Appendix 1. Protocol violation adjudication process

Introduction

Adjudication in clinical trials is intended to minimize subjective decisions and systematic errors in the assessment of key information such as patient eligibility, study outcomes and protocol adherence. Evaluating protocol adherence is an important methodological aspect of conducting clinical trials as non-adherence can bias findings. Non-adherent participants may have an inherently different prognosis or be less likely to benefit from (or be harmed by) the study intervention than adherent participants because of suboptimal/sub or supratherapeutic exposure.

No clear, standardized or universal definition of protocol adherence is accepted. As a result, investigators must tailor methods for assessing protocol adherence to the specific characteristics of their trial. This is particularly challenging when the intervention to be tested is complex or involves complex participants and settings such as critically ill patients.

In trials evaluating different hemoglobin (Hb) transfusion thresholds, a clinically significant difference of Hb levels between groups throughout the duration of the intervention is an important objective to demonstrate the fidelity of the interventions and may be considered as the ultimate and true measure of protocol adherence. Since a definitive conclusion on the Hb level difference between groups can only be made at the end of the study, investigators have to monitor, while conducting the study, different parameters to ensure overall adherence.

One critical parameter of protocol adherence is adherence to the transfusion threshold. However, transfusion thresholds need to be contextualized and adapted to the clinical environment, keeping in mind that not all situations in which the transfusion threshold is not respected can be seen as clinically important protocol violations that may bias the results and expose study participants to unnecessary risks. For example, to suspend transfusion in patients for whom a decision to withdraw life-sustaining therapies has been made should not be seen as a protocol deviation or a protocol violation as it represents a judicious use of scarce resources that is unlikely to bias the results.

Some protocol violations are unlikely to have the same impact in a given situation depending on whether it occurs in one study group or another. As an example, transfusing red blood cells (RBC) to a patient allocated to the liberal group while not reaching the transfusion threshold does not have the same impact as transfusing a patient in the restrictive group who did not reach the transfusion threshold. The former situation would result in a greater separation of the Hb curves between study groups while the later would do the opposite. On the opposite, not transfusing a patient of the liberal group who reached the transfusion

threshold would attenuate the difference of the Hb level curves between study groups, while not transfusing a patient allocated to the restrictive group would accentuate this difference.

Another parameter that may be monitored in transfusion threshold trials is the time between reaching the transfusion threshold and administration of the transfusion itself. In patients with traumatic brain injury, the underlying hypothesis of aiming for higher Hb levels is that the injured brain is particularly sensitive to ischemia. Therefore, minimizing the exposure time to low Hb levels may increase the benefits (if any) of targeting higher Hb levels. However, several clinical situations can delay transfusion, such as hospital-related (e.g., rationalization of blood bank services outside of business hours, institutional policy on Hb validation for transfusion), ICU-related (e.g., rationalization of some interventions overnight), or patient-related factors (e.g., difficult crossmatch). These factors are important and may vary across centres, especially in trials conducted in various jurisdictions.

In HEMOTION, we advocate a pragmatic approach where any deviation from the protocol will not be systematically classified as a protocol violation. Instead, deviations will trigger a rigorous and transparent adjudication process whose goal is to systematically assess if each deviation was truly avoidable or clinically important.

Protocol deviations

Protocol deviations will be classified into three categories for review by the adjudication committee:

1. Any situation where RBC transfusion occurred while the Hb threshold was not reached.

2. Any situation where more than one unit were transfused without reassessing the Hb level between transfusion.

3. Any situation where there delay between the Hb measurement and the RBC transfusion is greater than 3 hours or where an RBCs were not transfused despite reaching the transfusion threshold.

If a transfusion is suspended in the context of life-sustaining therapies withholding or withdrawal, this will not be considered as a protocol deviation or violation.

Adjudication process

The protocol violation adjudication committee will consist of two of the principal investigators and three other coinvestigators, including one blood banker, one anesthesiologist and one intensivist. The information to adjudicate the protocol deviations will be extracted from the protocol deviation form. If necessary, additional information will be obtained directly from the research team as per requested by the adjudication committee. We will perform a calibration exercise to reduce the variability in assessments among raters. Independently, all five

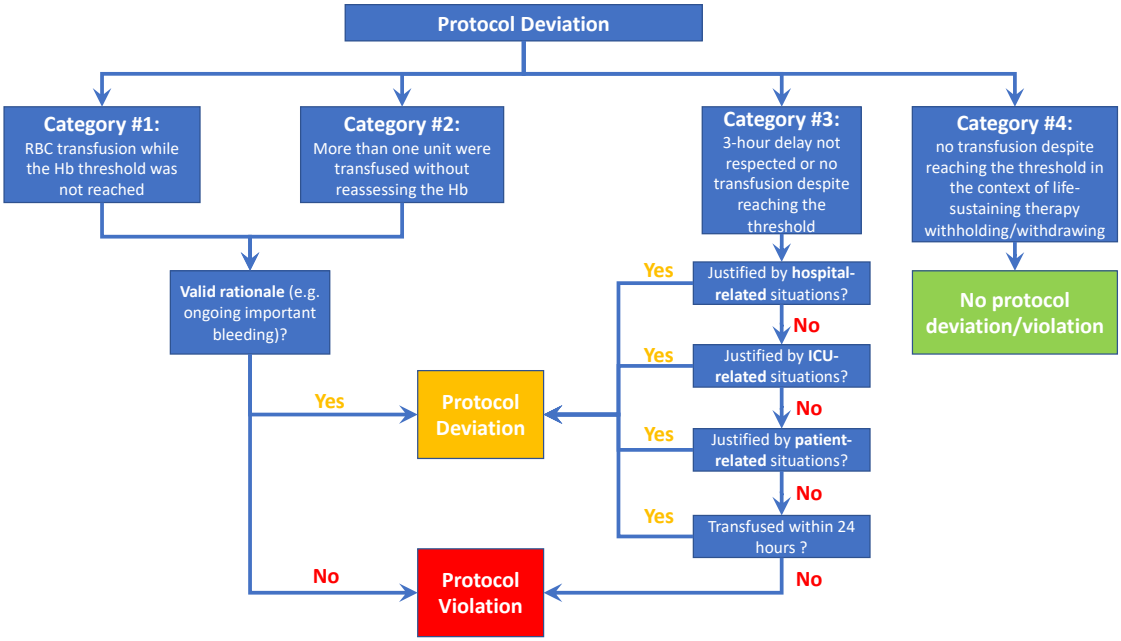
adjudicators will examine 20 *protocol deviations*, including at least three in each of the three above-mentioned deviation category (if the number of deviations per category is sufficient). Adjudicators will discuss their assessments and reasons for disagreement to attempt clarifying the adjudication process. Then, another set of 20 deviations will be evaluated. If the agreement for this set is excellent (kappa greater than 0.8), we will proceed with pairwise adjudication for the remainder of the trial. A pair of adjudicators, including at least one of the principal investigators, will independently assess each event. One of the two principal investigators will be randomly assigned to each deviation and paired with a randomly selected second adjudicator. All adjudicators will be independent and blinded to each other for their initial assessment. Disagreements between pairs of adjudicators will be resolved by further discussion and/or consultation with a third reviewer.

Definition of a protocol violation (see Figure 1)

1. Protocol deviations in which RBC transfusion occurred while the Hb threshold was not reached (**category #1**) will be reclassified as a protocol violation if no valid rationale is provided to justify the transfusion. Valid justifications include, but are not limited to, active bleeding or imminent or anticipated Hb drop below the transfusion threshold (e.g., Hb near the transfusion threshold and upcoming major surgery with high risk of bleeding). Adjudicators will then have to classify those events as either **protocol deviation** or **protocol violation**.
2. Protocol deviations in which more than one unit were transfused without reassessing the Hb level between transfusion (**category #2**) will be reclassified as a protocol violation if no valid rationale is provided to justify the transfusion. Valid justifications include, but are not limited to, active bleeding or extremely low Hb levels. Adjudicators will then have to classify those events as either **protocol deviation** or **protocol violation**.
3. Protocol deviations in which the three-hour delay between an RBC transfusion and the Hb measurement is not respected will remain classified as a protocol deviation if a valid rationale is provided to justify the delay. Valid justifications can be classified into three different categories (hospital-related, ICU-related, patient-related) and may include (without being limited to) the following scenarios:
    a. Hospital-related situations: rationalization of blood bank services outside of business hours, unavailability of blood due to orange code.
    b. ICU-related situations: rationalization of some interventions overnight due to limited staff issues, another more unstable patient requiring care, institutional policy on Hb validation for transfusion.
    c. Patient-related situations: difficult crossmatch, no IV access available.

    Subsequently, all transfusion delays that are not justified by either those three categories will be reclassified as a protocol violation only if the delay is greater than 24 hours.

Figure 1.


Protocol Deviation
Category #1: RBC transfusion while the Hb threshold was not reached
Category #2: More than one unit were transfused without reassessing the Hb
Category #3: 3-hour delay not respected or no transfusion despite reaching the threshold
Category #4: no transfusion despite reaching the threshold in the context of life-sustaining therapy withholding/withdrawing
Valid rationale (e.g. ongoing important bleeding)?
Yes
No
Protocol Deviation
Protocol Violation
Justified by hospital-related situations?
Justified by ICU-related situations?
Justified by patient-related situations?
Transfused within 24 hours ?
No protocol deviation/violation