Review of the collaboration's "R&D proposal for the preliminary and pre-construction phases"

Response to feedback

The LhARA Project Management Board

On behalf of the LhARA collaboration, the Project Management Board welcomes the feedback [1] of the reviewers following the review meetings held on the 30$^{\text{th}}$ August 2022[1], and 26$^{\text{th}}$ and 27$^{\text{th}}$ October 2022. This document provides the project team's response to each of the panel's recommendations.

1 Response to feedback

1.1 Review of radiobiology input for LHARA

Recommendations

1. **Ensure possibilities for in vivo research. This includes nearby animal facilities and possibility for small animal imaging thought into the facility.**

   The project team agrees that providing the capability to carry out *in-vivo* studies is an important element of the LhARA project. Efficient exploitation of the *in-vivo* end station will require appropriate access to animal facilities. To maximise the scientific programme that can be supported by the facility will require an appropriately high level of automated remote handling. This implies the need for in-situ imaging to ensure the correct positioning and exposure of the animal. These ideas will be developed through the peer-group consultation being carried out in work package 5.

2. **Ensure access to experimental reference beams (e.g. conventional proton beams and photon beams).**

   The project team agrees that comparison of the results obtained with the novel beams that LhARA will provide with those of conventional sources will be an essential part of the programme. Work has started on the preparation of a proposal to the Medical Research Council under the Developmental Pathway Funding Scheme for an initial programme of experimentation on conventional and laser-driven proton and ion beams. Our objective is to begin to investigate the radiobiology themes to which LhARA will provide access and to develop the techniques required to maximise the scientific potential of the LhARA facility. The "sister review to look at the instrumentation, diagnostics, novel end-station development, and radiobiological topics" identified in [2] will be scheduled taking into account the timescale of the review of the collaboration's proposal to the MRC DPFS scheme and the ongoing peer-group consultation being carried out by WP5.

[1] This link is to an Indico page for which the pass phrase is CCAP3008.

1.2 Review of LhARA collaboration's R&D proposal for the Preliminary Activity Phase – Report Accelerator and Technology Session

Recommendations

1. **Continue and strengthen the collaboration between the medical and radiobiology and the accelerator communities. This is vital in the refinement/revision of the parameters with the evolution of the project as R&D progresses and options are investigated.**

   In forging the LhARA collaboration a significant effort was made to assemble expertise from across the medical, radiation biology, and natural science communities. The project team is clear that strengthening the multidisciplinarity of the collaboration remains vital to the successful execution of the programme. Every effort will be made to maintain and enhance the collaboration's multidisciplinarity.

2. **Assess in depth possible challenges and limitations of the Gabor lens in addition to the required electron density and plasma transverse size as the required focusing linearity and, in turn, electron density homogeneity and possible beam pollution by other species.**

   In section 2.8 (paragraph that spans the bottom of page 7 and top of page 8) the reviewers noted the contributions made by the Swansea and Manchester groups to the Penning traps employed on the ALPHA experiment at CERN. The ALPHA Penning traps were of similar design to those proposed here and were used to cool anti-protons. Since the kinetic energy spread of the anti-protons was large, the presence of a strong magnetic field masked any lensing effects due to the non-neutral plasma. In contrast, the space-charge contained within the Penning traps envisaged for use in the LhARA project are required to focus the positive ion beam.

   The thermalised, low temperature, non-neutral plasmas that will be formed within the Gabor lens will naturally develop a uniform electron density. This has been observed in various systems (see e.g. Dubin and O'Niel [3]). In addition, perturbations to the uniform density distribution, referred to as plasma modes or plasma oscillations, typically have amplitudes $\ll 1\%$. Such oscillations have been observed under a multitude of conditions. Plasma modes are well understood for well confined plasma (see for example [4–8]).

   Many of the individual parameters required of the plasma in the LhARA Gabor lens (e.g. size or density) have been obtained in systems elsewhere. During the review, greater emphasis could have been placed on the fact that many existing systems have achieved the highly uniform density required for a Gabor lens. Much of the current experimental programme has focused upon parameters such as 'size' or 'lifetime', as these are intrinsically linked to plasma density; for instance, under 'poor' conditions, deleterious plasma modes will develop which, if unchecked, will grow, leading to an unstable plasma that is ultimately destroyed through expansion.

   The specifications for the test bench are such that it will allow the study of plasmas at various scales to allow the parameters required of the final lens design to be determined. The expected density and the behaviour of the plasma as multiple parameters are scaled simultaneously will be studied. Diagnostics are required to provide real-time, shot-to-shot, knowledge of the plasma and to allow feedback to damp deleterious plasma modes before they become an issue. Plasma diagnostics rely on various density perturbations. Therefore, the study of the behaviour of the plasma will include the study of density perturbations.

   The catalyst for the development of density perturbations is often 'pollution', whether by other species within the plasma (such as background gases) or the quality (e.g. lack of homogeneity and temporal fluctuations) of external fields. It is expected that ion-beam pollutants, such as multiple ion species, within the capture system will influence the trapped plasma. Since details of the kinematic distributions of such ion species are not yet available, a detailed evaluation can not yet be made. However, current estimates suggest that the various timescales involved are sufficiently disparate that the impact of ion-beam pollution on individual shots will be small. When operating the system at 10 Hz, there is significant time for plasma preparation (e.g. damping of induced density perturbations) between shots, if needed.

Resource limitations have led the project team to make extensive use of in-depth simulations to make sure that the formation of plasmas of a suitable size and density is possible. The simulations will also be used to study the conditions under which deleterious density perturbations develop within our parameter space. These studies will inform the design of a stable plasma-lens system. The first step towards the development of the in-depth simulation is the confirmation that the codes that will be employed capture the relevant physics with sufficient precision over the disparate timescales that are involved in LhARA.

The challenges expected along the route to the design of a Gabor lens for LhARA are recorded in the risk register. The experimental limitations (such as wall-to-plasma radius, or fraction of the Brillouin limit on the plasma density) are reasonably well identified and mitigating engineering solutions are expected to be implemented and studied using the test-bench. Further studies of new literature, extended computation, and possibly experimentation using existing apparatus, will be performed as resources become available. This combined experiment/simulation approach will provide the detailed understanding of the plasma dynamics required to allow the design of the LhARA Gabor lens to proceed with confidence.

3. **Continue the preliminary preparations to facilitate the implementation of a proton and ion capture system based on more conventional technology (normal conducting or superconducting solenoids and Wien filter) as a possible alternative to the Gabor lens system, if it becomes necessary. As part of the Conceptual Design Report it might be useful to define the time-line for decision on the choice of the design of the capture system consistent with the construction and operation deadlines.**

The project team continues to develop the beam transport and particle selection systems with the constraint that it be possible to exchange the Gabor lenses with solenoid magnets should this become necessary. The solutions therefore automatically map onto a solenoid-based system. Parameter limits are currently selected to allow the use of conventional warm magnets.

Progress of the Gabor-lens-development programme is monitored by the project team and the LhARA baseline document is discussed at each of the six-monthly LhARA collaborations meetings. If the collaboration assesses that the Gabor lens sub-project may not deliver to the required schedule, it is empowered to update the baseline and change the default focusing scheme to solenoids. The collaboration recognises the enormous potential benefits that a Gabor lens system offers and believes these benefits justify the attendant technical risk. Routes to additional funding have been identified that would enable increased spend in this work package to mitigate the risk. The project management team views this as one of the major challenges for the project, one which requires a parallel multi-year funding stream to bring its time-line into synchronisation with the remainder of the project. We expect to provide that additional effort within the current calendar year.

The project team acknowledges that an appropriate decision path with a clearly articulated time-line and decision points will be required as the project enters the pre-construction phase.

4. **Consider a preliminary design of a Rapid Cycling Synchrotron as a possible alternative to the FFA as post accelerator and compare costs, performance but also tunability and operability of the two options.**

The FFA provides rapid acceleration without the need to transfer energy into and out of the guiding dipole field. For the LhARA application this fixed-field solution accommodates the arbitrary time structure required to investigate the temporal dependence of the biological response to ionising radiation. In addition, the large dynamic aperture provides large acceptance for multiple ion species.

A rapid-cycling synchrotron can be designed to operate at the 10 Hz repetition rate specified in the LhARA baseline. However, the application of a rapid-cycling synchrotron at repetition rates of 100 Hz or above would be challenging. Therefore, the broader LhARA initiative, in which the technologies necessary to transform the clinical practice of particle-beam therapy will be demonstrated in a research facility, provides additional motivation for development of the FFA which will be able to accommodate such high repetition rates.

Despite the "in-principle advantages" of the FFA, the project team acknowledges the need to consider a preliminary design of a rapid-cycling synchrotron for the purposes noted by the panel. Tunablity and operability are not explicit parameters under consideration but these can be added to the list of metrics to be evaluated. The project team is actively pursuing avenues by which such a design can be developed within the limited resources that are presently available. An attractive option is to exploit the Framework Collaboration Agreement between CERN and the STFC which allows joint development of novel accelerator systems for medical application. The project team will continue to explore this option. A conventional high intensity synchrotron design is under development as part of the wider ITRF project. This design is based on the synchrotron being developed in the NIMMS2 project as part of the Framework Collaboration Agreement mentioned above. Explicit comparison of the synchrotron-based solution with the LhARA FFA design is a requirement in the ITRF project plan.

5. **A thorough study of direct space charge effects and their impact on beam loss and emittance increase should be carried out. The consequence of direct space charge effects on beam parameters after acceleration should be evaluated and used to estimate possible beam sizes at the end stations.**

   The project team welcome the panel's recommendation and agrees that a careful study of space-charge effects is essential. The status of the study of space-charge effects in LhARA was presented at the review. These studies have continued for the Stage 1 beam-line using GPT. An evaluation of alternative codes has just begun with a view to carrying out a more detailed and thorough investigation.

6. **It is recommended to seek compensation for the effect of the inflation considering the exceptional international situation.**

   The rules under which the LhARA project funded explicitly excluded consideration of inflation. The annual inflation in the UK for 2022 is slightly over 9%. The majority of the LhARA budget is assigned to staff. These costs are likely to rise less rapidly than the headline inflation rate as they are regulated through national pay negotiations. Non-staff costs are dominated by laser-facility-access and travel costs. A relatively small sum is allocated to the purchase of equipment. It is anticipated that the institutions providing access to lasers will stand by their quoted access costs. Travel and equipment have both increased at a rate markedly above the average national inflation rate, with some estimates showing travel and subsistence inflation peaking at over 50% but falling to 25% over the course of the year. If we assume salary inflation to be two thirds of the UK rate for 2022/23, i.e. 6%, then overall the appropriate inflation figure for the LhARA costs is between 7% and 8%.

7. **Contingency should be addressed at some level.**

   The current rules under which the LhARA project was funded explicitly exclude contingency and working margin.

   The majority of the project funding is provided by grants to universities. The grants are based on costs supplied by the universities and include an estimate of inflation and take account of averaged cost increases due to staff increments and the outcome of national pay bargaining. The project may reasonably expect the universities to stand by these costs. However, some will simply provide a fixed budget and leave the management of any problems that arise from higher than estimated costs to the institute PI. Under these conditions, both contingency and working margin are appropriate. The LhARA project team considers that, in the present Preliminary Activity, the lowest appropriate working margin would be 5–7% with an upper bound of 10%.

The project team have reviewed the project's risk register to estimate the costs of an appropriate programme of risk mitigation. This analysis allows an estimate of the contingency requirement to be made. We note that the combined total is large (60%), reflecting the fact that the project is in its initial stages and that the scope of the programme is limitted at present by the ITRF funding envelope. A project of this type would normally be considered to require a contingency of between 30% and 50%, the latter being indicated for an early-stage project such as LhARA where technical solutions are still being developed. The project risk table has been updated to include the costs of mitigation. The estimates of the cost of risk mitigation presented by work package below should be seen in the context of the comments made above.

WP1; Project Management: Work package 1 deals with project management. The only significant outstanding risk in WP1 relates to the cost of travel and subsistence. This part of the project budget was squeezed during the LhARA/ITRF alignment discussions. In addition, flights, train travel and accommodation have all experienced significant cost increases in the past year. We estimate a contingency of £30k would mitigate travel-cost risk for the LhARA Preliminary Activity project.

WP2; Laser-driven proton and ion source: The experimental risk in WP2 is largely related to the problem of managing the debris in the target area. There is the possibility of damage to large, expensive optics, the loss of which could prevent or delay further operation. £25k hardware contingency is appropriate. Additional contingency of £25k is required to mitigate the risk of loss of beam time due to facility failure or issues in commissioning test equipment. On the modelling side, the risks lie in the ability to access sufficient super-computer resources to allow simulation results to be generated and to support their interpretation. In this case the contingency of £30k would be applied to increase staffing and to secure additional super-computer access.

WP3; proton and ion capture: This part of the project carries the highest technical risk which results in risk to the overall project schedule. To effectively mitigate the technical risks to the successful development of the plasma lens requires a substantial parallel programme of research with its own staffing and equipment as well as an uplift to the staffing for the current programme. The mitigation plan includes the design and build of a parallel experimental system able to operate at higher voltage, the aim being to bring this online earlier than would otherwise be the case. Funds at the level of £500–£600k would make a significant impact, with an appropriate ramp to allow the team to be built up.

WP4; ion-acoustic dose profile measurement: Work package 4 is currently running with only post-graduate student and supervisory effort. The risk to the programme would be mitigated through the recruitment of postdoc effort, requiring investment at the level of £150k per annum. Experienced post-docs already employed at LhARA institutes could be deployed at more than one site, funded partly from the contingency funds and partly on other projects to allow a rapid up-tick in suitably qualified and experienced staff effort.

WP5; novel end-station development: The novel end-station development work package risk lies in its dependence on heavily loaded personnel. Funds to 'buy-out' more staff time would see immediate benefit. Investment of £50k–£70k would allow the relevant staff time to be roughly doubled. The additional resource would also be deployed to accelerate evaluation of the novel instrumentation required to interogate samples on the short timescales and high repetition rates required to maximise the scientific potential of the LhARA beams.

WP6; Facility design and integration: The integration and design work package risk is concentrated in the time pressures on key staff. Contingency funds would be focused on negotiating the release of key staff from other commitments and bringing in expertise at an earlier career stage to support an extension in the scope of the work. The estimated cost of these actions is £75k.

8. **The proposal has a high potential to validate and introduce innovative and disruptive concepts in the design of accelerators for medical applications. This requires a significant amount of Research and Development. The members of the Collaboration are aware of the need of raising additional funding through various channels (in the UK and outside), including the radiobiology and medical community. This commendable effort should be supported by all means.**

The project team welcome the panel's comment and are pro-actively seeking funding to enhance the LhARA programme across the natural and life sciences. Present initiatives include the preparation of a proposal to the UKRI Medical Research Council's Developmental Pathway Funding Scheme for an initial programme of experimentation using conventional and laser-driven proton and ion beams. The objective is to begin to investigate the radiobiology themes to which LhARA will provide access and to develop the techniques required to maximise the scientific potential of the LhARA facility.

The collaboration will contribute to and benefit from the FFA development work package of the "Muon consortium" bid the STFC Accelerator science research and development consortia outlines call. Development of laser-driven ion sources and plasma-lens capture work packages had been negotiated for inclusion in a laser-driven accelerator proposal. This proposal evolved into a laser-wake-field accelerator development consortium focused on the development of laser-wake-field electron acceleration and its application to X-ray free electron lasers.

The UK community interested in the development of laser-driven proton and ion beams has agreed to work together to develop a vision for the development of laser-driven ion beams for science and innovation and a road-map for its realisation. This will allow the community to respond to funding calls as they arise and to engage with subsequent STFC accelerator consortia calls.

Discussion has been initiatied of the possibility of developing a proposal to develop a successful ERC Synergy bid or other proposal to the EU or ERC to support European and UK members of the LhARA collaboration. While at an early stage, discussions have been initiated with laser-plasma and radiobiology groups in France, Germany, and Italy as well as with the medical and novel accelerator development teams at CERN. The present goal is that a proposal will be developed against an appropriate call for submission in 2024.

9. **The global accelerator community shares broad interest in many of the component technologies. Some outreaching engagements (such as those related to targetry, the Gabor lens and ion acoustic diagnostics) should be sustained for the entire duration of the programme.**

The collaboration agrees that the project should remain tightly coupled to global research and progress in the areas noted. The LhARA collaboration is active in seeking collaboration with groups with appropriate expertise as well as with groups that share the collaboration's vision and seek to develop the expertise necessary to contribute. The development of such collaborations and the engagement of groups with common areas of interest is a focus of LhARA programme management team.

10. **A clear definition by the interested users' community of minimum and optimum requirements to carry out the radiobiological experiments needed to better understand the phenomena relevant to ion therapy would be an additional asset.**

The collaboration has established a series of 4 peer-group consultation events that will take place during the first year of the Preliminary Activity. These consultation meetings will allow us to document the requirements of the facility identified by the panel. The first of these meetings was attended by approximately 50 members of the relevant peer group and generated significant input and discussion. Once completed, the outcomes of the consultation will be used to derive the specifications for the end-station, its instrumentation, and the sample/animal handling requirements. These specifications will be documented in the LhARA baseline document. We note that the LhARA beam will have unique temporal characteristics, the project team is determined to exploit the additional capability that this offers. To this end we have started an exercise to consult on potential fast instrumentation and diagnostics which may be applied in-situ and which can be developed for deployment at the point of treatment.

11. Continue the effort in the definition of the medical and radiobiology user requirements/expectations and irradiation modalities and their translation into specification of the beam parameters and of the beam diagnostic capabilities (including tolerances, precision, accuracy, etc.) Specification of minimum requirements necessary to start with the foreseen scientific programme and parameters for optimum exploitation would be useful.

The project agrees that a specification for the minimum requirements necessary to deliver the scientific programme is appropriate. The LhARA Science Board has recently been established. Its inaugural co-chairs have internationally recognised expertise in the fields of laser-driven acceleration and radiation biology. The Science Board will play an important role in the development of the specification the panel has identified.

12. The document describing the baseline parameters of the facility that the reviewers have been presented with, should be extended and regularly reviewed continuing the joint effort among medical, radiobiology and the accelerator communities sharing the ownership of the facility.

The LhARA baseline document is stored publicly on the LhARA wiki [9]. The document is reviewed before each collaboration meeting and any proposal to update the baseline is presented to the collaboration for discussion at the collaboration meeting. This process is important to ensure that all dependencies and consequences of proposed updates are fully explored. Collaboration meetings currently occur every six months. Should the need arise for an update between collaboration meetings, the proposed updates will be presented and reviewed at one of the regular “fortnightly meetings”. The Executive Board is then empowered to make any changes that are urgently required ahead of discussion at the next full collaboration meeting. Extension of the baseline document to include appropriate information on radiobiological and medical specifications will begin as the WP5 consultation exercise develops.

References

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