NATIONAL FAMILIAL HYPERCHOLESTEROLAEMIA REGISTRY

Charter, Protocol and Guidelines

Version 3.2

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Australian Atherosclerosis Society

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CONTENTS

This document is a statement of the scope, objectives and participants in the activities of the Familial Hypercholesterolaemia Registry (the Registry). It provides a delineation of roles and responsibilities, outlines the objectives, defines the governance structures and identifies the members of the Registry Advisory Board. The document serves as a reference of authority for the future activities of the Registry.

This charter has been developed in consultation with members of the Familial Hypercholesterolaemia Australasia Network.

➢ Background

Disease Description

Familial hypercholesterolaemia (FH) is an autosomal dominant disorder of absent or grossly malfunctioning low-density lipoprotein (LDL) receptors that causes severe elevations in total cholesterol and low-density lipoprotein cholesterol (LDLc). Heterozygous FH occurs in approximately 1 per 500 persons.

For the purposes of this Registry, Familial Hypercholesterolaemia will be inclusive of other forms of autosomal dominant hypercholesterolaemia (FDB, PCSK9 gain-of-function mutations).

More than 1000 mutations have been identified that have a meaningful impact on receptor function. LDL receptor function ranges from completely absent to approximately 25% of normal receptor activity. Five classes of mutations have been defined. The collection of more information on genetic typing will facilitate easy overview of different mutations in FH, to help in diagnosis of other FH patients and families.

Health Risks

FH is associated with a high risk for premature coronary artery disease. Early detection and aggressive management to lower the LDLc level helps prevent or slows the progression of coronary atherosclerosis. Moreover, if the first-degree relatives of a patient with FH are screened, other gene carriers can be identified and treated. Statistically, because the gene for FH is dominant, 50% of the patient's first-degree relatives will also have heterozygous FH.

Therapeutic Management

Among many people with FH, even high-potency statins do not allow attainment of recommended targets for LDLc concentration. Statins can also have dose-dependent side-effects, most notably skeletal muscle symptoms. Other therapeutics for FH include inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9), including the use of monoclonal antibodies and anti-sense oligonucleotides, small interfering RNAs, and inhibitory adnectins. However the efficacy and safety of all of these approaches have not been tested in people and clinical trials are needed.

Registries as enabling tools for Health Improvement

Disease registries offer technical solutions to storing, managing and accessing patient and clinical information to address a range of unmet clinical needs. The full potential of registries to

deliver improvements in clinical services and patient outcomes is often dependent on (1) levels of interoperability between existing data silos, (2) the use of harmonised data and approaches such that registry platforms can manage the consent process and flow of data between individual data sets (3) whether research groups are able to utilise the registry platforms and thereby translate research findings to best clinical practice. Such a paradigm for improving outcomes is dependent on strong networking across the various components of research and clinical services.

➢ Aims of the Registry

The aims of the National Registry for Familial Hypercholesterolaemia (the Registry) are to:

- Facilitate service planning by analyses and reporting of data collected by the Registry on prevalence, geographical distribution, genetic variants associated with disease, clinical features, clinical management and patient outcomes.
- Enable research by providing aggregate, de-identified data to research entities.
- Facilitate identification and recruitment of eligible volunteers for clinical trials.
- Promulgate new knowledge to inform best practice and care services.

To achieve these aims, the registry will collect, store, protect, curate, analyse, report and provide data on individuals and their family members who consent to participate in the Registry. Only individuals with FH and their affected and unaffected relatives are eligible to enrol in the Registry. Diagnosis of FH will be made genotypically or phenotypically as per the model of care developed by the FH Australasia Network[1]. Future expansion of the Registry may include other familial dyslipidaemias, such as familial combined hyperlipidaemia, and other inherited cardiovascular conditions, such as familial hypertrophic and dilated cardiomyopathies and long QT syndrome. Accordingly, the aims of the FH Registry align with those of the National Genetic Heart Disease Registry and with the National Registry for Rare Disease.

The Registry will collect and process data according to state and/or federal legislation and best practices and ensure currency of the data.

➢ Scope of the Registry

The Registry will include the following people:

- Individuals with diagnosed Familial Hypercholesterolaemia
- Individuals with suspected Familial Hypercholesterolaemia
- Children of individuals with diagnosed Familial Hypercholesterolaemia

[1] Watts GF, Sullivan DR, Poplawski N, van Bockxmeer F, Hamilton-Craig I, Clifton PM, O'Brien R, Bishop W, George P, Barter PJ, Bates T, Burnett JR, Coakley J, Davidson P, Emery J, Martin A, Farid W, Freeman L, Geelhoed E, Juniper A, Kidd A, Kostner K, Krass I, Livingston M, Maxwell S, O'Leary P, Owaimrin A, Redgrave TG, Reid N, Southwell L, Suthers G, Tonkin A, Towler S, Trent R. Familial hypercholesterolaemia: A model of care for Australasia. Atherosclerosis Supplements. 2011;12:221-263

- Undiagnosed family members of individuals diagnosed with or suspected to have Familial Hypercholesterolaemia

The Registry will link individuals with diagnosed or suspected Familial Hypercholesterolaemia with family members also included in the Registry.

Since inception, the Registry has enrolled over 1500 participants.

➢ Custodian

The national custodianship of the Registry will be assigned and endorsed by the Advisory Board of the Registry. The criteria for selecting the appropriate custodian include:

- Competence, skills and authority to discharge the custodianship responsibilities
- Understanding of the relevant legislation and policies
- Understanding of needs of all users
- Experience with and knowledge of Familial Hypercholesterolaemia and associated clinical considerations.

The Custodian is responsible for ensuring data quality issues and improvement processes are documented in accordance with the mandatory reporting requirements.

➢ Coordinator

The national coordinator will be assigned and endorsed by the Advisory Board of the Registry. The national coordinator will be responsible for ensuring cross-site coordination, over-arching data curation, including processes for data extraction. The national coordinator, in conjunction with the Custodian will have access to all data.

➢ Advisory Board

Chairperson

The chairperson of the National Advisory Board (the Board) will be elected by nominees proposed by the Familial Hypercholesterolaemia Australasia Network. A vice-chairperson will also be elected and will chair the board meeting in the absence of the chairperson. A question arising at a Committee meeting must be decided by a majority of votes, but, if there is no majority, the Chair will have a casting vote in addition to his or her deliberative vote. Minutes of the proceedings of each meeting will be taken by a nominated secretary, and circulated to all members after the meetings. The Familial Hypercholesterolaemia Australasia Network will provide secretariat support for the meetings of the Board.

Role

The Board will provide oversight on the governance of the registry and will be responsible for approving the responses of the registry to queries from research or other external parties. The role of the Board is to:

- Oversee all Registry activities
- Provide advice on the Registry management, scope, development and funding
- Provide advice on the collection and interpretation of data
- Monitor the scientific progress of the Registry
- Monitor the Registry data quality management processes and timelines of reporting
- Advise on scientific priorities
- Review all research and external data requests
- Review publications of the registry and advise on clinical issues
- Circulate and keep abreast of literature relevant to the research area including new publications and abstracts

Membership

Board members will usually be limited to a maximum of 16 people and will hold office for a maximum of 5 years. Members will include representatives from:

- Australian States and jurisdictional sites;
- Health consumer reference groups;
- Contributors of data to the Registry;
- Clinical specialties related to familial hypercholesterolaemia; and
- Legal and ethical sectors

Members of the Board are required to:

- develop and make available to the public an annual report on the activities and outputs of the Registry (see *Reporting Requirements* below)
- review all applications for access to the Registry
- sign confidentiality agreements if a third party requests them prior to having access to the inquiry of the third party

Meetings

It is intended that the Board will meet by teleconference or in person at least bi-annually. A quorum (as defined by 50% attendance by members) is required for meetings to proceed.

Reporting Requirements

Annual reporting

The Board will be responsible for issuing an annual report of the Registry and for ensuring that the report is made available on the Registry website. The annual report will strengthen the evidence base used by Australian health care providers for service planning through inclusion of data on prevalence, geographical distribution, clinical features, clinical management and patient outcomes.

Specific inquiries

The Board will respond to inquiries to the Registry within 30 calendar days upon receipt of the inquiry and will report the decision in writing to the third party. If the Board cannot reach a majority decision according to the Terms of Reference, the inquiry will be rejected or deferred pending re-application. In the case of a rejection or deferral, the Board will report the reason for and allow reconsideration of the application.

Agenda

Agendas and other documentation relevant to the business of the Advisory Board will be forwarded to members electronically prior to the next meeting.

Records of Meetings

Formal Minutes will be kept of all meetings and will be confirmed at the next subsequent meeting of the Advisory Board. Actions noted should be addressed by the relevant person(s) and progress discussed at the next meeting or prior if deemed urgent.

Conflicts of Interest

Conflicts of interest relating to the governance of the Registry will be recorded on a Conflicts of Interest Register and managed according to the *Conflicts of Interest Guidelines* of the respective Area Health Services and State Department of Health. Members of the Board will be specifically required to disclose all conflicts of interests and update disclosure statements on an annual basis.

Strategies to manage Conflicts of Interest include: restricting involvement in the matter if deemed appropriate, engagement of an independent third party, removing involvement in the matter altogether, relinquishing the personal or private interest and resignation as a last option.

➢ Data Access and Information Disclosure

Access to data for clinical trials

The Registry collects identifiable patient data for the purposes of the referring clinician being able to readily contact those who, based on their demographic, clinical and genetic data, meet the eligibility criteria for a specific clinical trial. The identifiable data will not be provided to third parties, disclosed, reported or published for any reason.

The National Coordinator will contact the site coordinator, who in turn, will ask the nominated clinician to contact the registrant to discuss the opportunity to participate in the trial. Access to personal information is restricted to those treating the patient, the clinical site coordinator and the national curator of the registry. Data will not be accessible across Registry sites to anyone other than the National Coordinator.

Access to patient identifying information is restricted to the treating clinician who enters the data, the coordinator of the site of registration and the national coordinator. Third parties will not be given direct access to patients or identifiable data under any conditions.

Access to de-identified data for research or feasibility of clinical trials

The Board will regulate the relationship of the Registry with third parties. Access to de-identified patient information is subject to approval by a jurisdiction human research ethics committee, recommendation by the Board, approval of the data custodian and the study objectives being aligned with Registry objectives

All applications must have prior approval by a jurisdiction ethics committee and may be made via submission to the Advisory Board of an Expression of Interest.

Access Agreement

An Access Agreement is required to be authorised by the third party and the Advisory Board, with copies to be held by the Custodian and circulated to the members of the Advisory Board. The agreement between the Registry and the third party must ensure that access to confidential health information by the third party is limited to the use specified, that appropriate safeguards are in place to protect information on the termination of the contract. The access agreement will include:

- acknowledgement that data derived from the Registry may be used for registering medicinal products through the Therapeutic Goods Administration (TGA), Food and Drug Administration (FDA) and European Medicines Evaluation Agency (EMEA)
- access by research and academic institutions will be provided free of charge. Any publications must acknowledge support by the Registry
- access by commercial companies may be charged a service fee agreed to by the company and the Board
- all parties agree with the ethical principle of benefit sharing, which requires that benefits resulting from any scientific research and its applications should be shared especially with the persons and groups that have taken part in the research

The Board will regulate the sharing of information with patients, clinical and genetic service providers in relation to:

- provision of de-identified aggregate to third parties;
- details of trials and research projects recruiting through Registry;
- information on other Registry and external related activities;
- any other way to return benefit in accordance with the ethical principal of benefit sharing

Sustainability

There may be fees payable for access by industry and other bodies as deemed appropriate by the board, utilised for grass roots infrastructure. In the future, further industry support will be sought to continue to support both the infrastructure and the National Coordinator position.

➢ List of Members and External Advisors

Members of the Board (limit of 16)

Name	Institution/Location	Email Contact
Bishop, Dr Warrick	Calvary Hospital, Tasmania	warrick@drwarrickbishop.com
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