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The Australian Aplastic Anaemia and other Bone Marrow Failure Syndromes Registry

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ABSTRACT

The bone marrow failure syndromes (BMFS) are a diverse group of acquired and inherited diseases which may manifest in cytopenias, haematological malignancy and/or syndromic multisystem disease. Patients with BMFS frequently experience poor outcomes, and improved treatment strategies are needed. Collation of clinical characteristics and patient outcomes in a national disease-specific registry represents a powerful tool to identify areas of need and support clinical and research collaboration. Novel treatment strategies such as gene therapy, particularly in rare diseases, will depend on the ability to identify eligible patients alongside the molecular genetic features of their disease that may be amenable to novel therapy. The Australian Aplastic Anaemia and other Bone Marrow Failure Syndromes Registry (AAR) aims to improve outcomes for all paediatric and adult patients with BMFS in Australia by describing the demographics,

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treatments (including supportive care) and outcomes, and serving as a resource for research and practice improvement.

1. Introduction

The bone marrow failure syndromes (BMFS) comprise a heterogeneous group of diseases in which hypoplasia of the haematopoietic elements of the bone marrow (BM) results in uni-lineage or multi-lineage cytopenias. Some patients with BMFS experience cytopenias as the sole manifestation of disease while others experience severe, multisystem syndromic disease. The differential diagnoses of patients with newly presenting BMF are vast and can be broadly categorised into acquired and inherited conditions. Acquired aplastic anaemia (aAA) is the most common form of BMF and is thought to result from autoimmune toxicity to the haematopoietic stem cells of the BM [1]. Conversely, inherited BMF (IBMF) and germline predisposition to haematological malignancy are closely related forms of heritable BM disease that have overlapping features [2].

Patients with these conditions frequently experience long diagnostic odysseys and poor outcomes. A unifying feature of the BMFS is an increased risk of developing haematological malignancy, namely myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML). Clonal evolution to MDS may occur in 15–20 % patients with aAA [3]. The cumulative incidence of AML in patients with Fanconi anemia is reported as 10–37 % by fifty years of age, with the most common age of leukaemia development being in teenage years or young adulthood [4]. In GATA2 deficiency syndrome, 75 % of all carriers with syndromic features will develop haematological malignancy; 75 % of diagnoses are MDS and 9 % are AML and the median age of onset is 17 years (range 0–78 years) [5]. Shortening the time to, and increasing the accuracy of, diagnosis is an important first step in improving outcomes. New strategies are required to assist with improved diagnosis and management of patients with BMFS and their families, but clinical trials of new interventions are challenging in these rare conditions.

1.1. Clinical registries and rare diseases

While individually the BMFS are rare diseases, collectively they are not so, and both incidence and prevalence will continue to rise with increasing awareness and access to genetic testing (particularly of inherited diseases). A crucial aspect to improving outcomes is collaborative efforts to collate clinical and variant databases with associated phenotypes, and documenting disease courses and natural history in the 'real world', i.e. outside clinical trials, of which there are very few in this area. This may take different forms such as disease-specific registries (e.g. the International Fanconi Anemia Registry, the North American Shwachman-Diamond Syndrome Registry and the Clinical Care Consortium of Telomere-Associated Ailments). In acquired disease, a consortium of interested clinicians comprising the North American Paediatric Aplastic Anemia Consortium, have collated cases and outcomes, and have contributed important published data [6,7]. A standardised approach to collecting information on rare diseases offers many benefits (Table 1). These networks and platforms also facilitate collaborative research efforts, such as clinical trials, which are essential but difficult to perform in BMFS. Clinical quality registries have been shown to provide valuable infrastructure which may be leveraged to permit real world research in an efficient and robust manner including registry based clinical trials, cohort sub-studies, biospecimen resources, and post-marketing surveillance of new therapies [8].

2. Methods

The Aplastic Anaemia and Other Bone Marrow Failure Syndromes Registry (AAR) was established in 2013 as a partnership between the Transfusion Research Unit in the School of Public Health and Preventive Medicine at Monash University in Melbourne, Australia, and participating hospitals and clinicians nationally. The School has expertise in clinical quality registries and the Transfusion Research Unit manages ten clinical registries dedicated to both malignant and non-malignant haematological diseases including the Myeloma and Related Diseases Registry [9], the Lymphoma and Related Diseases Registry [10] and the Thrombotic Microangiopathy Registry [11].

The AAR is a register of Australian patients of all ages who develop a BMFS in any clinical setting. Clinical data collection is undertaken by clinicians in specialist units at participating hospitals. Data management and analysis is undertaken by Monash

Table 1
Benefits of rare disease registries[a].

1. Standardised dataset and data collection format permits pooling of rare data
2. Platform to achieve meaningful participation from the community, and adequate sample size for analysis
3. Permits longitudinal data collection and comparison to historical or complementary cohorts
4. Network enables collaboration between interested clinicians, scientists and patients/community
5. Provides framework for collection of samples for biobanking and correlative studies, with full clinical annotation
6. May be used to facilitate translational research and plan and conduct clinical trials, including long-term follow-up
7. Facilitates documentation of knowledge lacking in many recently described germline conditions – incidence, prevalence, natural history, disease course and response to therapy, disease latency, phenotypic variability and reduced penetrance

[a] Adapted from Fox et al. [2].

University staff and interpreted with the input of specialist clinicians on the steering committee.

The **aims of the AAR** are to:

- Better define the incidence of acquired and inherited BMFS, including hereditary predisposition to haematological malignancy (HPHM), in Australia
- Provide information on the range of therapeutic strategies being employed in the treatment of BMFS patients, including immunosuppression, allogeneic haematopoietic stem cell transplant (alloSCT) and supportive care
- Document the specific inherited genetic causes that underlie IBMF and HPHM in Australia
- Explore factors influencing clinical outcomes
- Investigate the relationship of paroxysmal nocturnal haemoglobinuria (PNH) clones to disease progression and response to therapy in patients with BMFS
- Better define optimal management of patients with BMFS
- Inform and inspire future hypothesis-driven research in this area

2.1. Governance

Activities of the AAR are overseen by a national steering committee which provides guidance regarding projects and research according to documented Terms of Reference. Steering committee members include clinicians from across Australia with track records of leadership and expertise in BMFS diagnosis and management, including both adult and paediatric haematologists and those skilled in haematopoietic stem cell transplantation. There are close connections with individual consumers and community advocacy groups. The steering committee meets twice per year and as required to discuss progress, plans for registry development and any research project or question submitted to the AAR by colleagues nationally. A management committee comprised of AAR staff and clinicians meet fortnightly to discuss operational issues. Site investigators at participating centres take responsibility for identifying and inviting eligible patients and oversight of local data entry.

Ethics approval

The AAR has human research ethics committee (HREC) approval from Monash Health (AM/36494/MonH/13139A) under the national mutual acceptance (NMA) scheme. The NMA scheme permits the mutual acceptance of a single ethical review for multi-centre research studies conducted in publicly-funded health services. In 2020, all AAR participating hospital sites, except Western Australia, transferred their ethical review to NMA, greatly reducing the resources required to manage multiple individual HREC applications. The Western Australian Department of Health does not permit NMA for projects approved prior to 2017: these projects must remain under their approving HREC. The four Western Australian participating hospital sites are reviewed by a single Western Australian ethics committee. Local governance approval at all individual sites is still required to ensure institutional capacity and willingness to support AAR activity.

2.2. Informed consent

To maximise participation, simplify enrolment and minimise bias, the AAR utilises an 'opt out' approach. This is approved by the Australian National Health and Medical Research Council if it is deemed that public interest in a research study sufficiently outweighs the potential impingement on individual privacy, and has been shown to improve participation rates in epidemiological studies like registries. Clinicians at participating sites are responsible for identifying eligible patients, explaining the registry to them, inviting them to participate, and providing them the approved AAR information brochure. The AAR brochure describes the registry aims, the data collected and rationale for collection of information. It explains the "opt-out" consent model and provides information about how to decline enrolment, if wished, including contact details for the AAR Project Manager. Each brochure is individualised to the participating site with home hospital logo and local research governance coordinator details.

Funding

The AAR is currently jointly supported by Monash University and Maddie Riewoldt's Vision, a not-for-profit organization established in 2016 in memory of a young woman who died from complications of aAA treatment. Maddie Riewoldt's Vision aims to fund research to improve treatments for patients with BMFS and to support patients and families living with these diseases. On receipt of additional funding, a modest per-patient payment to sites was commenced in 2023 to support completion of both initial registration and long-term outcome data for all patients enrolled in the AAR.

2.3. Patient recruitment and participation

The AAR aims to enrol all adult and paediatric Australian patients with BMFS. Prospective data commencing from the time of presentation is sought, and it is envisaged that all patients will have long term follow up in the AAR until the time of death (Fig. 1). All Australian hospitals known to care for patients with BMFS have been approached regarding participation. The AAR is promoted to

patients and clinicians via the Maddie Riewoldt's Vision website and outreach, clinical networks, scientific presentations and educational events, and recruitment to registry-supported studies.

2.4. Data items collected by the registry

Selection of data items in a clinical registry is of critical importance in registry design. A balance must be struck between obtaining sufficient details to permit clinical utility and sufficient quality to enable robust outputs (such as analyses and publications), balanced against the challenge of the workload requested of local sites to complete initial and ongoing data entry. Clinicians on the steering committee determined critical data fields regarding demographics, diagnosis, co-morbidities, treatments and outcomes (summarised in Fig. 2). A user-friendly database was deemed of critical importance and great care is taken to provide clear instructions utilising drop-down boxes and branching logic where appropriate. Use of free-text entry fields is minimised where possible. For critical laboratory results which may be difficult to convey succinctly, or which are prone to error when manually entered, including bone marrow aspirate and trephine results, cytogenetic and molecular genetic results, it is requested that the primary result document is securely uploaded to the REDCap database. The AAR and other registries managed by the Transfusion Research Unit are currently exploring options for robust and reliable ways to extract and analyse data from hospital electronic medical records to minimise the burden of data entry for site staff.

3. Results

3.1. Current status

Currently there are 38 approved sites in Australia (Fig. 3). There are 383 enrolled patients in the AAR as of October 2023, including patients 279 with aAA and 96 patients with inherited BMF or HPHM. The aAA group includes 77 patients enrolled in the DIAAMOND clinical trial (see below). There are 6 patients in whom the BMF is unable to be confidently categorised and so are considered to have a diagnosis of 'BMF-unclassifiable' and a further 2 patients with non-aAA acquired BMF.

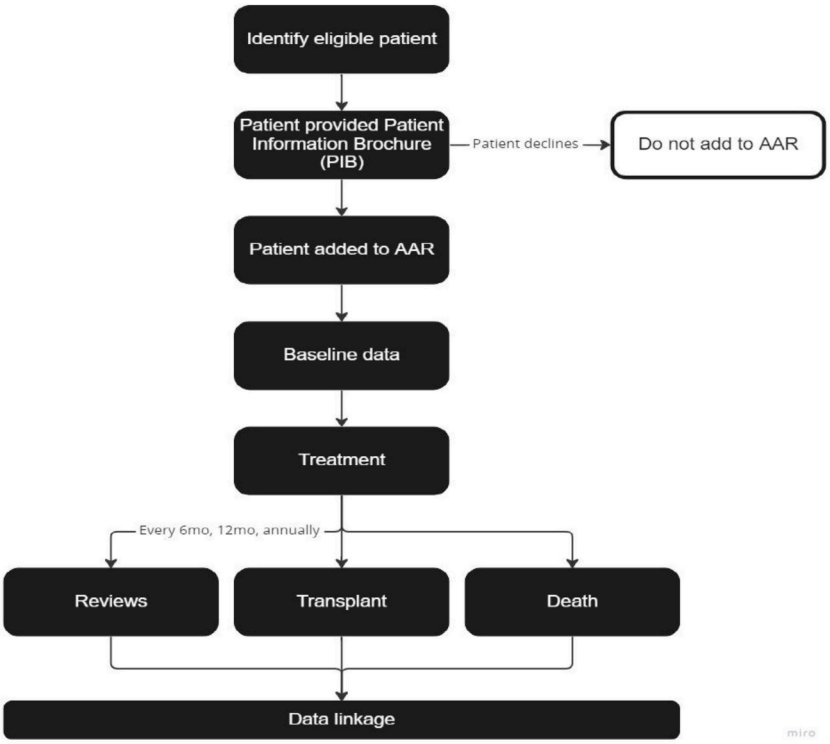

Fig. 1. Key AAR patient enrolment steps and time points.

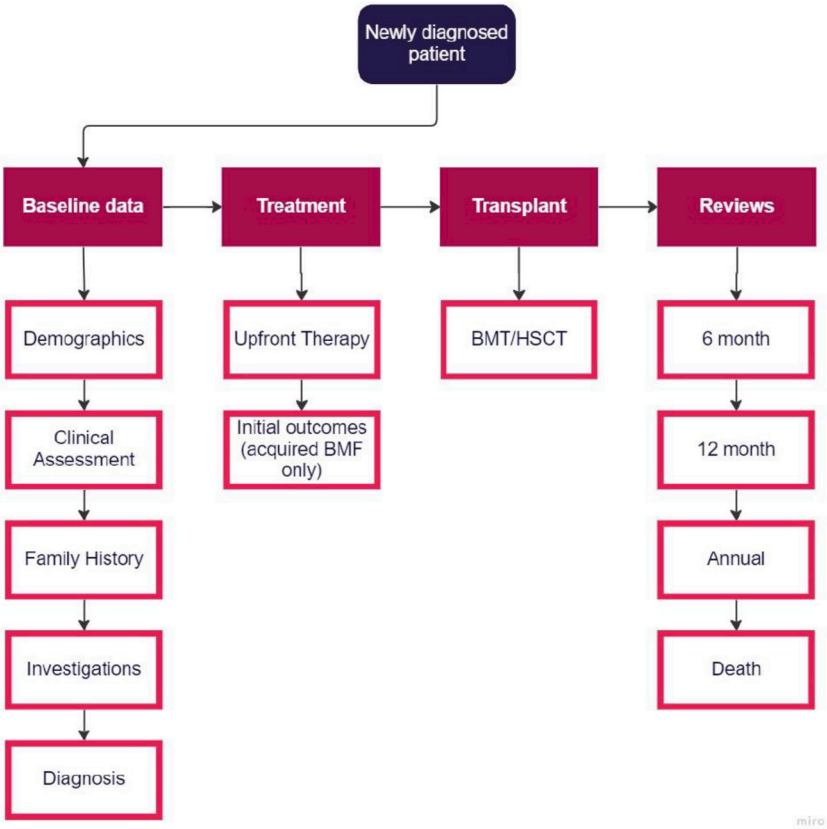

Fig. 2. AAR data collection overview.

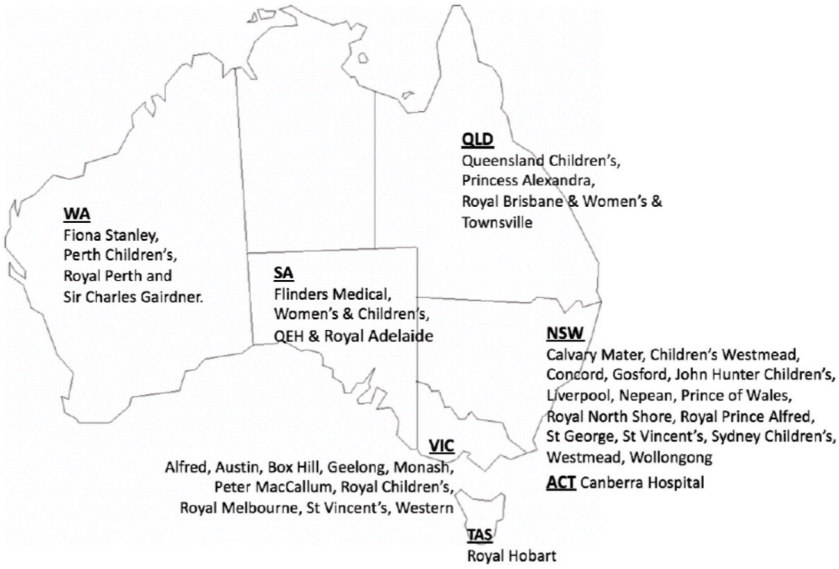

Fig. 3. Australian hospitals participating in the AAR.

Fig. 4. Evolution of the AAR
Legend: Diagnosis of aplastic anaemia, management and outcomes, utilising a national dataset trial (DIAAMOND), Diagnosis, discovery and novel phenotype characterisation using multimodal genomics in patients with inherited bone marrow failure and related disorders (IBMDx), Australian Marrow Failure Biobank (AMFB), national mutual acceptance scheme (NMA).

3.2. Registry evolution since establishment

The AAR has undergone several changes in response to observed utilisation of the registry and also to accommodate scientific developments (Fig. 4):

1. Enrolment of all patients with traditional BMFS (such as dyskeratosis congenita), including but not limited to aAA, was an aim of the AAR from its inception, however enrolment of these IBMFS patients was initially low. Therefore, in 2020 the name of the AAR was extended from the 'Aplastic Anaemia Registry' to the 'Aplastic Anaemia and Other Bone Marrow Failure Syndromes Registry', in recognition of the complex, evolving, and often misinterpreted nomenclature in these disease groups which had resulted in a strong bias to aAA patient enrolment to the registry.
2. The scope of the registry was expanded in the most recent version of the ethics submission (Version 3.0 August 2020). This increase in scope occurred to permit capture of patients with the large number of emerging inherited and acquired diseases underlying BMF presentations that have only recently been described. This includes the 'myeloid neoplasms with germline predisposition' which was incorporated for the first time in 2017 fourth edition of the World Health Organization Classification of Tumors of the Haematopoietic and Lymphoid Tissues [12] and which has been expanded upon in the most recent fifth edition [13]. In the same way as aAA/IBMF patients, these novel germline predisposition conditions may present with BMF, require genetic testing and counselling as do patients with traditional IBMFS and by definition harbour an increased risk of developing haematological malignancy. Some aspects of treatment across these diseases are the same; specifically, alloSCT offers the potential for cure of the haematological manifestations of these conditions. Emerging acquired BMF conditions, which are increasingly appreciated in the age of relatively easy access to next-generation sequencing (NGS) testing are also able to be incorporated. For example, it is highly desirable to capture and describe the clinical course and outcome of patients experiencing the recently described VEXAS syndrome, which constitutes an acquired life-threatening inflammatory illness attributable to the acquisition of somatic *UBA1* mutations in the haemopoietic compartment and potentially requiring alloSCT [14]. The AAR update permits flexibility to incorporate novel diseases and emerging genotype-phenotype associations as they are reported, thereby permitting documentation, research and collaborative efforts to improve treatment approaches.
3. In 2020 the AAR database was updated to a REDCap database. Study data are collected and managed using REDCap electronic data capture tool hosted and managed by Helix (Monash University) [15,16]. REDCap (Research Electronic Data Capture) is a flexible, secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

3.3. AAR infrastructure support of major research studies

1. The AAR infrastructure supports a clinical trial – the Diagnosis of aplastic anaemia, management and outcomes, utilising a national dataset (DIAAMOND) study. The DIAAMOND study are Phase II, single arm registry-based clinical trials examining the use of avatrombopag in both newly presenting ("FIRST") and relapsed ("NEXT") adult patients with severe aAA. It is funded by a competitive national grant from the Australian Government Medical Research Future Fund (MRFF). Correlative substudies are also underway. There are 12 sites nationally enrolling patients on the DIAAMOND trial. All trial participants are enrolled in the AAR,

which provides a framework for long term follow-up of patients with aAA. The trials are registered on the Australian Clinical Trials Registry at: DIAAMOND-FIRST (ACTRN12619001042134) and DIAAMOND-NEXT (ACTRN12619001043123). More information is available at: https://aaregistry.org.au/clinical-trials-diaamond

2. The IBMDx study is an MRFF-supported study of diagnosis, discovery and novel phenotype characterisation using multimodal genomics in patients with IBMF and related disorders. The IBMDx study provides whole genome/transcriptome sequencing in patients who are suspected of having a monogenic, germline cause of their BMF presentation. Patients enrolled in the IBMDx study are offered the opportunity to participate in the AAR, and again this offers the potential for long term follow up beyond the study completion date.
3. The Australian Marrow Failure Biobank (AMFB) represents a collaboration between the AAR and Biobanking Victoria, Monash University, funded by Maddie Riewoldt's Vision. The purpose of the AMFB is to provide a centralised, national, marrow failure resource that is available to the research community. The AAR serves as the repository for clinical data which accompanies the biological samples stored at Biobanking Victoria, together comprising the AMFB. Access to long-term clinical data and biological samples will permit insight into mechanisms of disease progression and facilitate research and investigations into novel therapeutic strategies such as gene editing and gene therapy. HREC approval has been secured, and pilot testing of the biobank processes are underway.

3.4. Challenges for the AAR

These are summarised in Table 2. Many of these are common to all rare diseases registries. Particular challenges for the AAR include that the diseases of interest are diverse with varying underlying pathologies and which may present at any stage of life; furthermore, many of these have only been described recently. The multiorgan manifestations of some BMFS result in extensive lists of potential symptoms and signs, which can be difficult to include in what is – ideally – a minimum dataset, or unfamiliar to some staff entering data. Family histories may be complex and challenging to capture in a simple and succinct way suitable for a registry. Many investigations are required to work up a new patient presenting with a BMFS. Prior to the genomic era, there was often significant diagnostic uncertainty and even with access to current comprehensive NGS technologies, so some patients have uncertain diagnoses and are labelled "BMFS-unclassifiable".

Although health-related quality of life is recognised as an important outcome for patients with BMFS, the AAR has not been able to collect this routinely, due to, until recently, the lack of disease-specific patient reported-outcome measures, as well as the practical challenges of prospectively collecting these data.

Patients may present to any healthcare setting and/or be managed at any hospital nationally – sometimes more than one centre – so the registry must be open to recruitment at as many sites as possible to capture a comprehensive picture across the country. This creates some challenges for both sites and the registry management group.

3.5. Further research

BMFS are rare diseases, so national and international collaborative research efforts in this space are highly desirable, delivering access to larger patient numbers for inclusion in trials and other studies, improving communication between researchers and clinicians and the community, and maximising outputs while reducing duplication of efforts. International disease-specific registries will permit feasibility assessment when considering applying novel therapies which depend on an understanding of a precise germline lesion (where one exists), and it will be imperative that de-identified patient data are confidentially and securely collated and curated to determine where and how new therapies, including novel gene strategies, may be trialled. Biobanks aligned with clinical registries will permit correlative studies to better understand disease mechanisms and develop and test new therapeutics for these important conditions. Incorporation of patient-reported outcome measures will allow prospective monitoring of health-related quality of life.

4. Practice points

- Patients with BMFS frequently experience poor outcomes and novel treatment strategies are required to improve morbidity and mortality
- Clinical registries represent a powerful way to collate and analyse data in rare diseases including identification of areas of need and permitting collaborative research efforts
- A comprehensive national clinical disease registry enables further research efforts including registry-based clinical trials (such as the DIAAMOND study) and development of a clinically-annotated specimen repository (such as the Australian Marrow Failure biobank)

5. Research agenda

- The natural histories of recently described, novel BMFS remain poorly understood (e.g. *SAMD9/SAMD9L* or *DDX41* predisposition to myeloid malignancy) and require molecular characterisation and longitudinal follow-up to understand and improve clinical outcomes.

Table 2
Challenges for rare diseases registries.

Challenge	Resolution	Examples
Awareness and engagement	Highlight value of registry platform and activities as national resources for rare diseases research to patients, clinicians, industry and policy-makers	Sites and clinicians have access to peer network, and own and registry aggregate data for benchmarking and practice improvement, projects for early career investigators, data on rare conditions where trials are difficult, supported by AAR team Newsletters, website and presentations for patient/community and clinical/research groups
Ethics and governance	'Opt out' consent approach enables broad patient participation, but some HREC & governance committees not familiar with model Streamlined ethics and governance arrangements	Investigators and registry project team engage with site staff and HREC and governance committees Seek written consent to obtain biological samples for biobank Clinical quality registries considered and classified as research activities Australian HREC system historically burdensome and time-consuming for registries – now transitioned to national mutual acceptance ethics arrangements
Recruitment and diagnostic classification	Diversity of clinical diagnoses, many still incompletely understood or characterised, addressed by greater access to precision diagnostics and genetic counselling	Link with clinical, consumer and community support groups to promote participation Flexible approach to eligibility criteria Biobank and research activities to support future improve diagnoses and follow-up
Sustainability	Site resources very limited (similar for all rare diseases) but alleviated by recent per-patient payments Securing ongoing registry funding always challenging until data mature and can generate analyses, peer-reviewed publications and reports for policy-makers	Stakeholder and site engagement activities, keeping all participants informed of progress and plans Per-patient payments: even modest support is valuable and permits managers to allocate staff time for data entry Leverage registry for clinical trials and other projects which can secure dedicated funding Communicate potential and how industry, clinicians, researchers, government policy-makers can access and use registry data
Data and access	Burden on sites to enter data for patients with diverse and complex clinical situations, and provide ongoing follow-up Maximising data access while maintaining data security Incorporate patient-reported outcome measures	Stakeholders involved in planning of registry scope and activities, including determination of minimum dataset Training for site staff, and access to ongoing support and resources, and data definitions Per-patient payments to sites for baseline and follow-up data Secure e-research platform permits authorised users to access and analyse data within secure environment
Research activities	Promoting research, especially early and before many patient outcomes available Leverage registry for clinical trials platform, biobank	Hold/participate in research meetings and promote registry research widely, share data via abstracts and publications Promote project and authorship opportunities, especially for early career researchers
	Patient experience and outcomes research, health economics evaluations	Incorporate patient-reported outcome measures and healthcare utilisation data to complement clinical dataset

*adapted from [10].

- The BMFS represent chronic, sometimes lifelong, diseases with significant impact on quality of life for patients and families. Patient-reported outcome measures provide a structured approach to understanding health outcomes from a patient perspective, and are a (largely) currently unmet need in the setting of BMFS care and research.
- Patients with BMFS have complex and costly healthcare needs, including comprehensive tests for diagnosis at time of initial presentation, haematological monitoring and transfusion support, lengthy inpatient stays for immunotherapy, chemotherapy and allogeneic stem cell transplant, or to treat disease manifestations such as infections, bleeding or solid tumors. Other care needs include genetic counselling for patients and family members, and fertility treatments including *in vitro* fertilisation and preimplantation genetic testing. These high-cost healthcare needs are ideally formally evaluated with health economics analyses to inform health policy-making and improved management strategies in an environment of scarce resources.

6. Summary

The benefits of clinical registries are now well established for both research and clinical practice improvement. The BMFS represent a diverse group of individually rare diseases in which patients frequently have poor outcomes. Establishing a national BMFS registry to inform disease prevalence, clinical features and areas of need facilitates collaborative efforts towards novel therapies and other research opportunities. The AAR has supported and encouraged national collaboration in BMFS in Australia, and is a vital tool to engage in international efforts for improved strategies in management of these challenging diseases.

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