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

**[HREC/17/PH/30]**

**Ultrarapid iron polymaltose infusion for iron deficiency anaemia: a pilot safety study**

**UltraRIIPH pilot 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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|  | **Principal Investigator:** |
|  | Iouri Banakh |
|  | **Associate Investigator(s):** |
|  | Martha Turek, Dr. Jong Chin, 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 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.  This will be an open-label pilot study aiming to explore the safety of iron polymaltose as an ultrarapid infusion in a general hospital population. Patients diagnosed with iron deficiency anaemia of any cause requiring iron replacement doses of up to 1500 mg will be enrolled into the study after obtaining consent. The required dose will be administered as an ultrarapid infusion firstly over 30 minutes and then, should no concerns arise, over 15 minutes in a second series of patients. 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.5  For this reason, the goal of this study is to test the safety of iron polymaltose administered over 30, and then potentially 15 minutes. If the safety of iron polymaltose administered as an ultrarapid infusion can be shown to be non-inferior to the slower infusions of 1 and 4 hours, and that of ferric carboxymaltose, then this could lead to significant benefit 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 14 times lower. If the pilot study is successful, funding will be sought for a fully powered study to show non-inferiority. A previous funding application for a fully powered randomised controlled study has been declined due to lack of insight into adverse event pathophysiology by reviewers and false belief that the administration safety results from similar products cannot be extrapolated to iron polymaltose despite similar pharmacokinetic and pharmacodynamics. This misunderstanding has been partly proven false with a recent study from Western Australia team.6 A pilot study such as this one will increase the likelihood of a successful grant application for a fully powered study that can lead to clinical practice application with confidence from clinicians in utilising this product this way more widely, than off-label and off any guidelines as is the current situation.6  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 2. Goddard AF, James MW, et al. Guidelines for the management of iron defiency anaemia. Gut. 2011; 60: 1309-16. 3. Garg M, Morrison G, Friedman A, Lau A. Lau D, Gibson PR. A rapid infusion protocol is safe for total dose iron polymaltose: time for a change. Intern Med J. 2011;41:548-54. 4. Banakh I, Lam A, Turek M, Htet TD, Vorlander C. et al. Rapid versus standar iron polymaltose infusions: a single centre safety study. J Pharm Pract Res. 2017; 47 (2): 103-109. doi: 10.1002/jppr.1236. 5. Bregman DB, Goodnough LT. Experience with intravenous ferric carboxymaltose in patients with iron deficiency anemia. Ther Adv Hematol. 2014;5: 48-60. 6. Browning RM, Alakeson N, O'Loughlin EJ. Efficacy and safety of ultra rapid iron polymaltose infusion during general anaesthesia. Anaesth Intensive Care. 2017; 45 (3): 320-325. |

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| **4.** | **Objectives \*** |
|  | The primary objective of this study is to explore the safety of iron polymaltose administered as an ultrarapid infusion over 30 and 15 minutes and compare 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 or 30 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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| **5.1** | **Principal Investigator** |

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

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| 6.2 | Study comparison and interventions \* |
|  | The study interventions include intravenous infusion of iron polymaltose up to 1500 mg in 250 mL sodium chloride 0.9% administered at ultrarapid rates: firstly over 30 minutes and then, should no safety concerns arise, over 15 minutes in a second case series. 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 iron replacement 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 Gastroenterology or General Medicine team seeing patients requiring iron infusions for management of inflammatory bowel disease and iron deficiency anaemia due to gastrointestinal bleeding. The required dose will be calculated by medical and pharmacy staff using established guidelines for iron polymaltose (last update 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 30 minutes (group 1) or 15 minutes (group 2). 10 participants per infusion rate group will be enrolled: first ten for 30-minute infusions (group 1), another ten for 15-minute infusions (group 2) if no safety issues arise with group 1 such as severe reactions above the rates observed in previous studies of rapid and slow infusion, which was at 1.1%.  The iron polymaltose infusion will be prepared by the Pharmacy Department, as per standard procedure, 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 (30 or 15 minutes), as specified by the monitoring medical staff member, who will also be one of the investigators. Participants will be monitored by a medical investigator for the duration of the infusion, with the remainder one hour observation period to be done by the nursing staff as per current iron polymaltose guidelines. Medical staff members will be called in case of any adverse events as per current guidelines as set by Peninsula Health. Monitoring will include pulse, blood pressure, temperature, and oxygen saturation prior to infusion and every 5 minutes for the duration of the infusion, then every 15 minutes during the 1 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. |
| 6.5 | Outcome(s) \* |
|  | The primary outcome is the overall adverse event rate in each group.  Secondary outcomes included the severity of adverse events, which will be graded as mild, moderate or severe. Mild reactions will be defined as those that do not require a change in the infusion rate, a change in treatment or prolongation of hospital stay. Moderate reactions will be defined as those that required a change in infusion rate or interruption to the infusion, or required minor treatment such as analgesia or requiring additional monitoring. Severe reactions will be defined as those that required the iron infusion to be stopped without an 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). Adverse events during the week after infusion administration, and their severity. |

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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 it (IBD, raised inflammatory markers, concurrent immunosuppression), * any adverse effects recorded in the notes or 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 reported by medical notes and as per patient phone call 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 June-Septmeber 2017. * Expected trial period is 3-4 months based on current rates of iron infusions prepared at the Pharmacy Department, permitting for patients declining to participate (October 2017-January 2018). * Interim safety data analysis after the first 10 patients at 30 minutes infusion rates will be conducted prior to progressing to the 15 minute infusion part of the safety study – October-November 2017. * The study data collection, analysis is anticipated to take 1 month January-February2018. * Study results write up 1-2 months February-March 2018. * 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 at the time of the iron infusion. |

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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 Peninsula Health confidential bin by an investigator.  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 \*** |
|  | Being a pilot study with a small sample size, this study will not be powered to achieve statistical significance; rather the analysis of outcome measures is for exploratory purposes only.  Adverse event rates will be compared using Fisher's exact test, and baseline parameters using Fisher's exact and student-t test or Kruskal Wallis 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 & Therapeutics Committee and the medication safety pharmacist. An interim results analysis and report will be provided to HREC and Drug and Therapeutics committee prior to progression to the second group of patients at the 15-minute infusion rates.  Participants will be monitored for adverse effects during the infusion and for the following hour by nursing staff as per existing iron polymaltose administration guideline. Any delayed adverse reactions for the next week may be documented in the patient’s history by nursing or treating teams and identified upon scanning through the DMR. 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. Participants discharged within a week of their infusion will be contacted 1 week after the infusion to check for any adverse event occurrence, their management and severity. Any severe reactions that occur during the study 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 5 hours with test dosing at even slower rates 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, and test doses are no longer recommended by the European Medicines Agency and is no longer included in the current iron polymaltose infusion guidelines. These findings have been incorporated into the hospital guideline and, as such, have become standard practice. This study aims to explore the safety of ultrarapid administration firstly over 30 minutes and then, should no concerns arise, over 15 minutes in a second group – further testing the hypothesis that ultrarapid rates are non-inferior in safety to the slower infusions.  Given the risk of adverse events, the study will require Human Research Ethic Committee (HREC) review and development of patient consent forms. |

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| **11.** | **Finance and resource use \*** |
|  | Nil. |

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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, medical and pharmacy staff after the investigator-led monitoring period. 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.  The main limitation will be the pilot-nature of the study itself, where any evaluation of outcomes cannot be determined with confidence nor statistical significance, and is therefore to be considered exploratory only. In order to be powered to 80% with a two sided alpha for significance at 0.05 for the primary end-point of identifying a change in the rate of severe adverse events up to 4%, the study would require 275 patients to be enrolled. Plans to expand the study will be pursued given the potential significant benefit for patients, infusion centres and hospitals with reduced medication and operational costs, should the results support the null hypothesis. |