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Rare Voices Australia 'Rare Disease Registry Workshop' 40th HGSA (Human Genetics Society of Australasia) Annual Scientific Meeting, Post Conference Workshop, Hobart, Tasmania, Australia, 9th August 2016

Rare Voices Australia

Rare Voices Australia (RVA) is Australia's National Alliance for rare diseases; a strong common voice calling for health policy/healthcare system that works for those with rare diseases. A non-profit, non-Government registered company, RVA is governed by an independent Board of Directors many of who have a personal as well as a professional connection to rare disease. RVA also has a Scientific Medical Advisory Committee (SMAC) made up of 13 members. Further detail is located on the RVA website.

Rare Voices Australia (RVA) undertook a national Roadshow in 2014 that involved round-table discussions with representatives from patient, healthcare, research, government and industry organisations with sessions in Queensland, Victoria, South Australia, New South Wales and Western Australia. The discussions focussed on the need, barriers and drivers for coordinated action on rare diseases and for a national plan. The state-based discussion records directly led to the key findings on the principles and objectives to progress a national plan. These findings were presented at a National Summit on Rare Diseases in March 2015 and form the Communique. This Communique was presented at the RVA Rare Disease Summit receiving endorsement not only from its attendees but from rare disease patient organisations, universities, research institutes and other stakeholders across Australia.

A key topic addressed within the Communique is data collection and use / rare disease registries. RVA is keen to facilitate further stakeholder input on this particular area of need to better advocate for the adoption of a National approach to a Rare Disease Registry.

Rare Disease Registries: Principles

Patient registries are ongoing, exhaustive systems of data collection of patients with the same disease from a geographically defined population over an extended period of time. By collecting patient data, patient registries constitute key instruments in supporting;

- Health service planning
- Increasing knowledge on rare diseases
- Support research by pooling data in order to achieve a sufficient sample size of epidemiological research, clinical research, surveillance of drugs used off-label, and post marketing orphan drug surveillance.

Patient registries are only one type of database collecting information on RD patients used to ask or answer research questions. Other types of databases include hospital databases, ad hoc surveys and observational studies, repositories of cases and patient association databases which despite all having the purpose of collecting patient data, have difference characteristics and applications. Patient registries are tools that require significant time, human resources as well as financial investment and sustainability. Collaborative efforts are paramount at the regional, national and international level to establish, manage and derive outcomes from patient registries.

The principles listed above are taken from the EURORDIS (European Organisation of Rare Disease) Rare Disease Registries Fact Sheet;
http://www.eurordis.org/sites/default/files/publications/Factsheet_registries.pdf

The State Plan of Western Australia also talks to rare disease registries.
http://ww2.health.wa.gov.au/~/media/Files/Corporate/Reports%20and%20publications/PDF/Rare-diseases-strategic-framework.ashx

Rationale

The RVA SMAC presented a rationale to the Human Genetic Society of Australasia (HGSA) to consider hosting a section of their scientific meeting talking to the topic of rare disease registries. As well as a session within the HGSA program, the Local Organisation Committee of HGSA agreed for RVA to host a satellite workshop after the conference.

An excerpt from the rationale presented to the HGSA LOC by SMAC Chair Prof Alan Bittles;

…The establishment of interactive National disease registries for specific disorders will facilitate more accurate and reproducible disease estimates, improved and accelerated disease diagnoses, and treatments that are notably more cost-effective. Access to comprehensive RD registries also will be of major importance in the identification of affected people resident in different States and Territories of Australia, and in New Zealand, thereby allowing the efficient design and testing of customized drug therapies for individual rare diseases.

The Rare Disease Registry Workshop was opened by RVA Executive Officer; Ms Nicole Millis, who gave background to Rare Voices Australia (RVA), the RVA roadshow, the RVA Rare Disease Summit and Communique leading to the importance of data collection and registries.
Chairing Panel: Prof John McNeil, Monash University/Alfred Hospital / RVA SMAC, Ms Megan Fookes, Rare Voices Australia, Dr Paul Lacaze, Monash University & A/Prof Yvonne Zurynski, University of Sydney/Westmead Hospital / RVA SMAC.

The focus of the workshop was to visit nine short papers that talked to a range of issues concerning rare disease registries as well as exploring the benefits of a rare disease registry in Australia to people diagnosed with a rare disease. In preparation for their talks, the presenters were asked to consider/ include the following;

- What are some of the challenges?
- How may we overcome such challenges?
- How can we ensure sustainability and ultimately bring benefit to all rare disease stakeholders but particularly the rare disease patients?

9 Short Papers/ Presentations
Key points are highlighted as follows;

1. **Introduction: The definition and prevalence of Rare Diseases in Australasia**
   Prof Alan Bittles, Centre for Comparative Genomics, Murdoch University and School of Medical Sciences, Edith Cowan University, Perth, Australia & RVA SMAC Chair

   - Rare Diseases need to be recognised as a national health priority. 'The burden of rare diseases, while largely hidden due to inadequate information systems, is unacceptably high for patients, families, and the community'. (Source RVA 2015)

- Rare Diseases – working definitions vary from country to country.
- Rare Diseases – overall profile
  - 27 different categories of disease, e.g. rare bone diseases, cardiac disorders, eye diseases.
  - 80% of Rare Diseases are genetic in origin
  - Remaining 20% comprise rare tumours, infectious diseases, and teratological disorders.
  - Approx. equal numbers manifest at birth or <15 years, and in adulthood.
- Rare Diseases in Australia
  - Australia: based on current estimated Australian population 24.1 million
  - As in Europe, Rare Diseases defined as a disorder with a prevalence of <1/2,000
  - 6,000 – 8,000 known named rare diseases
  - Approximately 4.7% of the population have one (or more) of these RDs
  - 1 in 17 Australians has a Rare Disease (Sources: Rare Voices Australia (2015); Australian Bureau of Statistics (2016)
- Rare Diseases in Australia: community & population perspectives
  - Indigenous 669,900 (2.8%)
    ~60-145 languages
  - Overseas-born 6.7 million (27.8%)
    >200 countries & ~300 languages
  - (Ultra) Rare Diseases may be unique to specific communities.
  - Distribution patterns of this nature have major genetic education, counselling and diagnostic implications.

2. **Disease registries and the EURORDIS-NORD-CORD Declaration**
   Prof Adam Jaffe, University of NSW / Sydney Children's Hospital, Randwick & RVA SMAC

- Adam talked to the declaration between EU, USA and Canada via their Alliance Rare Disease Organisations on the establishment and use of rare disease registries.
- Registry Definition: 'An organised system that uses observational study methods to collect uniform data to evaluate specific outcomes for a population that serves a scientific, clinical or policy purpose.'

- **Principles for Rare Disease Patient Registries**
  a. Patient registries recognised as a global priority in the field of Rare Diseases
  b. They should encompass the widest geographic scope possible
  c. Should be centred on a disease or group of diseases rather than therapeutic intervention
  d. Interoperability and harmonisation between registries should be consistently pursued
  e. Minimum set of common data elements should be consistently used
  f. Should be linked with biobank data
  g. Include data directly reported by patients along with healthcare professional data
  h. Public-private partnerships should be encouraged to ensure sustainability
  i. Patients should be equally involved with other stakeholders in the governance of the registries
  j. Rare Disease Patient Registries should serve as key instruments for building and empowering patient communities

3. **Application of disease registries in clinical practice and Rare Disease research**
   Prof John McNeil, Monash University/Alfred Hospital, Melbourne & RVA SMAC
   - Rare Diseases are by definition;
     - Rare therefore difficult to study and develop new and better treatments
     - Clinical trials are often difficult
     - Most information comes from case series
     - Often small populations.
     - Limited information about subtypes, natural history, safety of interventions
     - Inadequate information to support advocacy
   - Clinical registries are a way of overcoming these limitations typical to rare disease
     - Essentially a process for amalgamating data, using identical definitions and procedures
     - Multiple clinics send identical data to a registry provider stored, merged with outcome data and reported back to clinicians
   - Value Proposition
     - Data from a registry is highly valued
     - Useful tool for benchmarking
     - Comparing treatment approaches / outcomes from other clinicians
   - US Cystic Fibrosis Registry
     - Bell Curve
   - RD Registry is not just a data base
   - RD Registry projects are in place in the USA and Europe.
   - Australia could look to these as best practice of how to approach a RD registry
   - How to progress?
     There exists a publication put together by Monash University *'Operating Principles and Clinical Standards for Australian Clinical Quality Registries'*
   - Governance – outline a typical governance model
   - Learnings from mistakes
     - clinician ownership
     - minimal data burden
     - opt-out consent
     - data security paramount
     - real-time reporting
     - data access policy
   - Ethics Issues
     - Registries require personal medical information to be collected and pooled from large numbers of individuals.
     - Ideally this should only be undertaken with specific permission in advance from each individual whose data is involved.
     - Some ethics committees have equated participation in registries to participation in clinical trials and insisted that advance permission be sought before any patient's data is included.
     - The downside of seeking individual permission is that participation rates are likely to be low. This has been well documented in overseas studies (quote NEJM 2003).
     - When the participation rate is low there is strong likelihood that the resultant participants will be unrepresentative and the data therefore unsuited for quality improvement or benchmarking. In particular, it would not be acceptable for benchmarking of performance.

- To overcome the problems associated with low participation rates registries typically request approval for an 'opt out' approach for data collection. Under this approach patients are provided with a leaflet explaining the purposes and procedures of the registry, and told that their identity and some specific clinical information will be passed to the registry unless they contact the registry to register their objection. These procedures provide potential participants with a means for rejecting participation but experience shows that this option is rarely exercised.
- Registries also require publication policies

4. Tasmania: Rare Diseases from a physician perspective

Clinical A/Prof Robyn Wallace, Calvary Lenah Valley, Hobart

'Rare syndromes of intellectual disability in adults attending a specialised outpatient clinic for physical health care in Hobart- clinical aspects, registry aspects'

Tasmania – context of 'rare'

- Total population about 500,000 people, island
- 145 adult physicians;0-250 people with a single rare disease
- Up to 40,000 with rare diseases; up to 15,000 with intellectual disability, so about 7500 adults, mostly with rare conditions of intellectual disability
- Sensible to guess that every physician will see single patients with different rare conditions, but sub specialists may see relatively many
- Speculate that combination of "rare" plus "intellectual disability" scares many clinicians

Clinical Aspects –Adults with Rare Syndromes of Intellectual Disability

- Specialised Healthcare for Adults with Intellectual Disability (SHAID)
- Biopsychosocial physical health of adults with developmental disability review including ethology, logistics of hospital preparation, working with disability sector, NDIS; adult N = 7500?
- Teaching, small research, disability-health interface (NDIS, NDS, Syndrome groups, NDIS-RACP working party, other health and disability professionals)
- SHAID clinic several patients with the same rare condition, scope to see every adult patient with that condition or all adult patients with intellectual disability in Tasmania
- Goals: physical health, general, transition & syndrome specific clinics, public-private state-wide clinical service and base for help for Colleagues with patients with intellectual disability, health-disability engagement

Relevance and Benefits of SHAID type clinic and rare disease registry

- SHAID clinic could contribute to a Tasmanian Rare Disease registry (which would need to satisfy conditions)
- Allow pooling of data for public health purposes, speed up acquisition of knowledge, combining with other Australian states vs local aspects
- Definition of data, level of detail and scope required to be specified
- In particular research on phenotype and genotype relevant
- Data collected could help support policy and service development at local regional national and international levels
- Potential for intervention with off label or medications e.g. medicinal cannabis for intractable epilepsy, other research participants

- Consumer involvement and collaboration with support groups e.g. Prader Willi, Angelman, Fragile X
- Consent for participation issues to be considered, privacy, quality assurance, respect
- May contribute to reduction of fear of rare diseases by colleagues
- Feedback to providers from registry re outcomes as a result of t/heir input

Summary

- Up to 10-15,000 Tasmanians with rare conditions of intellectual disability
- Adult health services lacking; one specialised clinic in Hobart but potential for a statewide service for healthcare of adults with intellectual disability; ideally specialised service within generic health services providing care and consultation to colleagues
- Possible for inclusion of potentially all people with intellectual disability associated with genetic abnormalities into a quality Tasmanian Rare Disease registry could help with;
  - Research
  - refinement of genotypic-phenotypic associations
  - requirements for local services and education
  - opportunities for intervention trials
  - support for disability mainstream inclusion including healthcare
  - making rare not so frightening
- Values of Rare Diseases and Rare Disease Registry consistent with disability values

5. Charles Bonnet Syndrome: a not-so-rare disorder?
Mr Scot Muirden, Charles Bonnet Foundation, Sydney

- Scot gave some background to Charles Bonnet syndrome (CBS) the organisation that he is associated with CBS.
- CBS has no universally agreed upon set of diagnostic criteria
- Is CBS a rare disease? If not, where does it fit?
- A registry could assist to bring together the limited knowledge about this condition

6. Design and applications of the Rare Disease registry framework
Prof Matthew Bellgard, Murdoch University, Perth

- Registries must be able to adapt
  - Requirements change (attention to detail)
  - Technologies change
  - Knowledge base changes – upskill
  - Facilitate transdisciplinary clinical research
- Build registries with a view to get data out
- Technological Innovation (RDRF)
  - Repurpose ability
  - Interopability at many levels
  - Ability to share forms/ registries/DE/ Sections/PVs
  - Empower end user: Dynamic/configurable consent/ reporting/visualisation
  - Empower end user: Addition of Des/ Sections/Forms
  - Natural/ Treatment history studies of rare disease
- Patient Reporting: continuous reporting

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7. **Genomic technology & Mendelian phenotypes**
   Dr Paul Lacaze, Monash University, Melbourne

- Paul highlighted the progress of genomic technology and rare disease gene discovery
- More than 100,000 genetic variants are reported but penetrance is generally unknown for most of them
- Disease-centric clinical sampling but benefits to sampling healthy people
- Identify resilience against severe disease.

8. **Human Variome Project**
   Prof Ingrid Winship, University of Melbourne/Melbourne Health

Why create the HHT (or any other disease) Registry?

- Currently no database exists to gather health and clinical information from patients diagnosed with HHT
- To be able to meet the needs of the HHT population a greater awareness of HHT
- Economies of scale
- Optimise management
- Research platform
- Facilitate international clinical trials for HHT

Major projects HVP

Global Globin 2020

- systematic collection and sharing of variation data to fighting haemoglobinopathies (thalassaemia and sickle cell disease) in low- and middle-income countries.

BRCA Challenge -in collaboration with GA4GH

- Develop population-based assessment of allele frequencies of variants using available sequencing resources
- Build federated data collection methodology for pathogenic variants of BRCA1 & BRCA2
- Improve and refine penetrance for select mutations

UNESCO Ethics & Standards Project

- An overall statement on the current state of technical best practice and ethical considerations for the collection, curation, interpretation and sharing of human genomic variation information in the different UNESCO member states.

Accurate assignment of pathogenicity of variants

- Confirms clinical diagnosis
- Optimises individual management
- Allows predictive testing
- Optimises family management
- Allows prenatal or pre-implantation genetic diagnosis
- Optimises reproductive options
- Allows pharmaco-genomic testing
- Optimises pharmacologic management

Personalising medicine- preventive strategies informed by accurate interpretable data.

- Early detection
- Early intervention
- Targeted therapy
- Preventing predictable disease
- Preventing predictable complications of disease
- Preventing predictable complications of treatment
- Cost saving towards a sustainable health system
- Using genes to save lives!

9. Sharing rare disease genomic information for research and clinical care – The Melbourne Genomics and Vision Experience

A/Prof Clara Gaff, University of Melbourne/Melbourne Genome Health Alliance

Clara talked to the WES (Whole Exome Sequencing) being used to diagnose and re-evaluate some rare diseases. She gave an oversight of the work used by Genome Health Alliance and how a system for shared information has helped clinicians and researchers across Victoria.

- System for shared information and management across Victoria
  - Clinical Management
  - Re-analysis
  - Clinical Care
  - Research

- Impact of WES (Whole Exome Sequencing) on rare diseases (4 flagship RD's at this stage; Childhood syndromes, focal epilepsy, hereditary neuropathy and hereditary colorectal cancer
  - 7x increase in germline diagnosis
  - Singleton WES is more cost effective than standard care
  - Results change management (23/109 had an immediate change in management)

- Evidence of value of common approach
  - Patients agree to share data (293/315 (93%) consented for their data to be used for any research)
  - Reanalysis improves diagnostic rates (16 new diagnoses with 147 reanalyses in last 12 mths)
  - Researchers are accessing the data (15 researchers are accessing the data from the 4 flagships)
- Data Governance framework now agreed
- Common Genome data repository designed, built, implemented and integrated with lab systems
- 2000 patients to be tested across 11 patient indications

Open Discussion and Recommendations

The benefits of a National RD Registry seem to be clear from feedback to RVA and all the various stakeholders, including Government, agree to the concept in theory. The dialogue seems to always fall down when discussion turns to the challenges of governance, platforms, implementation and sustainability – issues around who owns the data, how will it be shared, who will enter the data, maintain the registry, how will it be funded...and many more questions.

It was acknowledged that the challenges were indeed difficult, however participants were urged to not be deterred by this, and if necessary think outside the square and the existing structures. Focus on what we could do collectively, and where we could come together rather than simply focus on what was difficult or what could not be done. Participants were encouraged to consider patient-centred approaches and remain solution-focused.

There was active discussion form a range of stakeholder perspectives and a commitment to a patient centred and collaborative approach. While at times the task seemed too challenging, participants persisted, determined to come away with some clear action items
Two proposals for further work/ focus came out of the Workshop;

1. Review existing Australian principles for registries and customise for rare disease i.e. *Operating Principles & Clinical Standards for Australian Clinical Quality Registries* Monash University.

2. Do an audit of all existing Australian rare disease registries, showing scope, purpose etc. This will be a very useful information seeking exercise but also potentially show areas of duplication and highlight opportunities for collaboration and improved efficiency.

This work will be driven by RVA's Scientific & Medical Advisory Committee (SMAC) who will outline steps/ plan for this work to occur.

Rare Voices Australia Ltd.
PO Box 138
Mentone Vic 3194, Australia
P +61 (0)497 003 104
E admin@rarevoices.com.au
W www.rarevoices.org.au
ABN 69 156 254 303