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The Australasian Radiopharmaceutical Trials Network (ARTnet) – Clinical Trials, Evidence and Opportunity.

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Recent advances in technology and discovery have led to Nuclear Medicine having a key role in Precision Health and individualised patient care. As we enter this era of promise and growth, we need to ensure that our specialty is well equipped to assess, evaluate and provide evidence for the clinical application of new imaging and therapeutic agents to translate from research/experimental applications to clinical practice. The challenge for Nuclear Medicine is how to obtain evidence of efficacy, cost-effectiveness and clinical indications, in order to progress from initial studies to an approved, Government or insurance funded imaging or therapeutic agent. This is particularly relevant for imaging studies and therapies which are not developed by companies, and where academic sites participate in investigator-initiated multi-centre trials aiming to develop evidence for regulatory approval.

The initial development of evidence for FDG PET was one of the first examples of multi-centre, prospective, academic trials aimed at generating data for regulatory approval. In 2001, the Australian PET Data Collection project was initiated to generate evidence of clinical impact and management change of PET in clinical practice. This multi-centre prospective trial program evaluated over 30,000 consecutive patients undergoing FDG PET across the country over a 2 year period, and trials evaluating management impact in oncology patients produced compelling data leading to Medicare approval of many clinical indications (1). In the US, the National Oncologic PET Registry was established in 2006 to evaluate data on the clinical utility of PET through a prospective data registry, and not only enabled Centres for Medicare and Medicaid Services (CMS) to support broad funding for PET in oncology, but provided compelling data on clinical utility (2). In addition, the SNMMI established the Clinical Trials Network (CTN) in 2008 to assist with developing new molecular imaging radiopharmaceuticals through scanner validation, clinical protocol and training programs (3). These programs are examples of how clinical evidence can be developed for Nuclear Medicine studies by academic groups. The challenge that has more recently emerged is that regulatory bodies require Health Technology Assessments to contain more detailed clinical and economic outcomes in order to approve new imaging and therapeutic radiopharmaceuticals, hence new approaches to generating these levels of evidence are required.

To address the need for a more comprehensive clinical trials program in Nuclear Medicine in Australia, the Australasian Radiopharmaceutical Trials Network (ARTnet) was formed in 2014. This was a joint initiative between the two professional Nuclear Medicine organisations, the Australian and New Zealand Society of Nuclear Medicine (ANZSNM) and Australasian Association of Nuclear Medicine Specialists (AANMS). ARTnet was launched with the mission statement: 'To promote and facilitate innovative collaborative clinical research utilising radiopharmaceuticals for imaging or therapy'. ARTnet's scientific committee incorporates Nuclear Medicine specialists, technologists, radiopharmaceutical scientists and physicists. ARTnet has implemented a broad-reaching program of scanner credentialling, site validation, defining radiopharmaceutical standard operating procedures (SOPs), central image interpretation, as well as scientific and protocol review.

PET and SPECT camera accreditation is an essential element of multicentre trials in which imaging datasets will be analyzed. The importance of this was highlighted with the PET camera

accreditation using ^{68}Ga in preparation for the proPSMA clinical trial (4). The accreditation process was performed using an IEC/NEMA-NU2 body phantom and standardised imaging instructions, and this uncovered an unanticipated issue with a large underestimate in ^{68}Ga SUV parameters, that was eventually found to be related to a factory shipped incorrect dose calibrator setting (5). Had this accreditation not been undertaken, there would have been an average of 15% variation in SUV parameters across sites in the trial, which would not be acceptable. ARTnet has also developed radiopharmaceutical production and QC manuals for clinical trials and has an accreditation process for sites that perform in-house production of radiopharmaceuticals.

ARTnet provides quality support and enabling for clinical trials, however the clinical trials are run as investigator-initiated studies, led by Principal Investigators, and funded by Government, charitable organisations or sponsored research grants. Trials are either Nuclear Medicine led studies or are performed collaboratively in close co-operation with other medical speciality and clinical trials groups.

The formation of ARTnet corresponded with the emergence of PSMA PET imaging, and this has been the focus of the initial successful ARTnet supported studies and publications. The first collaborative ARTnet supported study was a study of the management impact of PSMA PET imaging. This questionnaire-based study assessed management intent pre- and post-PSMA PET imaging and demonstrated a 51% management change in the overall cohort and a 62% management change in those patients who had PSMA PET performed for biochemical relapse (6). The clinical impact and influence on subsequent treatment decisions are important considerations in funding of a new imaging test and also provide inputs into cost analysis considerations.

The proPSMA study was the first large imaging trial where ARTnet was involved in site credentialling and study conduct. ProPSMA was a multicentre prospective randomised clinical trial of ^{68}Ga-PSMA PET imaging in 302 men with newly diagnosed prostate cancer with high risk features who were being considered for definitive treatment. This study was conducted at 10 clinical trial sites across Australia and completed recruitment ahead of schedule. The results of this trial showed that ^{68}Ga-PSMA PET had a 27% improvement in accuracy compared to staging with bone scan and contrast CT, and that PSMA PET was associated with higher reporter agreement and a lower radiation dose than current standard of care (4). This landmark study has provided comprehensive clinical evidence of superiority of ^{68}Ga-PSMA PET over conventional imaging in primary staging of prostate cancer.

ARTnet has provided site accreditation for radiopharmaceutical synthesis and PET camera performance for a series of academic, investigator-initiated prospective multi-centre trials of ^{177}Lu-PSMA in prostate cancer patients. The TheraP trial (7) was a multicentre randomised prospective phase II clinical trial comparing ^{177}Lu-PSMA (Lu-PSMA) vs cabazitaxel in men with metastatic castrate resistant prostate cancer progressing after docetaxel. There were 291 patients screened, with 200 eligible patients randomised to either Lu-PSMA or cabazitaxel, from 11 sites around Australia. The study demonstrated a significantly higher PSA-50 response rate in those assigned Lu-PSMA than cabazitaxel (65/99 [66%; 95%CI 56-75] vs 37/101 [37%; 95%CI 27-

46]; P<0.001), with less grade III/IV toxicity in the Lu-PSMA group than conventional chemotherapy (8). ARTnet is providing similar support for two further randomised phase II clinical trials with Lu-PSMA, the UpFront PSMA (NCT04343885) and ENZAp (NCT04419402) clinical trials.

Multi-centre imaging clinical trials just commencing where ARTnet is involved include the FET in glioblastoma trial (FIG Study), which is a prospective multicentre clinical trial of 210 patients at 10 sites designed to establish the role of FET PET in distinguishing pseudoprogression from true tumor progression and/or tumor recurrence, and impact on radiotherapy treatment planning (ACTRN12619001735145). This study will be supported by ARTnet for PET camera accreditation, radiopharmaceutical accreditation for sites undertaking in-house production, and assistance in centralized FET imaging review and analysis. Another study that is being co-ordinated by ARTnet is a prospective evaluation of a new quantitative SPECT bone reconstruction algorithm based on incorporating the CT scan into the reconstruction process compared to current state-of-the-art OSEM reconstruction with resolution recovery.

Collaboration has been pivotal in the success of the current multicentre trials in Australia. There is the opportunity for all nuclear medicine sites to participate in multicentre trials, thereby gaining experience with new imaging or therapeutic agents, and resulting in patients gaining access to these studies. ARTnet also provides a mechanism for young and less experienced researchers to become involved in clinical trials. We feel that this joint venture has been the success that it has to date because it was initiated and remains managed by the nuclear medicine clinician researchers who have created a multidisciplinary approach to research design and have been extremely willing to engage with other clinical trial groups. ARTnet has also been approached by other medical speciality clinical trial groups to give input into and participate in diagnostic and therapy focused multi-centre trials. Finally, there is also the opportunity for the ARTnet model to be extended to other countries, which could provide opportunities for broader collaborative networks in Nuclear Medicine clinical trials.

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