First draft:

### C3.2: Work package 2: Proton-acoustic imaging

Knowledge of the position of the Bragg peak in relation to anatomy is essential if PBT is to deliver a high dose to the target tumour and spare healthy tissue, rather than cause damage to healthy tissue and under-dosing of the tumour. Furthermore, for preclinical research to provide the radiobiology knowledge needed to take full advantage of the new accelerator, and for its optimal clinical use, a system is needed to measure the PB deposited-energy distribution in the tissue, preferably on a pulse-by-pulse basis. We will develop proto-acoustic imaging to fulfil both needs.

Proton-acoustic imaging works in a similar way to emerging medical photoacoustic imaging. It can localise the Bragg peak with submillimetre accuracy and potentially reconstruct a quantitative dose image by using acoustic waves that are emitted when deposited energy creates a temporally and spatially localised temperature (and hence pressure) rise. Our aim is *in-vivo* real-time 4D proton-acoustic dose localisation and quantitative imaging, for real-time pulse-to-pulse adaptive treatment as the beam is moved around and the absorbed dose varies. The ultrasound system used for dose imaging will also employ pre-existing or rapidly developing methods to create simultaneous co-registered multimodality ultrasound images, track tissue motion and register to planning CT or MRI. Conventional ultrasound and photoacoustic imaging will be available, with anatomy, perfusion, vascular density, blood oxygenation, hypoxia, elastography, speed of sound, molecular biomarker detection based on contrast agents and dose enhancement distribution from molecularly targeted dose enhancers. This approach is suitable for any organs where acoustic access is possible, including breast, prostate, liver, pancreas, pelvic, head and neck, etc. It is especially applicable to mini/micro-beam and FLASH irradiation which, in combination with the Bragg-peak energy deposition, generates an acoustic source that can be localised and quantified by passive ultrasound image reconstruction methods currently employed in photoacoustic imaging.

Although not a new concept, past performance of this type of imaging dosimetry has been limited, and this component of the project represents one of the ambitious high-risk, high-gain elements of the project. The main challenges, and our novel approaches to overcoming them, are:

* The proto-acoustic signals generated by tissue at existing PBT beam and pulsing regimen have thus far been extremely week, requiring impractically massive signal averaging and acquisition times to detect them. Although the ms‑duration PBT pulses employed to date fall within the stress-confinement limit defined by the dimensions of the Bragg peak, experience from photoacoustic imaging is that ns‑duration pulses generate much stronger signals. The strength and hence detectability of the acoustic signals will therefore be greatly enhanced by employing the unique features of laser-hybrid accelerator technology which will facilitate PBT pulses of 10 ‑ 40 ns duration. We will also take advantage of massively parallel ultrasound receive electronics and transducer arrays with tens of thousands of elements, and front-end compressive sensing, so that averaging-out of uncorrelated noise between array elements and signal enhancement is implicit in image reconstruction. Furthermore, techniques described below for overcoming the bandwidth limitations will enhance signal to noise ratio.
* The frequency content of proto-acoustic signals varies widely, depending on the spatiotemporal dose distribution and proton energy. To date, experimental proto-acoustic systems have been designed to detect the wave emitted along the PB axis, where the Bragg peak’s dimension causes kHz acoustic emissions which cannot take advantage of the most sensitive ultrasound transducers or those used for simultaneous ultrasound imaging. We will use flexible detector configurations and novel acoustic beamforming that take further advantage the unique features of this hybrid acceleratory technology by employing the natural variation in frequency content that exists with emitted wave direction, using the high (MHz) frequencies associated with cylindrical component of the emitted wave and which can be optimised for high sensitivity and high resolution ultrasound detection, adjustable by changing the PB (mini- or micro‑) beam size. Further flexibility in transducer array design, with interdigitated elements that vary in centre frequency and with location on the array according to wave direction, will also be utilised.
* The ultrasound transducers must permit dose and other imaging without disturbing simultaneous irradiation, in the treatment room without an operator to do the scanning. Our solution will be a flexible ultrasound detector system, based on inter-communicating subarrays with an organ-specific array configuration that provides acoustic data for volumetric image reconstruction as well as PBT access. For specific organs, aspects of existing technology can be used, such as the ring arrays currently used for whole-body photoacoustic imaging of mice or for clinical breast imaging. For abdominal and other organs, novel array configurations will be needed although advantage can be taken of simultaneous work around the world to develop conformable arrays for solving a multitude of diagnostic imaging problems.
* The acoustic properties for which compensation is needed to enable accurately localised and quantitative dose imaging, are patient specific. Novel speed of sound and attenuation imaging, which employ full-wavefield reconstruction methods, are currently being developed for diagnostic imaging. These will be used, where necessary taking advantage of novel ultrasound contrast microbubbles as beacon signals, to correct for acoustic wave aberrations and attenuation for dose-image resolution enhancement and quantification, respectively.

Lacking an appropriate source and co-optimised acoustic detectors, 15 months is insufficient for experimental proto-acoustics work. (Preliminary sources will, however, be available early in the phase-2 project). During the phase-1 project we will deliver:

* A review of proto-acoustics work, options and potential, with a preliminary required performance specification and key biological questions.
* Original findings from modelling using tools such as the GEANT4 (Monte Carlo) and k-Wave (thermoacoustic generation and propagation) libraries, based on known tissue characteristics, varied PB properties such as beam size, pulse length, particle energy, particle type and dose per pulse, and varied ultrasound detector characteristics as described above, to evaluate predicted dose imaging capabilities for the expected performance of the hybrid accelerator and to determine the ultrasound system requirements for phase-2.

A full plan for a phase-2 proposal based on the concepts outlined above and the outcome of the modelling.

1st revision:

### C3.2: Work package 2: Proton- and ion-acoustic imaging

**Knowledge of the position of the Bragg peak (BP) in relation to anatomy is essential for PBT** to be used to deliver a high dose to the target tumour and to spare healthy tissue. **Quantification of the deposited dose distribution is required for our clinical-system vision, and to perform biological measurements** in the PoP system. **We will develop proton- and ion-acoustic (proton-acoustic) imaging to fulfil both needs.**

Proton-acoustic imaging works in a similar way to emerging medical photoacoustic imaging. It can localise the BP with submillimetre accuracy, allowing a quantitative image of the dose to be reconstructed using the acoustic waves emitted when the energy deposited creates a temporally and spatially localised temperature (and hence pressure) rise. Our aim is *in-vivo* real-time 4D proton-acoustic dose localisation and quantitative imaging with simultaneous multimodality ultrasound and motion tracking. **Challenges will be met with fundamental ultrasound innovation**. Good signal-to-noise ratio will be achieved by using proton/ion pulses about 100 times shorter than those used hitherto, adjusting the mini-/micro-beam size to generate acoustic fields that allow highly sensitive ultrasound transducers with novel configurations and beamforming to use different frequencies for different wave directions, acoustic wavefield averaging using massively parallel ultrasound processing, and compressed sensing. Novel full-wavefield speed of sound and attenuation imaging will provide patient-specific correction for accurate BP localisation and dose-image quantification.

**Deliverables:**

* **Design report defining proton-acoustic systems for biological research and for clinical use.** This document will include a review of proton-acoustic literature, a preliminary performance specification, and an R&D roadmap.
* **Simulation of the performance of the proton-acoustic systems.** Original findings from modelling using tools such as GEANT4 (Monte Carlo) and k-Wave (thermoacoustic generation and propagation), based on known tissue characteristics and varied beam and ultrasound-detector characteristics to evaluate dose-imaging capabilities for the laser-hybrid accelerator and to determine the ultrasound system requirements for the Phase 2 programme.
* **A full plan for a phase-2 proposal** based on the concepts outlined above and the modelling.

STFC version:

+ demonstrator experiment

+ device for biologists to use

* In vitro (5 year)
* In vivo (beyond)

Hadron

Avio, Daresbury

Ken’s estimate for full (i.e. all w/ps) is £7M-£10M