Rare disease registries: a call to action

Paul Lacaze,1 Nicole Millis,2 Megan Fookes,2 Yvonne Zurynski,3,4 Adam Jaffe,5,6 Matthew Bellgard,7 Ingrid Winship,8,9 John McNeil1 and Alan H. Bittles1,10

1Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, 2Rare Voices Australia Ltd, 3Genetic Medicine and Family Cancer Clinic, Royal Melbourne Hospital, and 4Department of Medicine, University of Melbourne, Royal Melbourne Hospital, Melbourne, Victoria, 5Paediatrics and Child Health, Children’s Hospital, 6Australian Paediatric Surveillance Unit, The University of Sydney, 7Discipline of Paediatrics, School of Women’s and Children’s Health, Faculty of Medicine, University of New South Wales, and 8Respiratory Medicine, Sydney Children’s Hospital, Sydney, New South Wales, and 9Centre for Comparative Genomics (CCG), Murdoch University, and 10School of Medical and Health Sciences, Edith Cowan University, Perth, Western Australia

Key words
rare disease, registries, clinical registries, genetics.

Correspondence
Paul Lacaze, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, The Alfred Centre, 99 Commercial Road, Melbourne, Vic. 3004, Australia.
Email: paul.lacaze@monash.edu

Received 11 December 2016; accepted 1 June 2017.

Abstract

When registries collect accurate clinical data over time, they can act as fundamental support structures for patients and their families and powerful cost-effective instruments to support clinical trials and translational research to improve quality of care, quality of life and survival. Registries are critical for rare diseases (RD) with low prevalence and propensity for variation in treatment and outcomes. Rare Voices Australia is leading a call for action to the research and clinical community to prioritise RD data collection and develop an integrated RD Registry strategy for Australia. Financial, operational and governance challenges exist for establishing and maintaining RD registries. As a multidisciplinary team whose interests converge on RD, we highlight the need for the establishment of an Australian RD Registry Alliance. This ‘umbrella’ organisation will: (i) bring together existing RD registries across Australia; (ii) establish National RD Registry Standards to support interoperability and cohesion across registries; (iii) develop strategies to attract sustainable funding from government and other sources to maximise the utility of existing RD registries and support the development of new RD registries. The most important role for the Alliance would be to use the RD registries for translational research to address current knowledge gaps about RD and to improve the care for the over 1.4 million Australians estimated to live with RD.

The burden of rare diseases (RD) is unacceptably high for patients, families and the community in Australia and needs to be recognised as a national priority, with RD collectively affecting over 1.4 million Australians.1–3 Instead, the impact of RD remain largely hidden due to inadequate information systems of a healthcare system designed to respond to individual diseases with much larger patient numbers.

At present, even the most basic information about many RD, including incidence and prevalence, are merely estimates given the absence of systematic patient data collection (i.e. registries) for most RD in Australia. The need for a National RD Registry Strategy has been highlighted previously1,2,4,5 and more recently was echoed by Rare Voices Australia (RVA), the national alliance of people living with RD. Out of its Rare Disease Summit, RVA released a public Communique in 2014 highlighting the need for a national coordinated and collaborative approach, better data collection and information use for RD, with coordinated care and equitable access to services, diagnostics, treatment and research for RD. The Communique has now been endorsed by over 100 patient organisations6 and used to inform the recent ‘Fair for Rare’ campaign.7

For progress to be made towards achieving a National RD Registry Strategy in Australia, we need better coordination and alliances among existing RD registries and stakeholders. Stable, long-term government funding also is needed to ensure sustainability and to facilitate the significant networking and coordination efforts required. This coordinated approach to managing multiple RD registries under the same umbrella is likely to provide significant cost savings while maximising impact.

Data collection is critical for RD because the inherent features and lack of patient numbers for most RD result in a lack of data, evidence and knowledge. This has negative impacts, including delayed diagnosis, suboptimal

Funding: None.
Conflict of interest: None.
patient care and limited access to treatments, either because they have not been developed, or where available due to high costs and/or lack of government reimbursement. Registries are systems of uniform data collection to evaluate specified outcomes for a population defined by a disease, condition, or exposure, typically spanning different clinical or academic partnerships over an extended time period.\textsuperscript{5,9}

Registries are particularly important for rare or poorly understood diseases with small patient numbers, complex delayed diagnoses, a propensity for variable standards of care and limited treatment options.\textsuperscript{1,2} Registries act as a central networking point for all stakeholders around a particular RD, including patient advocacy groups, researchers, clinicians, industry and Government. Registries, if populated with accurate and high-quality clinical data over extended periods of time, enable health service planning, epidemiological research, clinical trial recruitment and post-marketing drug surveillance.

RD researchers and registry custodians from across Australia recently agreed to develop a National RD Registry Strategy, and given the limited resources and funding identified the following priorities:

1. Create an alliance of existing RD registries in Australia through the RVA-based network to begin sharing best practices, establishing standards, cohesion and higher interoperability;
2. Conduct an audit of appropriate existing RD registries and databases (this is underway with examples of Australian RD registries and databases provided in Table S1, Supporting information);
3. Define how best to establish a single National RD database to act as a central repository for RD, and define the consent, data capture and governance models, following FAIR principles\textsuperscript{10};
4. Develop strategies to minimise barriers for establishing new and more comprehensive registries for individual RD or related disease groups;
5. Consolidate a coordinated effort to attract sustainable government funding for RD registries.

The case for registries: benefits to patients and treating doctors: RD can be defined as disorders with a prevalence of \textless 1/2000.\textsuperscript{11} Some 6000-8000 known RD, approximately 80\% of which are genetic in origin, exist across 27 different disease categories, many with childhood onset, and the remaining 20\% comprise varying aetiologies.\textsuperscript{1,3,11} Although each individual RD is by definition infrequent, the combined health burden of all RD in Australia is significant, with an estimated \textgeq 6\% of the total population (or 1/17 people) affected, equating to at least 1.4 million Australians, that is, similar to the number of those in Australia with diabetes\textsuperscript{1-3} and matching the prevalence of RD in England.\textsuperscript{11} However, these estimates are limited by a scarcity of robust representative data, due to the lack of specialist registries and data collection systems.

Some RD, such as cystic fibrosis, have benefited from long-standing Australian registries; however, there are no standardised data collections or registries for most disorders. Therefore, there is uncertainty about basic information including: the number and prevalence of RD in the population; how many patients with a RD are receiving treatment; variation in the quality of care and health outcomes across the health systems; and the overall burden of RD nationally. Without registries or better patient data collection systems, it will continue to be difficult or impossible to ascertain even this basic, yet crucial information for RD in Australia.

Given the existence of so many different RD, it is impractical, cost-prohibitive and unrealistic to establish stand-alone high-quality clinical registries for each individual RD. Modular approaches and shared platforms are required to collect data on multiple RD or the grouping of related RD. A central database or repository for many RD in Australia would provide an important step towards better measurement of the burden of RD on the health system, and would provide basic information like incidence and prevalence for RD. A National RD database would not act as a clinical quality registry measuring outcomes and clinical variation for each RD, but instead would be a starting point to help collate basic data and then identify areas in need of further development and focus.

A National RD Registry Strategy should be consistent with the 10 key principles for RD Registries jointly declared by the European Organisation for Rare Diseases (EURORDIS), the National Organization for Rare Disorders (NORD) and the Canadian Organization for Rare Disorders (CORD)\textsuperscript{9} (Table 1).

**Epidemiology and impact of rare diseases:** Registries have the potential to provide widespread benefit to researchers, clinicians, governments, industry, patients, patient organisations and ultimately the community.\textsuperscript{12} For registries to be effective, data input must be complete and comprehensive over long periods of time. Only then can registries enable monitoring of disease prevalence, incidence, natural history, interventions and their safety and functional outcomes effectively. Registries can generate sufficient data on a given RD to make it appropriately visible to researchers, clinicians, governments and industry. Registries can facilitate planning and recruitment for clinical trials, enable post-market drug surveillance and allow the assessment of new interventions once established.
The evidence base for RD is limited because of their low individual prevalence, and consequent propensity for variations in treatment and outcomes. Registry data can be used to reduce variation in practice, and strengthen the evidence base by generating hypotheses for new interventions and facilitating clinical consensus and practice guidelines. For any given RD, without basic data available through a registry, it is often impossible to take the first critical steps towards improved management or new research.

For RD patients, diagnosis is often difficult or delayed, with misdiagnosis or inappropriate and ineffective treatment commonplace.13 Even with a correct diagnosis many RD have no effective treatment, and when treatment is available insufficient data may be cited by funding bodies as a reason not to approve reimbursement. This can make treatment inaccessible to RD patients. Registries enable the accumulation of relevant evidence required to break this cycle.

There are several additional value propositions for establishing an enhanced clinical RD registry model across Australia. Registry data, once collected, could be used for benchmarking in research and clinical practice, for coordination of research groups, to facilitate phenotype/genotype correlations across small patient groups, and to connect researchers and clinicians with international registry initiatives. Registries can also provide transparency for patient advocacy groups to raise the profile and understanding of RD in the community.

A national RD Registry strategy or alliance could improve consistency across RD registries, standardise governance and consent, and provide efficiencies by consolidating information technology platforms, and linking existing registries thereby improving interoperability, sustainability and reducing costs. It could support the harmonisation of data according to standardised definitions and procedures, enabling multiple clinics to transmit standardised data to a common national registry. Registries could effectively quantify and monitor the burden of RD in Australia, and identify areas for improvement once accurate data had been collected.

For the approximately 80% of RD that have a genetic aetiology, genomic analysis can have a major impact on diagnosis and research.14 Registries can assist genomic research by facilitating the collection of biospecimens and genomic test results. Genomics and bioinformatics have also helped to facilitate international initiatives, such as RD-Connect,15 the Human Variome Project,16 the Global Alliance for Genomic Health17,18 and Matchmaker Exchange,19 thus encouraging research groups to share vital phenotypic information and build international RD registry communities.15 To contribute significantly to international efforts, linkages of RD registries with biobanks should be encouraged. International data-sharing efforts are proving to be instrumental for advancing our understanding of causative genetic variation in RD.

The logistics and challenges of establishing RD registries: Registries face common challenges, including difficulties in reliable and complete data capture, multi-site research ethics and governance approvals, data harmonisation, data custodianship, access to reliable IT platforms and financial sustainability. Inconsistent approaches in state-based health systems, disparate hospital data collection methods and variable interpretation of the rules around data sharing are also problematic. These challenges are amplified for RD registries because there are fewer cases of individual RD, limiting information about RD subtypes, the natural history of each disorder, or the safety of interventions. This leads to inadequacy of available information to support effectively RD advocacy.

Governance and funding difficulties arise for RD registries because RD are collectively numerous, and even single RD spans multiple clinical specialties, making it difficult to achieve united advocacy and stable funding. Making the case for the sustainable funding of RD registries is challenging given the low frequency of specific RD and limited treatment options, potentially limiting interest from government and industry. RVA has an opportunity to unify many disparate disease groups to advocate for action to establish a cohesive national RD registry strategy and alliance.

Despite advances in genomics and bioinformatics and the associated hope these bring, many challenges still remain, including the accurate clinical interpretation of new sequence variants for RD,20 the variable penetrance of known RD mutations21 and the fact that many RD remain undiagnosed even after whole exome or genome
analysis. A push for increased international collaboration and consistent data sharing is a crucial aspect of continued progress, particularly for Australia, given its relatively small population and limited RD case numbers.10 The scale of ethnic diversity in Australia is also a challenge for genetic research, given ~3% of the Australian population is indigenous, and 28% are first generation immigrants from over 200 different countries.22

There is an opportunity to build on existing database frameworks and structures to support RD registries.23 Systems that simultaneously collect data on many different RD in children, such as paediatric surveillance units, are currently active in Australia, and have provided incidence estimates and clinical data on over 60 different RD.1,2 There is potential to expand these systems to support the enrolment of patients in RD registries to collect accurate data across more disease types. There is also an opportunity to collect more patient-reported outcome measures (PROMs), especially around quality of life, for RD where the collection of information from clinical centres may be more challenging. The Australian government has also developed a consumer-managed electronic health record system MyHealthRecord24 which may also provide future options for data collection or linkage. Implementing a national RD data system requires long-term planning and consensus among many stakeholders with regards to data collection, storage and sharing. International guidelines provide the foundation for this work.15

RD registries must also strive to capture data that are meaningful to patients and health professionals, for example, quality of life. In some cases, a parochial sense of ownership and a reticence to share for some Australian RD registries, has further restricted progress. To be sustainable, after data collection national RD registries must also be designed to deliver genuine and practical benefit to all stakeholders, including clinicians, researchers, government, health service providers, pharmaceutical companies, patient advocacy groups and most importantly to RD patients themselves.

Finally, a National RD framework will probably never be achievable without significant government funding to help network and link existing registries, and provide the long-term sustainability required to make registries effective. There has been long-held enthusiasm for a National RD Plan to help address the growing needs of this fragmented and under-served patient community.12,4,5 The new-found enthusiasm for RD registries is an important first step towards a national approach for RD in Australia. The RD research and registry community has aligned itself with RVA to create better national cohesion and a scalable framework to ensure that government funding provided for RD strategies is spent most effectively.

Acknowledgements

This manuscript arose from a collaborative Rare Disease Registry Workshop at the 2016 HGSA Conference. We would like to acknowledge the contributions of Clara Gaff, Monique Garcia, Susannah Ahern, Robyn Wallace, Scot Muirden and Geoff Sims for their input into this manuscript and initiative. We would also like to thank the members of the RVA Scientific Medical Advisory Committee as well as the Human Genetics Society of Australasia and the Human Variome Project.

References

4 Molster C, Youngs L, Hammond E, Dawkins H. Key outcomes from stakeholder workshops at a symposium to inform the development of an Australian national plan for rare diseases. Orphanet J Rare Dis 2012; 7: 50.
14 Chong JX, Buckingham KJ, Jhangiani SN, Boehm C, Sobreira N, Smith JD et al. The genetic basis of...
Supporting Information

Additional supporting information may be found in the online version of this article at the publisher’s web-site:

Table S1. Existing rare disease registries hosted and/or operated in Australia. NB This is not an exhaustive list.

doi:10.1111/imj.13536

PERSONAL VIEWPOINT

Cognitive challenges to minimising low value care

Ian A. Scott

Department of Internal Medicine and Clinical Epidemiology, Princess Alexandra Hospital, Brisbane, Queensland, Australia

Key words
cognitive bias, decision-making, low value care.

Correspondence
Ian A. Scott, Department of Internal Medicine and Clinical Epidemiology, Princess Alexandra Hospital, 199 Ipswich Road, Woolloongabba, Brisbane, Qld 4102, Australia. Email: ian.scott@health.qld.gov.au

Received 28 January 2017; accepted 12 March 2017.

Funding: None.
Conflict of interest: None.

Abstract

Clinical decisions often rely on pattern recognition, simple rules of thumb, tacit knowledge and habit. In many instances, such intuitive decisions are fast and accurate, but they can be subject to cognitive biases leading to delivery of care of low value at odds with scientific evidence of best practice. If programmes, such as EVOLVE (Evaluating Evidence, Enhancing Efficiencies) and Choosing Wisely are to have maximal impact in minimising low value care, such biases, and the factors that hide and accentuate them, need to be exposed and addressed in a collegiate and non-judgemental manner.