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.