**STUDY PROTOCOL**

# A cross-sectional study of the relationship between iron deficiency anaemia and chronic pain in patients presenting to a multidisciplinary pain centre in a tertiary referral teaching hospital

**Short Title:** (CANCAN) A **c**ross-sectional study of iron deficiency **an**aemia and **c**hronic p**a**i**n**


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**List of Abbreviations**

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| **IDA** | Iron Deficiency Anaemia |
| **ID** | Iron Deficiency |
| **WHO** | World Health Organisation |
| **BMI** | Body Mass Index |

## Introduction

Approximately 30% of the world's population suffer from anaemia, a condition characterised by decreased levels of red blood cells or haemoglobin in the blood, resulting in a reduced capacity to carry oxygen. Iron deficiency anaemia (IDA) is the most common type of anaemia, which is prevalent in Australia and worldwide. IDA is a significant public health problem in Australia as identified by the World Health Organisation (WHO), defining anaemia as a Hb level below 130g/L in men, 120g/L in women and 110g/L in pregnant women (Stevens, Finucane et al. 2013, World Health Organisation 2014).

Iron deficiency should be distinguished from other causes of anaemia due to the association with underlying conditions that mandate specific investigation. Treatment for this form of anaemia is simple, effective and safe (Pasricha, S et al. 2010). Anaemia with the presence of low mean corpuscular volume or mean corpuscular haemoglobin is expected to be due to iron deficiency and patients who are suspected, or iron deficiency should have iron studies performed.

There are many misconceptions in the diagnosis and management of iron deficiency (ID) (Munoz, Gomez-Ramirez et al. 2017). IDA is often overlooked, especially in people with chronic conditions. Patients with chronic pain can present with chronic inflammatory conditions and often experience a reduced health-related quality of life which is an important target of therapeutic interventions. Iron deficiency, even in the absence of anaemia, can be debilitating, and may exacerbate any underlying chronic disease, leading to increased morbidity and mortality (Cappellini, Comin-Colet et al. 2017). The most common symptoms of IDA are fatigue, weakness, dizziness, headache, lethargy, but it is hypothesised that IDA can also lead to pain. The effects of intravenous iron on health-related quality of life in patients with chronic heart failure and IDA have been studied (Comin-Colet, Lainscak et al. 2013) but there have been no studies to date regarding the incidence of IDA in the chronic pain population.

It has been well published that patients with chronic pain pose a heavy financial and social burden (Breivik et al. 2006, Langley et al. 2011, Leadley et al. 2012, Duenas et al. 2015), and can struggle with everyday tasks resulting in poor general well-being (Duenas M et al., 2016). Patients with chronic pain often have underlying chronic conditions such as irritable bowel syndrome or chronic inflammation. The need for ongoing pain medication, including non-steroidal anti-inflammatory drugs (NSAID) may cause occult bleeding. The often-debilitating pain experienced by these patients may cause a poor nutritional status. All these causes singular or combined may contribute to a higher prevalence of IDA in chronic pain patients.

Health institutions need to implement patient blood management strategies that align with the newly updated guidelines for clinical governance and quality improvement strategies in Australia (National Safety and Quality Health Service Standards. Second Ed; 2017). This revised standard will re-shape the way hospitals and healthcare services undertake patient blood management, with new focus placed on audit of processes for quality assurance activities and nation-wide accreditation. This shift away from a product-focused approach will result in implementation of patient-focused strategies and the need to measure success through patient-outcome based data and evidence of a collaborative, hospital-wide approach to treatment (Stevens, Finucane et al. 2013, World Health Organisation 2014).

## Aims and Objectives

### *Aims*

The aim of this observational pilot study is to describe the prevalence of anaemia, ID without anaemia and IDA in patients presenting to the Professor Tess Cramond Multidisciplinary Pain Centre at the Royal Brisbane and Women's Hospital (RBWH).

### *Primary Objective*

The primary objective is to measure the prevalence of anaemia versus IDA in patients who have a diagnosis of chronic pain for greater than 12 months.

***Secondary Objective***

The secondary objective is to measure patients pain levels by utilising the Visual Analogue Scale (VAS) and patients fatigue levels with the FACIT score. We will then assess patients' reported pain and fatigue scores, explore the relationship between IDA and pain, and to provide a baseline before planning a cohort study (Mann 2003).

## Study Design

A single centre, cross-sectional, observational study with a quantitative research design (Setia 2016) examining the relationship between iron deficiency anaemia and chronic pain in patients presenting to a multidisciplinary pain centre at the RBWH.

***Patient Population***

Patients attending outpatients' appointments in the Pain Centre will be identified by trained research personnel and invited to participate in the study. Patients will be recruited in order to satisfy a convenience sample of patients diagnosed with chronic pain. Participants will be given patient information sheets and informed consent will be obtained by trained research personnel. The refusal or reluctance to participate will be respected.

***Inclusion criteria:***

- Patients aged ≥18 years
- Patient experiencing Chronic pain for more than 12 months

***Exclusion criteria:***

- Patients with known or suspected blood disorders
- Pregnancy
- Known medication with iron supplements including intravenous iron
- Surgery within the last 6 months

## Methods

Patients presenting to the RBWH Professor Tess Cramond Multidisciplinary Pain Centre for treatment of a chronic pain condition that they have had for more than 12 months in duration, will be identified by trained research personnel and chronic pain personnel. Patients will be recruited in the clinic or identified prior to their scheduled appointment and telephoned to discuss their potential participation in the study, discuss any concerns, and gain their verbal consent to approach the patient on the day of their outpatients' appointment. Information to be discussed includes details of the Patient Information Sheet and a telephone script has been designed for this purpose. The phone calls will be conducted by trained research personnel.

On the appointment day, the patient will sign the consent form if agreeable, and will receive a copy of Patient Information Form and signed consent. Data collection and blood sampling (Pathology) will be performed. All data points will be recorded in REDCap, a secure electronic data program.

Each patient will have pain measured on the visual analogue scale and fatigue levels measured with the FACIT score. The Functional Assessment of Chronic Illness Therapy – fatigue scale (FACIT) is a 13-item tool designed to assess fatigue and its impact of daily living in several chronic diseases. A recent study has assessed the validity of this tool to evaluate the impact of new treatments for IDA. It

suggested that the FACIT-fatigue score is a conceptually relevant scale to use in patients with IDA, as its content is clear and meaningful to patients (Pasricha et al., 2010). Use of the Visual Analogue Scale is a commonly used tool amongst health care professionals due to its robust, sensitive and reproducible method of expressing pain severity (Price et al., 2011)

Blood sampling will then be obtained via routine venepuncture methods in line with hospital policy. This data will be used to calculate current pain levels, fatigue scores and iron levels in combination to determine the relationship between iron deficiency anaemia and chronic pain.

## Data Collection, processing and analysis

The trained research personnel will collect data from electronic records, other charts and the patient using a Research Electronic Data Capture Platform also known as REDCap. REDCap will be used for data entry and downloading data for analysis. All data will be deidentified data with a unique study number for each participant. REDCap is currently a free service for all MNHHS employees.

### *Data Collection*

The following parameters will be recorded for analysis:

- Patient demographics: Age, Gender, Height, weight, BMI, study number, medical record number
- Clinical details: Pain status (VAS), Medications, Interventions in situ as current care, Diet preferences, level of malnutrition (Subjective Global Assessment – SGA status), FACIT score
- Blood Tests: Full Blood Count, Serum iron, Serum ferritin, Serum transferrin, CRP

### *Blood Sampling*

Blood sampling will be obtained via routine venepuncture methods in line with hospital policy. This data will be used to calculate current pain levels, fatigue scores and iron levels in combination to determine the relationship between iron deficiency anaemia and chronic pain. As this is an observational study, any pathology results that require treatment will be sent to the patients nominated General Practitioner for follow-up care.

### *Sample Size*

A sample size of 80 will be obtained as a pilot sample in preparation for a larger cohort study. In the healthy Australian population, it is expected that approximately 20% of people have anaemia and 8.70% have iron deficient anaemia (non-pregnant women). Although the exact percentage of chronic pain patients with iron deficiency and anaemia is unknown, it is expected it may be similar or higher than the healthy population. The sample size chosen will be adequate in providing an estimate of the percentage with iron deficiency.

### *Statistical Analysis*

Descriptive statistical analyses will be performed. Categorical variables will be described using number (percent) and continuous variables using mean (standard deviation) or median (interquartile range) as appropriate. The relationship between iron deficiency anaemia and pain will be explored using a “Kruskall-Wallis test”. Test will be declared statistically significant at the two-sided $\alpha<0.05$ level. Analyses will be performed in STATA 15.

## Ethical Considerations

The participant's interests will be safeguarded by informing them that participation in the research project involves the collection of information about pain and anaemia status and includes blood analysis to diagnose anaemia. Their test results may reveal that they are anaemic with or without iron deficiency, and a referral letter will be sent to their treating GP for follow up and investigations. All information will be stored in a re-identifiable (or coded) format using your unique study number.

The collection of blood requires their specific consent for taking, storage, testing and analysis of these samples for research purposes. The samples will not be kept for further testing. Having a blood sample taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

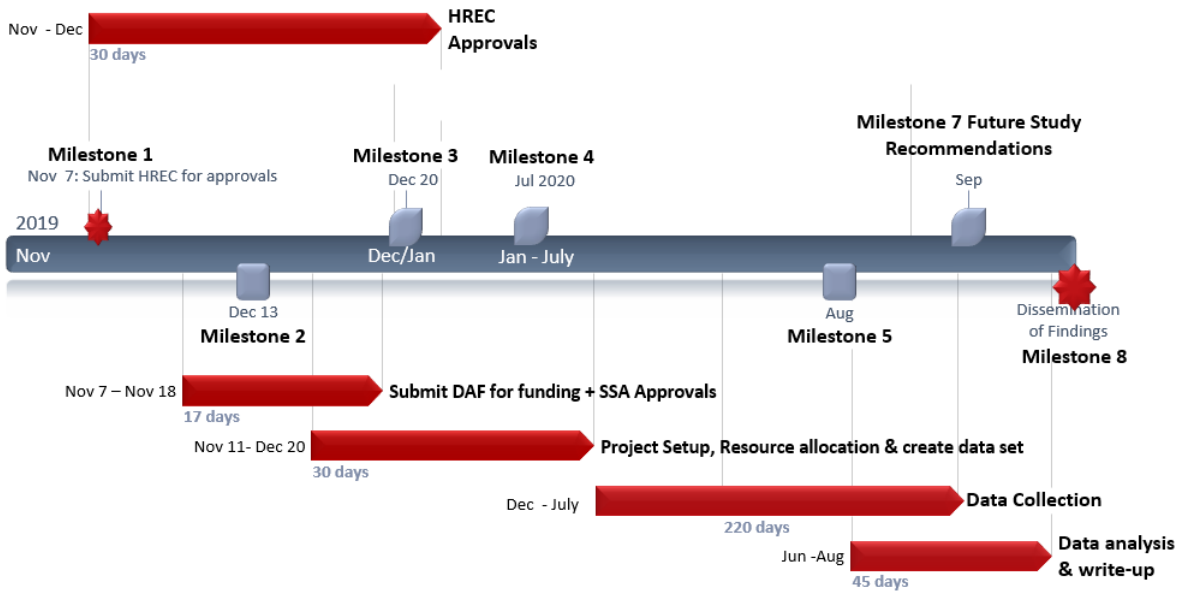
By signing the consent form they agree to the research team accessing health records if they are relevant to the participation in this research project. If they decide to withdraw from this research project a member of the research team will need to be notified prior to withdrawal.

Patients will receive a Patient Information Form and a copy of their signed consent to keep. Any information obtained for the purpose of this research project that can identify the participant will be treated as confidential and securely stored in password protected computers and programs (REDCap). It is anticipated that the results of this research project will be published and/or presented in a variety of forums, but the information will be provided in such a way so that they cannot be identified. Patients will not benefit financially from their involvement in this research project.

Any adverse events will be addressed and reported immediately to the HREC at RBWH. The ethical and governance aspects of this research project will require approval by the Royal Brisbane and Women's Hospital.

## Timeline and Resource Requirements

The duration of this project is expected to be completed within 12 months:



The staff of the Multidisciplinary Pain Centre are collaborators in this study, and liaison with key personnel will take place to facilitate the patient interview for consent, data collection and blood sampling.

The Pathology Department will be informed of the study and the required blood samples, as well as details of blood sample study labels.

All costs will be met by the Anaesthetic Research Department. It is expected to require a clinical research nurse (NG6), a research coordinator (NG7) and a UQ summer medical student (already allocated). Related staff and pathology costs have been requested via a Distribution Application Form (DAF) from Anaesthetic Tied Fund accounts at the RBWH Foundation, for $30,000.00.

## Outcomes and Significance

The study findings will be published in a professional journal and presented at local and international conferences. It is expected that this pilot trial will provide pertinent data for Chronic Pain patients and the prevalence of IDA in this specific population to improve health related quality of life, and to reduce pain and fatigue levels. It is our intention to follow up this initial study with a further multi-centred Randomised Control Trial to test the effects of iron treatments and the health and well-being outcomes in this population of patients.

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