transfusionoutcomes research collaborative

NAIT REGISTRY

Neonatal Alloimmune Thrombocytopenia (NAIT) Registry

PROTOCOL

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Background

Neonatal Alloimmune Thrombocytopenia (NAIT) is a significant cause of severe foetal and neonatal thrombocytopenia. It is estimated that 10% of cases are complicated by intracranial haemorrhage, and survivors may have life-long neurological consequences. Other serious (gut, skin and lung) haemorrhage occurs in many affected children, and may also have long-term sequelae. Although the number of affected pregnancies is relatively small, the disease burden for children affected by NAIT, their families, and the community is very large.

Currently there is no consensus regarding the true incidence or frequency of NAIT, optimal management, accurate incidence or impact of complications, useful clinical outcome data or standardisation of laboratory assessments. Lack of data hampers the design of clinical interventional studies and laboratory tests to improve diagnostics.

The relative rarity of these diseases makes both the accrual of data and material to support scientific studies and the establishment of high quality randomised prospective trials challenging.

Registry data would provide valuable information about patterns of IVIg and specialised platelet use (HPA-matched for intrauterine and neonatal transfusion) in NAIT. Opportunities to stratify and standardise therapy for optimal maternal and neonatal outcomes could achieve better use of these precious products. Registry data may also eventually permit stratification of testing and other interventions, avoiding costs and potential complications for some patients. Information generated from this registry will contribute to understanding of disease mechanisms and permit further focused research.

The Australian Red Cross Blood Service (the Blood Service) is Australia's national blood service. It provides a central point of contact for clinicians managing NAIT, including specialised diagnostic testing, clinical advice and provision of appropriate therapies including blood components and intravenous immunoglobulin (IVIg).

The Monash University Department of Epidemiology and Preventive Medicine (DEPM) currently maintain a number of major registries including VSTORM (the Victorian State Trauma Registry), VOTOR (the Victorian Orthopaedic Trauma Registry), and the Victorian Cardiac Surgical Register (ASCTS). In addition the Transfusion Research Unit within DEPM is responsible for the Thrombotic Thrombocytopenic Purpura registry (TTP), the Neonatal Alloimmune Thrombocytopenia (NAIT) Registry, the Aplastic Anaemia (AA) Registry, the Massive Transfusion Registry and the Venous Thromboembolism (VTE) Cohort Study.

Aims

The aims of the NAIT Registry are to:

1. Better define the incidence, natural history and clinical outcome of NAIT
2. Provide information on the range of therapeutic strategies being employed in the treatment of NAIT patients
3. Explore factors influencing clinical outcomes
4. Better define optimal management of NAIT patients
5. Inform and inspire future hypothesis-driven research in this area

Study Design

The NAIT Registry is a register of pregnant women who develop or have a history of NAIT and their children, both before and after birth. Clinical data collection will be undertaken by clinicians in specialist units at participating hospitals and some laboratory data will be collected by The Blood Service. Data management and analysis will be undertaken by the Department of Epidemiology and Preventive Medicine (DEPM), Monash University. The registry opened for data collection in March 2009.

Study Population

Patients who have been diagnosed with Neonatal Alloimmune Thrombocytopenia (NAIT) by their treating physician are eligible for inclusion in the Registry. Patients diagnosed with NAIT are treated at a limited number of hospitals with specialised facilities. Their requirement for specific blood component therapy will also enable cross reference with The Blood Service to ensure all eligible patients are captured by the registry.

Due to the nature of NAIT a diagnosis could be made while the baby is still in utero or just after birth. Once the baby is born treatment will usually conclude within the first 3 weeks of birth. After this time the child will no longer be affected by NAIT. The potential age of mothers is likely to be between 15 and 55 years.

Participants will not be excluded unless they choose to ‘opt-off’ the registry. It is anticipated that 20-30 cases will be identified each year across all participating hospitals.

Subject recruitment and enrolment

Recruitment strategies take advantage of the fact that diagnosis is dependent on specialised testing undertaken by The Blood Service. Most patients would require specialised products from The Blood Service, and patients are largely managed by a small group of highly specialised clinicians. Registry staff will maintain close interaction with key individuals working in relevant hospital clinical care areas to ensure notification of all patients.

Study Assessments

Assessments

Inclusion on the NAIT Registry does not involve any change in patient treatment or any procedures beyond those usually involved in the diagnosis and treatment of NAIT. No additional information will be collected from participants other than that routinely collected in the diagnosis and treatment of NAIT.

Potential Benefits

Participants in this project are not likely to receive direct benefit from participation. However, NAIT mothers may have future children who are diagnosed with NAIT. It is possible that outcomes of the project may enable improved management that could benefit some of the participants as well as future patients diagnosed with NAIT.

Data Collection

Clinical data collection will be undertaken by clinicians in specialist units at participating hospitals and some laboratory data will be collected by The Blood Service. Data management and analysis will be undertaken by the Department of Epidemiology and Preventive Medicine (DEPM), Monash University.

Patients are identified either by the treating clinician or by The Blood Service clinicians as a result of referral for specialised testing or provision of specialised products. Patient liaison and registration will take place in participating hospitals primarily through the treating clinical team. Data will be collected onto a web-based data collection form designed specifically for the study. It will record data in the following categories:

Maternal details

- Patient demographics
- Background (previous pregnancies including any NAIT affected pregnancies)
- Test results
- Maternal outcome

Paternal details

- Patient demographics
- Test results

Foetal details and antenatal management

Test results
Therapy
Foetal outcome

Neonatal details and postnatal management

- Patient demographics
- Clinical details
- Therapy
- Clinical outcome

Registry staff will be responsible for training clinicians to use this data collection form and performing random audits on 5 % of cases to ensure accurate extraction of data.

Data Management

Patient data will not be de-identified on entry to the registry. Neonatal Alloimmune Thrombocytopenia is a disease which may affect multiple children of the same mother, and where the treatment of a single child may span several doctors and institutions (e.g. with prenatal treatment at an obstetric unit, then neonatal treatment in a paediatric intensive care unit). There is also a familial association: for example sisters may both have NAIT affected children. All participants will be recruited independently on diagnosis of NAIT. Sisters will be identified as related unless a patient 'opts-off' the register so familial links can be made where they occur. Subsequent pregnancies may be treated at different institutions and by different clinicians. In order to completely describe the potential course of the disease, the ability to track an individual's progress across these transfers and further pregnancies is required, and this requires identified data.

It should be noted that the data to be collected remain the joint property of Monash University and The Blood Service. Data will not be used in a way that will allow individual patients to be identified. Publication will be restricted to statistical tabulation of aggregate data only. The data will be handled by an experienced university research unit with careful attention paid to privacy and security of the information. The DEPM and The Blood Service have impeccable track records in handling personal information.

Data collected as part of the registry will be managed according to guidelines stipulated by the Australian Therapeutic Goods Administration and conform to Commonwealth and State privacy principles. All registry data entry will be performed by data collectors off-site using a web-based interface. Hospital-level access is granted to only allow a data collector access to their own patient's information with logins assigned by registry IT staff via email. The web interface will be developed in Microsoft ASP.NET 2.0 and hosted on an IIS Web Server by the faculty's IT team at the Monash Clayton site. All data storage will be in a Microsoft SQL™ Server 2000 database located in the Department of Epidemiology and Preventive Medicine's (DEPM) server room. Access to this server room is available only to the Unit IT manager. In case of fire or loss of data, the database server is mirrored each day to a backup facility at the Monash Clayton campus. All traffic between the data

collector's browser, the web server and the database server are encrypted to 128 bits, and all passwords are encrypted in the database.

Registry information will only be available to the investigators named below for the purposes of developing aggregate data reports and analysis. These reports will be provided to the supervisory Steering Committee of the registry and to participating institutions in de-identified form.

Quality control

A number of validation measures will be incorporated into the web registry to ensure quality data entry. All mandatory fields will be required to be entered, and value and date text boxes have specified upper and lower limits. Fields dependent on the value of a parent item will be enabled and disabled accordingly and warning messages will appear for unknown or extreme values. Consistency checks will also be in place. Data entry will be verified independently by NAIT Registry staff. Data will be readily available for extraction and reporting to the Project Manager.

Audit

A comprehensive audit plan will be instituted to ensure a high standard of data acquisition across multiple sites using multiple data collectors. The audit plan will have two arms:

- Case accrual audits will be undertaken by cross-reference to testing and product provision by The Blood Service to ensure that all eligible cases are included.
- Random audits of 5 % of cases against source data will be undertaken to ensure accurate extraction of data. This audit will be undertaken by registry staff.

Performance figures will be reported back to data collectors and senior clinicians at each site.

Data Access/Usage

A protocol to facilitate access to researchers will be developed. In general access to NAIT Registry data will be provided to bona fide external researchers with the approval of the registry staff and the Steering Committee and with appropriate HREC approval. Participating clinicians or hospitals are at liberty to publish their own hospital data without any reference to the NAIT Registry.

Reporting

The registry will provide on-line Hospital Data Reports to participating clinicians and hospitals describing essential statistics relating to case accrual and outcome. A more detailed written report will be provided on an annual basis to clinicians, participating hospitals and their Ethics Committees. Six monthly quality assurance reports will be prepared for meetings of the Steering Committee.

Communication with Participating Institutions

In addition to the on-line Hospital Data Reports, communication will be maintained with stakeholders via newsletters, emails and an Annual Investigators' Meeting.

Publications

Publication of scientific manuscripts is a high priority for the registry. The data analyses may include national, state and institutional cohorts but will include only collective patient data. Publications will be prepared with input where appropriate from members of the steering committee and will be submitted for comment and approval of the Steering Committee. Final content, however, will be at the discretion of the authors. Publication sub-committees may be formed in particular areas of interest or expertise. In addition to publications, project data will be presented at Scientific Meetings and Conferences

Ethics

Ethics approval for participation in the Registry has been gained from Monash University Human Research Ethics Committee (MUHREC), and The Blood Service Human Research Ethics Committee (HREC). Ethics approval will be obtained from the Human Research Ethics Committee (HREC) at each of the participating hospitals.

'Opt-off' Consent

Written informed consent will not be obtained from patients prior to their details being included on the NAIT Registry. In this registry data collected will not exceed data routinely required by clinicians for management of patients with NAIT and will be handled by highly trained staff in a reputable epidemiological unit. The small impingement on privacy is substantially outweighed by the public interest in the improvements to patient care that may result from this project. It is the view of the project that it is impractical to seek informed, valid patient consent for participation in the project because of the difficulties that would be encountered given the nature of the condition and the type of information being collected. The integrity of the project also relies on a 100 % unbiased sample being collected. We know from previous work that obtaining consent would result in a potentially biased sample with less than 70% of patients included. There are specific patient types who are less likely to consent. As a result, it has been decided that the most appropriate approach is to provide an information brochure only and allow patients to 'opt-off' the registry by contacting registry staff.

Patient Information

Patients will not be contacted specifically by the registry. A brochure regarding the registry will be provided to patients during consultation, containing information about the registry and contact details for local investigators, the local ethics committee, and registry staff. The patient will be included on the registry and clinical information provided to the registry unless the patient decides to 'opt-off'. Patients will be able to 'opt-off' at the time of approach or at any time thereafter by

notifying registry staff using the 'opt-off' form and reply paid envelope provided with the patient brochure.

The number of patients who choose to 'opt-off' is not anticipated to be large. The project operates on the basis that consent will not be sought because it would be impracticable to do so. The information brochure will indicate that the Registry will maintain the strictest control over access to the information so as to ensure maximum protection of an individual's privacy. No information will be released about any individual unless required by law (e.g. pursuant to a court order, which is, in any event, unlikely given that more detailed and relevant information would be available at the treating hospital). Under no other circumstances would any information be made available to outside parties, or be used for other purposes by the Registry team.

Evidence of Consent Process

Evidence of the 'opt-off' consent process must be provided by the clinician. A comment in the patient's notes indicating that the patient has been informed about the registry and that information about them will be included unless they inform registry staff to the contrary will fulfil this obligation. Local investigators are required by the registry web portal to confirm that they have provided the patient with Patient and Families brochure with 'opt-off' information.

Contacts

Investigators

Dr Erica Wood: MB BS FRACP FRCPA

Dr Wood is a Transfusion Medicine specialist with clinical and laboratory experience in specialised transfusion support for patients with NAIT. Dr Wood has ongoing participation in research related to transfusion medicine and will provide supervision of Registry development including; case report forms, participation in data analysis at national level and is a member of the NAIT Registry Steering Committee.

NAIT Registry Coordinating Centre

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NAIT Registry Steering Committee

The Steering Committee consists of relevant stakeholders and clinical experts, the members include:

Dr Steve Cole **(Chair)**	Royal Women's Hospital, VIC
A/Prof. Mark Davies	Royal Brisbane and Women's Hospital, QLD
Dr Sunelle Engelbrecht	The Blood Service/ Monash University, VIC
Ms Rhonda Holdsworth	The Blood Service
Prof John McNeil	DEPM, Monash University, VIC
Dr Zoe McQuilten	Monash University, VIC
Dr Shelley Rowlands	Royal Women's Hospital, VIC
Dr Helen Savoia	Royal Women's Hospital, VIC
Dr Bronwyn Williams	Royal Brisbane and Women's Hospital, QLD
Dr Erica Wood	Monash University, VIC

The Steering Committee will meet at least twice per year; terms of reference of the committee include:

- Monitor the scientific progress of the project, including the data quality.
- Advise on the collection and interpretation of data.
- Assess and advise regarding performance outliers.
- Advise on scientific priorities to be addressed in data analysis and publication strategy.
- Engage in collaboration with registry staff in providing intellectual input into analysis of data and development of Registry publications where appropriate and advise on their scientific quality.

History of changes to NAIT Protocol

Version	Date	Author	Summary of Revisions
2.0	Feb 2009		Project Outline – Version 2
1	19/10/09	Dr Louise Phillips Ms Nikita Schembri	Original Project Protocol
2.0	14/7/10	Dr Rosemary McGinnes Dr Louise Phillips	Project Protocol Version 2 replaces both Protocol V1 and Project Outline V2 This document is based on the Project Outline. Sections introduced and information expanded and rearranged to improve readability. Ms Nikita Schembri removed as an investigator. Status of ethics applications removed. **No change to the study design**
3.0	01/07/12	Dr Simon Wilkins	Dr Simon Wilkins added as investigator. Removal of Dr Louise Phillips as an investigator. Addition of new Steering Committee chair (Steve Cole) and new members (Simon Wilkins, Sunelle Engelbrecht) and removal of SC members (Ben Saxon, Louise Phillips). Clarification of the role of Steering Committee in publications. **No change to the study design**
4.0	04/01/13	Dr Simon Wilkins	Dr Simon Wilkins removed as investigator and SC member. Updates to Steering Committee member affiliations. Update of contact information. **No change to the study design**.