T4P Protocol Appendix: Republic of Ireland

Study Title: The Threshold for Platelets study: a prospective randomised trial to define the platelet count below which critically ill patients should receive a platelet transfusion prior to an invasive procedure.

Short title: Threshold for Platelets (T4P)

Appendix Date and Version No: 09/JAN/2023, Version 1.0

[This document is an appendix to the T4P main protocol, to include participating sites within the Republic of Ireland. All procedures outlined in the T4P main protocol will be applicable to the Republic of Ireland, except where described in this document.]

1 Table of Contents

2 ABBREVIATIONS

CTU	Clinical Trials Unit
ICNARC	Intensive Care National Audit & Research Centre
INICUA	Irish National Intensive Care Unit Audit
SAE	Serious Adverse Event

3 STUDY DESIGN

3.1 Setting

3.1.1 Sites

Hospitals containing a critical care unit within the Irish National Intensive Care Unit Audit (INICUA) will be invited to take part in T4P. Study interventions will occur in the admitting critical care unit, in the Emergency Department prior to critical care unit admission, or where in the hospital the procedure takes place if it precedes a critical care unit admission.

3.1.1.1 Site requirements

In addition to those listed in the main T4P protocol:

- Active participation in the INICUA
- Willing to prepare and submit an application for site specific ethical approval

4 PROTOCOL PROCEDURES

4.1 Recruitment and consent

4.1.1 Consent procedures

The consent procedure for patients recruited in the Republic of Ireland are as follows:

4.1.1.1 Patient prospective informed consent

In the very rare situation where a patient has been deemed by the treating clinical team to have full mental capacity and is able to give informed consent at the point of meeting the eligibility criteria, they will be approached directly prior to randomisation for written or verbal consent to take part in T4P. If they provide verbal consent, they will then be followed up for full written informed consent, in line with the procedures outlined in section 4.1.1.2. If such a participant who gave prospective verbal consent subsequently loses mental capacity, the opinion of a substitute decision maker/relative must be sought to advise on their continuation in the trial (*see section 4.1.1.3*).

4.1.1.2 Patient consent to continue

Following randomisation, patients will be approached by a delegated member of the site research team once deemed to have full capacity to provide consent to continue. It is anticipated that this first

approach will occur within 24-48 hours of regaining capacity. A Participant Information and consent to continue form will be given to the patient. The form will provide information about the background/rationale for the trial, what participation means for the patient (e.g. data collection, follow-up questionnaires), confidentiality and data protection and the future availability of the trial results. Patients will be given time to read the form and have an opportunity to ask any questions they may have about participation in T4P.

A Consent to continue form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence. The Consent to continue form will also cover consent for access to medical records for ongoing data collection and follow-up.

After verifying that the Patient Information and Consent to continue Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes and the original kept in the Investigator Site File. If the patient is unable to physically sign the Consent Form (e.g. due to weakness, reduced dexterity), an independent witness (not involved in the trial) can sign on their behalf.

In the situation where a patient is approached in hospital but wishes to have more time to consider participation, they can request to be approached via the method detailed in section 4.1.1.4.

4.1.1.3 Deferred Assent by Substitute decision maker/Relative

It will usually not be possible to involve trial participants in the consenting process early on. Instead, consent will be obtained from patients once they have stabilised and are deemed to have capacity.
In the interim, once notified of the enrolment of a patient into T4P, a delegated member of the site research team will approach the substitute decision maker/relative (in person or via telephone) as soon as appropriate and practically possible to discuss the trial and seek their opinion as to the patients' likely wishes and feelings regarding participating in the trial. Ideally, this approach would take place within 24-48 hours of randomisation, but once the patient's medical situation is no longer an emergency.

Where approached in person, the substitute decision maker/relative will be provided with a Deferred Assent Form containing all of the information provided on the study, supplemented with information on why the substitute decision maker/relative has been approached at this stage. Substitute decision maker/relative will be given time to read the Deferred Assent form and have an opportunity to ask any questions they may have about the patients' participation in the T4P study.

A Deferred Assent form will be provided indicating that: the information given, orally and in writing, has been read and understood; the patients' participation is voluntary and can be withdrawn at any time without consequence; and that, in the substitute decision maker/relative's opinion, who know the will and preferences of the patient and would not object to taking part in the trial.

After verifying that the information in the Deferred Assent Form is understood, the person seeking the assent will invite the substitute decision maker/relative to sign this form and will then add their own name and countersign it. A copy will be given to the substitute decision maker/relative, a copy placed in the patient's medical notes and the original kept in the Investigator Site File.

If the substitute decision maker/relative advises that, in their opinion, the patient would not choose to participate in the trial, then the trial treatment will be stopped (if ongoing) and the substitute decision maker/relative asked whether, in their opinion, the patient would be willing to continue with ongoing data collection.

Where a substitute decision maker/relative is unable to visit the patient in hospital (e.g. due to infection control measures), this consultation may take place over the telephone. The consultation should be conducted by an experienced member of the site research team with knowledge of intensive care. The telephone consultation should be witnessed by another member of ICU research staff. The Deferred Assent form will be sent to the substitute decision maker/relative by post in a stamped addressed envelope. The outcome of the consultation will be documented and signed by person seeking opinion on the Deferred Assent Form, countersigned by the witness.

Upon patient recovery, the patient will be approached directly for consent to continue (*see section 4.1.1.2*). The patient's decision will be final, and will supersede the substitute decision maker/relative, where there is disagreement.

4.1.1.4 Discharge prior to consent/assent being confirmed

In the situation where the patient is discharged from hospital without gaining capacity prior to confirming their consent decision, an experienced member of the site research team with knowledge of intensive care will attempt a phone call to the patient after ultimate hospital discharge to: inform them of their involvement in T4P; provide information about the trial; and enquire when they are due back in clinic or an outpatients appointment and arrange to meet them at this time to go through the trial in details and obtain their consent to continue . The Patient Information & Consent to continue form will be sent to the patient by email or by post prior to meeting them in the clinic to allow them time to read the information. If there is no contact after 3 phone calls, we will attempt to contact the relative/substitute decision maker to confirm if the patient has capacity, if so, request a contact number, if not then is the substitute decision maker/relative still happy for the patient to remain in the study.

If the participant is transferred to another hospital participating in T4P before the consent procedures are complete, then the local research team will contact the research team at the receiving hospital to handover the consenting procedures.

If the participant is transferred to another hospital who are not participating in T4P before the consent procedures are complete, then the local research team will contact the receiving hospital for outcome

data. Meanwhile, substitute decision maker/relative opinion should be sought as appropriate. The patient consent to continue will be followed as appropriate following ultimate hospital discharge.

In the situation where a patient is discharged from hospital without regaining capacity, the substitute decision maker/relative decision will be final.

4.1.1.5 Refusal or withdrawals of consent/opinion

If a patient declines consent to continue, or a substitute decision maker/relative advises that they believe the patient would not choose to participate in the trial, and, if a patient or their substitute decision maker/relative withdraws consent/assent at any time during the trial - this decision will be respected and will be abided by. All data up to the point of this decision will be retained in the trial unless the patient or substitute decision maker/relative requests otherwise. Where possible, patients and substitute decision maker/relative will be asked if they are happy for data to continue to be collected from the medical records for the trial, emphasising that this will not require any further contact with the patient/substitute decision maker/relative about the trial.

5 SAFETY REPORTING

Please see section 12 of main T4P protocol for definitions and reporting procedures for adverse events. In addition, for sites within the Republic of Ireland:

5.1 Notifying the Ethics Committee

Any related and unexpected Serious Adverse Events (SAE) will be reportable to all participating site ethics committees within the Republic of Ireland.

5.2 Statutory reporting

Transfusion reactions that constitute a SAE should be reported as standard to the applicable blood products regulatory authority.

6 STATISTICAL AND DATA ANALYSIS

Statistical analysis is defined in section 13 of the main T4P protocol. All analyses will be pre-specified in a Statistical Analysis Plan published prior to the first interim analysis.

7 DATA MANAGEMENT

Trial data are collected on to the electronic Case Report Form. For further details, please see section 14 of the main T4P protocol. For participating sites within the Republic of Ireland:

7.1 Data collection

To maximise efficiency, trial data collection will be nested within the Irish National Intensive Care Unit Audit (INICUA). An INICUA Admission Number will be required by the Intensive Care National Audit and Research Centre (ICNARC) Clinical Trials Unit (CTU) to successfully enable data linkage to the INICUA national clinical audit. Identifiable data (including full name, contact details, date of birth) will not be sent from the Republic of Ireland to ICNARC CTU.

7.2 Questionnaire follow-up

Questionnaire follow-up will be coordinated as per 14.4 in the main protocol, by the local research teams in participating sites in the Republic of Ireland.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Approvals

T4P will receive favourable ethical opinion from each participating site in the Republic of Ireland.

8.2 Participant confidentiality

For participants recruited in the Republic of Ireland, an INICUA Admission Number will be required by the ICNARC CTU to successfully enable data linkage. Identifiable data (including full name, contact details, date of birth) will not be sent from the Republic of Ireland to ICNARC CTU as follow-up of participants will be coordinated with the Republic of Ireland by each participating hospital research team.

9 SERIOUS BREACHES

Serious breaches are defined in section 17 of the main T4P protocol. In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the Chief Investigator, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving local hospital ethics committee within the applicable local timeframe.

10 ETHICAL AND REGULATORY CONSIDERATIONS

Each participating site Principal Investigator shall submit once a year throughout the study, or on request, an Annual Progress Report to their local hospital Ethics Committee and Sponsor.

11 FINANCE AND INSURANCE

HSE clinical indemnity covers in respect of the clinical treatment that is provided in the Republic of Ireland. The University of Oxford has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).