apply for access to other,similar, laser systems e.g Gemini	2	3	6
WP3	6		Plasma Density	A low density will result in too long a focal length (& beamline)	4	4	16	Expert experimental design coupled with established and novel mitigation measures	4	3	12
WP4	7	4.1	Low acoustic signal	Insufficient acoustic signal to noise ratio.	3	5	15	Employ range of established techniques. Adaptively trade dose-map resolution for enhanced signal	3	3	9
WP6	8	6.6	Facility Integration	Delayed start/insufficient early resource.	3	5	15	Prioritise integration work package	1	4	4
WP5	9	5.1	End Station Specification	End station specification does not clearly specify requirements.	5	5	25	Early progress review, input from system designers to user consultation exercise	1	5	5

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 beam therapy (IBT). 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 IBT 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 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 LhARA system will be developed and produced in partnership with the industrial members of the collaboration. Active involvement in the R&D and LhARA 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 exploitation of LhARA. 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 (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 LhARA 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-beams (MBRT). 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 the use of automation and feedback to increase patient throughput to allow IBT 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 development of new strategies and therapies for tumours that are rare, difficult to treat, 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, and 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 LhARA 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, LhARA will 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 economics, and higher-education policy makes to promote bio-physical sciences will be important. In addition, clinical involvement of the NIH BRC network and cancer charities will widen the patient engagement.

LhARA is a “four-nation” project, therefore engagement with MPs, devolved assembly members, and their constituents to promote the societal benefits and job-creation opportunities that the LhARA initiative offers will be key.

A.8 Management plan

A.8.1 Programme organisation

The multidisciplinary LhARA collaboration's mission [1] is to harness the disruptive potential of laser-driven proton and ion sources to create a ground-breaking biomedical research facility [2, 3]. 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
- 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 15 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 16 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 review 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.

The Executive Board provides the management of the LhARA collaboration and is responsible for 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. The EB represents the collaboration in its relations with outside bodies. The EB is chaired by the LhARA spokespeople.

Figure 15: 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 such that LhARA serves the Ion Therapy Research Facility (ITRF) [4].

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

The present programme managers are:

- Jason Parsons (Biological Science), University of Liverpool;
- Colin Whyte (LhARA Project), University of Strathclyde.

As the LhARA initiative gets off the ground a programme manager for the "Impact: clinical and industrial" activity will need to be appointed.

Figure 16: Graphical representation of the institutes that make up the LhARA collaboration. The list of collaborating institutes is reproduced in Annex B.

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) [4] and defines the programme and resources required during the Preliminary Activity and the Preconstruction Phase.

The organisation of the LhARA project will be carried out in accordance with the STFC Project Management Handbook [132, 133] in by the LhARA collaboration in partnership with the STFC Daresbury and Rutherford Appleton Laboratories. The organisational structure of the LhARA project is shown in figure 17 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 advisory body for the LhARA Executive Board and LhARA Project Manager.

The PMB will be chaired by the LhARA Project Manager and include:

- The LhARA collaboration co-spokes people, one of whom will act as the Principal Investigator, the other as the Project Scientist;
- Work Package leaders; and
- Project Management Office representatives.

Additional expertise may be co-opted as required. The PMB collectively manages all aspects of the LhARA project.

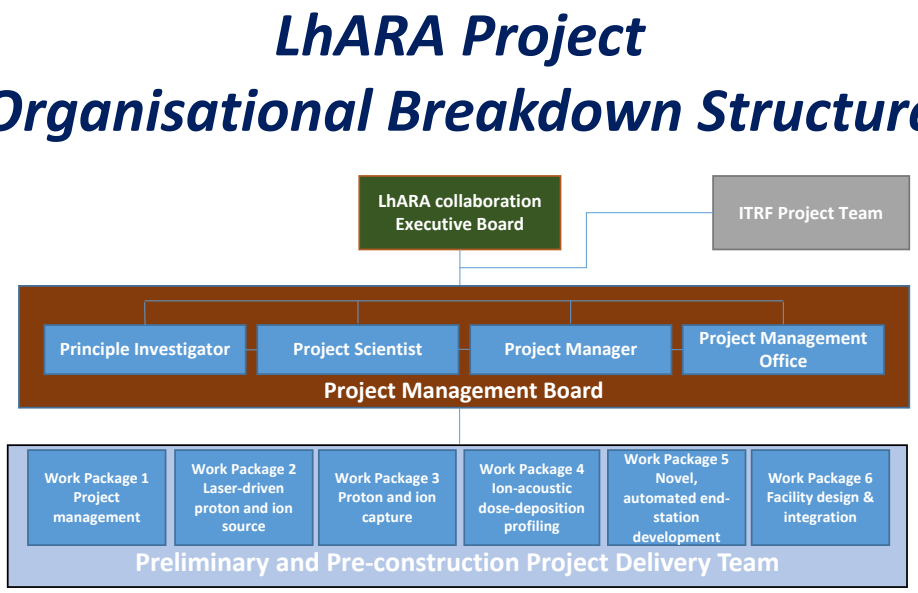

Figure 17: The organisational chart for the LhARA project. The functions of the Project Management Board are described in the text. The key roles within the project structure are indicated. The preliminary phase project is executed through six work packages, as indicated in the figure. The work content of each work package is defined in section A.2.1 to A.2.6.

The PMB will develop and maintain the LhARA Project Management Plan (PMP) will include all the plans and reference all the key project-management documentation required to deliver the project successfully. The PMP will include the 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 plans.

The PMB will meet monthly. Additional meetings focussed on specific technical and planning issues will occur more frequently with progress reported at the monthly PMG meetings by Work Package Managers.

The LhARA project has been underway for several years and produced a pre Conceptual Design Report [2, 3]. Further definition is proposed through the development of a full Conceptual Design Report. Technical Design Reports for LhARA Stages 1 and 2 will be produced in the Preconstruction Phase.

The Implementation Phase of the project will follow the Preconstruction Phase. During the Implementation Phase the PMB 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 reviews will be implemented during the concept and definition phases of the project. The reviews will focus on: what has been achieved; what are the key requirements for the next phase; what are the key decisions to be made; and whether the business is case still viable, i.e. can the desired benefits be achieved for an acceptable level of cost and risk? Gates will also be implemented at the end of each phase of work.

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, Principal Investigator, Project Scientist, and project delivery team.

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

The Principal Investigator: (PI) 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 Principal Investigator is:

- Kenneth Long; Imperial College London/STFC.

The Project Scientist: (PS) is responsible for ensuringn 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:

- Amato Giacca; Oxford Institute for Radiation Oncology, Oxford University.

Project Manager: is accountable to the LhARA Executive Board and forms the link to the ITRF Project Team. Together with the PI and PS, the Project Manager will maintain a continuous dialogue with the STFC 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 [132, 133].

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 [131] was held before publication of the pre-CDR [2] for the facility. A committee is being established to review the Preliminary Activity and the Preconstruction 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 [2]. This proposal builds on the pre-CDR and is designed to establish the conditions

for the technical-design phase of the LhARA project. 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) [134] 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 Activity. The present proposal also defines the work that must be carried out in the subsequent three-year Preconstruction Phase. An overview of the schedule for the development of the LhARA initiative in the Preliminary Activity and the Preconstruction Phase is shown in figure 18.

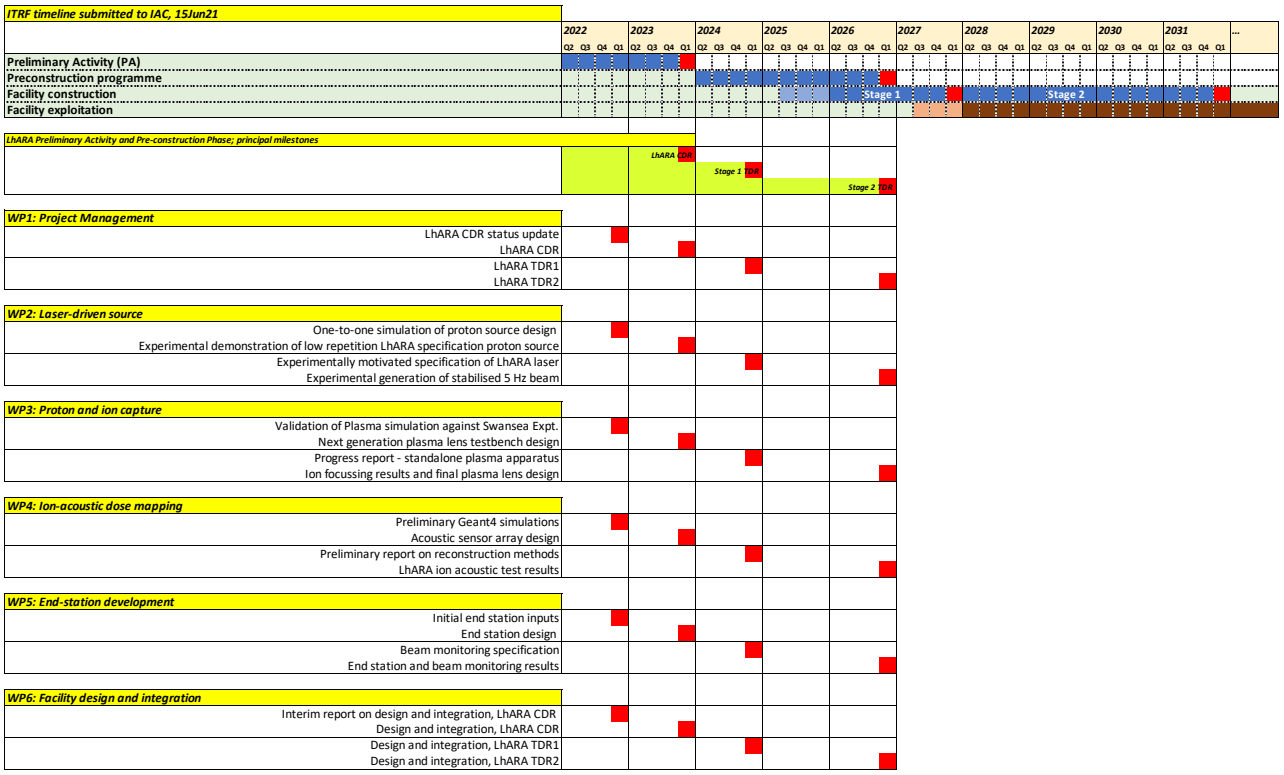

Figure 18: Waterfall chart showing the principal milestones that define the project proposed herein. The block entitled "ITRF timeline submitted to IAC, 15Jun21" shows the timeline for the development of the ITRF submitted to the UKRI's Infrastructure Advisory Committee. The block entitled "LhARA Preliminary Activity and Preconstruction Phase; principal milestones" shows the principal milestones of the LhARA Preliminary Activity and Preconstruction Phase proposed here. The subsequent blocks present the principal milestones that serve to specify each of the work packages.

The specification of the Preliminary and Preconstruction 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 18. The Preliminary Activity is assumed to take place over the first two years of the project while the Preconstruction Phase is assumed to take place over years three to five. The principal deliverables that define the project are:

Preliminary Activity:

- *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).

Preconstruction 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 Manager and Project Management Board) to support the Work Package managers in this task and to ensure that it is done. The Project Management Board

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 Management Board 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 will be based on Safety Readiness Reviews with checks and sign-off sheets by the technical leads of each discipline. Documentary evidence of adherence to 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 LhARA project's influence on the environment will be a key consideration throughout the project's 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 impact 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

The Work breakdown structure is already well developed through the refinement of the work packages during the writing of this proposal. Work packages objectives have been broken down into several components to allow costing of the required staff effort and equipment. These will be further refined and formalised within the project once funding is awarded. The Work Breakdown Structure of the Preconstruction Phase will be developed as the formal proposal is written in the last six months of the Preliminary Activity. This will necessarily draw on expertise from all the work package managers.

A.8.6 Critical path

The LhARA project has not yet reached the construction phase and the individual work packages do not yet show sufficient inter-dependancies for the concept of a critical path to yield meaningful data. As the project moves forward and such dependancies emerge, a critical path through the project will be determined and monitored in the usual way. It is anticipated that such a critical path will not emerge during the Preliminary Activity of the project. Due consideration will be given to the critical path when the Preconstruction Phase of the project is planned. Currently we expect this work to begin at month 18 of the Preliminary Activity of the project and continue through month 24.

A.8.7 Risk management plan

The Project delivery team is required to keep the Project Management Board apprised of potential risks, their consequences and the development of appropriate contingency plans. The Project Manager and Work Package Managers will report regularly on the evolution of the project risk register to the Project Management Board. 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 Board in a timely manner. Risk Management will be a standing agenda item at the Project Management Board and Executive Board meetings. Risks will be identified, captured, have mitigation controls implemented to reduce the risk likelihood or impact (or both), and will be 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 Project Management Board meeting; significant changes will be presented by the Project Managers in their report to the Project Management Board.

A.8.8 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 [132, 133]. 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 Manager and reviewed by the Project Management Board 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 Management Board.

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 Management Board and in turn by the Project Management Board. A change control mechanism will be established as the project enters the Preconstruction Phase.

A.8.9 Document control plan

Project documentation, including engineering drawings and specification documents, is collected in the "Technical Note" repository [135] that is maintained as part of the CCAP wiki [136]. The documentation source files (WORD, LaTeX, figures, spreadsheets etc.) are stored in a GIT repository [137]. 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 Management Board and Project Management Board.

A.8.10 Staffing strategy

Initial estimates of the staff effort required to deliver the LhARA facility were presented in the pre-CDR [2]. The effort break-down in terms of FTEs needed for the different roles specified in the pre-CDR project plan are shown in table 25. These estimates are reproduced here as a guide to the scale of the undertaking. It is reasonable to assume that more effort will be needed as the table includes only those positions and rolls identified in the pre-CDR. The development of a more robust staff-effort estimate will be carried out in WP6 and presented in the CDR at the end of year 2 of the programme proposed here.

The development of the LhARA Programme, which includes the development of radiation biology and biomedical impact activities will require further staff resources to be secured.

A.8.11 Availability of staff resources

Execution of the LhARA Project will require expertise in laser-driven particle sources, high power optics, accelerator science, RF and other electrical power systems, cryogenics engineering, advanced diagnostics, detectors and instrumentation, advanced beamline design, experimental systems design, automation, feedback and control, high-throughput, and high-performance computing. The institutes that make up the LhARA collaboration and the STFC has pools of expertise in all of these areas.

Type of position	Number of FTEs
Academic	10.7
Administrative	10.3
Engineering	27.9
Post-doctoral Research associate	61.2
Post-graduate student	50.7
Technical/support	5.1

Table 25: Breakdown of the staff effort estimated as required for the execution of the LhARA project. Table taken from the Management annex of [2].

The LhARA project and the wider LhARA Programme are significant activities. The collaboration recognises the need to develop a recruitment and staff-development strategy by which to build on the existing skill base. Of particular importance is the development of an appropriate depth of expertise at the interfaces between the existing skills sets. For example, the LhARA collaboration includes leading experts in laser-driven sources, novel accelerator development, and advanced instrumentation as well as internationally recognised radiation biologists, biophysicists, medical physicists and oncologists. For the full benefits of the programme to be realised staff with multidisciplinary expertise able to communicate effectively across the individual specialities will be required. LhARA personnel are active in the development of a number of multidisciplinary initiatives by which to create a cohort of scientists with the expertise necessary to deliver the LhARA Programme.

The novel technologies on which the LhARA design concept is based have either recently been implemented or are in the early stages of development and are being actively pursued in a number of locations in the UK, Europe and worldwide. The LhARA collaboration encompasses the key UK groups contributing in each of the novel technology-developments areas. The collaboration places great importance on its efforts to continue to develop links with strong laboratories overseas. With the resources requested in this proposal we will seek to establish further collaborations with Berkeley, SLAC, and a number of European institutes.

It will be important for all LhARA project staff to continue to develop their expertise and exchange ideas in these fast-moving areas through participating in, and organising, international workshops and collaborating on related development projects. The LhARA collaboration is well placed to do this, for instance the collaboration is active in the preparation of the ”Disruptive technologies for proton/ion oncology workshop” which will take place at RAL on the 28^{th} April 2022. There will also be great benefit to be obtained from encouraging short term visiting-scientist appointments across the collaboration, to establish student-exchange programmes, and to enhance the present CCAP seminar series to encompass areas of interest to the members of the collaboration.

A.8.12 Consideration of diversity issues

The collaboration recognises its responsibilities in the promotion of equality and diversity in the development of its activities. As employees, each member of the collaboration is responsible to their employer for their adherence to Equality and Diversity policy. Where work is being carried out outside the jurisdiction of a particular collaborating institute, the collaboration will be guided by the STFC Diversity Guide [138].

In the execution of the LhARA initiative it is necessary to distinguish a number of activities:

- Working at an individual’s home institution: in this case the regulations established by the individual’s employer will be in effect;
- Working on an “occasional” basis as a visitor to another institute: in this case it will be understood that

the by accepting to work as a visitor, the individual has agreed to be bound by the host institutes regulations; and

- The construction, execution, and exploitation of the LhARA project: The construction, commissioning, execution, and exploitation of LhARA will be significant activities extending over a number of years. Therefore, for the avoidance of uncertainty, collaboration members will be asked to sign an agreement that they agree to be bound by the host laboratories regulations. This agreement will be modelled on that in force for visiting scientists working at CERN. The model was used effectively in providing a framework for the work of MICE collaboration members when working on STFC Laboratory sites.

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 Management Board 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 Preconstruction Phase. These will be obtained through competitive tender based on a design specification worked-out in the Preliminary or Preconstruction Phases. As part of the Quality assurance management (section A.8.8), 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 Preconstruction Phase:

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, preconstruction, 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 Activity and implemented during the Preconstruction 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 [133]. 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 Preconstruction 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 Management Board and Project Management Board 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 Management Board meetings, the Project Management Board 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.