Reviewer's report

Title: Transfusion of Fresh Frozen Plasma in non-bleeding ICU patients: TOPIC TRIAL rationale and study design

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Reviewer: Jacques Lacroix

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Manuscript entitled “Transfusion of fresh frozen plasma in non-bleeding ICU patients: TOPIC trial – rationale and study design” by Marcella Müller et al.

Submitted to the journal “TRIALS”

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SUMMARY. – In this research protocol, Müller et al describe a multicenter randomized open-label blinded endpoint evaluation (PROBE) clinical trial with two arms. The acronym of the study is TOPIC. All consecutive non-bleeding patients admitted to a participating intensive care unit (ICU) who presented an international normalized ratio (INR) higher than 1.5 and lower then 3.0, and for whom an invasive procedure is scheduled, will be considered for recruitment. Consent will be obtained if no exclusion criterion is observed. Patients allocated to the control group will receive 12 mL/kg of fresh frozen plasma (FFP) before the invasive procedure is started. Patients in the experimental group will not receive any FFP transfusion before the procedure. The primary outcome measure is “relevant bleeding” during or shortly after the procedure. Secondary outcomes include minor bleeding, correction of INR, onset of acute lung injury, length of mechanical ventilation and of ICU stay, and costs. It is expected that the TOPIC trial will show that not receiving a FFP is safe in non-bleeding patients with an INR between 1.5 and 3.0.

MAJOR COMPULSARY REVISIONS

ABSTRACTS
• Methods. – I understand that TOPIC is a non-inferiority randomized clinical trial (RCT); please, write this in the abstract.

METHODS
• Study population. – Patients with “clinically overt bleeding” will be excluded. Please, provide an operational definition of “clinically overt bleeding”.
• Intervention and co-interventions. – Patients in the control group will receive a transfusion of FFP; I guess that time zero will be when the transfusion is started. What will be time zero in the experimental group (no FFP)?
• Compliance is not defined.
• How will be checked compliance is not described.
The section entitled “Protocol drop out” is somewhat misleading. A patient who makes the decision to leave the study is indeed a drop out, but only if s/he also makes the decision that no data can be collected; if it is not the case, such patient must be kept in the study and in the intent-to-treat analysis.

Non compliance should not be considered as a justification to exclude a patient from an intent-to-treat analysis, although they should be excluded from a per-protocol analysis.

More details on co-interventions would be helpful. It is great that the investigators plan to take into account a co-maneuver like ultrasound guidance. I think that they should consider collecting data on other co-interventions, like red-cell and platelets transfusion, plasma transfusion given during of shortly after the procedure, fluid balance (no supplementary fluids is given to patients allocated to the experimental group), etc.

What will happen if a patient goes from the ICU to the operating room on an emergency basis, or if a technique that can modulate the coagulation profile of the patient like hemofiltration or plasmapheresis is started?

Study End Points. – How will be monitored and who will monitor the primary outcome measure (bleeding) is unclear.

Please, define “PEEP score” and “circulatory overload”.

Please provide a reference to the “APACHE IV” score (I am aware only of the APACHE III score).

Statistical Analysis. – Will the statistical analysis be done on an intent-to-treat approach or a per-protocol approach? I suggest to do both because there is a debate presently on what is the best approach in the context of a non-inferiority RTC: some experts consider that both analyses must be done in such instance (Matilde Sanchez M, Chen X. Choosing the analysis population in non-inferiority studies: per protocol or intent-to-treat. Stat Med 2006 Apr 15;25(7):1169-81).

MINOR ESSENTIAL REVISIONS (not for publication).

Abstract (< 350 words).

• The acronym TOPIC must be defined.

• Methods. – It is written in the abstract that “costs” will be a secondary outcome; however, the outcome “costs” is not discussed in the body text of the protocol.

Discussion.

• Page 12, 1st line: define RCT.
List of abbreviations.

- Define the acronym RCT.

DISCRETIONARY REVISIONS.

- Up to 10 key words chosen according to the list of Medical Subject Headings (MeSH) provided by the Index Medicus, like “randomized clinical trial” must be added.

DECLARATION OF CONFLICT OF INTEREST
I declare that I have no competing interests.

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Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.