Preliminary details and descriptions

Name of project (and acronym or short name if relevant)	Ion Therapy Research Facility (ITRF)
Type of infrastructure project	**Establishment of new capability**
Submitting Council(s)/UKRI team(s)	☐ **AHRC** ☐ **BBSRC** ☐ **EPSRC** ☐ **ESRC** ☐ **Innovate UK** ☐ **MRC** ☐ **NERC** ☐ **Research England** ☒ **STFC** ☐ **E-infrastructure Team** ☐ **Large multidisciplinary facilities (STFC managed)**
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One-line description of the preliminary activity for use in summary tables to IAC, ExCo etc. [22 words]

To develop the specification and costs for ITRF, a facility which will elucidate the **biological impact of proton/ion beams** for **clinical practice**.

Long description of the preliminary activity [800 words, **please continue to the next box when full** – for IAC]

Background:

Conventional X-ray therapy is effective in eliminating the tumour in 40-50% of all patients treated with the intent to cure. Newer Ion Beam Therapy (IBT) instead uses highly-accelerated atomic particles such as protons and carbon ions to kill tumour cells. The physics of IBT permits higher-energy ions to be distributed precisely over the tumour with greater biological effectiveness than X-rays and with minimal normal-tissue interactions. The patient will benefit from reduced toxicity and therapy which can be delivered in a much shorter period of time. Our wide community engagement assures us that **future cancer treatment** to 2050 and beyond **will require advanced radiotherapy**—delivered in such a way as to overcome the ability of tumour cells to repair themselves, whilst also being highly protective of healthy tissues (reduce side effects), stimulating a systematic immune response - an **"in-situ cancer vaccine"**.

Globally there is no facility that can explore these domains adequately, both to understand the fundamental processes and to optimise radiation delivery in time, space, ion species, and energy spectrum, alone and in combination with new drugs. The UK has the capability to deliver such a facility and to become a hub for the global fight against cancer.

Objectives:

The Ion Therapy Research Facility (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. Bespoke end stations will allow great flexibility in the spatial, temporal, and spectral characteristics of the ion beams, tailored to enable the study of biology relevant for future treatment regimens such as FLASH (high dose rate) and spatially-fractionated radiotherapy. Fundamentally 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 the ITRF will promote the disruptive accelerator, diagnostic, imaging, and computing technologies required to radically transform clinical practice.

The **ITRF will place the UK** at the **forefront of the science and technology of particle therapy internationally**, **establish UK industry as a key player** in the delivery of novel clinical equipment/prototypes, and enable significantly enhanced **access to state-of-the-art IBT across the UK**. The ITRF will enhance the UK as the destination of choice for cutting-edge research.

Transformative, multidisciplinary approach:

Very high dose rate FLASH therapy may transform radiotherapy; new modalities in spatially-fractionated therapy could be disruptive in ion-beam therapy. A laser-hybrid proton/ion source, as proposed by the existing, UK-led, international LhARA collaboration (see figure 3), can deliver this and meet the needs of the ITRF. LhARA (see figure 1) is a hybrid system coupling a laser-driven proton/ion source to a novel, rapid-acceleration system. The delivery of the ITRF will require a multidisciplinary approach that includes oncologists, radiobiologists, accelerator, and instrumentation scientists; this expertise is present in the ITRF collaboration and its Advisory Board.

The Preliminary Activity (PA):

The PA will develop over 2 years the specification, design, and cost of the ITRF and present these in a full Conceptual Design Report (CDR), leading to a 2-year pre-construction TDR phase and the construction phase (see figure 2). The PA will be performed via two main work streams:

1. End-station specification and design:

Learning from previous and planned ion-research infrastructures, we will develop an end-station design and associated beam specification to support a definitive biomedical research programme. This activity will benefit from significant expertise at: MRC Oxford Institute of Radiation Oncology; Liverpool University's Institute of Systems, Molecular and Integrative Biology; Christie Hospital/Manchester University PRECISE proton therapy research group and research beamline. We envisage a staged plan first for high-throughput *in-vitro* and then small-animal *in-vivo* research to improve understanding of biological effectiveness and biologically-augmented treatment planning with AI/ML as part of a wider UK plan towards eventual clinical ion treatment. The potential and need for both transmission and Bragg-peak FLASH will also be assessed.

2. Conceptual Design Report, technology choice, technical-risk management:

A conceptual design study will be conducted to produce a full project plan including operating modality for national/international users, and a scientific, technological, economic, and societal impact assessment. This will feed into subsequent development of an Outline Business Case.

We will build upon UK expertise in the relevant accelerator technologies. Laser-source design will be led by Belfast/CLF/Imperial/Strathclyde; conventional acceleration by Cockcroft/JAI/STFC; novel dosimetry and instrumentation by Birmingham/ICR/Liverpool/Manchester/NPL/STFC/UCL; infrastructure and engineering integration by STFC. We recognise the significant challenges of our transformative technical approach, which will be managed as described later; our modular design allows the research end-station to be compatible with several accelerator source options.

Effective tensioning of the benefits and costs of parameter trade-offs, technology choices, and implementation strategies will be carried out through 6-monthly reviews via our Advisory Group. Technology choices will be supported by appropriate prototyping building on existing test infrastructures and instrumentation at Belfast/Birmingham/Christie/Imperial/Strathclyde and elsewhere.

Please describe the full infrastructure capability that this Preliminary Activity is exploring or working towards. The audience is the IAC.
This will be less developed, briefer and more uncertain than a Full Project proposal and the information required should be proportional to the scale of the investment.

[800 words, **please continue to the next box if full**]

Research objectives:

Our vision is to radically transform the technology available for IBT and to provide a blueprint for its dissemination both nationally and internationally. To realise this vision, the ITRF will:

- **Be a fully-automated, highly-flexible infrastructure to serve fundamental research** into the biological and biochemical impact of proton and ion beams on cells, tissues and organisms, aiming at reduced toxicity and enhanced cell killing; and
- **Demonstrate** in a research facility **the capability to deliver particle-beam therapy in completely new regimens,** by combining a variety of different ion species and exploring timing, rate, and size of the delivered dose fractions. The facility will also be capable of enabling the investigation of novel combination strategies (e.g. targeting DNA repair and the immune response, or via high-throughput screening) that maximize tumour radiosensitisation.

The collaboration we have forged and our Advisory Group are representative of the UK's multi-disciplinary network of clinical oncologists, medical, particle, plasma, laser, ultrasound, and optical physicists, accelerator, computer, and instrumentation scientists, radiobiologists, industrialists, and patient representatives **required to realise our vision**.

Research/innovation need:

1 in 2 people will develop cancer in the UK in their lifetime; globally, there will be 27.5 million cancer patients per year by 2040. Radiotherapy (RT) is used with 50% of cancer patients and around 40% of cures. The NHS plan to improve early cancer diagnoses implies an increasing need for interventions that will include RT. RT is second only to surgery in curative effect; chemotherapy/targeted therapy, which receives the majority of research support, is a distant third.

RT is today most commonly delivered with X-rays. However, there is increasing emphasis on the use of proton and ion beams where most dose is deposited in the end-of-range Bragg peak. Proton therapy may be conformed to the tumour whilst sparing nearby organs at risk; ion therapy may give yet further advantages—both from the higher energy transfer efficiency and the different biological response mechanisms. Ion therapy also enables advanced dose-imaging techniques such as He–C simultaneous imaging.

IBT offers a major advance over traditional X-ray therapy which relies heavily on the generation of free radicals from water to kill tumour cells. The generation of free radicals requires oxygen, and so hypoxic cells (common to many solid tumours), are more difficult to treat with X-rays. IBT can directly induce greater DNA damage without relying on free-radical creation, and thus reduces the problem of hypoxic cells. In addition, tumour cells that possess elevated levels of free-radical scavengers (that prevent free radical generation) are more effectively treated.

The benefits of IBT are widely recognised. The NHS recently invested £250M in proton-beam therapy at 2 UK sites and the Particle Therapy Co-Operative Group currently lists 90 proton-therapy facilities and 12 carbon-ion-therapy facilities most of which are located in high-income countries. Around 70% of cancer patients in low-and-middle-income countries cannot access RT.

The beam characteristics exploited in IBT facilities today rely mostly on low dose rates (<10 Gy/min) and a limited number of temporal and spatial schemes. IBT's clinical efficacy is dependent on the treatment modality and fractionation schedule. Recent work on proton FLASH indicates therapeutic benefit for X-ray dose rates over 100 Gy/s; these rates are possible at clinical proton facilities. Consideration must now be given to ion-beam facilities to explore their potential. Combined with spatial (e.g. minibeam) and spectral methods to elicit biologic and immune response, this is the rationale for the ITRF. Fundamental new biological understanding is needed to develop the clinical application using these novel beam modalities whilst minimizing collateral damage to normal tissues. The ITRF is thus part of the agenda for personalised medicine based on the biology of individual tumours, and provides a route for a radical transformation of IBT.

Through STFC, EPSRC and other councils, the UK has invested in several technologies for IBT, predominantly novel accelerator technologies such as laser/plasma techniques and fixed-field accelerators. Investment has also been made in the development of conventional technologies such as linacs, imaging systems, and high-energy electron FLASH. Several advanced radiotherapy networks have built industrial/clinical collaborations that have, for example, demonstrated the first commercial FLASH dosimeter. These developments leverage research-council investments in core programme areas and exploit partnerships with overseas partners, CERN, the Paul Scherrer Institute and the MedAustron ion-therapy centre. The technologies developed for, and demonstrated in, the ITRF are complementary to those of the core research-council programmes and can be "spun back in" to enhance research capability and for the provision of intense proton sources. Similarly, the ITRF will complement the research possible at the MC40 Cyclotron Facility in Birmingham, the research line at the Christie Hospital, and at the Clatterbridge Cancer Centre (with which ITRF developments can be shared).

The outstanding requirement for high-precision, well-characterised ion beams capable of penetration to depths of a few centimetres will be met by the ITRF.

When would the preliminary activity begin?	*Either* select one of – **2022/23** *Or* select one range **between 2022/23 and 2024/25**
How many financial years will it take to complete?	**2**
Is there likely to be an application for a second preliminary activity before that for a full infrastructure (if it is taken forward)?	**Yes**

The remainder of this form refers to the full infrastructure capability this Preliminary Activity is exploring or working towards (with the exception of one cost table).
This will understandably be briefer and more uncertain than a full project template. Much is optional to complete.

Project criteria

What would be the main benefits of proceeding with the full project? [200 words]

The ITRF will deliver **world-leading research** in ion-beam radiotherapy, in underpinning science (biology, biochemistry, treatment methodologies, imaging methods, planning) and technology development.

As yet there is no dedicated research infrastructure that can support both in-vitro and in-vivo studies. The ITRF is essential to meet this need in the UK; its funding will:

- **Maximise the benefit** from the UK's present investment in IBT;
- **Provide a platform for the future** of ion-beam therapy in the UK;
- **Maintain and enhance the UK's position of leadership** in radiobiology at the MRC-funded OIRO, Christie and elsewhere.

The ITRF will provide transformative proton and ion **research capabilities in the UK**. The technology choice will be **risk-managed** such that it is **feasible**, yet matches user need to drive a **step change** in capability.

The 2018 'Strategic Review of CRUK's Investment in Radiation Biology and Radiation Oncology' recommended that a national particle research facility 'would potentially transform (…) research in the UK'. Exploitation of the facility will allow substantial reductions in the treatment cost per-patient and the development of new treatment modalities. Implementation of the ITRF will create this transformation and develop the partnerships necessary for UK industry to deliver new clinical facilities in the UK and overseas.

What would be the main consequences of not taking this full project forward? [200 words]

Failure to take the project forward risks ceding the initiative to an overseas laboratory. The UK would be unable to take a lead in this field, its biological and medical researchers will lose the chance to have quick and easy access to an ion beam research facility, and the opportunity to build on the international leadership position established by UK researchers within the multidisciplinary collaboration will be lost. The opportunity to develop a roadmap for clinical implementation and evaluation would also be lost.

We have established the multidisciplinary collaboration necessary to transform clinical practice through the delivery of multi-ion particle beam therapy in completely new regimens. **We propose to demonstrate the novel technologies required, in a research facility dedicated to understanding the impact of particle beams on tissue.** The facility specification has been developed in consultation with world-renowned leaders in the biological and clinical exploitation of novel particle beams.

Across the world there are few comparable initiatives. Our new approach distinguishes itself from these by shifting the emphasis to high ion dose rate. The collaborations we have established brings together world-leading researchers from universities, national laboratories and hospitals, with the ambition and capability to deliver the step-change in capability required.

How has the <u>research or innovation area</u> been prioritised for the full infrastructure investment? Tick all that apply.	**☒ Community engagement (e.g. Statement of Need, workshop)** **☐ Infrastructure Roadmap theme or concept** **☐ Council's strategy or equivalent** **☐ Discipline or technology roadmap or strategy (e.g. European strategy for particle physics)** **☐ Government or UKRI strategy (e.g. Government's "Plan for Growth")** **☒ Other**

If relevant, comment briefly on how this has been done. [50 words]

The demand for such a research ITRF platform is evidenced primarily in a UK position paper *'Heavy charged particle beam therapy and related new radiotherapy technologies: The clinical potential, physics and technical developments required to deliver benefit for patients with cancer'*, BJR 93 (1116) 20200247.

How has the <u>proposal</u> been endorsed as a priority for the Council(s), Team or Community? Tick all that apply.	☒ **A Council's advisory committee (e.g. a science board, review panel)** ☒ **Council's Executive Board/Team** ☒ **Council's Council** ☐ **Other**

If relevant, comment briefly on how this has been done. [50 words]

The ITRF proposal was reviewed favourably by the STFC Science Board and Technology and Accelerator Advisory Board. The STFC Executive Board and STFC Council considered the ITRF proposal together with the recommendations of the SB and TAAB, endorsed the proposal and recommended its transmission to the UKRI Infrastructure Fund process.

How has the <u>full proposal</u> been independently reviewed? *Refer to guidance.* [100 words]

The case for an ion therapy research facility was published in the BJR following positive independent peer review. The LhARA initiative, and the preliminary conceptual design, was subjected to review by an independent, international expert panel composed of P. Bolton (Munich), M. Lamont (CERN), Y. Prezado (Curie Institut), F. Romano (INFN Catania). The review panel's positive report can be found on the LhARA website. The conceptual design was published in Frontiers in Physics following independent peer review. STFC panels and boards (PPRP, SB, TAAB, EB and Council) have also reviewed the proposal at various stages of its preparation.

Outline the strategic drivers for the full infrastructure project and how the project will help achieve the strategic goals. [200 words]

The UKRI Opportunities Report highlights the need for future technologies to improve health. Previous UKRI investment in accelerator research resulted in the first demonstrated fixed-field alternating gradient (FFAG) accelerator, EMMA, the basis of future FFAG designs for high-intensity particle physics, neutron science and healthcare applications. The UK is at the forefront of this technology (to be applied in ITRF), which is also being applied to future X-ray facility designs such as the UK-FEL. Similarly, the UK has a leading role in the science of laser-plasma acceleration, holding the record for TNSA foil proton acceleration. The proposed infrastructure would be the first combination of multi-ion generation and acceleration at high dose rate, greatly surpassing existing infrastructures in Europe and elsewhere. It would be the first demonstrator of high-dose-rate irradiation, enabling the first systematic *in-vitro* and *in-vivo* biological studies of multi-ion irradiation. There is broad global consensus for the need for such a facility (see referenced BJR paper), which would be complementary to lower-dose-rate facilities such as at MedAustron. The project would strongly leverage the deep UK experience in core accelerator technologies, and benefit from close collaboration with overseas collaborations on NIMMS; this co-development spreads costs amongst our partners and de-risks development.

Describe the potential benefits/impacts of the full infrastructure project. [300 words]

Particle therapy is a rapidly-growing branch of accelerator-based research that can both benefit patient care and stimulate UK-based technological innovation. (UK) Cockcroft Institute researchers developed the specification for the two recently-commissioned NHS proton treatment centres (£250M capital); the first (at The Christie, Manchester) started treating patients in 2018, and the UK will soon reach the planned 1500 patients per year, focusing on rare and paediatric cancers and conferring 11.2 quality-adjusted life years benefit for each patient. These researchers also specified, designed and procured the unique research beamline now operating at The Christie; this catalysed a 40-person research centre and strategic partnership with Varian focusing on the transformative area of high-intensity FLASH radiotherapy. Similar partnerships on electron therapy with Elekta, fully automated flexible multi-ion therapy (LhARA), and with CERN focus on targeted new treatment modalities.

Research at the ITRF is needed to optimise ion dose delivery to underpin future clinical facilities. The fundamental understanding of biology that will be afforded will open up new paradigms of individualized patient care for next-generation treatments. ITRF leverages the UK's leadership in high-intensity accelerators and associated technology (e.g. plasma, superconducting magnets, and beam delivery) and applies it with industry partnership to better understand how to treat those cancers difficult to address with conventional radiotherapy.

Our multidisciplinary approach coupled with managed prototyping provides a pathway for skills development in many fields ranging from biology, medical physics, engineering, accelerator science and particle physics. This develops a skilled and flexible workforce to support the NHS, industry, academic and the national laboratories. By drawing people with different knowledge and skills bases together it builds an environment that fosters creativity in a way that inevitably leads to new ideas and technologies that bring benefit not just to researchers but to the wider public.

Describe how this will enable a step change (transformation) in capability and how it fits in the existing infrastructure landscape. [200 words]

There is today no infrastructure in the UK, or indeed overseas, that can deliver multiple ion species over the range of conditions necessary to revolutionise biomedical research. The ITRF makes the step from today's lower-intensity capabilities (Surrey/Dalton Cumbria) and proton-only capabilities at Clatterbridge and Christie. A systems approach is taken to couple together the accelerator source with the necessary dosimetry, delivery, and computing for the next generation of treatment modalities. Proposals elsewhere seek to serve biomedical research (BIO-LEIR, GSI, ELIMEA/ELIMED). Our approach is transformational and distinguishes itself from other initiatives by:

- **Providing in a single facility** the capability to carry out biomedical research in completely new regimens by combining a variety of ion species from proton to neon in a single fraction, exploiting ultra-high dose rates and novel spectral-, spatial- and spectral-fractionation schemes; and
- **Demonstrating in an integrated facility** the technologies required to integrate patient, soft-tissue, and dose-deposition imaging with real-time treatment planning in an automatic system that triggers the delivery of dose tailored in real time to the individual patient.

Only UKRI can support an integrated project of this nature, which can foster a new interdisciplinary community across the component councils and their user bases.

Describe how the full project will be delivered, its feasibility and top risks and dependencies. [800 words, **please continue to the next box if full**]

Delivery approach: ITRF will be a new facility sited within the UK. The preliminary activity will settle the design scope of the infrastructure and its sustainable usage model, balanced against the user community demand. Modular costings based on 'greenfield' or existing sites will allow costings to be assessed against possible site decisions. We will utilise the standard STFC project management approach successfully applied in a number of recent projects, and work towards a CDR/TDR gateway process and Outline Business Case development with UKRI and advisory board oversight.

Delivery technology: There are three technologies shortlisted for the infrastructure: plasma/FFAG, synchrotron, linac. During the CDR phase these will be down-selected following a conceptual design and costing. We foresee a staged infrastructure (see accompanying figures) with a lower-energy (shallower depth, in-vitro) initial capability, followed by a higher-energy (larger depth) provision. Risks inherent in the use of novel high-dose-rate sources will be managed through design and prototyping carried out in parallel with the preliminary activity. We are already engaged in a number of relevant collaborations and projects to develop the key technologies (ion source, pre-acceleration, final acceleration) and associated components.

Delivery de-risking and dependencies: The CDR process will address critical risks, including: capture and transport of short-duration high flux pulses; dosimetry and dose-deposition imaging; end-station automation. The CDR process will tension the subsystem risk (e.g. FFAG design) with the user demand (e.g. required rate of energy change), informed by the design work of the CDR. Authorisation for biological research will be pursued following site selection, after the preliminary activity.

The preliminary risk matrix for the project is summarised:

Technical Challenges in the design and construction of the facility may introduce delays/cost over-runs.	H	Mitigation 1 – ensure the right expertise to successfully execute the project is on board incl. international partners; ensure there is an appropriate oversight committee to monitor project progress. Mitigation 2 – alternative technology options identified for major subsystems; CDR process manages final technology choice.
Budget Funding for all phases of the project may not be immediately available, therefore project may have to start at-risk	H	Mitigation – the project will pass through gateway stages, appropriately documented (CDR as first major deliverable) to ensure new knowledge is retained and key milestones are developed so that as appropriate the steps to reaching the eventual aims can be delivered in stages.
Stakeholders/governance Multiple stakeholders and interest groups may not agree on the facility specification, the transformational potential of the technological approaches, or scientific objectives of the programme.	M	Mitigation 1 – ensure that stakeholder relationships have a dedicated manager to ensure there is a common understanding of the project goals and outputs; clinical oversight to guide UK requirements. Mitigation 2 – initial Advisory Board terms of reference will be confirmed at beginning of Preliminary Activity, and board membership/leadership refreshed at each Gateway stage.

Market The ongoing market for ion and FLASH therapies is not yet established to commit commercial involvement.	M	Mitigation 1 – ensure that clinical viewpoint is included at each stage of the project to ensure alignment with market needs. Mitigation 2 – work with Advisory Board to establish case for ion therapy service. Mitigation 3 – establish partnerships with key commercial providers in important sub-systems that have generic use, e.g. dosimetry, source technology, instrumentation, computing methodology.

Can you confirm the full infrastructure will be open to users outside of those directly involved in the project (i.e. the host institution and funding partners)?	**Yes** **How?** ☒ **Excellence-driven (e.g. peer review)** ☐ **Market-driven (e.g. commercial)** ☐ **Unrestricted/open (e.g. data and digital services)** ☐ **Other**

If not covered elsewhere, briefly comment on how if you answered yes.
e.g. for unrestricted/open access, whether it is immediate or after an embargo period, quota expectations for market-driven access. Include reference to established pre-existing mechanisms or models. [100 words]

We envisage access similar to other comparable-scale infrastructures: the accelerator source will include a suite of the necessary diagnostic instrumentation to fully characterise the delivered ion species, which will enter a flexible *in-vitro* and *in-vivo* end-station area that allows interchangeable, modular experiments; this model has been successfully applied in other infrastructures and can also be applied to other developments such as in-beamline diagnostic development. Each experiment will benefit from an integrated group of both accelerator technologists and end users, supported by local site management. A user access panel will assess experimental proposals against the overall strategic aims of the infrastructure.

Describe the infrastructure's environmental impact, any mitigations, and the alignment with UKRI's environmental commitments. *Refer to guidance.*	[200 words]

Under the UKRI sustainability strategy, our preliminary activity occupies the 'five years of action' for sustainability, which means our CDR and planning will take into account UKRI objectives. This will be embedded into the CDR and future infrastructure in the following ways:

- Consideration from the project outset of sustainability in **procurement**, construction, operation and eventual decommissioning. Also, offsetting of **carbon** emissions using local associated planting and generation, e.g. roof solar.
- Consideration of the **re-use of existing equipment/infrastructure** (e.g. buildings, shielding, existing site provisions such as installed services) when selecting siting, overall design and construction method.
- **Modularity** of design cf. comparable STFC-designed infrastructure, to minimise design costs and to enable eventual recycling of major components, e.g. steelwork, radiation shielding.
- Incorporation of modern **sustainable practice** in design, construction and operation; for example, recycling of waste facility heat into local CHP.
- Consideration and adaptation of **operating schedule** to take account of likely peak energy demand and cost; use of local on-site power generation storage (e.g. battery) for smaller power systems.
- Utilisation of modern **sustainable accelerator technologies** to minimise power consumption, including the use of permanent-magnet systems and high-efficiency klystrons where possible.

Portfolio factors

Discipline balance

Select as many of the follow research areas that are significant to the output of your infrastructure proposal.
You should only select those that contribute to at least 10% of the output of the infrastructure.

Research and innovation area	
Histories, Cultures and Heritage	☐
Creative and Performing Arts	☐
Languages and Literature	☐
Human society	☐
Social relationships	☐
Psychology, Neurosciences & Mental Health	☐
Public Health, infections and immunity	☒
Preclinical Medicine	☒
Clinical Medicine	☒
Genes and STEM approaches to biology	☐
Molecular & Cellular biology, medicine and biotechnology	☒
Biological sciences	☒
Agriculture, fisheries and food	☐
Ecology	☐
Geosciences	☐
Atmospheric sciences	☐
Chemistry	☐
Physics and mathematical sciences	☒
Astronomy and Astrophysics	☐
Particle and Nuclear Physics	☐
Energy and clean growth	☐
Engineering and Technology	☒
Multidisciplinary structural analytics and imaging facilities	☒
Computational science, Artificial Intelligence (AI), compute and data	☒
Mobility, manufacturing and materials	☐

Type of activities **Which answer(s) best describe what will take place at/using the full infrastructure?** *You can select all that make a significant contribution (i.e. 10% or more of its function).*	☒ **Fundamental research** - Curiosity-driven research that advances human knowledge. Generating socio-economic impact is not the motivation ☒ **Use-inspired basic research** - Scientific research conducted with the clear ambition of solving known societal challenges or creating technologies for future economic applications ☒ **Applied and solution-oriented research** - research and development directly aimed at meeting public or business demands and at responding to well identified research and or technological problems ☒ **Provision of scientific services** - facilities designed to offer services to be directly used by the science community to efficiently carry out their research ☒ **Innovation** - development, demonstration and delivery of innovative (new to market) products, services or processes
If you selected Innovation, how will the infrastructure project support innovation? *Select all answers that make a significant contribution (i.e. 10% or more of the innovation function).*	☒ **Enabling industry engagement** ☒ **Supporting industry to advance products and ideas through TRL stages** ☒ **Supporting industry experimentation and prototyping** ☐ **Enabling industry commercialisation and development**

Location **Is there one or more particular institutions, facilities, UK regions or international locations where the infrastructure project must or ideally should be located?** *This applies to multiple locations for distributed models as well as single sites. Please consider the operational site(s) rather than user access if these differ (e.g. for a data infrastructure where access is virtual).* **Unless covered in earlier answers, state where any parts of the infrastructure project must or ideally should be located and explain why.** *List any host institution(s) if this has already been identified. If there is a primary 'hub' location in a distributed structure, please flag. If future locations will be decided by competition, please state.*	**For an infrastructure with a single site:** **Yes** **For a distributed infrastructure with multiple locations (e.g. network, hub and spoke):** **Choose an item.**

Please explain your answer (e.g. where and why)? [100 words]

STFC and the national laboratories have world-leading expertise in the construction, operation, and decommissioning of such a multidisciplinary user facility, and will support the construction of the ITRF at a suitable large-scale campus/laboratory site, ensuring input from key users of the technology; this will be decided as part of the Preliminary Activity and Outline Business Case through a transparent process described in the CDR. The expertise and capabilities that reside in national-laboratory personnel and in academic/clinical users will both be essential to the successful development, implementation and operation of the facility.

Collaboration **Will the infrastructure project encourage inter/ multidisciplinary collaboration and/ or cross business sector working?**	**Yes**

Unless covered in earlier answers, describe how. [100 words]

Our multidisciplinary collaboration includes clinical oncologists, medical, particle, plasma, laser, ultrasound, and optical physicists, accelerator, computer, and instrumentation scientists, radiobiologists, industrialists, and patient representatives with the competence and experience to deliver the proposed programme. The strong collaboration of 39 institutes includes 6 clinical departments, 10 university physics departments, 10 university biomedical and medical physics departments, 3 university accelerator centres, 1 university computing department, 1 university engineering department, 4 STFC laboratory departments, 3 commercial enterprises, and the NPL.

The collaboration benefits from strong research links through CERN/NIMMS, STFC/EPSRC radiotherapy networks, EU INSPIRE, CNRS Institut Curie in Paris and INFN Catania.

Strategic deployment, collaboration and connectivity **Will the proposal enable more strategic deployment, collaboration and/or connectivity of UK infrastructure?**	**Yes** **How?** ☒ **Better linkage/building local clusters** ☐ **Efficiency i.e. streamlining** ☒ **Building partnerships/developing networks** ☐ **Equipment sharing initiative** ☒ **Integrating innovation** ☒ **Broadening access/increasing awareness** ☐ **Other**

Unless covered in earlier answers, describe how. [100 words]

The proposed facility will connect together the existing and desired research activities and infrastructures of a number of UK research groups, that include the Liverpool, Manchester and Imperial radiobiology activities, the technical and instrumentation developments of Birmingham, Manchester, Liverpool, Imperial and STFC. This will build on the existing proton-only facilities already in operation at Christie, Birmingham, Surrey and Liverpool.

International **Does the project create opportunities for UK international leadership (e.g. hosting capability in the UK, drawing specific talent to the UK) or support strategic links and partnerships with key countries?**	**Yes** **How? Choose all that are relevant** ☒ **World-leading reputation** ☒ **Enabling the UK to take an international leadership role** ☒ **Hosting cutting-edge national facility** ☐ **Hosting an international capability in the UK part funded by other countries (e.g. HQ or new global facility)** ☐ **UK jointing International infrastructure requiring government-level sign up** ☒ **Attracting specific desired talent to the UK** ☐ **Global connections for scientific or partnership benefits aligned to UKRI or government strategy** ☐ **Supporting strategic links with key countries/ scientific diplomacy**

Please provide brief details if relevant: [100 words]

The ITRF will be the world's leading IBT infrastructure; there is nothing similar that exists today. The ITRF will provide the research that underpins future IBT treatment, and as such will connect the UK to strategic research towards future clinical facilities, such as the ongoing CERN/NIMMS study with which our collaboration is also working. A Collaboration Agreement is being negotiated with CERN to support bilateral collaboration on the CERN medical-accelerator programme and the ITRF. Early IBT technology demonstrations have already been conducted with other partners such as MedAustron.

Leverage **Does the project leverage funding from outside the UK public sector, i.e. private or third sector?** *Unless covered in earlier answers, describe how. State how much leverage (cash or in kind) and if this could be counted as foreign direct investment (FDI).*	**Yes** **How?** ☐ **Committed leverage to develop the infrastructure** ☐ **Committed leverage to operate the infrastructure** ☒ **Expectation of commercial/third sector revenue** ☐ **Tick if this is counted as foreign direct investment** ☒ **Other**

Please provide brief details, including amounts and whether its cash or in kind: [100 words]

Several radiotherapy technology companies are already engaged within our collaboration on relevant technologies, such as high-intensity proton/ion acceleration (Varian, Antaya), linac technology (Advanced Oncotherapy) and advanced dosimetry and instrumentation. We are in discussion with several interested companies that have expressed interest in the use of ITRF for IBT technology development.

Efficient use of resources **Will the project result in longer term savings of public money (i.e. this is an "invest to save" project)?**	**Yes** **How?** **☒ Generation and application of new research or innovation outputs** **☐ Increased efficiency compared to existing capability** **☐ Increased effectiveness compared to existing capability**

Unless covered in earlier answers, describe how and the extent of efficiency or effectiveness savings (over a specified time period if possible). Briefly describe any economic analysis done to demonstrate these savings. [200 words]

The overall goal of ITRF is to provide a clear optimisation of appropriate ion types, treatment modalities, and technologies required for future IBT treatment of patients. In so doing, this will constitute a de-risking of future investment in IBT clinical treatment.

Parties

List all parties involved where their agreement, participation and/or funding is needed to take the full project forward.

Lead Council/UKRI team(s) **Select the lead Council/UKRI team(s) behind the infrastructure project.** *If the project is considered an equal partnership between Councils/teams, select all that apply plus "equal partnership".*	☐ **AHRC** ☐ **BBSRC** ☐ **EPSRC** ☐ **ESRC** ☐ **Innovate UK** ☐ **MRC** ☐ **NERC** ☐ **Research England** ☒ **STFC** ☐ **E-infrastructure** ☐ **Large multidisciplinary facilities** ☐ **Equal lead** ☐ **To be decided**
Other Councils/UKRI teams involved **Select the other Councils/UKRI teams involved in the project (excluding equal partners which are selected above) or select "no other Councils/ teams are involved".** *Please ensure that discussion have taken place with any that have been ticked.*	☐ **AHRC** ☐ **BBSRC** ☐ **EPSRC** ☐ **ESRC** ☐ **Innovate UK** ☒ **MRC** ☐ **NERC** ☐ **Research England** ☐ **STFC** ☐ **E-infrastructure** ☐ **Large multidisciplinary facilities** ☐ **No others involved** ☐ **To be decided**

List here the names of any external/non-UKRI project partners.
These are partners whose agreement, participation or funding is needed to take the project forward. You only have to provide the names for this question. [100 words]

As well as UKRI-funded HEI and other partners, we also have as partners:
- Institut Curie,
- INFN-Catania

(the full partner list is shown on the accompanying figures)

Partner mapping

Complete this tab to indicate (yes/no) which types of organisations are directly involved in the full infrastructure project. *Your answers should be consistent with the partners listed in the previous tab.*

Are non-UKRI UK public sector organisations directly involved in the project?	**Yes**
Are international public sector organisations directly involved in the project?	**Yes**
Is industry directly involved in the project?	**Yes**
Are UK higher education institutions (HEIs) directly involved in the project?	**Yes**
Are international higher education institutions (HEIs) directly involved in the project?	**Yes**
Are non-profit/charitable organisations (not HEIs) directly involved in the project?	**Yes**

Timings

Complete this table to provide timings for project and to describe any external drivers of timings.
The timing information entered here will ensure the correct finance tables are generated for the project.

When would the <u>full project</u> begin?	**If there is a specific date driving the start of the project? select one of –** **2022/23** **If not, select one range:** **Choose an item.**
How many financial years will it take to complete?	**2**
If more than 10 years, specify:	

Brief explanation of why this project is timely if not already covered. *If this has already been described reference the relevant question.* [100 words]
The projected rapid increase in demand for particle beam therapy cannot be met through incremental development of technique alone. Novel, fully-automated techniques will be required to create the necessary capacity. Across the world there are a small number of initiatives that seek to develop novel particle-beam therapy technologies. This active research field is growing rapidly. Establishing a unique capability in the UK at the very start of this process will give the UK an edge. Development of the ITRF now will place UK researchers, UK industry, and the multidisciplinary collaboration at the forefront of the field worldwide.

Is there an <u>external</u> driver of decision timing? *If there is no fixed external driver of decision point timing is assumed to be flexible to enable financial management of the portfolio.*	**Yes** **Why?** ☐ **International agreement** ☐ **Commercial agreement** ☐ **Regulatory compliance** ☒ **Other**

If yes, please state when a decision is needed by and explain why the timing is fixed. [100 words]

The UK is presently at the forefront of research and development of the development of novel, laser-driven acceleration and the application of these technologies for the advancement of science and innovation. The development of these techniques for biomedical application is an active area of research being pursued by groups in Asia (principally Japan), Europe (including ELIMAIA at ELIMED), and the US. Failure to embark on the preliminary activity proposed here risks ceding the UK's present position of leadership and the opportunity to exploit the unique multidisciplinary activity established within the LhARA collaboration and more broadly within the UK research base.

Please provide a summary of high-level milestones. A detailed project plan is not required. [200 words]

ITRF development timeline (see accompanying Figure 2): the indicative timeline for the implementation and exploitation of the ITRF is based on preliminary work carried out by the multidisciplinary collaboration.

1: The present Preliminary Activity will deliver the full CDR for the ITRF.

2: 2-year pre-construction phase (resulting in a TDR),

3: Stage 1 of the facility (beam to the low-energy in-vitro end station) will be delivered over 2 years. Exploitation of the facility can then begin and operation for users will be scheduled in parallel to the construction of Stage 2 (beam to the high-energy *in-vitro* and *in-vivo* end stations).

Costs

Two types of costs are requested:

a) **Costs for the Preliminary Activity**
b) **Costs of the eventual Full Infrastructure that this activity is working toward or would enable**

Both require completion, although it is understood that there may be less certainty of the Full Infrastructure costs at this stage and that updated costs would be input in a future proposal for the full infrastructure.

Please refer to the guidance before completing tables.

Cost tables for the Preliminary Activity.

You must fill this in.

Table 1. Preliminary activity costs (£m)	Year																Total
	22/23	**23/24**	**24/25**	**25/26**	**26/27**	**27/28**	**28/29**	**29/30**	**30/31**	**31/32**	**32/33**	**33/34**	**34/35**	**35/36**	**36/37**	**37/38**	
Traditional capital costs																	
Traditional resource costs	0.7	1.3															2.0
All costs requested from Fund	0.7	1.3															2.0
Other funding agreed/anticipated																	

Cost tables for the full infrastructure that this activity would enable/is working toward.

You must fill this in if relevant. The main funder is this Infrastructure Fund. Please name any other funders. When filling in the cost table for other funders, please provide the totals for other funders.

If relevant, name of 2nd funder:		If relevant, name of 3rd funder:	
If relevant, name of 4th funder:		If relevant, name of 5th funder:	
Will you be providing point estimates or ranges? *Please refer to guidance.*		**Ranges**	

Complete one of the following two tables for UKRI Infrastructure Fund requirements depending on whether you are using point estimates or ranges.

UKRI Infrastructure Fund requirement (£m) Point estimates.		Year																Total
		22/23	**23/24**	**24/25**	**25/26**	**26/27**	**27/28**	**28/29**	**29/30**	**30/31**	**31/32**	**32/33**	**33/34**	**34/35**	**35/36**	**36/37**	**37/38**	
Traditional capital costs total																		
Traditional resource costs	ESA10 Programme CDEL																	
	ESA10 OpEx																	
	Total resource																	
All costs	Total																	

UKRI Infrastructure Fund requirement (£m) Range estimates.		Year																Total
		22/23	**23/24**	**24/25**	**25/26**	**26/27**	**27/28**	**28/29**	**29/30**	**30/31**	**31/32**	**32/33**	**33/34**	**34/35**	**35/36**	**36/37**	**37/38**	
Traditional capital costs	Lower																	
	Upper																	
Traditional resource costs	Lower																	
	Upper																	
All costs	Lower			1.5	2.0	4.0	7.0	13.0	16.0	10.0								53.5
	Upper			2.5	3.0	4.0	8.0	16.0	16.0	21.0	10.0							80.5

Please complete one of the following two tables for the total funding from all funders contributing to the full infrastructure project, if relevant.

Other funders (£m). Point estimates.	Year																Total
	22/23	**23/24**	**24/25**	**25/26**	**26/27**	**27/28**	**28/29**	**29/30**	**30/31**	**31/32**	**32/33**	**33/34**	**34/35**	**35/36**	**36/37**	**37/38**	
UKRI Infrastructure Fund																	
Non-UKRI funding source(s)																	
Total																	

Other funders (£m). Range estimates.		Year															Total
		22/23	**23/24**	**24/25**	**25/26**	**26/27**	**27/28**	**28/29**	**29/30**	**30/31**	**31/32**	**32/33**	**33/34**	**34/35**	**35/36**	**36/37**	**37/38**	
UKRI Infrastructure Fund	Lower																
	Upper																
Non-UKRI funding source(s)	Lower																
	Upper																
Total	Lower																
	Upper																

Contingency, financial sustainability and decommissioning

Refer to guidance.

Indicate how much (if any) of the project investment will be allocated to contingency and briefly explain the basis for that contingency. *Contingency can be expressed as an estimated % or specific figure.*	[100 words]
Based upon past and current experience of large, complex, accelerator projects of similar order of investment to ITRF, a contingency of 20% is typically allocated.	
Longer-term funding implications post cessation of the Infrastructure Fund project. **After project completion, how much would be spent per year on capital maintenance and on running costs (resource)?** *Explicitly cover what UKRI will be expected to contribute towards these longer-term costs. See guidance for further information.*	[100 words]
These costs will vary depending upon the technical solution which is selected during the Preliminary Activity. The assessment of these costs will be one of the Preliminary Activity deliverables.	
Briefly describe your assumptions on how UKRI's contribution to longer term maintenance/ running costs will be met. *See guidance for further information.*	[100 words]
A range of options for funding of these costs will be assessed as part of the Preliminary Activity and be discussed in the Outline Business Case. Particular attention will be given to the potential contributions from industrial partners, such as those who are already actively investing in related activities at STFC National Laboratories and hospital-based proton clinical facilities and research sites.	
Is there any future decommissioning cost associated with this activity?	**Yes**
If yes, briefly describe.	[50 words]
The costs will vary depending upon the technical solution which is selected during the Preliminary Activity. STFC has considerable recent and successful experience of decommissioning a number of particle accelerators at the STFC National Laboratories.	

Scalability

Refer to guidance.

Can the infrastructure project be scaled down? *If you answer no, it would be assumed that if there was less funding available that you have requested you would not be able to adapt the project to go ahead.*	**No**
If yes: describe how the infrastructure is scalable and what different scales would mean for research/ innovation outputs. *In your answer comment on the minimum viable intervention below which the project would no longer create a step change in capability.* [200 words]	
If yes: how much do you estimate it would cost to establish the minimum viable option? *Please provide your answer in £m. Ranges should be entered in the format X-Y. Do not include longer term running/ legacy costs.*	

Digital Research Infrastructure

Please refer to guidance.

Does the infrastructure require strong digital or data components?	**Yes**
If yes or possibly, what options have you considered to deliver this capability and if you have not chosen to utilize existing infrastructure, why? [100 words]	
ITRF aims to develop novel treatment modalities that involves optimised patient plans that utilise the enhanced radiobiological research that will be obtained. Development of optimised treatment planning together with the associated dosimetry and imaging development will require new applications of modern AI and Machine Learning techniques that utilise the significant computing infrastructure available at the Hartree Centre (Daresbury).	
If you are considering using existing digital infrastructure, has agreement to use this been obtained or is it still pending?	**No, this is pending**

Clearance and Handling

Please refer to guidance throughout.

Would the infrastructure project establish a new legal entity? *Answer yes even if this is one option under consideration and final decisions have yet to be made. See guidance for example legal entities.*	**No**
If yes, please describe. Unless covered in earlier answers, state what type of organisation is being proposed, why and if this is a definite decision or just an option under consideration. [100 words]	
Does UKRI need to sign a new MOU?	**No**
Is a request to deviate from pay and procurement frameworks likely?	**No**
If yes, please describe. *Unless covered in earlier answers, provide details of the flexibility in pay or procurement you need.* [100 words]	
Is Ministerial or central government agreement or action needed for reasons other than finance?	**No**
If yes describe. *Describe the agreement or action needed. If known, indicate whether approvals are likely to be routine or more complex.* [100 words]	
Has a UK Government Minister <u>publicly</u> made this a priority or already announced this? *This could be domestic project or an intergovernmental agreement.*	**No**

If yes, please describe.	[100 words]

Linking Infrastructure Fund projects

Please refer to guidance. *Optional*

Is the delivery of this infrastructure project dependent on other existing or planned infrastructures?	**No**
If yes list which ones.	
Are other existing or planned infrastructure projects dependent on this one?	**No**
If yes list which ones	

Any other comments? *Optional*

Please use this field to include any additional information that you would wish the infrastructure team and/or IAC to receive.	[200 words]