**Important Note:**

This is an observational study and does not involve any direct patient contact or treatment regimens, therefore the following Project Outline takes the place of the ‘Protocol’ and will be referred as the Project Outline in all Human Research Ethics documentation submitted for consideration.

**Background**

Myeloma, a malignant proliferation of plasma cells associated with anaemia, renal failure, hypercalcaemia and lytic bone lesions, has an age standardized incidence (ASI) rate of 5.6 per 100,000 in Australia, with a higher rate in males, and a median age at diagnosis of 70.\(^1\) Although the incidence rate of myeloma has not increased, its prevalence is expected to increase due to an ageing population and recent improvements in the overall survival of patients with the disease.\(^2\) Whilst myeloma accounts for 1.2% of all cancers, it was one of the ten most common cancers recorded as the primary reason for hospitalization in Australia in 2007-09.\(^1\)

The range of treatment options has changed dramatically over the last decade resulting in improved survival for patients with myeloma. In addition, a large number of second-generation and targeted therapies are under development, expanding the repertoire of agents that are likely to be available in the future. However, the optimal way to utilize these therapies, including combination of agents and treatment algorithms, is yet to be defined.

Despite improved overall and progression free survival through disease control with newer agents, the majority of patients with myeloma cannot be cured and live with the burden of disease or cumulative effect of treatments.\(^3\) Therefore, supportive care to maintain quality of life is also becoming increasingly important throughout the course of the disease.\(^4\)

Long-term patient follow-up and review of clinical (safety and efficacy) and correlative data outside of clinical trials will be highly valuable in informing optimal treatment strategies for myeloma and its related diseases. Clinical registries provide a useful mechanism to collect data on patterns of treatment and variation in outcomes (both survival and quality of life). They enable clinicians to benchmark against national and international standards and allow evaluation of the translation of advances in therapy (such as introduction in new targeted therapies) into long-term outcomes outside the setting of clinical trials.

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**Hypotheses**

There is substantial variation in the therapy provided to patients with myeloma including choice of induction therapy, choice of therapy for primary refractory disease, choice of therapy for relapsed disease and the use of maintenance therapy as well as timing for treatment commencement.

There is significant variation between hospitals in the quality of care patients with myeloma receive as measured by the following indicators:

- Proportion of patients receiving at least one novel agent with induction therapy as opposed to conventional chemotherapy (e.g. VAD)
- Proportion of eligible patients who are offered high dose therapy
- Proportion of patients who receive bisphosphonate therapy
- Proportion of eligible patients included in clinical trials
- Proportion of patients with primary refractory disease included in clinical trial
- Proportion of patients prescribed thromboprophylaxis
- Proportion of patients who receive vaccinations for streptococcus pneumonia and haemophilus influenzae

The outcomes for myeloma patients residing in non-metropolitan areas are inferior compared with patients residing in metropolitan areas.

High-risk myeloma patients (as defined by cytogenetic abnormalities) have improved outcomes if treated with the following rather than ‘standard’ therapy:

- Bortezomib included in induction therapy
- Allogeneic transplant

Patients who have heavy marrow plasma cell infiltration (>40%) at diagnosis but who are not considered symptomatic based on CRAB criteria rapidly progress to symptomatic myeloma without therapy (and therefore should commence treatment at diagnosis).

**Aims**

The aims of the Myeloma & Related Diseases Registry are to:

- monitor access to care
- benchmark outcomes nationally and internationally
- explore variation in practice, process and outcome measures
- monitor trends in incidence and survival
- explore the factors that influence outcomes including survival and quality of life
- act as a resource for clinical trials
Study Design

The Myeloma & Related Diseases Registry (MRDR) will be a register of patients diagnosed with myeloma or related diseases. Data collection will be undertaken by clinicians at participating hospitals. Data management and analysis will be undertaken by the Department of Epidemiology and Preventive Medicine (DEPM), Monash University and interpreted with the input of specialist clinicians on the Steering Committee. The Registry will begin collecting data in 2012.

Study Population

Inclusion criteria

Patients with a new diagnosis of myeloma and monoclonal gammopathy of undetermined significance (MGUS) will be included. The feasibility of including prevalent as well as incident cases will be determined in the Development Phase by the Steering Committee. Participants will not be excluded unless they choose to ‘opt-off’ the Registry.

Source of registrants

Treating clinicians at participating institutions will be responsible for identifying patients. Registry staff will maintain close interaction with key individuals working in relevant hospital clinical care areas to ensure notification of all patients.

Study Assessments

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

Potential Benefits

Participants in this project are not likely to receive direct benefit from participation. It is possible that outcomes of this project may enable improved management that could benefit some of the participants as well as future patients diagnosed with myeloma or related diseases.

Data Collection

Clinicians (or staff under their direction) at participating hospitals will undertake data collection. Data collection web-forms will be developed specifically for the registry. The data collection form will incorporate features to allow clinicians to use the Web-Database to record clinical notes, which can be printed and kept within patient medical records. This is intended to reduce the burden of data collection for clinicians.
A minimum data set limited to epidemiologically sound variables will be developed. Data will be recorded in the following categories:

- Patient identifiers (for linkage)
- Demographic Details
- Laboratory and imaging results at diagnosis
- Therapy
- Outcomes (overall and progression free survival, duration of response and time to next treatment)
- Long-term Outcomes (through linkage with Cancer and Death Registries)

**Data Management**

Data collected will be managed according to guidelines stipulated by the Australian Therapeutic Goods Administration and conform to Commonwealth and State privacy principles.

Hospital-level access to the database is granted to only allow a data collector access to their own patients, with logins assigned by Central Project 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 Monash University 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.

**Quality Control**

A number of validation measures will be incorporated into the web database 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 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.

1. Participating hospital registrations will be triangulated with administrative data sets and central cancer incident registry notifications to ensure that all eligible patients have been notified to the Registry.

2. Random audits of 5% of cases against source data will be undertaken to ensure accurate extraction of data. DEPM staff will undertake this audit.

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

A Steering Committee will be established with a membership consisting of relevant stakeholders, clinical experts and a working group from Monash Department of Epidemiology & Preventive Medicine (DEPM).

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
- Review publications of the project and advise on their scientific quality
- Review all research and external data requests

Reporting

The MRDR 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 regular Newsletters, emails and an Annual Investigator’s Meeting.

Publications

Publication of scientific manuscripts is a high priority for the project. Publications will be provided for comment and approval to 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. Publications arising from the registry will only report de-identified and aggregated patient data to ensure that no individual patient can be reasonably identified.

Ethics

Ethical approval for participation in the MRDR will be gained from Monash University Human Research Ethics Committee (MUHREC) and the Human Research Ethics Committee (HREC) of each participating hospital.

Written informed consent will not be obtained from patients prior to inclusion; however patients will be able to “opt-off” the registry by contacting registry staff. This approach is consistent with comparable registries in Australia, and allows collection of valid data from an unbiased sample. It is established that “opt-in” consent would result in a biased sample with less than 70% of patients included.
The data collected for the registry will not exceed data routinely required by clinicians for management of patients 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.

Patients will be informed about the nature of the registry through a patient brochure. This will provide the names of a contact person at the registry who will be able to answer questions about the nature and purpose of the project. It will also provide the name of a local Ethics Committee contact person who can be contacted by those with particular concern. The number of patients who choose to ‘opt-off’ is not anticipated to be large. 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 identifiable information will be released about any individual unless required by law (e.g. pursuant to a court order, which is unlikely given that more detailed and relevant information would be available at the treating hospital) or if a patient seeks care from more than one participating hospital, in which case information related to diagnosis and the treatment received will be shared between the sites. Access to registry data may be provided to bona fide researchers with prior approval from registry staff, the MRDR steering committee and the ethics committee from each hospital involved in accordance with the MRDR Data Access Policy Version 1.0. Under no other circumstances would any individual information be made available to outside parties, or be used for other purposes by the registry team.

**Data Ownership/Access/Usage**

The data collected by the MRDR remains the property of Monash University. A protocol to facilitate access to researchers has been developed (Myeloma and Related Diseases Registry Data Access Policy Version 1.0). In general, access to registry data will be provided to bona fide external researchers with the approval of the project staff and the Steering Committee. Participating clinicians or hospitals are at liberty to publish their own hospital data without any reference to the registry.

**Confidentiality & Intellectual Property**

The intellectual property rights attaching to all material created or prepared by the Monash Department of Epidemiology & Preventive Medicine (DEPM) in connection with performance of the MRDR shall vest in DEPM.

**Timeline**

**Pre-development Phase**
- Secure funding
- Finalise project plan
- Establish Steering Committee

**Development phase**
- Finalise data set and data dictionary
- Web-database construction
• Establish contacts at 6 pilot hospitals
• Ethics submission at Monash University and pilot hospitals

_Implementation Phase_  
Dec 2012-
• Data collection commences at 6 pilot sites
• Amendments made to web-database as required including additional reporting functions
• Identify additional sites for inclusion in the Registry

_Expansion Phase_  
June 2013-
• Ethics submission at additional sites
• Data collection commences at additional sites
• Test and develop new or improved measures of outcome

_Investigators_

_Choice Investigators_

Professor Andrew Spencer  DM FRACP FRCPA, Head of Service, Malignant Haematology & Stem Cell Transplantation, Alfred Health – Southern Health Haematology Consortium, and Department of Clinical Haematology, Monash University

Dr Zoe McQuilten  MBBS (HONS) FRACP FRCPA, Clinical Research Fellow, Department of Epidemiology and Preventive Medicine, Monash University

_Steering Committee_

Professor Andrew Spencer (Chair) (Alfred Health and Monash University)

Dr Bradley Augustson (Sir Charles Gairdner Hospital)

Dr Hilary Blacklock (Middlemore Hospital, Auckland)

Professor Joy Ho (Royal Prince Alfred Hospital)

Dr Noemi Horvath (Royal Adelaide Hospital)

Professor John McNeil (Monash University)

Dr Zoe McQuilten (Monash University)

Dr Peter Mollee (Princess Alexandra Hospital)

Dr Louise Phillips (Calembeena Consulting)

Dr Hang Quach (Monash Medical Centre and Alfred Health)

_Myeloma & Related Diseases Registry Operations Committee_

TBA
## History of changes to Project Outline for the Myeloma & Related Diseases Registry

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Author</th>
<th>Summary of Revisions</th>
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<tr>
<td>1.0</td>
<td>10/11/2011</td>
<td>Dr Zoe McQuilten Dr Louise Phillips</td>
<td>Project Outline created</td>
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<tr>
<td>1.1</td>
<td>18/01/2012</td>
<td>Dr Zoe McQuilten</td>
<td>Project Outline completed</td>
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<tr>
<td>1.2</td>
<td>04/06/2012</td>
<td>Naomi Aoki</td>
<td>Amendment to Governance, Ethics and Data Access information regarding access to patient information.</td>
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<tr>
<td>1.3</td>
<td>20/06/2012</td>
<td>Naomi Aoki</td>
<td>Amendment to Chief Investigators to reflect staff changes</td>
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<tr>
<td>1.4</td>
<td>19/10/2012</td>
<td>Ieva Ozolins</td>
<td>Update to timeline, addition of John McNeil to Steering Committee</td>
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