

Submission

2016 National Research Infrastructure Roadmap

Capability Issues Paper

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

Yes. The following areas have not been well represented in the issues paper:

1. Real time access to clinical data for researchers and data linkage provided by TIA's Australian Therapeutic Pipeline member BioGrid Australia
2. Novel Preclinical Testing Methodologies
3. Clinical Trials
4. Vaccine Production and Testing

Addressing these areas in turn we provide the following supporting information:

1. Real time access to clinical data for researchers and data linkage provided by TIA's Australian Therapeutic Pipeline member BioGrid Australia

Within the Health and Medical Science capability, the need for real-time data linkage of hospital/ clinic based clinical, bio-specimen, pathology, imaging and genomic data (i.e. Real-World Data or RWD) to enable analysis to generate Real-World Evidence (RWE) is not addressed. A critical gap in health data is data on patient outcomes. While patient registries play an important role and provide valuable data, it is expensive and time-consuming to collect these data. Data on patient outcomes exists as part of what is already collected as RWD, but is not easily useable as it is distributed across many healthcare and other organisations. Real-time data linkage of many health datasets will provide capability that distils RWE on patient outcomes from RWD, will improve patient outcomes and will support a precision medicine approach to health care.

It is therefore critical that health and medical research data linkage infrastructure and capability expands beyond the current administrative and registry static data linkage platforms to include real-time linkage of much richer clinical and clinically relevant data to provide evidence on patient outcomes that supports more informed and efficient decision-making in health care. To date, solutions to enable this have not been facilitated, and BioGrid Australia can assist.

A cost-effective solution to support a national framework for biobanking and data integration to support Translating Health Discovery (THD) is possible due to the success of a well established and proven operational federated national data linkage platform, BioGrid Australia. BioGrid specialises in real-time linkage of hospital/clinic-based and managed clinical and research data such as treatment outcome, genomic, bio-specimen, imaging and patient administration data systems (i.e. Real-World Data or RWD). These capabilities will enable analysis to generate Real-World Evidence (RWE). RWE will improve patient outcomes and support a precision medicine approach to health care. It is critical that health research data linkage infrastructure and capability expands beyond administrative and registry static data linkage to include real-time linkage of hospital based data to support more informed and efficient decision-making in health care.

Commencing in 2003 and considering other facilities globally, BioGrid Australia is still unique; its data linkage platform with its unique legal and ethical framework should be leveraged even further to progress a national approach for data integration that can support THD and Translating Health and Medical Research (THMR) projects via the Australian Therapeutic Pipeline (Pipeline). BioGrid Australia is a trusted and reliable partner in health and medical research capability with 34 members representing 66 sites across all Australian States and the ACT.

Data and information are of value to the Pipeline. Of particular importance will be the unique opportunity the Pipeline in Australia offers in yielding RWD about the potential/real impact of new products on real world population groups with multiple morbidities given the current and projected prevalence of chronic complex conditions in an ageing population. Data linkages via BioGrid and other data linkage platforms such as PHRN are critical to provide access to individual clinical and population level data.

Further investment in infrastructure to support more clinical data linkages would enable Pipeline members to access hospital/clinic-based clinical and genomic data that could enable:

- Pre-clinical innovation through using clinical and genomic data for pre-selection and adding a data validation phase;
- Biobanking through use of clinical and genomic data to enhance the biobank sample with clinical annotation;
- Clinical trials and biomarker biostatistics through use of clinical and genomic data to identify patients for trials, enhance recruitment and provide clinically rich annotated data; and
- Biological and cell therapies platforms through using clinical and genomic data for pre-selection of patients for clinical trials.

With BioGrid as a member of the Pipeline, THD projects and Pipeline members would be able to leverage the capabilities of BioGrid to access relevant clinical and genomic data to enhance THD projects.

BioGrid's unparalleled experience in federated real-time data linkage is very highly regarded by the recently funded Australian Genomic Health Alliance (AGHA). BioGrid's work with the Melbourne Genomic Health Alliance linking clinical phenotypic data with genomic data informed what is feasible regarding making relevant disparate data available in the clinic to assist clinician decision making. BioGrid is now a national platform partner of the AGHA. Several of the Pipeline members are also AGHA investigators along with BioGrid.

2. Novel Preclinical Testing Methodologies

The productivity of the health and medical research sector is now acknowledged to be significantly hindered through lack of reproducibility in research and the high attrition rate for therapeutic candidates.

- Between 80-90% of preclinical research has been said to not be reproducible by industry;
- Of 10,000 compounds first considered for a therapeutic application only one will make it to the public as a medicine.
- Approximately 80% of all therapeutic candidates fail in clinical trials
- 30% of these failures are due to toxicity related issues.
- These are large systemic issues which can be addressed at least in part, through access to independent quality accredited facilities.

The two major challenges are:

(1) Reproducibility:

TIA has through the support of NCRIS established a research quality management resource, iQDOCs, which has over 560 quality templates. To the best of our knowledge it is the world's largest quality document resource. This resource enables facilities to meet ISO standards and comply with the codes of GLP, GMP and GCP. It is hoped that future NCRIS programs would support access to quality and regulatory staffing to better enable the compliance of our facilities with the regulatory requirements. Whilst template documentation clearly reduces the cost to facilities seeking to gain GMP compliance it is the expertise that facilities require when building a quality management system.

(2) Attrition rate and failing late:

Over the last 5-10 years there have been a parallel effort in the US through government agencies such as NIH/NCATS, industry, and many academic centres to address the high attrition rate associated with the progress of drug candidates along the Pipeline and the poor correlation between early stage research findings and the realities of large clinical trial studies. Improving the success rate and importantly failing drug candidates early offers the potential to vastly improve the efficiency of our investment in health and medical research.

In planning for the next 5-10 years of investment in national research infrastructure provisions should be made to enable Australia to lead the adoption and (where appropriate) development of the next generation of translational research infrastructures.

Several potentially complementary approaches have been taken to address this issue by **Re-engineering drug development through research infrastructure**. They provide the potential to reduce the requirement for animals in preclinical testing. These Novel disruptive technologies are based on tissue and cell based screening including:

- Tissue on-a-chip technologies (as promoted by NCATS - <http://www.ncats.nih.gov/tissuechip>).
- This will enable human tissue to be screened against drug candidate libraries.
- The combination of various organs on chips will facilitate a whole of body screening process.
- This technology represents a future substitute for animal testing and will reduce the costs and time involved in drug development.

3. Clinical Trials

Up to 30% of Australia's research effort is in the field of health and medical research. Clinical trials are a necessary step for all therapeutic candidates and these trials are a precursor to health and often commercial impacts. To realise the benefits of our investment in health and medical research we propose that the committee consider strengthening our Nation's capacity in this critical area.

- Clinical trial infrastructure has been supported by the NCRIS program through TIA.
- Investments have been made into the establishment of a phase I clinical trial centre (the first accessible centre in NSW),
- Clinical trial management software, molecular pathology capabilities and the national clinical trial registry have been pivotal developments
- Underpinning the importance of this clinical and commercial clinical trial infrastructure to translation and commercialisation of discovery.

In the US and Europe the significance of clinical trials has been recognised with NCATS investing heavily into the area through its CTSA (<https://ncats.nih.gov/files/ctsa-factsheet.pdf>). The CTSA creates linkages between key centres, utilises clinical informatics, supports patient recruitment, clinical trial management software and quality documentation. In Europe the European Commission funded European Clinical Research Infrastructures Network (ECRIN, <http://www.ecri.org/>) supports clinical trials through

improving access to patients, facilities, medical expertise, methodological standards, tools and procedures. ECRIN supports protocol evaluation, trial management and quality assurance.

NCATS and ECRIN are collaborators of TIA, an opportunity exists to strengthen Australia's role internationally in clinical trials through strengthening these international partnerships. These international partners could interact through a NCRIS funded hub and spoke programme which would leverage the resources of local initiatives such as the NH&MRC Clinical Trials Centre and its Australian and New Zealand Clinical Trial Registry, the Australian Clinical Trials Alliance and the Paediatric Clinical Trials Network and its NCRIS funded clinical trial management resource, WebSpirit.

4. Vaccine Production and Testing

Australia has not invested significantly into vaccine production and testing capabilities despite its global reputation through the success of the influenza and cervical cancer vaccines. Capabilities in antigen production, characterisation, vaccine formulation, process developed and validation could be established and networked to facilitate a vaccine production platform.

- In Europe and the United States vaccine R&D platforms have been developed.
- In Europe the European Advancing Translational Research in Medicine (EATRIS) has a platform (<http://www.eatris.eu/platforms/vaccines.html>) which according to their website, "provides the critical expertise and infrastructure in translational vaccinology to advance candidates up to phase IIa trials.
- All processes required to complete non-clinical development (e.g. antigen production, adjuvantation, delivery/formulation, safety, immunogenicity, efficacy) and to obtain proof-of-concept in humans (e.g. process development, GMP production, clinical trial application and phase I studies) are covered"¹.
- In the US the National Institutes of Health has through its National Institute for Allergies and Infectious Diseases established a vaccine research centre with a Vaccine Production Program Laboratory (<http://www.niaid.nih.gov/LabsAndResources/labs/aboutlabs/VRC/vaccineProductionProgramLaboratory/Pages/default.aspx>) which has since its inception in 2001, "overseen the manufacture of over 68 bulk pharmaceutical compounds formulated into 40 different vaccine and therapeutic products. These products include candidate vaccines for HIV, influenza, filoviruses including Ebola and Marburg, and alphaviruses including chikungunya, SARS, and West Nile."

There is an opportunity to minimise government contributions through strategic collaborations with industry that complements any public investment in necessary infrastructure and expertise in this area.

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

The governance section is brief but does outline important points. Further to this we would add compliance with best practices as outlined by both the Australian Institute of Company Directors and relevant guidelines for publicly funded not-for-profits. One area that may not be addressed through the major headings is supporting the process of grant allocation through balancing independent yet consultative decision making frameworks.

It is vital that all governance arrangements are supported through a scientific approach to the evaluation of current and emerging need including a full mapping of national capabilities and research

¹ TRANSVAC is another relevant vaccine initiative in Europe - <http://www.transvac.org/>

requirements. There would be some value in this initiative being conducted independently of both agencies and facilities who may benefit from the result.

Establishment of a collaborative framework that structures the relationships between NCRIS funded agencies would further promote collaboration.

Governance arrangements could, whilst aiming to deliver programme requirements for NCRIS, also support broader goals such as those enabling outcomes in health and medical research and other government programmes. An operationally focussed framework for managing research projects between government programmes could deliver synergies through the identification of new projects and the facilitated development of these projects.

Collaborative interdepartmental relationships could be developed to support developments in research infrastructure agency management arrangements to support answering systemic questions whilst delivering programme requirements.

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

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

Yes. In some circumstances access vouchers can be a more efficient use of public funds. Infrastructure establishment costs for some capability areas do not warrant local investment due to the absence of widespread research community need. Niche research areas are an example where research may be of high quality, the need is clearly articulated but the numbers of researchers utilising the service are small. Access vouchers to infrastructure which is not available locally would enable Australian researchers to access high end quality infrastructure and to develop international research collaborations. Access to some infrastructure could be provided through collaboration agreements already established between NCRIS funded agencies. TIA has for example established a collaborative between Australia's national compound library, Compounds Australia and the equivalent resource in Europe, EU-OPENSREEN.

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

Yes. A holistic approach to infrastructure development ensuring the delivery of quality outcomes is fundamental and hence requires operational and technical expert resourcing to be included where they are essential to providing access and utilisation of the physical/tangible infrastructure.

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

Facilities in our consortium provide technical and operational expertise which can be utilised to deliver:

- Technical – TIA capabilities can educate researchers in relation to the use of drug screening machinery, preclinical testing and other translational research investigations. This would support the structuring and completion of individual technical investigations.
- Specialist – lifting researcher awareness of the process of drug development. TIA's expert committees could support this initiative. We note that the Global Translational Health Research Consortium (of which TIA is a founding member) is currently developing an education initiative to which TIA will contribute in kind.

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

A whole of project approach should be implemented for future investments.

- This could see funds from Government, philanthropy, patient advocacy groups and industry placed into a management fund which would be administered by lead agencies.
- The fund would cover capital investment, maintenance costs such as equipment service contracts, whole of life soft infrastructure requirements (for base level staffing) and
- Provide the resourcing necessary to meet essential expert and operational requirements necessary to support the infrastructure investment.

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

Reproducibility of research is a global issue which can be addressed in part through regulatory compliance. Compliance in the translational research field is generally a pre-requisite for quality outcomes however some capability areas may not require this level of formalisation, an example being medicinal chemistry.

The flexibility required in early research investigations is not always consistent with the structure entailed in quality systems. Other interventions such as support around implantation of scientific methodologies, access to quality materials (e.g., validated cell lines) may be a more efficient way of delivering quality research outcomes.

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

Two international examples include the Canadian Centre for Drug Research and Development (CDRD) and the NIH's CTSA program. Both initiatives leverage translational research infrastructure to deliver commercial and clinical outcomes.

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

The capacity to leverage translational research infrastructure through a national public private partnership is an important initiative to roll out. TIA submitted a proposal to the Australian Government describing this in 2012 following the National Translational Health Research Forum. Examples of such partnerships include CDRD and the significantly larger (\$3.5B) but project focused Innovative Medicines Initiative.

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

A number of key issues have been in our view correctly identified such as biological and cell therapies, biobanking and data linkage. However, in terms of the methodology we propose that:

- Identification of these areas could be better supported through the use of metrics given that it is most likely to provide an accurate indication of utilisation.
- National research infrastructure must not only support areas of emerging need but also, fundamentally, areas of demand.
- In other sectors supply chains aim to ensure supply is correlated to demand,

- This is possible in the research sector through mapping of research activity (which has been completed by TIA for the area of health and medical research).

TIA believes research infrastructure must meet Quality Management standards to ensure research projects are conducted in compliant and accredited facilities. This is crucial to improving reproducibility and demonstrated efficacy. The NCRIS program has already foreseen the value of this area through its investment in TIA's iQDOCs, an online resource for quality documentation.

- This resource is the largest of its type in the world offering over 560 documents for use by researchers and facility owners.
- The system promises to not only reduce the unnecessary duplication information in quality systems but it also offers the opportunity to implement efficiently the best available modules of information into research infrastructure providers.
- Prior to development of this online resource implementation of a Good Manufacturing Practice compliant system would take approximately two years and cost in excess of \$400,000 for one site.
- TIA need to expand the content of this resource to better serve the requirements of researchers and infrastructure access providers, and
- To maintain its currency to provide access to up-to-date standards and accreditation requirements.

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

The Global Translational Health Research Collaboration involving the, NIH/NCATs, the European Commission funded EATRIS, the Canadian Centre for Drug Research and Development, the United Kingdoms' MRC-T and Therapeutic Innovation Australia.