GOVERNMENT OF WESTERN AUSTRALIA

Sustainable Health Review

Public Submission Cover Sheet

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Roger Price 03/10/2017

Submission Guidance

You are encouraged to address the following question:

In the context of the Sustainable Health Review Terms of Reference listed below, what is needed to develop a more sustainable, patient centred health system in WA?

- Leveraging existing investment in Primary, Secondary and Tertiary healthcare, as well as new initiatives to improve patient centred service delivery, pathways and transition;
- The mix of services provided across the system, including gaps in service provision, sub-acute, step-down, community and other out-of-hospital services across WA to deliver care in the most appropriate setting and to maximise health outcomes and value to the public;
- Ways to encourage and drive digital innovation, the use of new technology, research and data to support patient centred care and improved performance;
- Opportunities to drive partnerships across sectors and all levels of government to reduce duplication and to deliver integrated and coordinated care;
- Ways to drive improvements in safety and quality for patients, value and financial sustainability, including cost drivers, allocative and technical efficiencies;
- The key enablers of new efficiencies and change, including, research, productivity, teaching and training, culture, leadership development, procurement and improved performance monitoring;
- Any further opportunities concerning patient centred service delivery and the sustainability of the WA health system.

Sustainable Long Term Supply of Critical Diagnostic Positron Emission Tomography (PET) Imaging Agents to WA Patients

A submission to the Sustainable Health Review: October 2017

EXECUTIVE SUMMARY

- **Rising demand for PET imaging in WA.** Positron emission tomography (PET) imaging is vital for the diagnosis and management of a broad range of cancers and increasingly in neurological diseases. In particular, PET imaging is used in the selection and monitoring of cancer treatments. Demand for PET scans in WA has exceeded 10%/yr for over a decade, with 40% further growth expected by mid-2020; equivalent then to about 21,000 individual patient scans per year.
- **SCGH facility is unique in WA**. The RAPID facility at Sir Charles Gairdner Hospital (SCGH) is the long-term sole provider for all of WA's PET radiopharmaceuticals requiring a Medical Cyclotron for production - about 95% of demand. Facilities are now 15 years old and have absorbed multifold increases in State-wide patient demand. It is not feasible to import PET radiopharmaceuticals from outside WA because of the very short radioactive half-life ('shelf-life') of such products – between 10 & 110 minutes.
- **Significant failure must not be allowed to occur**. Failure of WA's single Medical Cyclotron, operating every day of the working week, for more than a few days could lead to unacceptable delays in PET scans for seriously ill patients, with only a trickle of emergency doses from the Eastern States, at great cost and variable supply.
- **Production below international standards**. Also, according to the Therapeutic Goods Administration (TGA), PET radiopharmaceuticals should be manufactured according to an international standard called Good Manufacturing Practice (GMP); not possible in WA because of the age of the SCGH facility. Consequently, WA patients are currently barred from receiving the benefits of some recent advances in PET imaging, particularly for neurological diseases such as Alzheimer's disease. WA is the only state in WA (barring Tasmania) without GMP radiopharmaceutical production facilities.
- **Rising radiation dose to workers**. Furthermore, defects in the current facility plus relentless increase in demand will put the Hospital staff who work in this facility increasingly at risk of unacceptable radiation exposures over the next three years. Protection of these staff is becoming increasingly difficult, with the emerging sole option being systematic reduction in the operating hours of the Medical Cyclotron. Current planned downtime is 12 days/yr, but this will rise to at least 20 days/yr in 2020. This will directly limit the capacity of the facility to meet future demands for PET imaging - the scope of which is expanding rapidly, as shown by the Table at the end of this submission.
- **Initiating the conversation**. Our Area Health Service has acknowledged these risks by placing the Medical Cyclotron and its Lab on the Risk Registers of both SCGH&OPH and NMHS. A Business Case Analysis (BCA) for guaranteeing supply of PET radiopharmaceuticals to WA patients for the next 25 years has been submitted. It explores several options and is supported by an accurately costed Master Plan (MP). At the time of writing, the BCA & MP had been passed to the Assistant Director General: of Health, Purchasing & System Performance, for consideration.
- **KEY SUMMARY**. WA's aging non-GMP PET lab and single Medical Cyclotron, though capable of operating with enhancements for another 20 years, **cannot without capital investment (including a second Cyclotron) reliably respond beyond mid-2020** to the relentless growth in demand for existing and new PET radiopharmaceuticals, or the opportunities for internationally-linked clinical research using PET agents that must be produced under GMP. Even the 2020 deadline may require curtailment of some productions, restriction on introduction of new imaging agents, plus a possible rationing of supply of some agents to more urgent clinical cases.

BACKGROUND

Unique Role of WA's sole Medical Cyclotron & its Radiopharmaceutical Labs

1. The Radiopharmaceutical Production & Development (RAPID) Laboratories of Medical Technology & Physics (MTP), SCGH have been the sole statewide supplier of cyclotron-derived positron emission tomography (PET) radiopharmaceuticals since the inception of the service in 2003, providing products to public hospitals and to private imaging centres.
2. These products must be manufactured within WA, since it is not feasible to import more than a handful of doses from outside the State (at significant expense, and with variably reliable delivery). This is because of the short radioactive half-life of such products.
3. A 'natural monopoly' for supply of PET radiopharmaceuticals has arisen around SCGH over the last 14 years because of the necessity for investment in a Medical Cyclotron and the limited market provided by the relatively small 'captive' WA population.
4. RAPID serves two Public Hospitals, five private imaging centres (including Bunbury), one major research centre, plus the preclinical Cancer Imaging Facility of the Perkins Institute.
5. **If RAPID's production fails on any day, about 70-80 patients across the State have their PET scans cancelled.**

Increasing Scope & Volume of Production

6. Growth has been 10-14% per year consistently, since operations began in 2003. Now >15,000 patient doses are delivered per year, as shown in Figure 1. If current trends are extrapolated, 21,000 patient doses will be manufactured in 2020 (increase of 40%).

7. The PET radiopharmaceuticals available to patients in WA are shown in the Appendix. It is seen that PET imaging contributes to the management of a wide range of serious illnesses. Approximately one new PET imaging product is introduced per year to the scope of production, with (for example) an [^{1}8F] radiotracer for Alzheimer's disease diagnosis & staging being made available for clinical evaluation in 2018.

8. Recently, RAPID has assumed the additional role of producing therapy radiopharmaceuticals for prostate and neuroendocrine tumour *molecular radiotherapeutic treatment* – to be deployed in SCGH from early 2018, and expected to escalate rapidly in terms of patient demand.

Stress on Human and Equipment Resources

9. Minor radiation incidents involving workers and arising from increased radioactivity of daily productions have increased over the last 2 years. These have been managed in-house by engineering modifications to existing plant and by increased Medical Physics area monitoring. No breaches of any regulations have occurred. However, as the magnitude of daily produced radioactivity increases (see Figure) the capacity to effectively respond to future incidents is becoming more difficult.

10. The *duty cycle* of the Cyclotron is decreasing because of longer scheduled shutdowns for increasing regular maintenance, in proportion to total operational hours. Also, longer "cool-down" times prior to maintenance intervention are increasingly required, due to higher levels of residual radioactivity at shutdown. By 2020, total *planned*

Cyclotron downtime will be *at least* 20 working days per year (currently about 12). This will inevitably reduce services to patients.

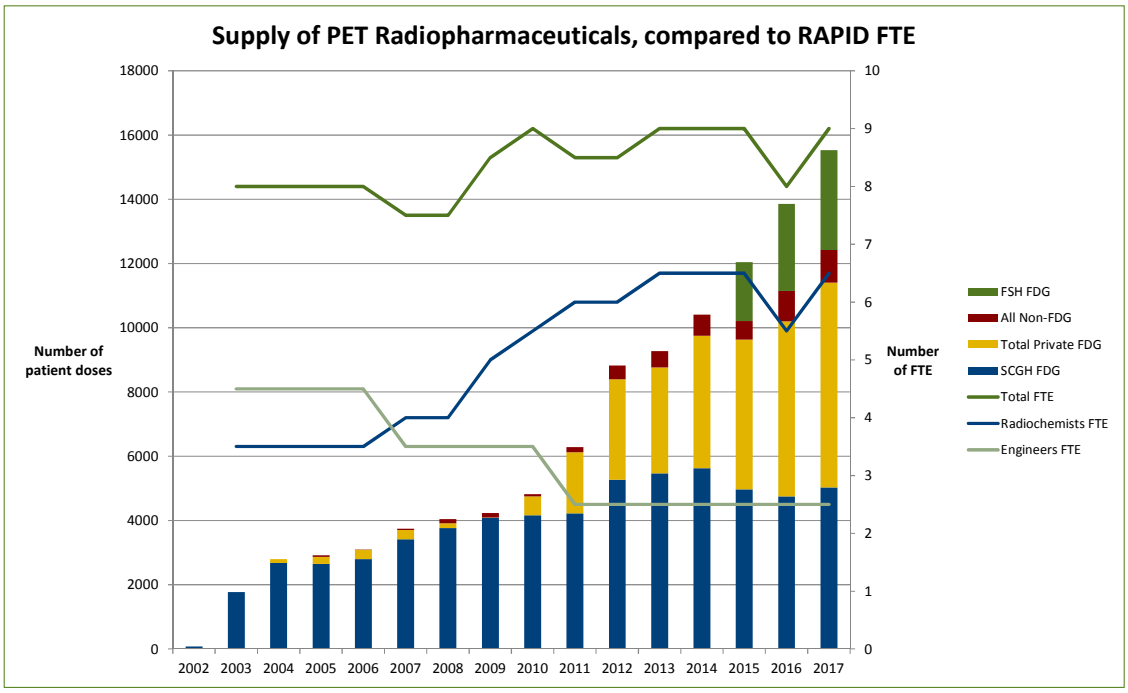

Figure 1. Growth in demand for cyclotron-derived PET radiopharmaceuticals expressed in patient doses per year, since commissioning of WA's only Medical Cyclotron in 2003. Radiopharmaceutical products are divided into public vs. private imaging centres; SCGH FDG vs. FSH FDG doses; and FDG doses vs. all other PET doses. (FDG is the most widely used PET agent – see App.)

Increasing Risk of Significant Failure with Consequent Increases in Worker Radiation Doses & Disruption of Patient Services

11. Radiation doses to Cyclotron Engineers are traditionally kept within regulatory limits by the high reliability of the Cyclotron and a relatively infrequent need for *unplanned* interventions – *each of which requires Engineers to actually crawl into the radioactive Cyclotron centre*. Significant failure would mean that staff would be required to assume more dose, OR wait a much longer "down" period before entering the Cyclotron precinct. Comprehensive personal shielding against penetrating (i.e., high-energy) Cyclotron radioactivity when in the bunker on maintenance duty is not feasible – the radiation requires centimetre (not millimetre) thicknesses of lead shielding to stop it.

12. RAPID management's *only* option in the coming years to avoid unacceptable exposure to Cyclotron Engineering staff in particular, but also possibly to Radiochemist production staff is to; (i) progressively reduce the duty cycle of the Cyclotron ('10', above) or (ii) temporarily retire staff from active production until their time-averaged radiation doses are acceptable. In any event, these actions would directly negatively impact on patient access to PET imaging in WA.

13. *The very good historical operational record of WA's ageing Cyclotron obscures the serious consequences of its potential significant failure.* The nearest technical support is in Belgium. Though the RAPID Engineering Team is one of the world's best (their advice is sought internationally) serious technical failure could shut down PET imaging in WA for weeks and cost >$100k in technical support from overseas – in the interest of the fastest possible rehabilitation of the Service.

14. **We estimate that the current RAPID plant (principally but not completely constrained by the capacity of the Cyclotron) will reach its production expansion limit by mid-2020 at the very latest, and management will very likely need to progressively restrict certain non-FDG productions before then, plus increase Cyclotron planned down-time.**

'Natural Monopoly' has Strategic Consequences and Responsibilities

15. A Medical Cyclotron & 'joined-at-the-hip' Radiopharmaceutical Labs are a major industrial investment for a 'greenfield' enterprise. National (TGA) & State (Radiological Council) regulatory approvals alone can take several months to a year to achieve, even for an expertly constructed enterprise and unlimited professional inputs.

16. Such a new enterprise would be required to operate under the code of Good Manufacturing Practice (GMP) – unlike RAPID Labs currently (see below). For a 'greenfield' plant, from 'spade in the ground' to actual approved production would take a minimum of 2 years. (Recall that only a trickle of PET doses can be flown to WA, and at high cost and low reliability – judged by experience). *Thus, any intention of RAPID Labs to restrict production growth or implement any other limiting changes to production would need to be announced to public and private stakeholders with at least two years' lead-time*, to encourage an alternative or augmented long term supply solution, without interruption to the existing services.

Lack of GMP Facilities: Risk to WA Health Revenue, Research Initiatives & Introduction of Innovative Products

17. Currently, WA Health receives $1.6 M revenue from FDG sales to private cameras, though the product is not produced under GMP conditions. This is effectively a longstanding concession by the TGA. *Continuation of this is predicated on no alternate supplier in WA being capable of producing FDG under GMP Certification*.

18. Lack of a GMP PET radiopharmaceutical production centre in WA continues to eliminate some opportunities for WA clinical investigators to initiate or participate in clinical trials because the required PET radiopharmaceuticals are prohibited by their patent owners from being produced in non-GMP certified labs. Examples include all common 'radiofluorinated' beta-amyloid plaque labels for Alzheimer's disease – which are currently effectively barred to WA patients.

19. Thus it will be increasingly difficult to introduce new imaging radiopharmaceuticals to WA because of the lack of GMP facilities, but also because RAPID Labs are reaching their limit in scope of production. RAPID currently regularly produces 9 different radiofluorine, radiocarbon and radiogallium labels, as well as (less frequently) several other agents including those for preclinical studies. *RAPID Labs are the busiest in Australia when judged on a combination of product scope and volume.*

BROAD RECOMMENDATIONS

- That the options for expanding the current RAPID facilities on the QEII MC site, including establishing a GMP-certified precinct, plus also a co-located second Medical Cyclotron be considered.

- That the comprehensively costed Business Plan plus its associated Master Plan, submitted in July 2017 to the Northern Metropolitan Health Service and passed on to the Office of the Director General of Health, be considered as the basis for devising a

State strategic plan, to ensure safe and adequate service provision of PET imaging products to WA patients for the next two decades.

CONSEQUENCES OF NOT PROCEEDING

- Inability to respond to increased demand from both the public and private PET imaging sectors. Possible embarrassment to WA Health & WA Gov't through insufficient warning given to now-dependent private PET imaging practices.

- Prospect of progressive reduction in Cyclotron operational days, to avoid rising radiation doses to Cyclotron engineers, and also ultimately to all RAPID Lab workers; leading to reduced patient access.

- Possibility of serious breakdown of WA's only Cyclotron, cancelling PET scans in WA for weeks.

- Lack of GMP facilities, restricting clinical research opportunities (particularly in oncology & neurology) through inability to produce radiotracers at GMP level.

- Restrictions in ability to introduce "new horizon" PET radiopharmaceuticals in cancer, neurology & cardiology.

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MTP, SCGH is an ISO9001 Certified Organisation

03 October, 2017.

(see Appendix over page)

APPENDIX

Current Scope of Service in Diagnostic PET Imaging Agents in WA

Current clinical investigations employing PET radioisotopes, in oncology, cardiology and neurology.

*** Provided by RAPID Labs, SCGH currently or capable of re-instigation.
** To be introduced by mid- 2018, responding to clinical demand.
* Expected to be introduced by 2019-2022, depending on demand.

Other PET radiopharmaceuticals, plus many compounds not mentioned that are under development worldwide can be produced, given sufficient clinical justification.

PET Isotope	Diagnostic Test	Clinical Agent	Purpose, Indications & Interpretation
Cancer			
^{11}C ***	Cancer: brain	[^{11}C]methionine (MET)	For mapping primary gliomas, recurrent tumours and brain metastases; difference between tumour recurrence & radiation necrosis
^{18}F ***	Cancer: glucose hypermetabolism	[^{18}F]Fluorodeoxyglucose (FDG; Sect. [6.17.1)	Detect cellular hypermetabolism, a signature of many common cancers; myocardial hibernation; abnormal metabolism associated with foci of epileptic seizures
^{18}F ***	Cancer: cellular proliferation	[^{18}F]Fluorodeoxythymidine (FLT)	Thymidine analog; an indirect measure of DNA replication and thus tumour cell proliferation through identifying substrates for thymidine kinase (TK). Increased mitotic rate, cell multiplication and lack of differentiation are tumour characteristics. Marker for early therapy assessment.
^{18}F ***	Cancer: cell membrane synthesis; parathyroid adenoma	[^{18}F]Fluoroethylcholine (FCH)	Identifying substrates for choline kinase. Choline is a precursor of phosphatidylcholine, an essential element of phospholipids of the cell membrane. Identifies rapidly growing tumors, in hepatocellular carcinoma and primary & metastatic brain tumors. Also for localization of parathyroid adenomas
^{18}F ***	Cancer: primary brain tumours	[^{18}F]Fluoroethyltyrosine (FET)	Labeled artificial amino acid taken up by tumour cells but not incorporated into proteins. For evaluation of patients with primary brain tumors, particularly glioma; the most frequently occurring.
^{18}F *	Cancer: estrogen receptors	[^{18}F]Fluoroestradiol (FES)	Estragen-receptor-positive (ER+) specific tracer, used in clinical equivocal breast cancer workup; especially sensitive to bone metastases

^{18}F ***	Cancer: hypoxia	[^{18}F]Fluoromisonidazole (FMISO)	Identifies tumor hypoxia; a key factor in tumor progression and therapy resistance. Used to image rapidly growing tumours. Useful for predicting outcomes in sarcoma and head & neck cancers following EBRT or chemotherapy
^{64}Cu *	Cancer: hypoxia	[^{64}Cu]-ATSM	Identifies tumor hypoxia; a key factor in tumor progression and therapy resistance.
^{68}Ga ***	Cancer: prostate	[^{68}Ga]PSMA-ligand	For imaging recurrent prostate cancer, particularly metastases. Ligand can take various forms. PSMA-HBED-CC is the most common (Sect. [12.9.6.10])
^{68}Ga ***	Neuroendocrine tumours (NET)	[^{68}Ga]Octreoetate	Octreotate is a somatostatin (II) analogue and ligand for the SSII receptor. For mapping NETs, particularly metastatic disease
Brain & nervous system			
^{11}C ***	Brain: dementia (□-amyloid)	[^{11}C]PiB	To estimate β-amyloid neuritic plaque density in patients with cognitive impairment being evaluated for Alzheimer's disease (AD)
^{18}F **	Brain: dementia (β-amyloid)	[^{18}F]flutemetamol, [^{18}F]florbetapir & [^{18}F]florbetaben [^{18}F] NAV-4694	To estimate β-amyloid neuritic plaque density in patients with cognitive impairment being evaluated for AD
^{18}F *	Brain: dementia (tau proteins)	[^{18}F] AV-1451 & emerging functionally similar compounds	For staging of AD & exploring interactions between β-amyloid, tau-protein pathology & neurodegeneration
^{11}C *	Brain: microglial activation	[^{11}C]PK11195	Marker for peripheral benzodiazepine receptor sites; measures microglia activation through expression of the translocator protein (TSPO); for assessing neuroinflammatory glial response to the degenerative process in PD
^{15}O *	Brain: blood flow/perfusion	[^{15}O]water	Dynamic study (typically 25 frames over 600 s) of cerebral blood flow
^{15}O *	Brain: oxygen metabolism	^{15}O^{16}O administered by inhalation	'Gold standard' for quantitative assessment of oxygen uptake and metabolism in the brain. Used to assess cerebrovascular disease.
^{18}F ***	PD & related; medullary carcinoma and NETs	[^{18}F]Dihydroxyfluoro phenylalanine (FDOPA)	Structurally similar to tyrosine; pumped into cells by the neutral amino-acid carrier. Used to map dopamine precursor in PD and to distinguish essential tremor. Also for staging medullary thyroid carcinoma, GI cancers, pheochromocytomas and other NETs
Cardiovascular system			

^{13}N ***	Heart function	[^{13}N]Ammonia	To evaluate myocardial perfusion in patients with suspected or confirmed
^{82}Rb *	Heart function	[^{82}Rb] as the chloride; derived from generator	Myocardial perfusion agent for distinguishing abnormal regions in cases of suspected myocardial infarction (Sect. [6.13.2]). A potassium analogue, similar to ^{201}Tl (Table [6.5])
Musculoskeletal system			
^{18}F ***	Bone metabolism	[^{18}F] sodium	Map areas of altered osteogenesis; bone tumours (particularly metastases), trauma and also calcifying soft tissues. Incorporated with mineralizing osteoid. Similar indications as ^{99m}Tc MDP (see Table [12.5])

AD = Alzheimer's disease. PD = Parkinson's disease. PiB = Pittsburgh compound B, an analogue of thioflavin T. PSMA = Prostrate specific membrane antigen. NET = neuroendocrine tumour.

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