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Impact of Biobanks on Research Outcomes in Rare Diseases : A Systematic Review

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Impact of Biobanks on Research Outcomes in Rare Diseases： A Systematic Review

A thesis submitted for the partial fulfilment of the requirements for the degree of

Master of Science (Human Biology)

by

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Declaration

I certify that this thesis does not, to the best of my knowledge and belief:

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_███████████_____ Monique Garcia, 26th July 2018

Abstract

Rare diseases (RDs) are a global priority yet are still under researched. When combined, RDs are common, with individual diseases numbering approximately 5,000-8,000, equating to approximately 7% of the population in Europe. Extrapolating this figure for Australia suggests that about 1.2 million people are affected by RDs, with about 400,000 of those being children. The WA Rare Diseases Strategic Framework 2015-2018, the first strategy for rare diseases in Australia, recognises that in order to alleviate the significant burden of rare diseases, innovative translational tools that facilitate research into new diagnostic and therapeutic strategies should be given priority.

Registries facilitate clinical, epidemiological, and post-marketing surveillance research for RD, collecting information from individuals with a particular disease, and storing these data in an organised system. Registries can lead to a greater understanding of the natural history of disease, consensus-driven treatment protocols, informed policy making and, in turn, improved patient outcomes. Despite these benefits, registries are limited in their capacity to conduct basic research, attributed to the fact that most registries do not collect and store patient and donor specimens appropriately to capture or preserve important biological information (such as DNA, RNA and proteins) for basic research, a prerequisite for translating scientific discoveries into diagnostic tools and therapies for clinical practice.

Biobanks (BB) are gradually becoming more recognised as invaluable tools to drive basic and translational research for RDs. BBs collect and store biological specimens with matched clinical data and patient metadata in an organised system, distributing samples and data to the scientific community, enabling "omics" studies. This is especially important considering the field of drug innovation for RDs has, in recent years, become progressively focused on 'omics-type research, and that more than 80% of RDs have a genetic component RDs have recently been referred to as "fundamental diseases", highlighting their unique capacity in providing opportunities to investigate the "extremes of human pathology". For example, research of LDL-receptors in familial hypercholesterolemia, a rare disease, led to the discovery of statins, a drug therapy that is now also routinely used to prevent heart disease.

This Masters research thesis examined the research outcomes of two specific research strategies: registries linked to BBs and registries without BBs, and found that whilst registries without BBs had the capacity to uncover the natural history of disease, develop best practice, replace clinical trials, and improve patient outcomes, they were limited in their capacity to conduct basic research. Registries, when annexed to BBs, had the key infrastructure required to make novel Omics discoveries, identify and validate biomarkers, uncover novel genes, and develop new therapeutic strategies. The results of this Masters research thesis suggest that the role of basic research in RD research is vital; scientists must first understand the pathways of disease before they can develop appropriate interventions. Linkage of BBs to RD registries will provide the enhanced resources required for the effective translation of basic research into clinical practice.

Publications

Article associated with this thesis:

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Russell AC, Šimurina M, **Garcia M**, Novokmet M, Wang Y., Rudan I., Campbell H, Lauc G, Thomas MG, Wang W. (2017). The N-glycosylation of immunoglobulin G as a novel biomarker of Parkinson's disease. *Glycobiology*, 2017, 27(5), 501-510.

Presentations

Conference oral guest presentations associated with this thesis:

Garcia, M., Downs, J., Russell, A., & Wang, W. (2015). The Australian Early Onset Scoliosis Biobank Initiative. Presentation (and winner) at the **Three Minute Thesis Competition, Edith Cowan University, Western Australia**

Garcia, M., Downs, J., Russell, A., & Wang, W. (2015). The Australian Early Onset Scoliosis Biobank Initiative. Presentation at the **Growing Spine Conference, Sydney, Australia**

Garcia, M., Downs, J., Russell, A., & Wang, W. (2015). The International Early Onset Scoliosis Biobank Initiative. Presentation at the **Growing Spine Study Group meeting, Boston, USA**

Garcia, M., Downs, J., Russell, A., & Wang, W. (2016). The International Early Onset Scoliosis Biobank Initiative - genetics. Presentation at the **International consortium for Scoliosis Genetics, Singapore, Singapore**

Garcia, M., Downs, J., Russell, A., & Wang, W. (2017). The International Early Onset Scoliosis Biobank Initiative. Presentation at the **Oxford Spine Meeting, Oxford University, Oxford**

Garcia, M., Downs, J., Russell, A., & Wang, W. (2017). The Nathan Project for Rare Diseases. Presentation at **Fondazione Telethon (Telethon Network of Genetic Biobanks, Eurobiobank, RD-Connect), Milan, Italy**

Garcia, M., Downs, J., Russell, A., & Wang, W. (2017). The Nathan Project for Rare Diseases. Presentation at **the International Congress for Early Onset Scoliosis, San Diego, USA**

Conference oral guest presentations associated with this thesis:

Garcia, M., Downs, J., Russell, A., & Wang, W. (2016). The Early Onset Scoliosis Biobank Initiative. Presentation at the **Spine Society of Australasia, Melbourne, Australia**

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Finally, to my three beautiful children Nathan, Callum, and Emma. My life. My wish and dream for all three of you is to live your lives as fearlessly as you can. Know that you can achieve anything you set your mind to, and that you really can live the life your dream of. Work hard, be passionate, and stay focused. Help others. But most of all, have fun! I love you all!

To Chris Meredith, a very special now retired lecturer from ECU. I remember my first day of university, so completely overwhelmed by forensic genetics, that I realised I was not smart enough for university. Chris, you encouraged me to believe in myself, and said I had brains coming out of my ears. Moving onto my PhD, I smile at how far I have come. Without you as my lecturer and friend, I would not still be here at university, believing in my wildest dreams!!!

To children who do not have the luxury of quitting their rare disease when the going gets tough, I dedicate my life to helping this cause in any way I can. May this thesis and important work inspire others to do the same.

This study was partially supported by the Nathan Project.

 Nathan Garcia

Keep our faith.

Abbreviations

RD/s	Rare Disease/s
BB/s	Biobank/s
JBI	Joanna Briggs Institute
JBI-QARI	Joanna Briggs Institute Qualitative Assessment and Review Instrument
WHO	World Health Organisation
ICD	International Classification of Diseases
OMIM	Online Mendelian Inheritance in Man
DNA	Deoxyribonucleic Acid
CREST	Cancer of Respiratory Tract Biorepository
NSCLC	Non-small Cell Lung Cancer
CT	Computed Topography
RNA	Ribonucleic Acid
MiRNA	MicroRNA
qPCR	Quantitative Polymerase Chain Reaction
TREAT-NMD	Network for Neuromuscular Diseases
DMD	Duchene Muscular Dystrophy
FT	Fondazione Telethon
TNGB	Telethon Network of Genetic Biobanks
ADA-SCID	Severe Combined Immunodeficiency due to Adenosine Deaminase Deficiency
RCT	Randomised Controlled Trials
CAPS	The Cryopyrin-associated Periodic Syndrome Registry
EBB	EuroBioBank
UK	United Kingdom
PAH	Pulmonary Arterial Hypertension
USA	United States of America
NGS	Next-Generation Sequencing
CNDR	Canadian Neuromuscular Disease Registry
TB-CHW	Tumour Bank at the Children's Hospital Westmead
EURORDIS	European Organisation for Rare Diseases
NORD	National Organization for Rare Disorders
CORD	Canadian Organization for Rare Disorders

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1. Introduction – Rare Diseases, Registries, and Biobanks

1.1 Rare Diseases

Rare diseases (RDs), also known as "orphan" or "neglected" diseases, each occur in small percentages of the population. The European Union (EU) consumer- endorsed definition of RDs is diseases with "life-threatening or chronically debilitating diseases which are of such low prevalence (1 in 2,000 people) that special combined efforts are needed to address them" (European Commission, 2013). "RDs are variant phenotypes created by the experiment of nature and misfortunes of the environment" – Professor Wei Wang. The phenomes can be defined at any level of biological systems: molecules, organelles, cells, tissues, or organs. Paradoxically when combined, RDs are common, with individual diseases numbering approximately 6,000-8,000, and those affected equating to around 7% of the population, or 30 million people in Europe (European Commission, 2013). Extrapolating this figure for Australia suggests approximately 1.4 million people are affected by RDs (Department of Health, Australia, 2015). RDs occur across 27 disease categories, with newborns and children the most frequently affected (Lacaze et al, 2017). Approximately 80% of all RD have a genetic component, are often disabling, incurable, painful, and cause great suffering (Jaffe et al, 2010). Very few RD have effective treatments. These factors make the diagnosis, management, and treatment of RD patients inherently challenging. This has a significant impact on patients, clinicians and the health system.

Diagnosis of RD

The impact of receiving a RD diagnosis is often a devastating experience for families (Zurynski et al, 2017). For RD patients, diagnosis is often delayed, attributable to a lack of available information and knowledge by treating clinicians (Jaffe et al, 2010). Moreover, misdiagnosis of the disease is not uncommon (Zurynski et al, 2017). A recent study surveyed 462 families who had a child with a RD under the age of 19. The results highlighted the consequences of a delayed diagnosis for families, which included the need to consult multiple clinicians in order to find answers for their children (Zurynski et al, 2017). The research found 41% of families consulted three to five doctors, 16% consulted six to ten doctors, and 11% consulted over ten doctors (Zurynski et al, 2017). The study also showed that 8% of children did not receive a diagnosis for over 3 years. Frustration, anxiety, progression of disease, and delayed treatment have been reported by parents as common yet serious consequences resulting from a delayed diagnosis (Zurynski et al, 2017). The most common perceived reason for a delayed diagnosis by parents is lack of knowledge of RD by health care professionals (Zurynski et al, 2017).

Management of RD

RD are complex to manage and often require a multidisciplinary team of healthcare providers (Elliot & Zurynski, 2015). It has been recognised that General Practitioners (GP) play a crucial role in the overall management of RD (Elliot & Zurynski, 2015). Research shows that approximately 80% of all children with RD visited their GPs more than once in the prior 12 months (Elliot & Zurynski, 2015). The role of GPs may include case coordination, care plans, and specialist referrals. Indeed, GPs can assist in accelerating the process of an earlier diagnosis by referring their patients to specialist's sooner (Elliot & Zurynski, 2015).

Treatment of RD

For RDs, it is not uncommon for inappropriate and inefficacious treatments to be used (Zurynski et al, 2017). Obtaining a correct diagnosis may be of little value to the patient, as very few RDs have available or effective treatments (Lacaze et al, 2017). Indeed, until recently, there has been a reluctance from pharmaceutical companies to show interest in developing therapies for RD, as the market is so small (Elliot & Zurynski, 2015).

Impact of RD

It is known that families are severely affected by the negative consequences of RDs, and have been referred to as a "medical disenfranchised population that falls through the cracks of every healthcare system in the world" (Myers et al, 2003). Healthcare systems themselves, however, are also significantly impacted by RD. For example, in Western Australia (WA), a recent data linkage study found 467 rare diseases were logged in hospital records, accounting for 2% of the WA population (Walker et al, 2016). The study also showed approximately 10% of all hospital admissions in WA were related to rare diseases. Moreover, RDs accounted for 10.5% of total WA hospital expenditure ($395 million) over one year (Walker et al, 2016). Despite the very large number of RDs in existence, there are only approximately 400 drugs approved worldwide (Kakkis et al, 2015). As a result, RDs place a significant burden on the healthcare system, with greater dependency on hospital resources being observed in this cohort (Department of Health, Australia, 2015). This demonstrates marked disparity between the RD population and the total cost to the state health system, underscoring the substantial financial burden RDs place on society.

It has been recognised that to alleviate the burden of RDs, substantial research into new diagnostic and therapeutic strategies are needed. In response, the *WA Rare Diseases Strategic Framework 2015-2018* developed the first strategy for RDs in Australia. Among its many objectives, the framework strives to improve the health and wellbeing of those affected by RD through the advancement of RD planning in Australia, and by fostering world class clinical and translational research. The framework highlighted the importance of developing registries in RD research (Department of Health, Australia, 2015). More recently, Rare Voices Australia (RVA) created a public Communique, calling for a national plan for RD registries to be developed (Lacaze et al, 2017).

RDs pose challenges not only for health systems but also for research activities. Researchers are faced with limited samples numbers that are scattered geographically, disease classifications which are often unclear, and a general lack of interest and funding in RD. As a result of these deficiencies, RDs have become priority areas for many public health programs throughout the world (the National Organization for Rare Disorders (NORD), European Organisation for Rare Diseases (EURORDIS), WA Health Department). Data collection, such as clinical data, is crucial in the field of RD as without collecting this basic data, improving the management of the disease or furthering research will not be possible (Lacaze et al, 2017). Orphanet, an online catalogue of over 6,000 RDs and directory of expert resources for participating countries, recently stated that registries are "the only way to pool data in order to achieve a sufficient sample size for epidemiological and/or clinical research" (Orphanet, 2016).

1.1.2 Registries

Registries are information systems that collects data from patients. The type of information collected is dependent on the registries aims, objectives, and scope. A registry may be specific to a disease, population, or an intervention. Data collection for RD is not dissimilar to that of common disease registries. RD registries seek to collect a uniform set of data for each patient (Glickich et al, 2014). Registries can enable epidemiological research, post-marketing drug surveillance, and assist in health service delivery planning (Lacaze et al, 2017). In addition to collecting clinical data, RD registries should aim to collect information that offers meaning to both patients and clinicians regarding quality of life (Lacaze et al, 2017). Ultimately, a RD registry aims to improve patient outcomes. Unfortunately, in Australia, the true incidence and prevalence for RD are unknown (Lacaze et al, 2017). This can be attributed, in part, to a lack of RD registries to collect clinical patient information (Lacaze et al, 2017). National and international registries for RDs are often required as the patient numbers in local jurisdictions for each RD are too few. Thus, they bring together patients to facilitate research (Department of Health, Australia, 2015). One successful Australian registry, for

example, the Australian Rett Syndrome Database, established in 1993 to investigate the rare neurodevelopmental disorder, has led to a greater understanding of the natural history of disease, impact of treatment, and facilitated more than 100 research publications on Rett syndrome (Downs and Leonard, 2016).

1.1.3   Biobanks

As well as clinical data, some RD registries also collect biological samples such as blood. Samples are processed and stored in specialised freezers in universities or institutes set up as a Biobank (BB). Biobanks, also referred to as "biological specimen banks", "tissue banks" or "biorepositories", link a patient's biological sample to their clinical data, providing detailed phenotypic and genotypic information. The aim of a BB is to then make samples and data available to the scientific community for further studies. The United Kingdom BB is one of the world's largest BBs with over 500,000 participants aged between 40-69 years (Elliot & Peakman, 2008). The open-access resource enables investigations of genetic and environmental cause of diseases to improve the prevention, diagnosis, and treatment of diseases affecting the greater community (Sudlow et al, 2015).

Recently, research into RDs has been shown to have a significant impact in the acceleration of drug discoveries (Pariser & Gahl, 2014). As a result, RDs have been referred to as "fundamental diseases", providing opportunities to investigate the "extremes of human pathology" whilst also affording unique insights into normal and abnormal human physiology (Pariser & Gahl, 2014; Hall & Sireau, 2014). This leads to a greater understanding of biological pathways and the identification of therapeutic strategies not only for RDs, but also common diseases (Monaco et al, 2015). For example, research of low-density lipoprotein (LDL)-receptors in familial hypercholesterolemia, a RD, led to the discovery of statins, a drug therapy that is now routinely used to prevent heart disease (Hall & Sireau, 2014).

Whilst BBs require significant commitment, planning and long-term funding, the benefits of drug discovery far outweigh the costs (Li et al, 2016). Indeed, their true value is not reflected in the cost of associated infrastructure, such as freezers. Rather, a BBs true value is found in the information they capture and provide. This is especially so with RDs, where "every sample counts" (Zhou & Catchpoole, 2009).

BB's are becoming an increasingly important resource for rare disease research. Biobanks are established with 6 key principles in mind – resources, appropriateness, sustainability, privacy, confidentiality and trust. Biobanks aim to provide a resource for research purposes that is valued by

society. Biobanks aim to ensure their procedures (collection, transport, storage, access, use, and disposal) involving participants' samples are data are appropriate from a scientific, legal, and ethical standpoint. It is prudent the custodian of the biobank develops a business plan to secure sustainability of the biobank. Participant's privacy is considered paramount in any biobank, with data remaining confidential. Biobanks need to operate in a transparent and respectful manner, gaining the trust and ongoing involvement of the public.

Three main categories of biobanks exist, including disease-specific, population, and pathology biobanks (Graham et al, 2014). Disease-specific biobanks (e.g. the International Early Onset Scoliosis Biobank) refers to bio specimens collected for a specific phenotype or group of phenotypes (Olson, 2014), and are commonly used for RD (Graham et al, 2014). New technologies, such as next generation sequencing, have enabled research (derived from samples stored in biobanks) to identify new genes, gene mutations, biomarkers, understand genotype-phenotype correlations, and uncover aetiologies of RD (Graham et al, 2014). BB's also facilitate precision medicine, a new classification of medicine designed to personalise treatments through targeted therapy.

1.3   Overview, specific aims and hypotheses

Area of research strength

This Master's thesis research aligns with the Australian government's research priority of Promoting Population Health and Well-being, the WA Rare Diseases Strategy 2014-2018, and Edith Cowan University's (ECU's) research area of Health and Wellness.

Aims

Overall aim: This Master's thesis research aimed to identify the impact of BBs and interventions derived from BB infrastructure on research outcomes in RDs, and compare research outcomes in RDs that are or are not associated with a BB infrastructure.

Specific aims

- To identify the impact of registries linked to biobanks on rare disease research outcomes
- To compare the differences between registries with and without biobanks on research outcomes and to explore what factors give rise to these differences
- To provide recommendations for practice and policy

Rare disease registries, when annexed to biobanks, accelerate rare disease research outcomes.

Significance

The lack of aetiological research for fundamental diseases have made them a priority area in many basic sciences, applied sciences and public health programs throughout the world (European Commission, 2018; Eurordis, 2018). The term rare disease has recently been coined "fundamental diseases" (Hall & Sireau, 2014) highlighting their importance and unique capability in discovering the cellular pathways of other conditions, including common diseases. Up until recently, fundamental diseases have been inherently difficult to study. Biobanks are becoming an increasingly important resource for fundamental disease research. With the advent of new "omics" technologies, fundamental disease biobanks may hold the key to new discoveries for rare diseases (Lochmuller et al, 2017).

2. Methods

2.1 Research Design

A Systematic Review and Meta-aggregation was conducted using the preferred reporting items for systematic reviews and meta-analyses (the PRISMA statement) (Moher et al, 2009). The Joanna Briggs Institute Qualitative Assessment and Review Instrument (JBI-QARI) method of meta-aggregation was used for critical appraisal of articles, data extraction, and synthesis of data (Hannes and Lockwood, 2011). This qualitative method was developed to mirror the Cochrane's collaboration processes for quantitative systematic reviews.

2.1.1 Search Strategy

All articles from 1991, to include the pre-genomic and genomic era, to the end of 2016 published in English were considered. This served to capture the establishment of biobanks in the early 2000s. PubMed, Medline, Scopus and Web of Science databases were utilised. The following search terms were used: Rare diseases OR neglected diseases OR orphan diseases AND Biological Specimen Bank OR tissue bank OR registries/standards* OR registries/therapies* OR biobank* OR biorepository (in Figure 1).

2.1.2 Eligibility Criteria

Original research papers that reported clinical, epidemiological, basic or translational research findings derived from data contained in a RD registry with or without a BB. All study designs were

included. Retrieved articles were initially screened by title and abstract, and if potentially eligible, their full-text was reviewed.

2.1.3   Critical Appraisal

Articles selected for inclusion were assessed using the critical appraisal instruments by JBI-QARI. Two researchers performed the critical appraisal and compared results. In the instance of a disagreement, a third party was sought, and consensus was reached. Recorded information for each article included: date of publication, title, authors, citation, and abstract for later review.

2.1.4   Data Extraction

A comprehensive data extraction coding sheet was first developed and pilot-tested on 3 randomly-selected included studies, and refined accordingly. Four domains were developed for the coding sheet – study quality, methodology, type of intervention, and data/specimen collection fields. Each article was read in its entirety and findings were extracted using the online data extraction software by the JBI-QARI. Findings were recorded as verbatim quotes of the author's interpretation of results. An illustration (direct quote) was included to support each finding. Findings were assigned a level of plausibility (unequivocal or credible).

2.1.5   Data Synthesis

Data was synthesised using meta-aggregation analysis (Lockwood et al, 2015). The findings were grouped through similarity of meaning. Categories were developed to describe the concepts of each group of findings, with at least two findings per category. The categories were then grouped into a synthesised finding with at least two categories per synthesis. Categories were then grouped into six themes: basic science, translational science, clinical observation, clinical treatment, study quality, and facilitators and barriers. The synthesised findings constituted the set of recommendations for practice and policy. The search retrieved 432 citations; 311 were excluded, with full text retrieved for 109. Of those, 79 did not meet the eligibility criteria. A total of 30 articles were included in the review (Figure 6). Ethics declaration was obtained at the completion of the review.
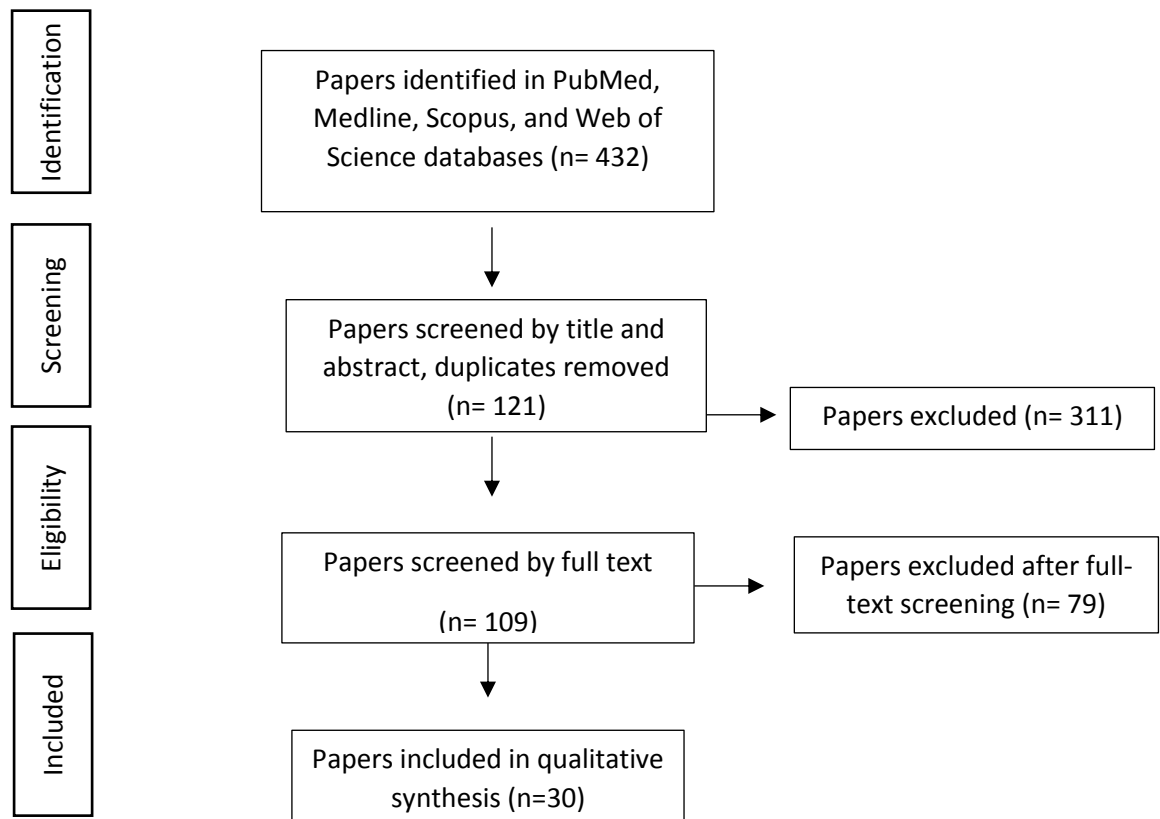
Figure 1. Flow diagram for article section and inclusion of review

3   Results

The search returned a total of 30 articles. There were 15 RD registries with a BB, and 11 RD registries without a BB. Of the 15 RD registries with a BB, 9 were international networks, 5 were national networks, and 1 was a single site initiative. Of the 11 RD registries without a BB, 6 were international networks, and 5 were national networks. The registries were European (n=12), International (n=7), North American (n=4), Australian and New Zealand (n=2), and Canadian (n=1). Twenty-one registries were established since 2000, with 9 established since 2010. Studies were mainly prospective and longitudinal in design, with only a few registries collecting retrospective or cross-sectional data. Disease categories included cancer, genetic, neuromuscular, neurological, lung diseases, cardiovascular, urogenital/renal, autoimmune, autoinflammatory, endocrine, blood and hereditary ocular diseases.

3.1   Study Quality

Registry cohorts ranged from paediatrics to adults or included both children and adults. Registry cohort sizes ranged from 23 to greater than 13,500 participants. The total number of biospecimens collected ranged from 46 to over 500,000. The number of research projects from RD registries and BBs ranged from 1 to 784, with the number of research publications ranging from 1 to 255 since the project started.

Twenty registries listed their funding sources: four were funded by the European Commission; three were funded by pharmaceutical companies; two by each of the following including the Department of Health, foundations, institutes, and research trusts; and one from each of the following including a university, charity, society, and benefactor funds; and one from a variety of sources. Four registries reported funding amounts ($170K per annum, 1.22 M, 1.6M, unrestricted funding). Nineteen registries reported that their data and samples are available to researchers. All 26 registries specified the RD name of interest, yet only five used the World Health Organisation (WHO) International Classification of Disease (ICD) or the Online Mendelian Inheritance in Man (OMIM) coding systems. A list of the registries, and their association with BBs at the time the original article was published, can be found in Tables 1 and 2.

Table 1: List of rare disease registries and whether or not they are associated with a biobank

Study ID	Author	Title	Registry with Biobank	Registry only	Themes associated with resource
N1-001	O'Souji, C	The Children's Oncology Rare and Cutaneous NHL registry	2		CO, CT, B
N1-002	Mora, M	The Eurobiobank Network	2		BS, T, CT, F, B
N1-003	Filacomo, M	Telethon Network of Genetic Biobanks	2		BS, T, CO, F, B
N1-004	Ebner, K	The European ARPKD registry	2		CO, CT, F

N1-005	Blain, D	Eyegene	2		BS, CT, F
N1-006	Bush, A	European Management Platform for Childhood Interstitial Lung Diseases	2		CT, F
N1-007	Martin, N	The UK JDM Cohort Biomarker Study and Repository Juvenile Dermatomyositis (UK and Ireland) Cohort Biomarker Study and Repository for Idiopathic Inflammatory Myopathies	2		CO, CT, F, B
N1-008	Fisher, C	The PTS Registry and Biobank Network - an AOSpine Knowledge Forum Tumour Study	2		BS, CO, CT, F, B
N1-009	Ugolini,	The CREST Biorepository	1		F
N1-010	Brandenburg, V	The German Calciphylaxis Registry	1		BS, CO, CT, F, B
N1-011	Struik, M	The Dutch Lymphangioleiomyomatosis (LAM) Registry	1		F
N1-012	Squitieri, J	Italian Huntington Disease Patients - Data and Tissue Bank	1		F
N1-013	Li, J	Friedrich's Ataxia Fibroblast Repository	1		F
N1-014	Zhou, L	The Tumour Bank at the Children's Hospital Westmead (TB-CHW)	0		F
N1-015	Bladen, C	The TREAT-NMD Duchenne Muscular Dystrophy Registries		2	CT, B
N1-016	Webb, S	The European Registry of Cushing's Syndrome (ERCUSYN) Registry		2	CO, CT, F
N1-017	Sharkey, E	The NF1 Patient Registry Initiative		2	CO

N1-018	Rodger, S	The TREAT-NMD Care and Trial Site Registry		2	BS, CO, F, B
N1-019	Tilson, H	The Cryopyrin-associated Periodic Syndrome (CAPS) Registry		2	T, CO, CT, F, B
N1-020	Mistry, P	The International Collaborative Gaucher Group (ICGG) Gaucher registry		2	CO, CT
N1-021	Evangelista, T	The UK Facioscapulohumeral Muscular Dystrophy Patient Registry		1	BS, CO, CT, F, B
N1-022	Hilbert, J	The National Registry of Myotonic Dystrophy (MD) and Facioscapulohumeral (FSHD)		1	BS, CO, F
N1-023	Fasnacht, M	The Swiss Registry for Pulmonary Arterial Hypertension		1	BS, CO, CT, F
N1-024	Downs, J Leonard H, Louise, S	The Australian Rett Syndrome Database The InterRett Database		1 2	CO, F
N1-025	Korngut, L	The Canadian Neuromuscular Disease Registry (CNDR)		1	F, B
N1 -026	Fehr, S	The International CDKL5 Disorder Database		2	CO, F
N1-027	Akbarnia, B	The Growing Spine Study Group		2	CO, CT, F

BS-Basic Science   T-Translational Science CO-Clinical Observation

CT-Clinical Treatment   F-Facilitators   B-Barriers

0–Single site   1–National registry   2–International registry

3.1.1   Increased Research Activity

There is overwhelming evidence that RD registries significantly increase research projects, and this is amplified when it is a member of a network. Comparatively, RD registries with BBs generate quantifiably more research activity and publications than RD registries without BBs. For example, the

use of samples from a European BB network has been acknowledged in 255 publications from 2004-2013 (Mora et al., 2015). An Italian network provided thousands of samples to national and international researchers over a 5-year period (Filocamo et al., 2013). This led to 784 research projects, with over 250 scientific publications from 2008-2012 (Filocamo et al., 2013). In this review, the articles analysed reported the number of research projects and enquiries totalled 898 for RD registries with BBs, compared to 172 for RD registries without BBs. This is a 5-fold increase in research projects utilising RD registries with BBs. Further, the articles analysed in this review reported research publications totalling 571 for RD registries with BBs, compared to 26 for RD registries without BBs. This is a 21-fold increase for RD registries with BBs (Figure 7).
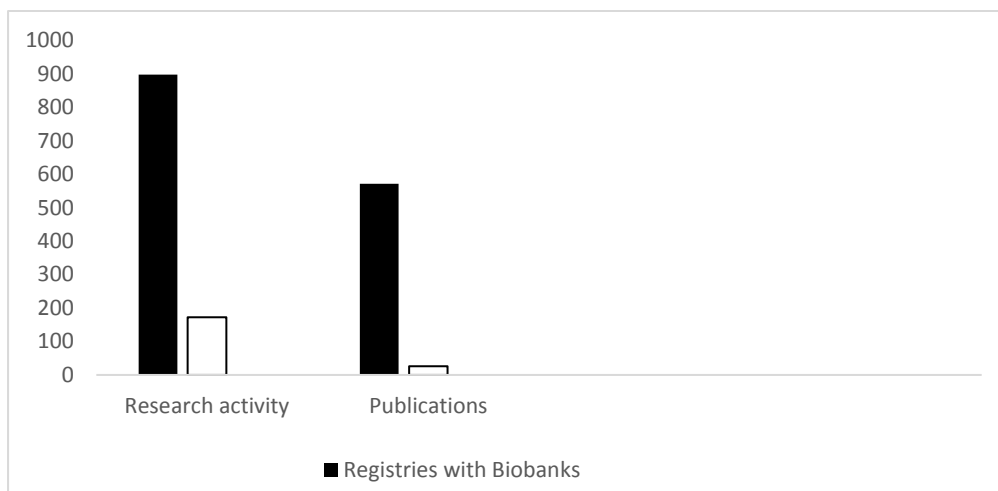
Figure 2. Research impact of RD registries with and without BB

3.1.2   Synthesised Themes

The synthesis generated 480 findings, 34 categories, and 6 themes. The themes were titled basic science, translational science, clinical observation, clinical treatment, study quality, and facilitators and barriers. An example of the meta-aggregation for this study is illustrated in Figure 3 and 4.

Illustration from study – Martin, N – Rheumatology (2011)

The establishment of the JDRG has provided a forum for regular communication between members, and facilitated discussion regarding treatment approaches. There is emerging evidence that this had led to a gradual shift in practice from the initial cohort. Treatment for JDM is not yet evidence based but the group has facilitated emerging consensus. Standardizing treatment protocols are currently under discussion and will hopefully be adopted by the group, providing a more secure basis for assessing outcome and the basis of future therapeutic studies. P141

Finding - This study has led to a shift in practice through achieving consensus and beginning the standardisation of treatment protocols.

Category – Guidelines for treatment

Figure 3. Direct quotes are recorded verbatim, summarised into findings, and assigned into a category.

Finding	Category	Synthesised finding
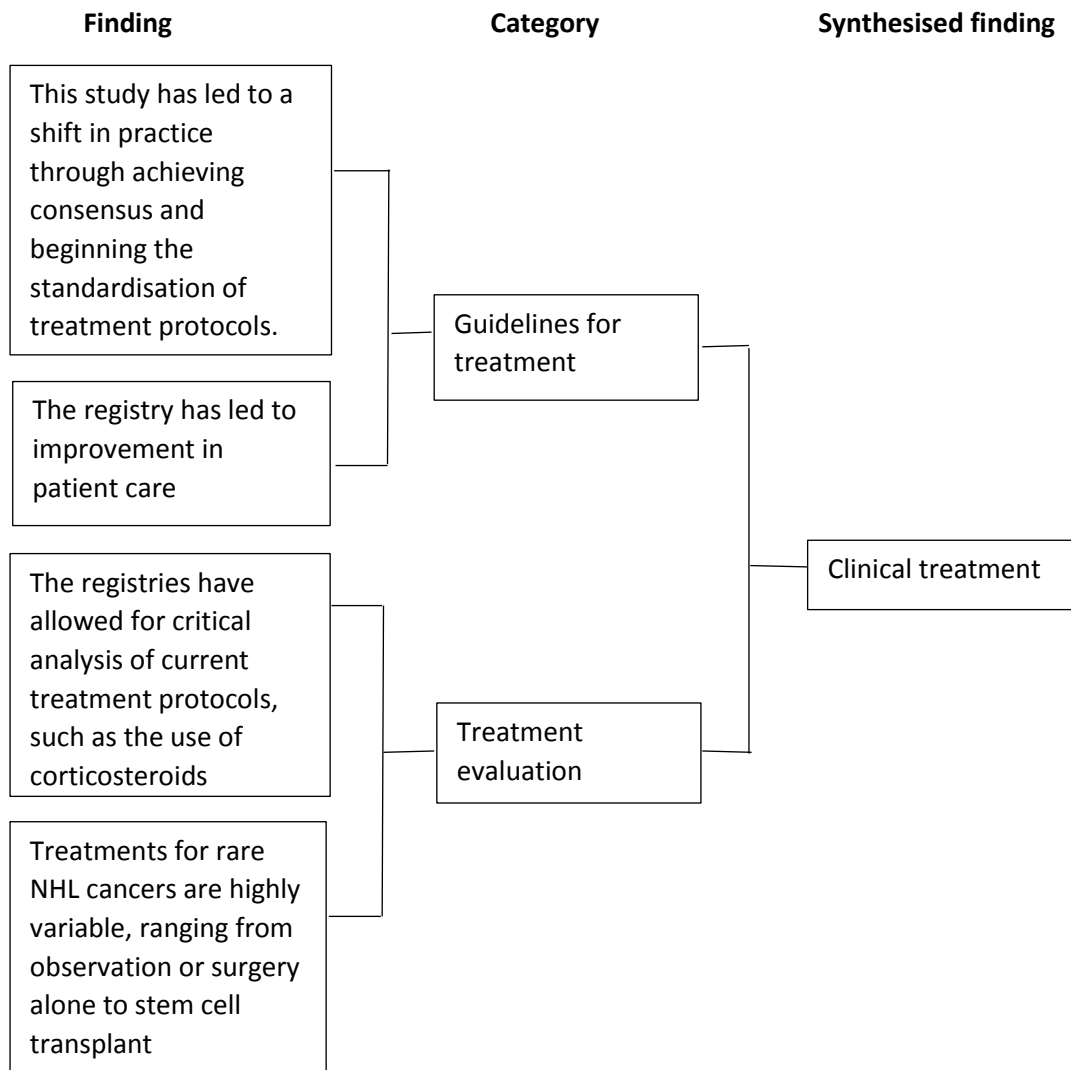
Figure 4. Meta-aggregation example – Findings from study number 7, 15, 15, and 1

3.2.1 Omics

This review found that registries linked to BBs impacted on RD research outcomes by facilitating Omics studies and discoveries, leading to scientific advancement. No evidence of basic science research being conducted in registries without a BB was found. This can be attributed to the fact that registries without BBs do not collect biological samples; therefore, they lack the ability to conduct basic science investigations. Conversely, registries with BBs collect, and have access to, biological samples, such as blood for DNA and fibroblasts for cell lines. As a result, registries with BBs can conduct laboratory studies (such as investigating the aetiopathogenesis of disease). Basic science is the first step in the translational science process, with discoveries made in this stage having the potential for future development into new diagnostic tools and therapies, relevant for clinical practice.

The basic science discoveries included the characterisation of new syndromes, biomarker discovery and validation, elucidation of biological pathways involved in disease, molecular modelling of pathogenic variants, characterisation of epigenetic factors involved in disease expression, genotype-phenotype correlations, molecular analysis of DNA methylation, chromatin structure, gene-transfection and gene-silencing studies, studies involving growth factors and cytokines, identification of new gene and novel mutations, and exon-skipping (Mora et al., 2015; Blain, Goetz, Ayyagari, & Tumminia, 2013; Filocamo et al., 2013).

3.2.1.1 Case Example –Omics

In 2011, utilising samples entirely from the Cancer of Respiratory Tract (CREST) biorepository that was primarily established to study mesothelioma (a rare and serious form of lung cancer), a study was conducted to evaluate new biomarkers for non-small cell lung cancer (NSCLC), the most common form of lung cancer (Foss et al, 2011). A large proportion of lung cancers (>75%) are detected in the later stages of the disease, attributable to a lack of appropriate screening tools for large numbers of people. Whilst computed topography (CT) screening has been used for at-risk individuals, it is not ideal. For example, approximately 50% of tumours detected by CT are benign, and for every death prevented using this method, two invasive procedures resulting from false-positive results will occur. Late detection using current methods has resulted in poor prognoses for lung cancer patients. Conversely, early detection leads to improved patient outcomes. Therefore, the rationale for biomarker development in lung cancer was for earlier detection of NSCLC, which may lead to improved survival rates. The study aimed to identify serum-based biomarkers for NSCLC. Blood-serum was obtained from 22 participants (11 with early-stage NSCLC and 11 controls) provided by the CREST biorepository. Using microRNA (miRNA) profiling on total RNA, the study found the expression of two miRNAs (has-miR-1254 and has-miR-574-5p) to be significantly elevated in NSCLC cases when compared to controls. Quantitative polymerase chain reaction (qPCR) validated the results, with the authors concluding the findings justified additional consideration and validation of these serum-based biomarkers for early-stage non-small cell lung cancer. The CREST biorepository demonstrates how RD BBs can impact on outcomes (biomarker development) in basic science, not only for RDs (mesothelioma), but also common disease (NSCLC). Moreover, the CREST biorepository stores blood samples over many years, and includes banked samples from individuals prior to their lung cancer diagnosis. This makes RD BBs invaluable for testing the applicability of NSCLC serum-based biomarkers, an opportunity not afforded to other biomarker studies.

3.3. Translational Science

3.3.1 Availability of Biospecimens for Research

This review found that registries linked to BB impacted on RD research outcomes in translational science by contributing biological specimens to research projects, leading to new therapies to treat

RD. Registries without BB could not contribute biological specimens, and so lacked the capacity to contribute to the development of new diagnostic tools and therapies. The registries with BB in this review donated biological samples to pharmaceutical companies (such as Pfizer), consortiums, and international studies (Filacomo et al, 2013).

3.3.2   Clinical Trials

This review found that registries both with and without BBs impacted on RD research outcomes in clinical trials with regards to increased patient recruitment and novel safety monitoring approaches. It was found that RD registries can not only be used in place of randomised controlled trials (RCT), they are often more advantageous (Tilson et al, 2013). Unlike RCTs, registries are unrestricted in their cohort size, and have no dictated treatment regimens or strict inclusion criteria (Tilson et al., 2013). Registries have the capacity to collect information from patients in a real world setting during routine clinical care, and because they are observational, all patients receiving treatment can be included, irrespective of dosage. This brings sound external validity as 'registry enrolled patients' generally have an increased baseline risk than 'RCT enrolled patients'. Further, the research period of registries is longer than RCTs, allowing long-term follow up of new approved therapies.

3.3.2.1 Case Example – Clinical Trials

The Cryopyrin-associated periodic syndrome (CAPS) registry is an example of a registry being used in place of a RCT for post-marketing purposes (Tilson et al, 2013). CAPS are a group of rare, hereditary autoinflammatory diseases. Symptoms, such as fever and systemic inflammation, present as recurrent episodes throughout the entire lifetime of the patient, and can become life-threatening. Canakinumab, a monoclonal IL-1-β antibody, is an approved treatment for CAPS patients. Like all RDs, the clinical development of Canakinumab recruited a very limited number of patients; therefore, post-approval monitoring to assess the short and long-term safety and efficacy was critical. The CAPS registry was established in 2009 as an online, observational registry with the aim of gathering information regarding the natural history of disease as well as the beneficial and adverse effects of treatment over a 5-year period. With no exclusion criteria, protocol-mandated visits, or procedures, physicians successfully collected data from 241 CAPS patients over 5 years during routine visits to clinic, significantly more than the original drug approved dossier of 78 CAPS patients over a 3.5-year period. An update of the safety profile of Canakinumab in 2013-2014 reported no new or unexpected safety concerns, with no loss of efficacy of the drug (Hoffman et al, 2016). Moreover, the findings were consistent with the previous clinical trials.

3.4   Clinical Observation

3.4.1 Epidemiology and Studies of Phenotype

This review found that registries both with and without BBs impacted on RD research outcomes with regards to epidemiological studies, providing further insight into the disease. This review found that RD registries can gain insights into the incidence/prevalence of the disorder and survival, natural history, relationships between genotype and phenotype, and understand the burden of disease. Captured epidemiological data in this review included age, characterisation of symptoms, gender distribution, ethnic background, provision of care at different sites, diagnosis of patient, and data pertaining specifically to the disease of interest (Fascnacht, Tolsa, & Beghetti, 2007; Tilson et al., 2013; Evangelista et al., 2016; Hilbert et al., 2012; Rodger et al., 2013; Brandenburg et al., 2016; Fisher et al., 2014).

3.4.1.1 Case Example –Epidemiology and Studies of Phenotype

TREAT-NMD, a registry network for neuromuscular diseases, provides evidence of how RD initiatives can impact on genetic epidemiological outcomes. Duchenne Muscular Dystrophy (DMD) is a progressive neuromuscular disease caused by mutations in the DMD gene, leading to a depletion of dystrophin within the muscle (Hoffman et al, 2012). The TREAT-NMD DMD global database is thought to be the world's largest cohort of DMD mutations, containing over 7,000 mutations (Bladen et al, 2015). The initiative collects and compares information regarding DMD mutations (such as location of mutation). Gaining an insight into the type and frequency of mutations that cause DMD is invaluable for genetic diagnosis, basic science, clinical care, and personalised/targeted therapy (Bladen et al, 2015).

Analysis of the TREAT-NMD DMD Global database showed that, regardless of geographical location, the most prevalent mutation are large deletions (68%) with exon 45 being the most common deletion (reported 316 times). Of the 7,149 mutations, 5,684 (80%) are insertion/deletion (INDELS) mutations, and 1,445 (20%) are small point mutations. Half of all small point mutations (10% of total mutations) are nonsense mutations: point mutations that lead to a premature 'stop' codon being introduced into the amino acid sequence. This usually results in a non-functional protein, causing disease. A potential DMD therapy that has achieved marketing approval is nonsense stop codon read-through therapy (Welch et al, 2007). This treatment selectively induces ribosomal read-through of premature stop codons but not normal stop codons. The database identified 317 mutations (4%) with a premature TGA stop codon, 215 (3%) with a TAG stop codon, and 194 (3%) with a TAA stop codon, that would potentially benefit from this available therapy. Another therapy for DMD is exon-skipping technology (van Ommen and Aartsma-Rus, 2013). Exon-skipping takes advantage of the fact that internally deleted dystrophins can be partly functional (van Ommen and Aartsma-Rus, 2013). Mutations were identified in the database that would potentially benefit from exon-skipping, such as skipping of exon 51 (14% of all mutations) and 53 (10%). This example highlights how registries can impact on epidemiological outcomes and can assist in identifying patients who may benefit from already existing therapies.

3.4.2 Natural History of Disease

Registries both with and without BB impacted on the natural history of disease by gaining insight into the natural course of disease. This is important as it assists researchers in developing preventive strategies from a general framework. Registries in this review observed factors that accelerated or slowed development of disease, understood better the resultant disease sequalae, and made new findings regarding disease progression.

3.4.2.1 Case Example – Natural History of Disease

A novel finding regarding the natural history of disease was uncovered through the German Calciphylaxis registry (Brandenburg et al, 2016). Calciphylaxis is a very RD that carries a high mortality. It is frequently found in patients with end-stage renal disease on dialysis, and manifests as severe skin ulcerations and calcification of cutaneous arterioles (Brandenburg et al, 2016). The German registry was established to identify potential risk factors for disease, clinical practice methods, and biomarker analysis. This was achieved by collecting clinical information as well as blood samples, stored in the registry's BB. Whilst the registry validated previous reports that end-stage renal disease appears to predispose patients to Calciphylaxis, the novel finding came from the laboratory testing on patient samples, which measured serum calcium, phosphorus and parathyroid hormone levels. The biochemistry results found that parathyroid hormone levels in Calciphylaxis patients were unexpectedly low. The authors recommended that future studies need to explore the trend and time course of these biochemistry markers (calcium, phosphorus, and parathyroid hormone) in the months leading up to Calciphylaxis development.

3.4.3 Diagnosis, Survival Rates, Patient Outcomes

Registries with- and without- BBs impacted on clinical observation outcomes in regards to diagnosis, survival rates and patient outcomes. Registries in this review observed long delays between symptom onset and diagnosis, with multiple consults by specialists observed prior to gaining a confirmed diagnosis. Registries with BBs had the capacity to store samples for clinicians from undiagnosed patients with the view at future diagnosis, providing retrospective diagnoses. Survival rates could be established for various diseases, as well as outcomes at follow-ups in this review.

3.4.3.1 Case Example – Diagnosis, Survival Rates, Patient Outcomes

The International Collaborative Gaucher Group registry provides an example of how registries can establish survival rates (Mistry et al, 2015). Gaucher disease is a rare, heterogeneous inborn error of metabolism with three main phenotypic categories. Among its other manifestations, Gaucher disease type 1 is characterised by splenomegaly. A sub-study from the registry established that Gaucher disease type 1 has a 9-year reduced life-expectancy compared to that of the normal population, possibly as a result of the impact of splenectomy (Mistry et al, 2015).

3.5   Clinical Treatment

3.5.1   Diagnostics

This review found that RD registries contributed to observing which participating centres lacked appropriate diagnostic criteria, whilst also supporting the development of new diagnostic testing methodologies.

3.5.1.1 Case Example – Diagnostics

The EuroBioBank (EBB), the first BB network in Europe (and also a partner of the TNGB) collects, processes and stores biological samples (such as DNA and tissue) for provision to the RD scientific community (Mora et al, 2013). One partner of the EBB, known as the Instituto Nazionale Neurologico Carlo Besta, provides samples for new diagnostic tests when they become available. This provides another utility of a BB by way of supporting diagnostic development.

3.5.2   Guidelines for Treatment

Registries both with and without BB impact on clinical treatment. Rare diseases commonly lack evidence-based treatment protocols, attributed to the low number of patients seen at any one centre. Registries in this review facilitated multi-centre collaboration, which in turn led to discussions among experts regarding treatment protocols and best practice. This contributed to the management of disease, impacting on patient outcomes.

3.5.2.1 Case Example - Guidelines for Treatment

The Juvenile Myositis registry is one such example of how registries can impact on treatment guidelines (Martin et al, 2011). Juvenile Myositis is a group of rare, chronic inflammatory disorders in childhood, affecting muscles and other organs. This disorder is associated with a high level of morbidity and mortality. There is a severe lack of evidence-based treatments for Juvenile Myositis, with almost no level-1 evidence from trials regarding therapies, and little is known about the underlying mechanisms of the disease. Through collaboration with multiple centres, the registry facilitated discussion among experts regarding current treatments. It was observed that early management of Juvenile Myositis improved treatment outcomes, whereas a delay in treatment led to poorer outcomes. The outcome was a shift in practice; specifically, widespread adoption of earlier and more aggressive treatments. In addition, the assessment process for children with Juvenile Myositis changed in participating centres as a result of the registry. The registry employed the Childhood Myositis Assessment Scale, a tool previously validated to assess muscle function, as part of their data collection process. As a result, this assessment tool has since gained widespread use throughout the UK for management of Juvenile Myositis, and is now part of routine clinical practice in participating centres. The registry is currently working on establishing treatment protocols for this disease.

3.5.3 Treatment Evaluation

Registries both with and without BBs impacted on treatment evaluation for RD. Existing therapies and surgical interventions, and their outcomes, were observed. This led to a greater understanding of which therapies affected disease course.

3.5.3.1 Case Example – Treatment Evaluation

The Swiss Registry for Pulmonary Arterial Hypertension (PAH) collects information pertaining to paediatric PAH, a rare condition leading to high blood pressure in the lungs of affected children (Fasnacht et al, 2007). PAH has a poor prognosis if left untreated. Information regarding treatment outcomes for paediatric PAH are scarce. The Swiss registry evaluated treatment outcomes from 23 paediatric PAH patients, with a median follow-up of 3.47 years. Therapies included Bosentan, Sildenafil, and inhaled Iloprost, administered in isolation or in combination. Whilst the treatments were heterogeneous, it was found that the majority of PAH patients achieved stabilisation of their condition under these current available therapies. Further, some patients demonstrated an increased exercise tolerance with improved functional status on these therapies. The authors highlighted the usefulness of such a registry for gathering vital information on therapies for RD.

3.6 Facilitators

3.6.1 Benefits to Stakeholders

Registries with and without BBs benefit stakeholders. This review found that participants, patient advocacy groups, researchers, and clinicians all benefited from participation in RD registries.

3.6.1.1 Case Example – Benefits to Stakeholders

Eyegene, a registry and BB dedicated to phenotyping and genotyping rare inherited eye diseases, provides a comprehensive example of how registries benefit numerous stakeholders (Blain et al, 2013). Established by the National Eye Institute, Eyegene's reach encompasses the USA and Canada. Patients diagnosed with genetic eye diseases are clinically characterised, and have their DNA stored in a BB. Research is then conducted into the underlying pathogenesis of disease. Patients participating in the initiative benefit by being involved in current research which may elucidate the genetic cause of their condition. Eyegene found that patients chose to participate in research studies even when they knew the genetic cause of their disease. Patient support groups presented clinically characterised, previously genotyped individuals to Eyegene for participation, benefiting by expanding their access to research. Clinicians referring their patients to Eyegene benefited by receiving a molecular diagnosis of their patient, confirming the initial clinical diagnosis. Eyegene has provided diagnostic results to over 55% of participants enrolled, and has over 4,400 samples stored with Eyegene. This may help to better monitor and manage respective inherited eye conditions. Furthermore, through Eyegene, both clinicians and patients gain access to information regarding the availability of clinical trials. Finally, the scientific community benefited from Eyegene by accessing clinical data linked to biological samples, which progressed research in the field of inherited eye diseases. For example, Eyegene initially tested 20 genes over 9 disease categories, but now tests more than 100 genes over 35 categories, the result of gene discovery through the network.

3.6.2 Collaborations

This review found collaborations between registries and various stakeholders are vital to the success of the registries aims and objectives. The registries collaborated with numerous groups including hospital sites, academic centres, clinicians, patients, scientists, patient advocacy groups, pharmaceutical and diagnostic industries, societies, foundations and other registries. Collaboration was local, regional, national, or international. Collaborative approaches facilitated review and discussion of treatment protocols, improving treatment outcomes. Continuous engagement assisted

clinicians with follow-up, with more complete data being reported. International collaborations increased patient cohort size, leading to increased interest from industry.

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3.6.2.1 Case Example – Collaborations

The approval of Strimvelis required extensive collaboration between numerous stakeholders, establishing a new paradigm for RD research. Cooperation was facilitated between academia, not-for-profit organisations, and the pharmaceutical/biotech industry, evidencing how this transparent collaboration overcame the numerous barriers associated with drug development for RDs (Aiuti et al, 2017). The combined efforts that accelerated the commercialisation of Strimvelis resulted in a "turning point for the field" and has charted a "clear path" for similar gene therapy developments (Aiuti et al., 2017). The success of the methods developed for the success of Strimvelis extends beyond the obvious benefits to the patient, with the strategies employed for quality assessment, manufacturing, administration of the drug in the clinical setting, and policies for drug cost and reimbursement serving as a precedent for future efforts. (Aiuti et al, 2017).

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3.6.3   Engagement

Engagement strategies reported by the registries included the international nature of the registry, ongoing communication between the registry and participating sites, collaboration, methods of recruitment, using data collection forms in place of clinical notes to ease the burden of form filling, inclusion of any interested clinics to increase participant numbers, and equal sharing of funding leading to continuation of data collection even when the funding ceased.

3.6.3.1 Case Example – Engagement

The TNGB attributed 4 major strengths to the success of their national network (Filacomo et al, 2013). Firstly, the Coordination Office, managed by the Coordinator of the entire network, ensured harmonisation and standardisation of all operating procedures (including collection, processing, and storage of samples and data) throughout the BB. The TNGB reported that maintaining interoperability throughout the BB has prevented siloing and disorganisation from individual efforts. Secondly, a unique collaborative model between the TNGB and various patient support groups for RD in Italy was established. Patient support groups have always had representation on the advisory board since the inception of the network, providing insight and feedback on governance issues such as ethics, consent, and confidentiality. In addition to this role, a "coordinator emeritus" was appointed to support the coordinator by the TNGB to liaise between the patient support groups in Uniamo, an Italian federation of over 100 RD associations. The coordinator emeritus initiated meetings and workshops with the aim of fostering trust and interest among patients and their families regarding the concept of the BB, and how it can provide a resource for future RD research. The TNGB reported that there is a significant increase of interest in the BB, and that patient and family involvement have been vital for both reaching a critical mass of biological samples, as well as taking the patients' needs and concerns into account. Thirdly, the TNGB used a novel approach in dedicating a specific patient support group to one of the BB in the network. Termed a "framework agreement" and there are now six such agreements in place. Within the framework, patient groups can promote and cofound research projects with the BB they are partnered with, with two projects now developed as a result of this agreement. Lastly, the TNGB attributes another strength to its success through its online catalogue. The "virtual biobank" lists all samples stored within the BB network online, making some 75,900 samples visible to the international scientific community.

3.6.4 Recruitment

Registries in this review employed novel methods for recruitment of RD patients. This lateral thinking is especially important given the small number of patients scattered geographically.

3.6.4.1 Case Example – Recruitment

The Canadian Neuromuscular Disease Registry (CNDR) is a national registry established in 2011 (Korngut et al, 2013). The CNDR was established to bridge the gaps of knowledge for rare, neuromuscular diseases in Canada. The registry utilised a novel recruitment approach to "cast the net" as far as possible and reach patients affected by neuromuscular disease. Blended recruitment, the term given to this model, offers several methods for recruiting patients. In addition to the traditional approach of clinicians enrolling patients during routine visits to clinic, the CNDR also offers direct self-registration through the registries main office, with the option of patients registering themselves through the CNDR public website, connecting interested patients with CNDR staff at head office. Blended recruitment offers a novel approach to recruitment, enabling both clinicians and patients to recruit through several means. As a result, the CNDR recruited 253 Duchenne and Becker Muscular Dystrophy patients, 161 myotonic dystrophy patients, and 71 ALS patients. Enrolment extended to 12 provinces and territories, confirming the feasibility and efficacy of blended recruitment for RD registries.

3.6.5   Pro-active Marketing

A strategic, targeted, pro-active marketing approach demonstrated how even a single BB site can have a significant impact on RD research outcomes, and can contribute to key research studies throughout the world.

3.6.5.1 Case Example – Pro-active Marketing

The Tumour Bank at the Children's Hospital Westmead (TB-CHW) is a single site BB with a research focus on rare paediatric malignancies (Zhou & Catchpoole, 2015). They have been pro-active when forming collaborations. The TB-CHW actively sought out international, leading world experts whose research and results would most likely lead to a greater understanding of childhood cancer through the addition of TB-CHW samples. This novel approach has facilitated 84 research projects around the world, resulting in over 40 genomic-based research publications (Zhou & Catchpoole, 2015). Interestingly, 76% of research publications were from collaborations between international researchers, underscoring the importance of a single site RD registry with a BB to the international research community (Zhou & Catchpoole, 2015).

3.7 Barriers

3.7.1 Challenges

Challenges reported by the registries in this review included incomplete data sets, data accuracy (error), study design, lack of follow-up, lack of standardisation, and funding restrictions. Another challenge was the ability to reach, recruit and capture all patient cases. It was also found that BBs that cover a broad range of diseases are limited in their ability to reach a critical mass for a particular disease diagnosis or category.

3.7.1.1 Case Example – Challenges

Whilst the advent of next-generation sequencing (NGS) provides unparalleled opportunities for RD research, the TNGB found limitations when implementing this technology due to legal and ethical concerns (Filacomo et al, 2013). It was noted their current informed consent was restricted to that patient's particular disease, and lacked the necessary broad consent to implement NGS. Moreover, governing the sheer volume of information generated by NGS required additional considerations. This was especially so when managing "incidental findings". In response, the TNGB collaborated with experts in order to accelerate national regulations for BB.

Theme	Category	Identified in RD registries linked to BB	Identified in RD registries without BB
Basic Science	Omics	✓	
	Biomarker development	✓	
	Subcohort identification	✓	
	Epidemiology	✓	✓
Translational science	Increased number of research projects	✓	✓
	Randomised controlled trials	✓	✓
	Biospecimen contribution to studies	✓	
Clinical observation	Diagnosis/survival rate	✓	✓
	Natural history of disease	✓	✓
Clinical treatment	Diagnostics	✓	✓
	Guidelines for treatment	✓	✓
	Treatment evaluation	✓	✓
Facilitators	Benefits to stakeholders	✓	✓
	Collaborations	✓	✓
	Strengths	✓	✓
Barriers	Limitations	✓	✓
	Other	✓	✓
Study quality	Research period	✓	✓
	Recruited participants	✓	✓
	Samples collected	✓	
	Research projects	✓	✓
	Publications	✓	✓
	Confidentiality	✓	✓

Table 3. Synthesized Themes and Categories identified in RD registries with and without BB

# 4	Discussion

This systematic review sought to identify the impact of BBs on research outcomes in registries for RDs. We analysed and compared the research endpoints of two specific populations: registries with BBs and registries without BBs. Findings were grouped into themes: basic science, translational science, clinical observation, clinical treatment, study quality, and facilitators and barriers. We observed key differences among the research endpoint variables between registries with and without BBs. Most notably, registries with BBs included basic science as a research endpoint, observed to lie exclusively within the domain of registries with BBs. This review found that the inclusion of basic science as a research endpoint variable in registries has significant and far-reaching consequences by way of facilitating translational research, leading to the discovery and development of new treatments and therapies for RDs.

RD registries are often the only resource for the disease of interest (Gliklich & Dreyer, 2010). Registries are gradually being recognised as a global priority in RD research; the essential "building blocks" for RD epidemiological, clinical research, and post-marketing studies (Eurordis, 2011). In this review, RD registries without BBs facilitated epidemiological research, clinical research, and post-marketing surveillance studies. Furthermore, registries were found to not only replace clinical trials, but to offer several benefits to them, including no restrictions in cohort size and no dictated treatment regimens. This provided sound external validity, with patients being observed over longer periods of time in "real-world" settings, an important finding. Rare disease registries led to a greater understanding of the natural history of disease, consensus-driven treatment protocols, and ultimately improved patient outcomes.

An important consideration is that some registries collect the results of genetic testing and therefore store phenotype/genotype data, but not biological samples. This does not constitute a BB per se, as the registry cannot conduct basic research. For example, the Australian Cystic Fibrosis registry collected phenotypic/genotypic data from 3087 patients, allowing stratified genetic analysis in 91.7% of all registry members (Ahem et al, 2015). It is also important to note that clinical quality registries are set up specifically not to do research.

Despite these benefits, registries without BBs in this review were restricted in their smaller capacity to contribute to basic research, attributable to a lack of infrastructure required to conduct the necessary laboratory-based investigations. Further, basic research studies are made possible through the availability of human biological specimens (Zhou & Catchpoole, 2015). It is only through the collection and investigation of human biological samples matched to clinical data that novel diagnostic, prognostic, and therapeutic avenues can be developed (Fisher et al, 2013). This is

particularly important considering drug innovation for RD has, in recent years, become progressively focused on Omics studies, with the identification of molecular targets leading to the development of new therapies (Gahl, 2014).

Registries linked to BBs contributed more to basic research. Findings included novel Omics discoveries, biomarker development (screening, validation, replication and clinical trial), gene identification, elucidation of biological and cellular pathways, models for drug-screening, and therapeutic discoveries. As 80% of RD have a genetic component, genomic analyses may assist in not only obtaining a correct diagnosis but also contribute to RD genomic research (Chong et al, 2015). Furthermore, conducting genomics research can contribute to our knowledge of gene regulation and function, as well as gaining an understanding of the underlying biological pathways of disease that can then be translated into developing new therapies (Chong et al, 2015).

The development of new therapies for RDs is critically significant as they can be of a life-saving nature. This is best demonstrated by Strimvelis, the first *ex vivo* stem-cell gene-therapy for children to gain marketing approval anywhere in the world (Aiuti et al, 2017). In spite of the ground-breaking success of Strimvelis, Fondazione Telethon remains committed to its original focus of basic research, stating "basic science is the foundation on which future treatments will be developed" (Monaco & Faccio, 2017). This provides a powerful message to RD stakeholders; scientists must first understand the pathways of disease before they can develop appropriate interventions.

The premise that basic science is the key component in RD registries for the discovery and development of new therapies is consistent with statements from; the Eurordis position paper on research priorities for rare diseases 2014-2020, which states "basic research is the prerequisite of any therapeutic advance and of any new public health decision"; a recent joint declaration by the European Organisation for Rare Diseases (EURORDIS), the National Organization for Rare Disorders (NORD) and the Canadian Organization for Rare Disorders (CORD) 10 key principles for RD patient registries, which states "Rare Disease Patient Registries data should be linked with corresponding biobank data", adding that RD registries provide the key infrastructure for translating basic research into new therapies; and the *WA Rare Diseases Strategic Framework 2015-2018*, which recognises patient registries as a priority for research, supporting the development and integration of patient registries with BBs (Eurordis, 2011; Eurordis, 2012; Department of Health, 2015).

Whilst linkage of BBs to registries have been identified as important for translational research, in reality, BB are expensive (Hoffman et al, 2013). A recent survey of 456 BB found that 71% of respondents interviewed were concerned about funding (Cadigan et al, 2013). The associated costs of BB vary dependent on the size and structure of the BB. For example, a small resource involving a

single freezer in a university laboratory will have a vastly different structure (and hence, costs) to a national BB collecting samples from multiple sites (Vaught et al, 2010). Methods to reduce BB costs was suggested through the implementation of a cost-accounting tool for BB, specifically, two mathematical models designed to address production costs and request costs (Gonzalez-Sanchez et al, 2014). Consideration of multiple factors including numbers and types of samples stored, size of BB, concentration strategies in BB networks, as well as demand of researchers and international strategies of the BB may serve to decrease associated costs and improve financial sustainability of the BB (Gonzalaz-Sanchez et al, 2014). Implementing such a tool may assist to reduce the costs/barriers for RD registries wanting to incorporate a BB into their resource. However, this must be accompanied by appropriate levels of commitment from major national and international funding bodies.

In addition to these findings, this review found several factors which, when utilised, served to strengthen the success of RD registries.

The collaborative effort of Strimvelis provided a new paradigm for RD research. Strimvelis required open coordination and collaboration between academic institutions, bio-tech companies, the pharmaceutical industry, and not-for-profit organisations in order to overcome the numerous and often insurmountable obstacles in developing a new therapy for RD (Auiti et al, 2017).

The strengths of the TNGB included appointing a Coordinating Officer to lead the project to develop standardisation of data sets, operating procedures and policies, which enabled harmonisation and standardisation of all participating sites. A Coordinator Emeritus supported the Coordinating Officer by liaising with patient support groups, which increased patient interest and participation in the resource. The TNGB provided an effective model of collaboration between disease-specific BB and patient organisations, the importance of which must be underscored (Baldo et al, 2016). Patient organisation interest in the disease-specific BB led to their want to donate biological specimens. As a result, 13 written agreements were formalised. The agreements allowed the formation of RD genetic samples and their clinical data to be available to the scientific community (Baldo et al, 2016).

The TNGB provided visibility of the resource through their website and "virtual biobank" online catalogue. This is similar to the RD-Connect sample catalogue, which provides a detailed inventory of available biological samples in participating BB. These online catalogues allow researchers to see, select and apply to access the biological samples of interest (Gianotti et al, 2018). RD-Connect have also developed the "RD-Connect Registry and Biobank Finder", a unique tool to assist RD researchers find BB and registries. The finder currently has data for 222 registries and 21 BB (Giantotti et al,

2018). These catalogues are of great importance as they facilitate RD research on an international scale, making samples and data easier to located and access.

Another finding was the novel approach of "blended recruitment". Blended recruitment "casts the net" as wide as possible to recruit the maximum number of patients. This approach utilises several recruitment methods including direct enrolment of the patient by the clinician, as well as indirect enrolment by the patient themselves through head office of the registry or through the study's website. Through this unique strategy, the CNDR could recruit more patients than would have otherwise been possible through traditional means. The TB-CHW provided evidence of how a single site BB can still have a significant impact on contributing to international research for RD, attributed to its pro-active, targeted marketing of available samples to leading experts. Another important finding was the recognition of the need for broad consent to accommodate advancements in NGS technologies. A review of the ethics process was required by the TNGB, with broad consent requiring consideration in the management of large volumes of data, return of results, and incidental findings.

A limitation of this study is that our chosen search terms used to locate all necessary and relevant RD registries and associated BBs may have led to a "filed-effect" of articles, precluding other valuable studies from our review by default. Meanwhile a scenario of BBs without registry should also be considered to more fully articulate the role of BBs. Whilst we have done our best to conduct a comprehensive and exhaustive search for all RD registries and BBs, we acknowledge there may be other RD registries and BB initiatives that were missed, attributed to the fact that they were outside our search term criteria.

Whilst this review provides unequivocal evidence of the impact BBs linked to registries have for RDs, countries, like Australia, are yet to act to remedy the situation. This is despite a call to action from peak bodies and the strong enthusiasm from clinicians, researchers, and patients themselves. Indeed, this enthusiasm is not enough to effect meaningful change, with real support from the government urgently needed to make any real progress (Lacaze et al, 2017). Whilst there are individual research efforts throughout the country, the number of RD registries in Australia is few and still largely unknown. It is known individual research efforts can lead to siloing of information and disorganisation. Further, there is no central, coordinated effort to collect, store, and distribute biological samples for the scientific community, nor do efforts exist to link such a resource to the clinical data stored in registries. Moreover, there is a general lack of funding and interest to change the current climate of RDs. However, the lack of basic research activity for RDs in countries such as Australia is itself a unique opportunity as there is the ability to begin a national approach from a "clean slate". The concept of establishing a National RD Biobank Network for Australia has been

supported in the WA RD strategic framework (Department of Health, 2015). The validity and feasibility of such an initiative has been successfully demonstrated by similar models in other countries. For example, the Telethon Network of Genetic Biobanks has linked 11 individual BB throughout Italy, storing in excess of 100,000 biological samples for more than 950 rare genetic diseases. Australia needs a dedicated and passionate group of researchers to form a steering committee and drive a similar venture, through the guidance of existing national RD and BB experts. Criteria for inclusion could be for the disease to a) be confirmed as rare according to Orphanet criteria, b) have a genetic component, and c) to collaborate with an existing international registry. This strategy will enable access to existing protocols, provide support, and bring enthusiastic researchers together. Recruitment could be through referral from either the patient's specialist or General Practitioner. Data collection would depend on each international registry/BB. One possible model for sample collection would be, in the first instance, to form agreements with existing BB in each state, storing samples according to the expertise of that BB. For example, a BB specialising in musculoskeletal conditions could store the nation's samples for rare genetic musculoskeletal diseases. Establishing minimum sample numbers (for example, agreeing to store a maximum of 200 samples in each BB) could be an economic strategy for the network, as BB facilities may be able to provide a few shelves of a freezer at low cost, or even in kind. It is only once RD registries are linked to BBs we will have the appropriate resources required for the effective translation of basic research into clinical practice. This has the capacity to lead to new diagnostic tools and therapies, ultimately improving patient outcomes and alleviating the significant burden associated with RD for clinicians, hospitals, society, and most importantly, the patients and their families.

4.1 RECOMMENDATIONS:

The following evidence-based recommendations are derived from this systematic review and align with the WA Rare Disease Strategic Framework 2015-2018, and the joint declaration of 10 key principles for RD patient registries by the European Organisation for Rare Diseases (EURORDIS), the National Organization for Rare Disorders (NORD) and the Canadian Organization for Rare Disorders (CORD).

1. Established (RD) disease-specific registries without BBs should be identified, with an agreement reached to include Omics investigations as a research endpoint[20]

2. Existing BB infrastructure that specialises in the registries disease of interest should be identified and linked to the RD registry with agreements made to store samples[24]

3. A coordination office should be established in order to govern the project and achieve harmonisation throughout the network at national or international level[19]

4. A steering group should be created and consist of representatives from the following stakeholders; patients, patient support groups, clinicians, and researchers[19]

5. Engagement strategies should be employed by the registries and include ongoing communication between the registry and participating sites[34]

6. The network should develop a generic patient information sheet with a single "broad consent" to encompass every RD, compliant with but streamlining the human research ethics processes[29]

7. The network should adopt a "blended recruitment" approach, ensuring the largest possible geographical reach, with direct (patient) or indirect (clinician) enrolment[34]

8. Data collection forms should be used in place of clinical notes where possible to ease the burden of form filling and increase compliance[29]

9. The network should have a website and online catalogue of all available samples for the RD scientific community[19]

10. It is recommended the registries adopt a pro-active, targeted marketing approach, liaising with national and international leading experts[14]

11. Equal sharing of funding for each site should be considered as this leads to continuation of data collection even when the funding ceased[29]

4.2   Limitations

A limitation of this study is that our chosen search terms used to locate all necessary and relevant RD registries and associated BBs may have precluded other valuable studies from our review by default. In addition, there is potential that additional databases have been newly established due to the study of RD growing in momentum. There is also the limitation of relying on published literature from which we drew our findings. It should be acknowledged that there are existing registries that are active but do not publish, and that should be taken into account when interpreting our results.

A second limitation in our study was that all resources under analysis were classified as registries. Whilst all resources collected data, we did not consider the different levels of registries. As a result,

databases with minimum, basic, and common data sets were classified as registries and compared with epidemiological, clinical care, and comprehensive registries. In this study, a patient registry was defined as an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes. A registry database is a file (or files) derived from the registry (Glickich at al, 2010). Patient registries represent a useful tool for a number of purposes. Their ideal use and their role in evidence development, design, operations, and evaluation resemble but differ from clinical trials in a number of substantive ways, and therefore they should not be evaluated with the same constructs. That said, our coming updated meta-analysis will consider and compare registries with similar study design and data sets, which will strengthen the overall assumption of such analyses.

Another limitation of this study was not considering the possibility that biobanks may not be associated to registries. Although this study is centred around the comparison between registries associated or not associated to biobanks, the Biobank which is not associated to registry should not be neglected. Our coming updated meta-analysis will focus on this scenario as one additional category.

4.3 Future directions

The findings of this systematic review highlights the importance of annexing BB to established RD registries with regards to providing a valuable resource for future omics research. As highlighted in the literature review at the start of this thesis, establishing a BB takes considerable planning, coordingation, effort, resources, and time. Despite this, our findings indicate that BB are vital for progressing omics-based research.

5   Overall summary

5.1   Findings

It was shown in the systematic review that registries without BBs had the capacity to uncover the natural history of disease, develop best practice, replace clinical trials, and improve patient outcomes, but they were limited in their capacity to conduct basic research. Registries, when annexed to BBs, had the key infrastructure required to make novel Omics discoveries, identify and validate biomarkers, uncover novel genes, and develop new therapeutic strategies. The role of basic research in RD research is vital; scientists must first understand the pathways of disease before they

can develop appropriate interventions. This is especially important considering drug innovation for RD has, in recent years, become progressively focused on Omics studies. It is only once RD registries are linked to BBs we will have the appropriate resources required for the effective translation of basic research into clinical practice.

The systematic review also found that registries benefited numerous stakeholders. Broad consent, harmonisation and standardisation of procedures, blended recruitment, and pro-active marketing aided in the success of research outcomes.

5.2 Strengths

A strength of this study was the methodology used. Meta-aggregation allowed us to qualitatively identify that registries without BBs were limited in their capacity to conduct basic research. Through categorizing our findings based on similarities of meaning, we were able to synthesize groups of findings using a clear evidence base. We found that that linkage of RD registries with BBs provides researchers with the necessary resources required for basic science investigations. Basic science is a vital pre-requisite for translational medicine, and has the capacity to lead to new diagnostic tools and therapies in the clinical setting. RD research is important not only for rare diseases, but also for also common diseases, e.g., research of low-density lipoprotein (LDL)-receptors in the RD known as familial hypercholesterolemia led to the discovery of statins, a drug therapy that is now used routinely to prevent heart disease. Linkage of BBs to RD registries are essential for the discovery of new diagnostic tools and therapies, and ultimately improves patient outcomes and alleviates the significant burden associated with RD for clinicians, hospitals, society, and most importantly, the patients and their families.

5.3 Implications for Future Research

From this Master's thesis research findings, a set of recommendations for future RD research were developed. These recommendations can be immediately applied to both practice and policy. Employing these recommendations in the future will be an especially important factor in accelerating RD research findings, particularly with regards to Omics research. Adopting these recommendations will be a useful tool for designing an effective pathway for moving research findings along the translational research continuum at optimal speed, and translating basic science findings into new therapeutics. Considering the development of drug therapies on average is 10

years (from bench to bedside), adopting strategies which can accelerate this pathway is a clear benefit for all involved in RD, particularly the patients and their families.

Following these recommendations, a clear and practical next step would be to annex an established BB to an established international RD registry. For example, the Growing Spine Study Group (GSSG) is an international, disease- specific RD registry that collects clinical data from Early Onset Scoliosis (EOS) from 30 sites in 9 countries throughout the world. The GSSG has now commenced sample collection, storing samples centrally in an established BB in each country. For example, in North America, samples are collected, transported, and stored in a BB at Texas Scottish Rite Hospital; a participating site of the GSSG. This offers several advantages for accelerating research outcomes. The first is that clinical data is already being collected, and would complement sample collection well. This is an important consideration as samples must have matched clinical data to add real value in determining genotypic/phenotypic relationships. The second is that there are already strong advocates in the registry for the disease, namely, participating clinicians, researchers, and patients. The third is the minimal cost associated with collecting samples through this pathway. Samples numbers collected for EOS are small, and can be stored in one section of a freezer. This model has the potential to accelerate research outcomes by minimising the burden of cost, time, and effort in setting up such a resource.

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