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Dear Dr Lakin

In 2010, we published results from our large (20,211 patients) international multi-centre trial (the CRASH-2 trial) of tranexamic acid (TXA) in bleeding trauma patients. TXA reduced death due to bleeding and all-cause mortality. Pre-specified sub-group analyses showed that early treatment (within 3 hours of injury) was most effective. There was no effect on mortality when TXA is given after three hours and it seemed to increase deaths due to bleeding. Trauma care guidelines in many countries now recommend TXA in all bleeding trauma patients who are within 3 hours of injury.

Moore and colleagues believe that there is a sub-group of patients with fibrinolytic shutdown (a state that can be identified with a new diagnostic test) and that despite being within 3 hours of injury, patients in this subgroup are harmed by TXA. In the spirit of scientific openness, I agreed to share the CRASH-2 trial data with Moore's team so that they could test their hypothesis. My only condition was that before receiving the dataset, they document their planned analysis in a protocol. I did this for important scientific reasons. Within any large dataset there are a number of apparent but in fact spurious subgroup differences. Preparing an analysis plan in advance avoids the risk that many different analyses are carried out with a post-hoc focus on the ones that support the particular hypothesis. Such a selective use of the play of chance is considered to be the most important form of scientific misconduct in clinical trials (see attached). Moore and colleagues agreed with my proposal and as soon as they sent me their analysis protocol, I sent to them the full trial dataset. The current analyses are funded by the company that makes the diagnostic test.

The planned analysis did not show a sub-group of patients harmed by TXA. Indeed, TXA reduced mortality by the same amount in all of the planned subgroups.

Planned subgroup	Relative risk reduction with TXA
P-hyperfibrinolytic	RR=0.87
P-physiologic	RR=0.88
P-shutdown	RR=0.87

However, Moore and colleagues then conducted went on to conduct further analyses that were not pre-specified. It is not clear how many analyses were conducted but one of them showed that if the shutdown subgroup is further sub-divided into those who received more than one unit of red blood cells, TXA appears to increase the risk of death compared with placebo (and presumably, TXA is even more beneficial in those that do not receive red blood cells). They then drafted a paper that emphasized this 'finding.' That the pre-specified analysis did not provide evidence for the shutdown hypothesis was not mentioned in the abstract and hardly in the entire paper (see paper attached). When asked to remove the post-hoc analysis and report only the pre-specified analyses, Moore and colleagues said they believed that they had an ethical responsibility to report them.

I believe in the principle of data sharing. I also believe in good science and to avoid the dangers of spurious sub-group results, I asked the investigators to pre-specify their analyses. The reported analyses were not pre-specified. Moreover, the sub-group variable (receipt of blood) is an outcome measure. Methodological guidelines recommend that subgroup analyses use variables defined at randomization. Those based on factors that emerge during follow-up violate the principles of randomization and are less valid.

This is not an ethical dilemma. This is a breach of trust and poor science. Drawing selective attention to a post-hoc, scientifically dubious sub-group result could discourage some doctors from offering patients a safe and effective treatment and patients could die as a consequence.

Yours sincerely

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March 20, 2017

Re: Review of draft journal article – "Clinical predictors of fibrinolysis phenotypes warrant a selective use of tranexamic acid in trauma: a secondary analysis of the CRASH-2 study.

Review Panel: **Dr. R. Traystman, PhD, VC for Research**
Dr. J. Repine, MD, Chair of the Research Ethics Committee
Dr. A. Lakin, PhD, Research Integrity Officer

At the request of Drs. Roberts, Moore and Sauaia, a review team was established to consider if a manuscript drafted by Dr. Moore and his team based on a secondary analysis of the CRASH-2 data should be published.

The review panel met on 3/15/17 to review the various documents provided by the two sides of this issue.

Considerations of the review team include:

1. **Dr. Roberts asked Dr. Moore and his team beforehand to provide the specific analysis that they planned to do with the sub-set of data. The analysis plan provided did not include the specific sub-set analysis addressed in the draft paper. Dr. Moore's team acknowledged that fact.**

2. **The specific sub-set analysis did not use variables defined at randomization but instead used outcome measures. The scientific value of the proposed paper is, therefore, questionable based on the accepted standards of the field with respect to post-hoc analyses.**

3. **The ethical question of whether or how best to treat trauma patients or sub-sets of patients does not seem to be addressed with scientific rigor by this paper. The results outlined appear to be hypothesis generating only.**

Determination:

1. **Dr. Moore and his team should only have access to the CRASH-2 data for a specific purpose. The team did not describe this specific analysis as part of the proposal requested beforehand by Dr. Roberts. Indeed, there is some concern on the part of the panel that Dr. Moore and his group used data provided by Dr. Roberts for a purpose that was not approved by Dr. Roberts. Dr. Roberts was quite careful in indicating precisely what the data could be used for and Dr. Moore and his group used the data for a different purpose.**

2. **Therefore, unless Dr. Robert's agrees to the use of the data in this manner, the manuscript cannot be published for ethical reasons.**

3. With Dr. Robert's permission, this data could be used for a grant application to conduct a prospective clinical trial specifically designed to answer this specific research question.

4. The review panel did not believe that there were patient treatment implications that would mitigate the other concerns outlined above.

5. The review panel also speculate that authorship issues may arise since Dr. Robert's is listed as a co-author and the journal will likely need approval of all authors to publish the manuscript.

Conclusion:

1. The recommendation to Dr. Moore and his team is to consider how best to prospectively answer this important question rather than publish the current draft manuscript, unless Dr. Roberts approves. .

Sincerely,

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