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Study Profile

Design of the Familial Hypercholesterolaemia Australasia Network Registry: Creating Opportunities for Greater International Collaboration

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Familial Hypercholesterolemia (FH) is the most common and serious monogenic disorder of lipoprotein metabolism that leads to premature coronary heart disease. There are over 65,000 people estimated to have FH in Australia, but many remain undiagnosed. Patients with FH are often undertreated, but with early detection, cascade family testing and adequate treatment, patient outcomes can improve. Patient registries are key tools for providing new information on FH and enhancing care worldwide. The development and design of the FH Australasia Network Registry is a crucial component in the comprehensive model of care for FH, which aims to provide a standardized, high-quality and cost-effective system of care that is likely to have the highest impact on patient outcomes. Informed by stakeholder engagement, the FH Australasia Network Registry was collaboratively developed by government, patient and clinical networks and research groups. The open-source, web-based Rare Disease Registry Framework was the architecture chosen for this registry owing to its open-source standards, modular design, interoperability, scalability and security features; all these are key components required to meet the ever changing clinical demands across regions. This paper provides a high level blueprint for other countries and jurisdictions to help inform and map out the critical features of an FH registry to meet their particular health system needs.

Key words: Disease registry, Familial hypercholesterolaemia, Interoperable, Model of care, Registry framework

Introduction

Familial Hypercholesterolaemia

Familial Hypercholesterolaemia (FH) is a relatively common genetic disorder that is associated with premature coronary heart disease (CHD)[1, 2]. FH is the most common and serious monogenic disorder of lipoprotein metabolism, and causes severe elevation of total and low-density lipoprotein cholesterol (LDL-C) levels from birth[3, 4]. Heterozygous FH (HeFH) occurs in as many as 1 in 200 people[2], while the prevalence of homozygous FH (HoFH) has recently been estimated to be as high as 1 in 160,000–300,000 people[5] for most populations. Higher frequencies of FH occur in first-degree relatives (1 in 2) of index cases, and in populations subject to a "founder gene effect," such as Afrikaners and Ashkenazi Jews[4].

Under-diagnosis of FH is a problem worldwide, with estimates of FH affecting as many as 34.3 million people, with $<1\%$ of cases diagnosed in most countries[6, 7]. This represents a major gap in care, as 1 in 2 untreated men and 1 in 6 untreated women develop fatal CHD by the age of 60 years. Early diagnosis and treatment can delay the manifestation of atherosclerosis, with the introduction of statins improving the life expectancy of patients with FH which now approaches that of the general population. However, the standardized mortality rate for CHD still remains higher[8, 9]. HoFH requires therapeutic intervention within the first decade of life due to the development of aggressive CHD during childhood and adolescence, without which they will generally sustain a fatal myocardial infarction before the age of 30 years[10].

In Australia, at least 65,000 people are estimated to have FH with the vast majority undiagnosed, and in many diagnosed cases, patients are receiving inadequate treatment[1, 11]. The Western-Pacific and South-East Asia regions have the highest estimated population density of FH in the world[12]. Cascade family screening, by which all first-degree relatives of identified index patients are screened for FH, is of critical importance for early diagnosis and treatment of FH to delay or prevent the onset of premature CHD, yet is not often widely performed[13]. Only three national genetic cascade screening programs are currently operating in the Netherlands, Spain, and Wales, while advanced regional and local programs are operating in a number of countries including Australia, New Zealand, Slovenia, Czech Republic, and Malaysia[14].

To bridge this major gap in CHD prevention, the Commonwealth Government funded a flagship program under the Australian Better Health Initiative (ABHI), that resulted in the development of models of care for FH in Western Australia (WA)[15]. Building on a WA health model of care, the FH Australasia Network published a comprehensive model of care for FH with the aim to provide a standardized, high-quality, and cost-effective system of care that is likely to have the highest impact on patient outcomes[11], which was followed by the integrated guidance of care for FH by the International FH Foundation[16]. One important feature identified as essential to the implementation and effective provision of services, is a patient registry to store clinical and family data[13, 15, 17].

The Importance of Registries

Patient registries capture relevant patient information, including clinical and molecular information. Registries are clinical, information rich resources that are essential for the integration of research into clinical practice and translation into therapeutic solutions[18]. In populations with chronic disease, it has been demonstrated that patient outcomes improve with the use of models of care that integrate patient and clinical information with evidence-based treatments[19, 20]. As such, the American Heart Association has called for an expansion of clinical registry programmes[21]. A recent review of current studies of FH patients also concluded that complete national and international FH registries are key instruments for providing new information on FH and enhancing the care of FH patients worldwide[22].

Over the last 30 years, several national FH registries (**Table 1**) and cascade screening programs have been established in various countries, most notably in the United Kingdom (The Simon Broome Register[23, 24, 25] and The National Paediatric FH Register[26]), the Netherlands (Dutch Lipid Clinic Network[27]), Norway (Registry of the Medical Genetics Laboratory[28]/ Unit of Cardiac and Cardiovascular Genetics Registry[29, 30]), the United States (CASCADE FH[31, 32] and MED-PED[33]), Canada (British Columbia FH Registry[34]), and Spain (SAFEHEART Study[35, 36]). Recently, the importance of establishing regional FH registries has been noted for the Middle Eastern and North African Region[37], and France has also recently created a cohort of FH patients from across the country[38]. The European Atherosclerosis Society (EAS) recently launched a global "call to arms" initiative to integrate efforts from major FH registries around the world to generate large-scale data on the detection and

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Table 1. Details of existing FH Registries

Type: DNA positive indicates a molecular genetic diagnosis of FH. Clinical indicates a clinical diagnosis of FH by DLCNS or other criteria. Hybrid indicates a mixture of molecular genetic and clinical diagnosis for inclusion in the registry.

Country/ Region	Registry	Type	Time-frame	Number (year confirmed)	System	Further details
UK	The Simon Broome Register of FH[23-25]	Hybrid	1980-	3,382 heFH patients from 21 lipid clinics	SPSS	Developed the Simon Broome Criteria to determine definite or probable FH status. Reported significant decreases in excess coronary heart disease mortality for patients who received early diagnosis and treatment.
USA	Make Early Diagnosis, Prevent Early Deaths (MEDPED)[33]	Hybrid	1989-2004	~8,000 definite or probable FH patients[31]		MEDPED criteria created and validated to estimate the probability of FH.
Norway	Unit of Cardiac and Cardiovascular Genetics Registry[28-30]	DNA positive	1992-	7,091 (2016)	Filemaker from Apple	Registry data can be linked to several other National health registries to assess mortality, cardiovascular disease and pregnancy outcomes in FH patients.
The Netherlands	Dutch Lipid Clinic Network[27]	Hybrid	1994-	>30,000[31]	PASS Clinical ® Vascular	Developed and validated a set of diagnostic criteria for FH.
Czech Republic	Czech MED-PED Registry	Hybrid	1998-	6919 (2016)	Online database (PAGEWISER)	MedPed project initiative.
Spain	Spanish FH Longitudinal Cohort Study (SAFEHEART)[35, 36]	Hybrid	2004-	4,615 (2016)	Dinahosting (network server)	Approximately 3,000 individuals have a positive genetic test. The registry is run by the Fundación HF. Website: https://www.colesterolfamiliar.org/
Wales and England	Pass Database[54, 55]	Hybrid	2010-	2587 (2016)	PASS Clinical ® Vascular	
UK	The National Paediatric FH Register[26]	Clinical	2012-	380 (2016)	Electronic data capture	Established to collect baseline and long-term follow-up data on all children (0-18 years) with FH in the UK. Approximately 60% have a DNA family mutation recorded.
USA	CASCADE FH[31, 32]	Hybrid	2013-	3,030 (2016)	Bespoke built in partnership with the Duke Clinical Research Institute.	A national, multicentre initiative that longitudinally tracks FH therapy, family screening, clinical outcomes and patient-reported outcomes.
Canada	FH Canada Registry[34]	Hybrid	2014-	738 (2016); 2900 expected by the end of 2016	iCAPTURE (bespoke built) from the James Hogg Research Centre, UBC	Started in 2014 from the existing British Columbia FH Registry[6]. Established to diagnose, educate and treat individuals with heFHheFH. Website: www.fhcanada.net
France	French Cohort of patients with FH[38]	Clinical	2015-	~3,263 (2016)	Integralis	Primary objective is to create a cohort of French patients with FH to evaluate screening and clinical management.
Taiwan	Taiwan Familial Hypercholesterolemia Registry Study	Hybrid	2015-	500 (2016)	Clinical Study Information System (CIMS)	Organised by the Taiwan Society of Lipid & Atherosclerosis.
International	European Atherosclerosis Society (EAS) FH Studies Collaboration (FHSC)[39, 56]	Hybrid	2015-	Data to be received from 10/2016.	Bespoke system	A global initiative from the EAS that, through a consortium of major FH registries worldwide, aims to generate large-scale robust data. Investigators from over 5 countries have formally committed to contribute their data to date.
International	Homozygous autosomal dominant hypercholsterolemia (HoADH) International Clinical Collaboration (HICC)	Hybrid	2015-		REDCap	The HICC will evaluate the true prevalence and phenotypic and genetic characterisation of HoADH.

management of FH (EAS FH Studies Collaboration (FHSC)[39]).

Bamimore *et al.*[37] noted that there is no "standard rule" for building a FH registry; however, they suggest following the consensus-based guidance for the management of FH[16] as the starting point. A number of public and commercially available systems have been utilized in the creation of FH registries to date (see Table 1 for an overview). For example, PASS Clinical Vascular is a commercially available software package for clinical management and cascade screening, used in Latvia, Germany, Ireland, the United Kingdom, and the Netherlands[40]. REDCap is a web-based application for building and managing online surveys and databases that is free to non-profit organizations that are members of the REDCap consortium[41], used in some Japanese Atherosclerosis Society registry projects.

Registry Design

There are several fundamental factors that need to be considered when designing a registry including purpose, ethical and legal requirements, documentation, governance, design, and sustainability[42]. With a wide range of bespoke, commercially available, and open source tools available for the establishment of registries, choosing which system to use can be difficult due to the diverse range of functionality and technology choices offered[18].

To this point, several groups have recently developed key criteria for robust and sustainable registry implementation including, the Joint Declaration of 10 Key Principles for Rare Disease Patient Registries issued by the European Organisation for Rare Diseases (EURORDIS), the National Organisation for Rare Diseases (NORD), and the Canadian Organization for Rare Disease (CORD)[43], the recommendations published by the European Union Committee of Experts on Rare Diseases[44], and Rare Disease and Patient Registry Checklists to guide future registry development[18, 45, 46].

These recommendations and checklists highlight the effective sharing of data, and the ability to link patients, samples, and analyses are essential to the success of disease research and improving outcomes for patients. This has led to international initiatives to harmonize legacy systems such as the European Union Framework Program 7, RD-Connect (http://rd-connect.eu/), established to develop an integrated platform that connects key infrastructure tools such as databases, registries, biobanks, and clinical bioinformatics[47].

The open-source Rare Disease Registry Framework (RDRF) was therefore developed as a viable solution to registry development[18, 48-50]. Rather than focusing on the deployment of single, stand-alone registries, the RDRF enables the dynamic creation of web-based patient registries without the need for software development[18, 48-50]. By incorporating key criteria required for a registry such as modular design, interoperability, and security features, the RDRF allows the deployment of national and international registries that are able to meet ever-changing clinical demands.

Aim

This paper details the development and design of the FH Australasia Network Registry utilizing the RDRF. It provides a high level blueprint for other countries and jurisdictions to help inform and map out the critical features of a FH registry to meet their particular health system needs. The primary purpose of the FH Australasia Network Registry is to collate data to facilitate clinical service planning and to inform clinical best practices[17]. The registry will also enable research on aggregated data and the identification of eligible volunteers for clinical trials. The specific aims include:

1. Facilitate data collection to inform best practices, models of care, and health service planning;
2. Data analyses and reporting by the registry on estimated prevalence; geographical distribution, genetic variants associated with disease, clinical features, clinical management and patient outcomes;
3. Enable research by providing aggregate, de-identified data to research entities;
4. Facilitate identification and recruitment of eligible volunteers for clinical trials; and
5. Coordinate and administer education to registrants and participating centers.

Methods

Development of the FH Australasia Network Registry

Extensive stakeholder engagements led to the recognition of the need to improve outcomes for Australian and New Zealand FH patients under the ABHI. This resulted in the establishment of clinical models of care[11, 15] and the development of a simple relational database. Through an iterative process, an international registry previously titled the "Australia and New Zealand FH Registry (ANZFHR)"[17] was developed. The registry was collaboratively developed by the Office of Population and Health Genomics (Department of Health, Government of Western Australia), the FH Australasia Network (Australian Atherosclerosis Society), clinical networks, and the Centre

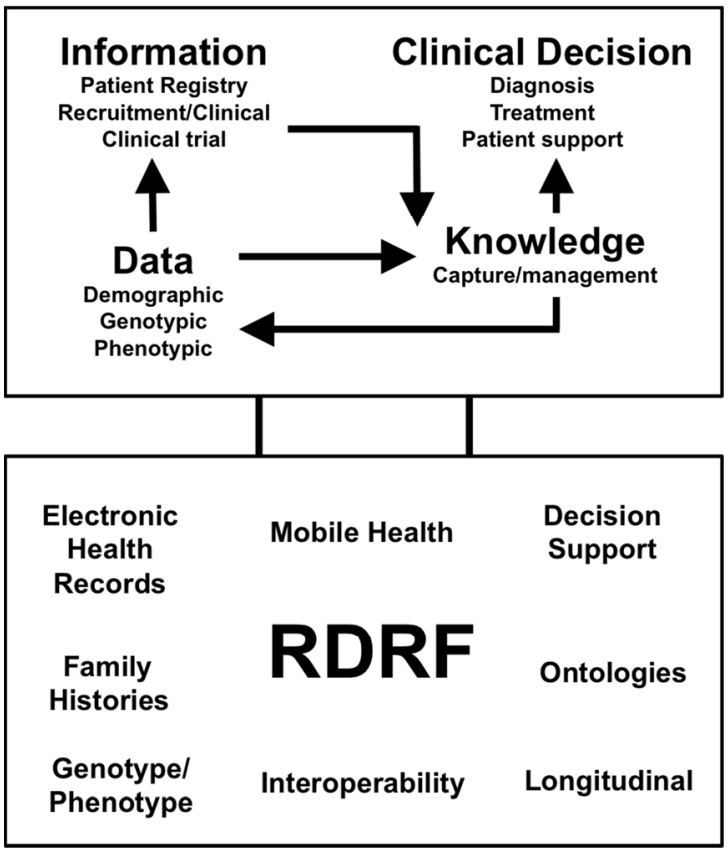

Fig. 1. The Rare Disease Registry Framework (RDRF) is a cloud-technology based platform that is focused on analytics

The RDRF facilitates the capture of information in the form of patient registries or clinical trials through the capture and storage of data (demographics, genotypic and phenotypic), which then in turn informs knowledge such as clinical decisions (diagnosis, treatment, and patient support). The RDRF is designed to "talk" and connect to other systems such as biobanks, registries and Electronic Health Records to capture data and ultimately provide decision support.

for Comparative Genomics (Murdoch University)[13, 17].

The Registry Framework

The RDRF allows the efficient deployment of web-based registries that can be modified dynamically as registry requirements evolve[18, 48-50]. The RDRF not only facilitates the effective capture, storage, management, and access of patient information, it is designed to be interoperable to capture, import, and store data from other systems such as the RD-Connect platform[49] (see **Fig. 1**). The ability to re-use data elements (DEs) across multiple registries greatly assists with the standardization of data capture, allowing for effective data sharing for research purposes.

The RDRF fulfills the key criteria required for sustainable registry development[18, 43, 44, 46], has continued to evolve since first described by Bellgard *et al.*[18, 48-50]. Additional features and enhancements of the RDRF were implemented specific to the FH Australasia Network Registry, described in Napier *et al.*[51].

Modular Design

The modular design of the RDRF enables simple configuration and creation of DEs, Sections, and Forms, such that FH Australasia Network Registry can continue to evolve over time. Currently, the patient data captured by the registry includes demographics and clinical information for each patient captured by the "Demographics" and "Consents" modules and six additional Forms titled Clinical Data, Medications, Genetic Data, Imaging, Apheresis and Follow Up (**Table 2**, also see Napier *et al.*[51]).

Interoperability

The ability for patient registries to communicate and share data with systems such as other registries or

Table 2. Capture of patient data in the FH Australasia Network Registry

FORM NAME	SUMMARY
Consents	Customisable consent sections easily allow new consent questions to be added or existing questions to be amended. Consent is captured via boolean Data Elements (DEs) presented as check boxes. A file DE allows the upload of a hard copy of a consent document if required.
Demographics	Patient's personal and contact details are captured, along with details of their doctors. For Index Patients, a Patient Relatives section is also present, which stores the details of relatives and allows a Patient Relative to be created in the registry. A Pedigree section allows the upload of family pedigree files and the capture of details on founder effect origin and the number of first, second and third degree relatives. The family linkage module, which details the relationships of Patient Relatives to Index Patients, is also accessed from this form.
Clinical Data	Clinical data is captured through various DEs, including family history, clinical history, physical examination, plasma LDL-cholesterol, biochemistry profile, risk factors and clinical trials. Derived DEs are utilised which allow automatic calculations of the 'Dutch Lipid Clinic Network Score', 'FH Diagnostic category', 'LDL-cholesterol adjusted for treatment', and 'BMI'.
Medications	Details on patient's medications and drug intolerances are captured. Multi-sections, which allow the addition of the same section, are utilised to add additional drug intolerances if required.
Genetic Data	This form captures a patient's genetic data, such as the genotype and gene variants. Laboratory Reports can also be uploaded to the registry through the use of a file DE.
Imaging	This form captures details of various imaging tests, such as carotid ultrasonography, echocardiograms, coronary artery calcium scores, angiograms, and nuclear perfusion scans. Multi-sections are utilised so additional tests may be easily added as required.
Apheresis	This form captures the type, frequency and complications related to apheresis through a multi-section.
Follow-Up	This form captures additional clinical data at follow up assessments, such as events, hypertension, diabetes, antithrombotic, biochemistry profiles, and death.

biobanks is critical. Interoperability in the RDRF is achieved through an application programming interface (API), which can interrogate other systems via their API's. In addition, the RDRF is able to share and re-use DEs, sections, and forms across multiple registries, assisting in the standardization of data capture.

Security

The RDRF provides distinct levels of inbuilt security, including Secure Socket Layer security encrypting all web traffic to and from the application, Cross-Site Request Forgery checking (a method of ensuring falsifying form submissions are near impossible), and the storage of identifying patient demographic data in a distinct database to any clinical data (refer to Napier *et al.*[51]) [18, 48, 50]. In addition, all user log-ins (successful and failed) are also recorded within the RDRF. The RDRF also has multiple levels of access with configurable permission levels (role based security model), which restricts the visibility of forms and fields to specified user groups.

Governance and Access

Standard international ethical principles[52], supplemented by local legislation and requirements, were followed when initiating and deploying the FH Australasia Network Registry. The FH Australasia Network Registry is hosted and maintained at Murdoch University, WA, with strategic direction and oversight provided by an advisory board of key stakeholders (FH Australasia Network Registry Advisory Board). A charter, protocol, and guidelines for the registry were developed by the WA Department of Health in conjunction with the FH Australasia Network and Australian Atherosclerosis Society, and are available from https://fhregistry-international.com.

The FH Australasia Network Registry is a multicenter collaboration, coordinated through the FH Australasia Network, with a national coordinator responsible for ensuring cross-site coordination. A principal investigator from each State or jurisdictional clinical service is responsible for the data collation of their patients. Applications for access to data are considered for approval by the FH Australasia Network Registry Advisory Board.

Discussion

In this paper, we describe the development and design of an international clinical registry for FH in Australia and New Zealand, the FH Australasia Network Registry. The open-source nature and modular design of the RDRF, upon which the registry is deployed, contributes to its long-term sustainability. A key merit of the RDRF is that is has an open-source license (GNU GPL v3), which allows it to be freely shared. The RDRF is therefore more flexible as it is not bound by licensing agreements like other registry systems such as PASS Clinical Vascular and REDCap. The RDRF is also much more cost effective in comparison to commercial software such as PASS Clinical Vascular. New features can also be easily incorporated into an existing registry as they are made available, which allows for the continual evolution over time as required. For example, a dynamic application to draw patient pedigrees based on the diagnosis status and relationships of patients can be designed and implemented in a future release of the RDRF.

The FH Australasia Network Registry also provides a great opportunity for recruiting participants and planning clinical trials. Information can be easily gathered for future clinical trials, simply by defining a new "Clinical Trials" form and DEs customized to capture the appropriate data in the RDRF. Existing features, as well as DEs and sections defined for the FH Australasia Network Registry, can also be utilized and shared by other registries. The RDRF has been endorsed by RD-Connect (see: http://rd-connect.eu/tools-resources/rare-disease-registry-framework-rdrf/), which emphasizes the value and long-term sustainability of the RDRF, and its ability to be interoperable with other registries and systems.

Through its multi-level user access, the FH Australasia Network Registry also has the ability to easily convert to a multi-national FH registry. As additional countries from across the Australasia-Pacific region join this registry, access will be easily configured through the use of customizable working groups and user permissions.

The FH Australasia Network Registry, deployed utilizing the RDRF, is a secure and comprehensive clinical registry that allows harmonization of data collection across different states, clinical jurisdictions, and countries. The RDRF is highly interactive and flexible, and has the ability to connect to other registries, systems, and data repositories, thus distinguishing the FH Australasia Network Registry from other FH registries developed to date. The full potential of this registry will be realized through its ability to connect with other data linkage systems.

The FH Australasia Network Registry has many functions. It is not only a repository of data, it also serves to support clinicians, researchers and patient groups, enables improvements to models of care, education, and communication, and helps focus and drive research and the development of new treatments.

Conclusion

The features described and the processes articulated in the development of the FH Australasia Network Registry encompasses the key features that should be considered when choosing a system for building patient registries. The FH Australasia Network Registry can be readily adapted to other conditions related to FH, such as familial combined hyperlipidemia and elevated lipoprotein(a)[53]. This framework is also applicable to other inherited cardiovascular conditions, such as familial hypertrophic cardiomyopathy.

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Familial Hypercholesterolaemia Model of Care. The key outcome of this Flagship project was a national framework for the early detection and treatment of familial hypercholesterolemia in affected Australian families. The authors wish to thank Professors Peter O'Leary and John Burnett for their dedication and commitment to leading the pilot programs and developing the model of care framework and the context for the clinical enabling registry described in this paper.

Conflicts of Interest

Warrick Bishop has been supported by Amgen for educational and advisory board work. David Sullivan has been supported by Amgen, Abbott, AstraZenica, MS&D, Sanofi, and NHMRC for clinical research, and by Abbott, MS&D, Pfizer, and NPS for education and consultancy work. Gerald F Watts has received honoraria for lectures, research studies or scientific advisory boards from Merck Sharp and Dohme, Novartis, Kowa, Amgen, Sanofi, and Regeneron.

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