South Australian Health and Medical Research Institute Submission

2016 National Research Infrastructure Roadmap Capability Issues Paper

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Background

Australia's future lies in innovation, and pioneering medical research represents a huge opportunity.

Proton therapy is a non-invasive form of cancer treatment for localised disease and is delivered in an outpatient setting. The physical properties of proton interactions with matter are advantageous for radiotherapy applications in comparison to X-ray beams which are the current standard of care in Australia. An increasing number of proton therapy units are being installed in Europe, Northern America and East Asia. However, despite the many advantages, proton therapy is not currently available in a clinical setting in the southern hemisphere. Securing this technology has the potential to move Australia to a strong position of regional and international leadership, and make Australia a destination for complex cancer treatment options for Australian and international cancer patients.

Question 1: Are there other capability areas that should be considered?

A National Proton Therapy Facility (housed in the proposed SAHMRI 2 building) will allow for patient treatment and research outcomes currently not available in the southern hemisphere whilst bringing together national and international researchers.

Question 2: Are these governance characteristics appropriate and are there other factors that should be considered for optimal governance for national research infrastructure.

A comprehensive Governance Plan of the National Proton Therapy Facility in South Australia has been completed by Ernst and Young and available on request. The Plan includes a Proton Therapy Facility with 3 gantries, will one gantry dedicated to research. The Plan also demonstrates an ability to deliver proton therapy to Australian patients with no out of pocket fee, whilst also providing access to private and fee paying patients. The 25 year operational plan enhances revenue generation with incorporation of whole-of-life costs including self-funded equipment upgrades and replacement.

The Governance Plan also incorporates details of the Project Team and Advisory Board with representation from research, university and public health sectors, ANSTO and RANZCR with representation from each State of Australia.

Question 3: Should national research infrastructure investment assist with access to international facilities?

Yes, it will formalise existing strategic links currently in place developed by the Royal Adelaide Hospital and SAHMRI to international and national research and health centres. International collaboration will continue through the operational phase with research partnerships and Australian patients no longer required to travel overseas for treatment. Research proposals developed prior to commencement of operations will further develop into multi centre international collaborations. A third phase will allow remote planning and mentorship through skill and expertise to other health care centres within the region.

Question 4: What are the conditions or scenarios where access to international facilities should be prioritised over developing national facilities?

Access to international facilities remains important in the years prior to commencement of proton therapy treatment in Australia, however as public and professional awareness to the benefits of proton therapy increases, there is a concern of increasing costs to the Federal government in treating Australian patients overseas.

Question 5: Should research workforce skills be considered a research infrastructure issue?

Yes, whilst there has been some media and announcements in relation to a potential proton therapy infrastructure centres within Australia; there is also a requirement of a skilled and experienced workforce. Over the past 5 years South Australia has developed a highly experienced team with the necessary expertise. Whilst key positions can be recruited from overseas, there is an availability risk and increased costs associated.

Question 6: How can national research infrastructure assist in training and skills development?

The South Australia Facility will have leaders with the necessary qualifications and skills available on Day 1 of the project, with an ability to further develop and train staff for other proton therapy centres in the future for the region.

Question 7: What responsibility should research institutions have in supporting the development of infrastructure ready researchers and technical specialists?

Research institutions must have the necessary workforce infrastructure from inception but also facilitate adequate ongoing training as the program evolves over time to optimise research opportunities. As the software and hardware technology involves, it is expected that technical specialists have skills that allow the adoption of more advanced treatment techniques using the existing machine technology.

Question 8: What principles should be applied for access to national research infrastructure, and are there situations when these should not apply?

Research infrastructure is a national resource. If the Governance plan has no Federal investment then a State or private funder will need to recover the true cost of any treatment or research from the user. The SAHMRI2 plan with minimal Federal Government investment allows full access to the facility to the Australian population.

Question 9: What should the criteria and funding arrangements for defunding or decommissioning look like?

The opportunity to develop a plan for a self-sustainable model exists with the requirement of a small initial seed funding. This model has defined co investment and acknowledges that the Federal government will not be encumbered with ongoing funding decisions. The project will transition to self-supported funding over the first 3-5 years of operations including the funds required to maintain the technology, avoiding obsolescence.

Question 10: What financing models should the Government consider to support investment in national research infrastructure?

Federal Government support for SAHMRI 1 has allowed us to create a consortium with industry and key health researchers the benefit of which allows the proton therapy facility to be built in SAHMRI 2 with minimal Federal Government funding. The Federal Government involvement could be in the form of an initial small capital expenditure investment or developing a Medicare item number for a bundled proton therapy payment. These options have been further explored in the Ernst and Young comprehensive business case.

Question 11: When should capabilities be expected to address standard and accreditation requirements?

A Particle Therapy Centre must meet EPA and RANZCR requirements prior to commencement. All patient treatment accreditation requirements must be approved and in place prior to operations. The machine technology should meet TGA or like standard requirements.

Question 12: Are there international or global models that represent best practice for national research infrastructure that could be considered?

Proton therapy centres operate across the USA, Europe and Japan. SAHMRI has established strong links to international researchers, whilst the clinical team from the Royal Adelaide Hospital has affiliation and networking links to MGH and Scripps in the USA. The clinical team of the Royal Adelaide Hospital have collaborated with medical professionals and key personnel in the he UK and Denmark National Proton Therapy Centres regarding the optimal infrastructure model.

Question 13: In considering whole of life investment including decommissioning or defunding for national research infrastructure are there examples domestic or international that should be examined?

Question 14: Are there alternative financing options, including international models that the Government could consider to support investment in national research infrastructure?

SAHMRI will receive at least four international proposals from vendors in the proton therapy machine industry for funding which will detail the extent of Government involvement of a National Proton Therapy Facility in South Australia.

Health and Medical Sciences

Question 15: Are the identified emerging directions and research infrastructure capabilities for Health and Medical Sciences right? Are there any missing or additional needed?

There is not currently a National facility offering proton therapy in Australia. This represents both a clinical and research need that has not been met. In addition, there is the possibility of a significant workforce issue in Australia for the future. Currently, Australian patients seek Federal Government funding of $180,000 to $250,000 per patient for a 6 week treatment course overseas in the USA or Europe. South Australia, through joint partnership between SAHMRI and SA Health (Royal Adelaide Hospital) has the capability to deliver such a facility.

Whilst there are cyclotron machines in Australia, the energy from these facilities is not appropriate for clinical treatment of malignancies. In addition, there is currently no public accelerator in Australia for the delivery of proton therapy to cancer patients. Proton therapy has the ability to deliver higher therapeutic doses of radiation to tumours with pencil beam precision. For a significant number of people with difficult cancer of the head and neck, brain, eye, central nervous system, skull base, sarcomas, gastrointestinal and spinal cord there is no comparable curative treatment alternative, there are at least 600-800 patients per year in this category. Of most significance however is the benefit to the paediatric population. Children with cancer suffer the greatest long-term harm from conventional x-ray therapy as their organs are still growing and developing.

A National Proton Therapy Facility incorporated in SAHMRI2 has the potential to move Australia to a clear position of national and international leadership bringing clear benefits to a significant number of Australian patients per annum whilst attracting international recognition in research and development. With a current worldwide shortage of skilled clinicians in this field, the health economic benefits to South Australia and Australia through academic education and training are significant.

A comprehensive business case and 25 year operation plan has been developed by Ernst and Young (and available on request) for a National Proton Facility in South Australia has State and Federal Government support. The business case identifies a self-sustaining health economics model with significant further cost recovery from research, and fee paying national and international patients. Proton therapy is delivered in an outpatient setting with the business case demonstrating cost comparable with delivery costs of Image

Guided Radiotherapy. Australia should set a new priority to not only look at the cost of new technology with a strong commitment to revenue opportunity. South Australia's clinical team and skilled expertise is highly sought after in SE Asia who have committed a strong link for collaborations with SAHMRI2/Royal Adelaide Hospital and a National Proton Centre in South Australia. This will allow Australia's existing reputation for health care excellence to further leveraged and reduce health care costs within Australia.

Other states within Australia are exploring proton therapy facilities, some on a private model rather than a comprehensive national facility for all Australians.

What would a National Facility in South Australia look like?

- Housed in SAHMRI2 and co-located with the $2b world class new Royal Adelaide Hospital (RAH) and proposed Women and Children's Hospital (major teaching hospitals for adult and paediatric) together with the three universities of South Australia with international affiliation and linkages to world class clinical and research activities from the same site.
- The proposed SAHMRI2/National Proton Therapy Facility has generated expressions of interest from a variety of fields including -
    - A National Digital Health Hub in collaboration with the University of South Australia will provide opportunity for SAHMRI to explore data analytics, in both data analysis with seamless links to neighbours in the SE Asia. Driven by Health in South Australia, this collaboration will link experts in industry and the university sector.
- Research and clinical team - Medical physicists at the RAH have been heavily involved with the program for a number of years, with some having completed research including a PhD thesis in proton tomography and have conjunct appointments in the USA centres. RAH Radiation Oncologists have been supported by the RANZCR through the Thomas Baker Fellowship to Massachusetts General Hospital Boston, McLaren Hospital (Michigan) to further develop a proton therapy program in Australia. RAH radiation therapists have received training and are currently undertaking numerous dose comparative studies to investigate the optimal use of proton therapy. This has led to informed clinical decision making regarding the need to refer for overseas treatment. Establishing a National Facility in SA would enable optimisation of the existing resources and skills currently in place, as well as attracting expertise from outside Australia.

- The SA project team now have strong proposals to treat patients from south-east Asia which helps to underpin some of the operational costs of the facility. This support is specific to a National Proton Therapy in South Australia, recognising and acknowledging the expertise and skill of clinicians and professionals based in this State. It would not affect the capacity to treat all Australian patients in urgent need for proton therapy. Similarly, we have preliminary but firm proposals for training and service development of future sites in China. This would establish Australia as the focus for cancer treatment and training in SE Asia, including China. Clinicians, physicists, radiation therapists as well as key project architects, builders and project planners from around the country would be able to participate.

- A National Hadron Group comprises representation from all states, RANZCR, and consumers. The Hadron Group supports the SA plan- a patient focused national centre with full research opportunities. The support of both ANSTO and the Hadron group for the SA proposal is a significant endorsement of the National Proton Facility in this State.
- Additional key international experts have pledged support for our centre. Prof. Torunn Yock, the worlds most experienced and published paediatric and breast cancer proton therapy expert has indicated their commitment to undertake a sabbatical funded by MGH to help us establish the national centre. Dr Yock has just published a highly recognised article on the benefits of proton radiotherapy in the paediatric population *[The Lancet Oncology article PIIS1470-2045(15)00167-9]* *http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)00167-9/fulltext*
- National and International support from professional organisations and committees including the Cancer Council, CanSpeak Australia, Cancer Voices Australia and the Royal Australian & New Zealand College of Radiology as well as affiliation, endorsement and support from the University of Australia; Flinders University, University of Adelaide, University of South Australia as well as the Australian National University, RMIT University, University of Wollongong, University of Melbourne, University of Sydney as well as international institutions such as Harvard University, Massachusetts General Hospital. (Attachment 1)
- Comprehensive MOC and operational plan for the National Centre developed through a strong affiliation with these institutions.
- High level discussions have been held with various health professionals and stakeholders in NSW and Qld relation to a National Proton Facility from South Australia.
- The RANZCR and the Australian Nuclear Science and Technology Organisation have independently endorsed the South Australian strategic plan for delivering an integrated national centre.
- Geographically centrally located within Australia, South Australia provides affordable treatment and associated support facilities for cancer patients. The proposed proton therapy facility will be located in a world-class precinct of healthcare, research and development co-locating with the new Royal Adelaide Hospital and SAHMRI.
- A century of contribution of eminent South Australians has been significant to the development of proton therapy treatment. Sir Mark Oliphant, Governor of South Australia received government support to develop the first proton synchrotron in Australia. The medical application of Sir William Bragg's discovery that proton beams deliver a high dose of radiation at depth in matter has revolutionised the field of radiation oncology. The term 'Bragg Peak' continues to be used today in proton radiation therapy. Sir William Henry Bragg and his son Sir Willam Lawrence Bragg were joint Noble Prize recipients.
  https://www.adelaide.edu.au/seek-light/stories/bragg.html
- A National Proton Therapy Facility incorporated in SAHMRI2 has the potential to move Australia to a clear position of national and international leadership bringing clear benefits to a significant number of Australian patients per annum whilst attracting international recognition in research and

development. With a current worldwide shortage of skilled clinicians in this field, the health economic benefits to South Australia and Australia through academic education and training are significant.

- The business case for a National Proton Facility in South Australia has State and Federal Government support and the business case identifies a self-sustaining health economics model with significant further cost recovery from research, and fee paying national and international patients.

Opportunity for world-leading research

Proton therapy shows great promise for successful targeted treatment of tumours that are difficult to treat because of their close proximity to extremely radiation sensitive normal tissues, but could be applicable to a wide range of cancers. However, proton therapy is still largely in the development phase and many important research questions remain unanswered compared to more conventional x-ray therapy, the radiobiology of the interaction of protons with both tumour and normal tissues is largely unknown. Research required to fill this knowledge gap includes both in vitro and in vivo study of gene transcription and signalling responses to proton irradiation in different cells and tissues radiation induced bystander effects, roles of hypoxia, the ability of the host to undergo a host vs tumour response and other immune system responses, potential for secondary tumours in normal tissue, and the interaction of proton therapy responses with radiotherapy or chemotherapy modalities, new therapeutic for radiosensitisation of the tumour tissue and radioprotection of normal tissue, as well as the many challenges related to the physics of dosimetry optimisation. These areas of research will provide the information required to inform the clinical trial design for the future. The South Australian multidisciplinary team of researchers has the required expertise in radiobiology, immunology, pharmacology, genetics and molecular biology to extend research to study the biological effects of proton therapy in a variety of cancers and normal tissue, the medical physics expertise to design the appropriate dosimetry optimisation and the clinical expertise to design clinical radiotherapy trials. As patients are treated in the National Proton Therapy Facility in South Australia and other facilities around the world, we are uniquely placed to undertake survivorship research, particularly around the issues of chronic disease management and studies of co-morbidities in patients treated with proton therapy, as well as undertaking behavioural research in secondary prevention strategies.

Question 16: Are there any international research infrastructure collaborations or emerging projects that Australia should engage in over the next ten years and beyond?

A National Proton Therapy Facility housed in the proposed SAHMRI 2 provides clear linkages to world class researchers and data collection.

- Comprehensive Model of Care and operational plan for the National Centre developed through a strong affiliation with international institutions such as Massachusetts General Hospital (Boston, US) and Scripps Radiation Therapy Centre (San Diego, US).
- The Radiation Therapy Oncology Group (RTOG), the peak research body in the US, provides the infrastructure for radiotherapy clinical research including proton therapy. There is an opportunity for

Australian patients to be enrolled in such trials, which would involve quality assurance and data collection of such a program.

- The Royal Australian and New Zealand College of Radiologists and the Australian Nuclear Science and Technology Organisation have independently endorsed the South Australian strategic plan for delivering an integrated national centre with a focus on meeting research and clinical needs.
- Significant collaboration with Radiobiologists in Dresden, Germany and Chiba, Japan investigating the interaction between particle irradiation and cell biology.

Considerable breadth of disciplinary expertise across multiple institutions both nationally and internationally would allow Australia to engage in further collaborative research over the next 10 years.

Question 17: Is there anything else that needs to be included or considered in the 2016 Roadmap for the Health and Medical Sciences capability area?

Whilst there are a number of cyclotrons in Australia capable of producing radioisotopes including the facility in the current SAHMRI it would be prudent to strengthen the link and leverage from the current cyclotron expertise. There is an opportunity to conduct clinical research using positron emission tomography (PET) to determine real time tumour response to fractionated proton therapy. This in turn would enable treatment adaptation during a course of therapy.

Additionally, in South Australia, a growing group of engineers and technicians are quietly manufacturing some of the world's leading edge radio frequency equipment, but a severed shortage of skills coming out of the State and National Universities means that Australian Companies are being forced to relocate overseas. **Tomco Technology** specialises in the design and manufacture of radio frequency power amplifiers for scientific and commercial uses including in particle accelerators, MRI machines and radars used in weather prediction and climate change.

Tomco Technologies have the contract to supply a component that can be used in proton therapy equipment. Whilst the company has doubled its workforce in 2014 on the back of new export contracts in the US, Germany and Russia, finding suitably qualified staff has been difficult. The scientific market as opposed to commercial has been resilient to recent financial crisis. (Attachment 2)

Other collaborative discussions have been held with vendors and suppliers in **New Zealand** in relation to manufacture of various components for the proton machine.

Environment and Natural Resource Management

Question 18: Are the identified emerging directions and research infrastructure capabilities for Environment and Natural Resource Management right? Are there any missing or additional needed?

Question 19: Are there any international research infrastructure collaborations or emerging projects that Australia should engage in over the next ten years and beyond?

Question 20: Is there anything else that needs to be included or considered in the 2016 Roadmap for the Environment and Natural Resource Management capability area?

Advanced Physics, Chemistry, Mathematics and Materials

Question 21: Are the identified emerging directions and research infrastructure capabilities for Advanced Physics, Chemistry, Mathematics and Materials right? Are there any missing or additional needed?

Therapeutic ion accelerators capable of accelerating protons and heavier species are an emerging direction in the management of cancer. While there are several ion accelerators operating to produce radioisotopes for medical use in Australia, the accelerators required to generate energetic ions capable of therapy are significantly larger and require greater infrastructure. Proton therapy, the most widespread application of ion therapy, is rapidly expanding in developed countries within North America, Europe, East Asia and South-east Asia. Australia currently does not offer proton therapy. It is important that Australian patients are offered the most up-to-date and technologically advanced cancer treatment options made possible by advanced physics.

Question 22: Are there any international research infrastructure collaborations or emerging projects that Australia should engage in over the next ten years and beyond?

Development of imaging for proton therapy is an important area of research required to fully utilize the potential physical benefits of proton therapy over conventional X-ray therapy. Proton computed tomography (pCT) is a form of medical imaging in which the source of radiation is a high energy proton beam, as opposed to a conventional kilovoltage X-ray beam. Proton CT has the advantage of providing more relevant information about the properties of patient tissues for accurate planning of a proton radiotherapy treatment in comparison to conventional X-ray CT. Realization of a clinical pCT system requires a collaboration of high energy physics, high performance computing, applied mathematics and medical physics. Because of the multidisciplinary nature of the research, an international collaboration is required.

Carbon ion accelerator facilities are several times larger and more expensive than proton accelerators and are thus restricted to only several sites worldwide. It is important that Australia become actively involved in this new treatment direction, which may reduce side-effects of cancer treatment and reduced total treatment time. Proton therapy is commonly the stepping stone to carbon ion therapy and this should be the direction in which Australia moves in the next decade.

Question 23: Is there anything else that needs to be included or considered in the 2016 Roadmap for the Advanced Physics, Chemistry, Mathematics and Materials capability area?

See response to 21.

Understanding Cultures and Communities

Question 24: Are the identified emerging directions and research infrastructure capabilities for Understanding Cultures and Communities right? Are there any missing or additional needed?

Question 25: Are there any international research infrastructure collaborations or emerging projects that Australia should engage in over the next ten years and beyond?

Question 26: Is there anything else that needs to be included or considered in the 2016 Roadmap for the Understanding Cultures and Communities capability area?

National Security

Question 27: Are the identified emerging directions and research infrastructure capabilities for National Security right? Are there any missing or additional needed?

Question 28: Are there any international research infrastructure collaborations or emerging projects that Australia should engage in over the next ten years and beyond?

Question 29: Is there anything else that needs to be included or considered in the 2016 Roadmap for the National Security capability area?

Underpinning Research Infrastructure

Question 30: Are the identified emerging directions and research infrastructure capabilities for Underpinning Research Infrastructure right? Are there any missing or additional needed?

Question 31: Are there any international research infrastructure collaborations or emerging projects that Australia should engage in over the next ten years and beyond?

Question 32: Is there anything else that needs to be included or considered in the 2016 Roadmap for the Underpinning Research Infrastructure capability area?

Data for Research and Discoverability

Question 33: Are the identified emerging directions and research infrastructure capabilities for Data for Research and Discoverability right? Are there any missing or additional needed?

Question 34: Are there any international research infrastructure collaborations or emerging projects that Australia should engage in over the next ten years and beyond?

Specifically in the area of big data the Digital Health Hub (see response in Question 15) will address any potential opportunities to mine clinical and research data. There a number of RTOG (Radiotherapy Oncology Group) Clinical Trials where there is an opportunity to collaborate and use their existing research infrastructure. This would include quality assurance of any clinical programme and data collection.

Question 35: Is there anything else that needs to be included or considered in the 2016 Roadmap for the Data for Research and Discoverability capability area?

Other comments

If you believe that there are issues not addressed in this Issues Paper or the associated questions, please provide your comments under this heading noting the overall 20 page limit of submissions.