TRICS IV AUSTRALIA & HEPCIDIN AND IRON STORAGE SUB-STUDY

FREQUENTLY ASKED QUESTIONS (FAQs)

Version Date: 01-Feb-2023

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Protocol Questions

1. **What are the main differences from TRICS III?**

   There is an age range incorporated into the inclusion criteria of 18-65 years of age. The pre-op EuroSCORE is to be determined using the EuroSCORE I calculator and in Australia, we have an additional component of a sub-study called the Hepcidin and Iron Storage Sub-Study.

2. **Our site has moved to using EuroSCORE II. Do we still have to use EuroSCORE I?**

   Yes, all sites are required to use the EuroSCORE I calculator when screening patients as this is consistent with the tool used for the other TRICS studies. EuroSCORE will be calculated within the eCRF on REDCap, and a paper version will be provided in the TRICS IV Manual of Operations.

3. **Our patient was randomised, but then their surgery was delayed to a later date. How should we proceed?**

   Please inform the Trial Coordinating Centre if this occurs and we will discuss the next steps on a case-by-case basis, as a Protocol Deviation may need to be logged.

4. **Our patient who reached the Liberal transfusion trigger was transfused 1 x unit of RBC yesterday. However, following a repeat Hb (post-transfusion) and a repeat on bloods early this morning the patient remains below the trigger. This patient may be discharged today. Would this be considered a non-adherent event if they did *not* receive a second transfusion prior to discharge?**

   If the patient meets a Hb trigger and they are discharged from hospital without receiving a transfusion prior to the end of the protocol defined time period (2/18/40 hours), this will not be considered a non-adherent event and you do not need to report the event in REDCap.

5. **When and where should we send the Screening Log for this study?**

   The Screening Log should be emailed on the *first week of each month* to the Data Management and Coordination Centre in Canada (TRICSIV@unityhealth.to). Please ensure that the Patient's Initials (column B) are removed (de-identified) before sending a copy of the screening log.

6. **What constitutes 'chest closure' as we are unsure if its closure of sternum with wires or skin closure?**

   Chest closure is once the sternum is closed.

7. Where should we send the ECGs that we collect for TRICS IV?

Please email all study ECGs directly to the Data Management and Coordination Centre in Canada - TRICSIV@unityhealth.to.

8. If a patient is being held in ICU due to bed availability, should the ward trigger threshold for the liberal group apply?

Patients who are waiting to be transferred from the ICU to the ward can be transfused using ward triggers.

9. If a patient triggers in the ICU and is then transferred to the ward within the 18 hour window, does this reset the trigger the ward value?

Patients in the ICU can follow the ward triggers if they are (i) ward-ready at the time the trigger haemoglobin is measured (even if they remain in the ICU for a longer period), or (ii) if they are transferred to the ward within 18 hours after the trigger is met.

10. Is co-enrollment into another study permitted?

There is no objection to co-enrollment – all observational studies are acceptable as are most interventional ones as long as the studies do not interfere with red cell transfusion guidelines (the intervention) or primary outcome.
Trials permitted for co-enrollment: **CALIPSO, BLENDER**
Trials not permitted: **CLIP II**
Please email the Trial Coordinating Centre (bhavita.patel@unimelb.edu.au) to check on specific studies that you wish to co-enroll into.

11. Our patient was randomised to the restrictive arm of the trial and required multiple transfusions of RBC's intra-operatively and another unit this morning in ICU. We are checking the Hb results from ABG's to see which units were given within the protocol-defined time periods and which were given when Hb levels were higher. Is this a deviation or a non-adherence event?

This is a protocol deviation and will need to be logged in the Protocol Deviation Log provided in the ISF. Data for these transfusions can still be entered as normal in REDCap. Non-adherence will be considered to have occurred if (1) a RBC transfusion is given without a protocol-defined Hb trigger being met, or (2) a RBC transfusion is not given subsequent to a "trigger event", and the Hb remains below the threshold at the end of the protocol-defined period (or a repeated Hb value was not performed during the protocol-defined time period).

12. Should we only exclude patients that require cardiopulmonary bypass straight from the cath labs?

The consent process and stress in these acutely urgent cases means that these patients are not appropriate to recruit.

13. **Should we exclude patients that have an angiogram and remain in hospital for surgery?**

    No, you can recruit inpatients as long as you have time to enable informed consent and get the needed preop tests done.

14. **Should we exclude patients that have diagnosed disease that transfer to our hospital from another hospital for surgery?**

    No, you can recruit inpatients from transfers as long as you have time to enable informed consent and get the needed preop tests done.

15. **How many times can the protocol be suspended? Do we need to record all transfusions given during the suspension period?**

    The protocol can be suspended more than once, *but only* if a **new** episode of bleeding or haemodynamic instability related to bleeding occurs. Once a decision is made to suspend the protocol, RBCs can be transfused at the discretion of the attending physician, and RBC transfusions administered during this time will not be considered non-adherent. The suspension may only continue until haemodynamic instability resolves or after 24 hours, **whichever occurs first.** All transfusions should be recorded in the *RBC Transfusion form* as separate transfusions, and you can indicate on this form that the event was *adherent* and that the protocol was suspended.

    All transfusions given during the period of a protocol suspension are adherent, so you do not need to complete the 'non-adherence' form in these cases.

16. **We have a patient who has agreed to take part in the trial and has increased dimensions of aortic root and ascending aorta and is having AVR & Aortic Root Replacement surgery. Can this be classified as 'surgery on thoracic aorta' in EuroSCORE I?**

    Yes, aortic root replacement involving the insertion of a synthetic aortic graft (e.g. a Dacron graft) to replace the aortic root and/or part of the ascending thoracic aorta fits under the definition of surgery on the Thoracic aorta as part of EuroSCORE I coding for TRICS IV.

Study set-up Questions

1. **What is required to get started on the trial?**

    For sites to get started, we will require site contact details, a signed/dated CV and a valid GCP certificate from the nominated Principal Investigator and coordinators at each site. We will provide start-up packs for local governance submissions and a Clinical Trial Research Agreement (CTRA) will be in place between The University of Melbourne and each site.

2. **Will there be a separate consent form for the sub-study?**

No, there will be one combined consent form for both the TRICS IV trial and the Hepcidin and Iron Storage Sub-Study.

3. What are the per patient payments for the study?

The per patient payment for TRICS IV Australia is $900 AUD and includes the processing of bloods and iron study tests that are routinely performed as part of standard care.

- $700 AUD (excluding GST) per patient for all screening, enrolments, preoperative, intraoperative and postoperative data points to hospital discharge or postoperative Day 28. Where the data is not yet complete, the payment for that patient will be applicable in a later quarter following completion of all data entry.
- $200 AUD will be paid upon completion of six month follow-up data.
- A support payment of up to $1000 AUD for Ethics and/or governance submissions will be payable once.

Additional funds will be available for the shipping and analysis of the Hepcidin and sTfR samples.

4. Is there provision in the budget for an archiving fee to be paid?

All archiving fees are to be paid from the $900 per patient payment.

5. What is required in order for our site to be activated?

The Trial Coordinating Centre requires the following documents from sites prior to being activated:

- ***Signed and dated CV's*** for the Principal Investigator, Co-Investigators and Research Coordinators
- ***GCP certificates*** for the Principal Investigator, Co-Investigators and Research Coordinators
- ***Governance approval letter***
- ***HREC Membership List***
- ***Site approved Patient Information Consent Form (PICF)***
- ***Signed Protocol Agreement page***
- ***Clinical Trial Research Agreement*** (fully executed)
- ***Medical Licenses***
- ***Study Task Delegation Log***
- ***REDCap Account Activation forms***
- ***Site Contact Sheet***
- ***Local Lab Certificate/ Accreditation***
- ***Local Lab Reference Ranges***

6. When can we schedule our Site Initiation Visit?

The Site Initiation Visit (SIV) will be scheduled once the Data Management and Coordination Centre (DCC) in Canada have approved all of the site activation documents (listed above).

7. What will happen during the Site Initiation Visit?

The SIV will take place over Zoom and will include training on both the TRICS IV and Hepcidin Sub-Study Protocols, as well as a demonstration of the REDCap database.

8. **When will we receive our Site Activation notice?**

   The Data Management and Coordination Centre (DCC) in Canada will issue a formal letter activating sites upon receiving all of the essential study activation documents, a fully executed CTRA and completion of the SIV.

9. **Where can I access trial forms and templates?**

   Each site will be sent an Investigator Site File (ISF) which contains all of the forms, templates and logs required for the main TRICS IV trial and the Sub-Study. The ISF can also be accessed via Dropbox (https://bit.ly/3KM3PoB).

10. **We are interested in participating in TRICS IV. Is there funding available for New Zealand sites or would we need to apply separately?**

    Currently all our ethics and funding is Australian-based due to the nature of our specific NHMRC-MRFF grant. Sites in New Zealand will require their own ethics approval and funding. Please get in touch with the Trial Coordination Centre (bhavita.patel@unimelb.edu.au) to discuss further as we would be happy to offer expertise and organisational support.

Sub-Study Questions

1. **Is participation in the Sub-Study mandatory?**

   Yes, recruitment to the Hepcidin and Iron Storage Sub-Study will be done at the same time as the recruitment to the main TRICS IV trial.

2. **Why has the primary outcome changed to Days Alive and Out of Hospital (DAOH) at 30 days?**

   We felt that it would be more consistent with the majority of other studies to change from DAOH 28 days to 30 days. The changes will not affect any other outcomes or processes, and the 28-day measures for the main TRICS IV study will be collected just the same.

3. **Is there additional funding available for the Sub-Study?**

   We would like to help sites as much as possible, but we have limited additional funding. Extra funds for the shipping and analysis of the Hepcidin and sTfR samples are available and we will cover reasonable costs.

4. **If we need to perform some of the blood tests outside of routine care, will there be additional funding to support this?**

   We have obtained additional funding to cover blood tests outside of routine care and sites will be offered up to $125 AUD per patient for these tests. This is in addition to the $900 AUD per patient payment offered which covers the expected laboratory tests set out in the main TRICS IV trial protocol and the Sub-Study Addendum which are to be performed as part of standard care at no additional cost.

5. What tubes are required to collect the Hepcidin and Soluble Transferrin Receptor (sTfR) samples?

Blood for Hepcidin and sTfR should be collected in a Serum Separation Tube (SST) and filled to the maximum limit (i.e. 2 x 1ml per tube).

6. Is the Trial Coordinating Centre supplying Cryotubes/vials and labels?

We would advise sites check with their Pathology department if they can supply cryovials and cryolabels for the vials. The Trial Coordinating Centre can provide a template for labels on request, which can be printed on standard Avery labels (65 to a sheet), with tape placed over the sticker once it is on the vial.

7. Our site does not have the facility to obtain a reticulocyte haemoglobin concentration. Do we still have to collect this result?

We would encourage sites to explore alternative methods with their Pathology department for obtaining this result as there are a range of machines that are available to provide this value. For example:

- Reticulocyte haemoglobin content (CHr) on Siemens Advia 2120 machines;
- Reticulocyte haemoglobin (Ret-He) on Sysmex XE/XN machines;
- Mean reticulocyte haemoglobin content (MCHr) on Abbott Sapphire machines;
- Reticulocyte haemoglobin expression (RHE) on Mindray BC 6800 machines;
- Reticulocyte haemoglobin cellular content (RHCc) on ABX-Horiba Pentra Nexus DX machines;
- Red Cell Size Factor (RSf) on Beckman Coulter analysers (to be converted to CHr values of Siemens Advia machines based on correlation studies)

These results may often be reported manually rather than on an electronic system. We would be happy to work with sites and their Pathology departments to determine the feasibility of collecting this result.

8. What tubes should be used for the Holotranscobalamin and Vitamin B12 tests?

Holotranscobalamin and Vitamin B12 are the same test. They have both been documented in the Manual of Operations because some sites perform one test and not the other. You will only be required to process one tube for this result (i.e. Holotranscobalamin or Vitamin B12).

9. Most of our cardiac patients are not having face-to-face postop follow-up due to COVID-19, and the majority are having telehealth appointments. Therefore, we are not able to collect the Day 30 Reticulocyte Haemoglobin result. Are there any solutions for this?

We would strongly encourage patients to return to site for a blood test if able to be performed and is convenient. For regional patients, they can be given a pathology slip to get FBE's done at a local lab facility, as long as the research team is able to obtain the test results.

10. We have spun and stored our own sample for our TRICS IV patient using our own supply of cryotubes. Can you confirm that you would like us to store these on site to be batch shipped at the end of patient recruitment?

Yes, we are requesting sites to store these samples until we are ready to ship for analysis at the end of patient recruitment. We will provide sites with the laboratory addresses and details for shipment once we are ready.

11. **Several of our patients reside a distance from the hospital. We have looked into getting one of the external NATA-accredited pathology labs to perform the Day 30 tests. Is this appropriate in terms of conducting the study?**

    Yes, we are happy for the Day 30 tests to be performed externally, as long as there are processes in place to be able to obtain the results. Please get in touch with the Trial Coordinating Centre (bhavita.patel@unimelb.edu.au) if you would like us to liaise directly with the external labs.

12. **If our patient is not able to come back to complete the Day 30 Reticulocyte Haemoglobin, would you deem them ineligible for the Sub-Study?**

    As much as we would like sites to try and obtain the Day 30 Reticulocyte Haemoglobin result (perhaps by providing patients with a pathology slip prior to discharge), we are no longer mandating this test to be completed for the Day 30 follow-up period. The patient would still be eligible for the Sub-Study.

13. **With regards to the estimated venesected blood loss calculator, can you please clarify if we are calculating study specific bloods only?**

    We would like an estimate value for all postop bloods.

Data Entry Questions

1. **Where do we enter data for the Sub-Study?**

   All data will be entered directly into REDCap and separate forms have been built into the database for the Sub-Study. There will not be a paper CRF for this study.

2. **Who will provide access to the REDCap database?**

   The Data Management and Coordination Centre in Canada will grant access to the REDCap database. Any staff members who are required to complete data entry for the trial will need to complete and return a REDCap Account Activation Form prior to receiving access.

3. **When should we enter values for Hepcidin and Soluble Transferrin Receptor (sTfR)?**

   Sites do not need to enter values for Hepcidin and sTfR as they will not be available until the end of the study. There will be a facility available on REDCap to enter these values once available and the relevant forms will be left unlocked.

4. **What if we are unable to enter some of the data or some data is missing?**

   The Data Management and Coordination Centre in Canada will be monitoring data entry in the REDCap database. They will be able to flag any data points that are missing. For data points that are not measured, sites can leave the fields blank in the eCRF and the Data Manager in Canada will query any blank fields. Alternatively, there will be a facility available on REDCap to reply to the query and confirm that the value is not available and the reason why.

5. **The lowest mixed venous pO_2 and lowest mixed venous O_2 saturation values are unlikely to be collected intraoperatively as the bloods that are collected intra-op are routinely arterial gases. Is it OK to leave these values empty on the eCRF?**

   It is OK to leave these fields empty. The Data Manager in Canada will query any blank fields, and sites need to respond saying the data is unavailable or provide further information on the missing data.

6. **Preoperative transfusions: How far back should we collect transfusions?**

   We ask that you record any transfusions given in the immediate preoperative hospitalisation period that leads to surgery (whether that is days, weeks or months). For out-patients, we ask that you record any transfusions given in the last month.

7. **For IV fluids, our patient received both 4% albumin and 20% albumin, but I can only enter one of these in the eCRF. How should we record this?**

   Enter the *average concentration % over the total volume;* for example, if 100ml of 5% and 100ml of 25% were administered, then you would enter 200ml of 15% albumin. We would advise you also use the *TRICS IV – Unit Conversions Albumin Calculator* located in the ISF to derive this number.

8. **Is there a data dictionary available for the trial?**

   Unfortunately the Data Management and Coordination Centre in Canada does not share the data dictionary with sites. There is a data entry guideline available in the Investigator Site File. Please get in touch with the Trial Coordinating Centre (bhavita.patel@unimelb.edu.au) with any specific queries.