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| **1.** | **Front Page \*** |

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**Ultrarapid iron polymaltose infusion for iron deficiency anaemia: a single centre study**

**UltraRIIPH single centre study**

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|  | **STATEMENT OF COMPLIANCE** |
|  | This study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC [National Statement on Ethical Conduct in Human Research](http://www.nhmrc.gov.au/guidelines-publications/e72) (2007) and (if applicable) the [Note for Guidance on Good Clinical Practice](http://www.tga.gov.au/sites/default/files/ich13595an.pdf) (CPMP/ICH-135/95). |

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|  | **Associate Investigator(s):** |
|  | Martha Turek, Dr Daniel Niewodowski, Dr Rumes Kanna Sriamareswaran, Dr Fiona Yeaman, Lilian Vo, Dr Travis Churchill |

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| **2.** | **Synopsis (250 – 300 words)** |
|  | Iron deficiency anaemia is a common condition that frequently requires intravenous treatment in patients with chronic conditions. Two formulations of intravenous iron are available in Australia that are used for total body iron replacement. However, the newer ferric carboxymaltose is limited by high cost and a maximum dose of 1000 mg per week over 15 minutes. Iron polymaltose has the advantage of being cost-effective with the ability to provide total body iron replacement in one administration of up to 1500 mg over 1 hour or greater amounts over 4 hours. A pilot study in 2017-2018 demonstrated safety of delivering iron polymaltose at doses up to and including 1500 mg over 30 and 15 minutes.This will be an open-label, single centre study aiming to confirm the safety of iron polymaltose administered as an ultrarapid (15-minute) infusion in a general hospital population. Patients diagnosed with iron deficiency anaemia of any cause requiring replacement with iron polymaltose doses up to 1500 mg will be enrolled into the study after obtaining consent. Rates and severity of adverse events will be compared to those previously published for iron polymaltose administered over 1 hour and 4 hours, as well as to previously published safety outcomes for ferric carboxymaltose infusions. |

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| **3.** | **Introduction / Background \*** |
|  | Iron deficiency anaemia is a common condition among the general population and patients admitted to hospitals.1-4 Correction of iron deficiency leads to improved quality of life with reduction in symptoms of anaemia, improved sensitivity to erythropoietin stimulating agents (ESAs) in patients with renal impairment as well as resolution of other related conditions.1-4 Total body iron replacement is a common practice in hospital settings for patients who are unable to tolerate oral iron supplements due to adverse effects, malabsorptive conditions, poor medication adherence, as well as conditions such as chronic renal failure (CRF), malignancies and continuing blood loss.3,4 Previous research has demonstrated the safety of iron polymaltose up to 1500 mg administered as a rapid 1-hour infusion in management of iron deficiency anaemia.3-4 However, despite the safety of this drug, its competitor, ferric carboxymaltose, is frequently used at a greater cost and with the limitation of a capped maximum dose of 1000 mg per week. The primary advantage of ferric carboxymaltose over iron polymaltose is the ultrarapid administration rate over 15 minutes.5For this reason, a pilot study was conducted in 2017-2018 demonstrating the safety of iron polymaltose administered over 30 and 15 minutes for dose up to and including 1500 mg.6 This study aims to confirm the result of the pilot ultrarapid administered iron polymaltose, which will compare the safety to the slower infusions of 1 and 4 hours, and to that of ferric carboxymaltose. Confirmation could lead to significant benefits for patients requiring total body iron replacement in a treatment session over a shorter period of time, as well as a significant benefit for infusion centres and hospitals with reduced nursing time and direct medication costs, which are 12 times lower.References:1. Pasricha SR, Flecknoe-Brown SC, Allen KJ, Gibson PR, McMahon LP, Olynyk JK, et al. Diagnosis and management of iron deficiency anaemia: a clinical update. MJA. 2010; 193: 525-32
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| **4.** | **Objectives \*** |
|  | The primary objective of this study is to confirm the safety of iron polymaltose administered as an ultrarapid infusion over 15 minutes, as has been demonstrated in the pilot study, and to compare the rates and severity of adverse events to the previously determined published rates of iron polymaltose administered over 1 hour and 4 hours.The secondary objective will be to compare these rates to previously published safety outcomes for ferric carboxymaltose infusions.The primary hypothesis is that there are no differences in adverse event rates between iron polymaltose infusions administered over 15 minutes compared to infusions administered over 1 hour and over 4 hours. Previous study results suggest that the adverse events appear to be related to supra-therapeutic dosing without consideration of patients’ weights or the iron content of any blood transfusions prior to iron replacement and not the infusion rates. Our secondary hypothesis is that there are also no differences in adverse event rates compared to infusions of ferric carboxymaltose administered over 15 minutes. |

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| **5.** | **Personnel** |

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| **6.** | **Study Design \*** |
| 6.1 | Study Description \* |
|  | This study is an open-label, double arm Phase 4 safety study. |

**Study Design \***Study Description \* |
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|  | This study is an open-label, single-centre, Phase 4 safety study. |

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| 6.2 | Study comparison and interventions \* |
|  | The study interventions include intravenous infusions of iron polymaltose up to 1500 mg in 250 mL sodium chloride 0.9% administered at ultrarapid rates over 15 minutes. The rates and severity of adverse events will be compared to those previously published for iron polymaltose administered over 1 hour and 4 hours, and for ferric carboxymaltose infusions. |

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| 6.3 | Participants \* |
|  | Inclusion criteria:* Frankston Hospital patients diagnosed with iron deficiency anaemia of any cause requiring replacement with iron polymaltose doses of up to 1500 mg.
* Treating team provided consent for their patient to be approached to participate.
* Patients able to provide informed consent.

Exclusion criteria:* Patients requiring doses greater than 1500 mg of iron polymaltose.
* Patients unable to give informed consent.
* Patients unable to read English.
* Treating team declining for their patient to be approached to participate in the study.
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| 6.4 | Study procedure \* |
|  | Participants will be screened for via the receipt of iron polymaltose infusion orders by the Pharmacy Department as well as by the General Medicine and Cardiology registrars seeing patients requiring iron infusions for management of inflammatory bowel disease and iron deficiency anaemia due to gastrointestinal bleeding or heart failure. The required dose will be calculated by medical and pharmacy staff using established guidelines for iron polymaltose (last updated May 2016). Approval for potential enrolment of eligible participants will be sought from the treating teams by investigators. If approved eligible participants will be approached whilst on the inpatient ward by an investigator to obtain written consent with a Participant Information Sheet/Consent Form (PICF) prior to receiving the iron infusion order at an amended infusion rate of over 15 minutes. Patients referred from community settings to infusion centres will also be contacted on receipt of intravenous iron infusion orders. The iron polymaltose infusions will be prepared by the Pharmacy Department as per standard procedures, with the required dose diluted in 250 mL sodium chloride 0.9%. It will be administered intravenously by nursing staff at the trial ultrarapid rate (15 minutes), as specified by the investigators. Nursing staff will monitor participants for the duration of the infusion and for the 1 hour observation period after the end of the infusion. Medical staff members will be called in case of any moderate to severe adverse events requiring changes to the iron infusion rate. Monitoring will include pulse, blood pressure, temperature, and oxygen saturation prior to infusion, every 5 minutes for the duration of the infusion, then every 15 minutes during the hour post-infusion monitoring with documentation of any perceived adverse events. Participants who experience adverse events will be able to complete the infusion at a slower rate or, if the reactions are severe, will have their infusions stopped and restarted only after medical review and if considered safe, as per previous rapid iron infusion study procedures.Rates of mild, moderate and severe adverse events will be collected along with any adverse event treatments or adjustments to infusion rates, number of units of blood transfused if required, patient demographics, past history, indication for iron infusion and pathology results, if available.Participants will be contacted via telephone or in person (if still hospitalised) by the study investigators to document any adverse events during occurring in the week after the infusion. These delayed adverse events will be compared to the previous results of rapid iron polymaltose infusions and that of ferric carboxymaltose. |
| 6.5 | Outcome(s) \* |
|  | The primary outcome is the overall adverse event rate during the iron polymaltose infusions. Secondary outcomes include the adverse event rate during the week post-infusion as well as severity of adverse events, graded as mild, moderate or severe. During the infusion: mild reactions will be defined as those that do not require a change in the infusion rate, treatment or prolongation of hospital stay; moderate reactions will be defined as those that require an interruption or change to infusion rate, minor treatment such as analgesia or additional monitoring; and severe reactions will be defined as those that require the iron infusion to be stopped without intention to restart and where patients require urgent medical attention with administration of resuscitation or severe allergic reaction medications such as adrenaline, hydrocortisone or parenteral antihistamine, or prolongation of hospitalisation (more than 1 day). During the week post infusion, adverse events will be graded as: mild for those not requiring treatment; moderate where minor treatment was required; and severe for those requiring attention of a local doctor or hospital presentation.  |

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| 6.6 | Data Collection \* |
|  | Investigators will collect data from the patient’s history and/or digitised medical records (DMR) and the electronic medication management system (CLOVeR). All data will be recorded on data collection forms in a de-identified manner and include:* patient demographics (age, gender, weight), cause of iron deficiency (if known), pre-infusion blood test results (FBE, Iron studies, SeCr, CRP), any recent blood transfusions in last 2 weeks (with number of units), comorbidities, preadmission medications, any pre-medications used,
* iron polymaltose dose and infusion rate, risk factors for adverse effects to iron (IBD, raised inflammatory markers, concurrent immunosuppression),
* any adverse effects observed during the monitoring period, any treatments of adverse effects to the iron infusions, any adjustments made to infusion rates or whether they required cessation +/- restarting.
* adverse events during the week after infusion administration, and their severity as per direct patient follow-up.
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| 6.7 | Expected Duration of trial and start times  |
|  | * Human Research Ethic Committee (HREC) review – estimated time of 4 months.
* Expected trial period is 12-18 months based on current rates of iron infusions prepared at the Pharmacy Department, permitting for patients declining to participate.
* Interim safety data analysis after the first 50 patients will be conducted before further study progress. Results to be compared to previous rapid and standard infusion adverse event rates as well as severities of adverse events.
* Study data collection, analysis – 2 months.
* Study results write up – 2 months.
* The results will be submitted to HREC and Drugs and Therapeutics Committee and, if considered significant, submitted to a medical or pharmaceutical journal for publication.
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| 6.8 | Participant withdrawal  |
|  | Participants may choose to withdraw their consent at any time, they must inform a member of the research team who will be available before and after the iron infusion, as well contactable via phone at individual participating sites.  |

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| **7.** | **Data Management \*** |
|  | All data will be de-identified at the time of data entry on data collection forms. Hard copies of data collections forms, consent forms and withdrawal of participation forms will be stored at the Pharmacy Department for 7 years, accessible only by the investigating team. These records will then be destroyed by placement into a confidential bin by investigators. An electronic copy of the results will be kept on the Peninsula Health Pharmacy M:\ drive in a de-identified format. |

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| **8.** | **Statistical considerations / Planned Analysis \*** |
|  | Based on previous study results of sufficiently powered studies, an overall adverse event rate of 8-9% is expected, with an acceptable safety rate of up to 4% for severe adverse events as was used by the original rapid infusion study conducted in Victoria (including Peninsula Health) in 2009. Calculated participant number of 172 patients will be required to power the study to 80% with a 2-sided alpha of 0.05 to detect a 3% increase in severe reactions, and 249 participants will be required to detect a 7% increase in overall adverse effects. The original rapid infusion study of 100 participants had a rate of any adverse events of 24%, which was considered acceptable for inclusion into hospital guidelines for clinical use. A total of 300 participants will targeted for enrolment into this study, to allow for 10-20% drop out rate or loss to follow up for 1 week adverse effect data collection. Adverse event rates will be compared using Fisher's exact test and Mann-Witney U test, and baseline parameters using Fisher's exact and student-t test or Mann-Witney U test if non-normally distributed data is identified.  |

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| **9.** | **Quality Assurance, monitoring and safety**  |
|  | The results will be reported to the Drugs and Therapeutics Committee. An interim results analysis and report will be provided to HRECs and Drugs and Therapeutics Committees prior to study progression beyond the first 50 participants.Participants will be monitored for adverse effects during the infusion and for the following hour by nursing staff. Participants who experience adverse events will be able to complete the infusion at a slower rate or, if the reactions are severe, will have their infusions stopped and restarted only after medical review and if considered safe as per current procedures. Delayed adverse reactions for the week after infusion will be collected by direct participant contact to check for any adverse event occurrence, their management and severity.If the rate of severe reactions that occur during the study exceeds 4% at any point during the study the study will stopped. Any severe reactions occurring during the infusions will be reviewed by an ICU consultant (as an independent adjudicator) prior to considering continuation of the study. |

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| **10.** | **Ethical issues** |
|  | Iron polymaltose infusions were typically administered over 4-5 hours with test dosing at even slower rate for the first 15 minutes. Recent research has determined that safety is not compromised at faster infusion rates over 1 hour for doses up to 1500 mg. Test doses are no longer recommended by the European Medicines Agency, nor are they included in the current iron polymaltose infusion guidelines at Peninsula Health. These findings have been incorporated into the hospital guideline and, as such, have become standard practice. This study aims to explore the safety of iron polymaltose ultrarapid administration over 15 minutes as a follow-up to the successful pilot study, which identified no safety issues. Given the risk of adverse events, the study will require HREC review and development of patient consent forms. |

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| **11.** | **Finance and resource use \*** |
|  | Iron polymaltose will be provided by the hospital as per current procedures. No additional funding was obtained for the conduct of this study. Principal investigator and associate investigators will contribute their own time for patient enrolment, data collection and analysis, and subsequent distribution of results. |

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| **12.** | **Publication / Authorship** |
|  | Authorship has been determined in accordance with the Australian Code for the Responsible Conduct of Research (2007) and Peninsula Health Authorship Policy.The results of this study will be submitted for publication at a medical or pharmaceutical journal.  |

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| **13.** | **Limitations of the study & future directions** |
|  | The study may be limited by accuracy in documentation of adverse events by nursing staff. Another limitation of this study is the ability to detect delayed reactions, as many patients are admitted solely for iron infusions and discharged usually after an hour of observation post-infusion, limiting the ability of this study to identify reactions that occur during the infusion or the 1-hour observation period. Delayed reactions will be biased by patient recall.If the results indicate non-inferior safety profile for the ultrarapid infusion, the results will be used to update iron polymaltose infusion guidelines to reduce infusion times from 1 hour to 15 minutes for iron polymaltose doses up to and including 1500 mg. Clinicians using infusion centres for iron deficiency anaemia management will be notified of the results of the study with an offer to improve their patient care with a single total body iron replacement dose of iron polymaltose instead of multiple admissions for ferric carboxymaltose. |