

1.c (2): Do the RESUS dosing and administration guidelines provide adequate assurance of a reasonable risk to benefit ratio?

Review #7

At this point, the dosing guidelines seem reasonable and it is difficult to see how they might be better refined until human data emerge.

1.d i: Has the sponsor provided adequate evidence to guide EMTs as to whether declining pulse oximetry values are due to interference by HBOC-201 or other reasons that reflect pathophysiological causes for reductions in arterial Hb O2 saturation?

No, there appears to be no discussion of this problem. However, the only practical and obligated response by the EMTs to this situation would be to increase the inspired O2 to its limit. If lung function is normal or near normal, then increased O2 extraction by the product, increased extraction due to ongoing blood losses and/or hypoperfusion would not lead to arterial O2 desaturation. Any other maneuvers, except with the exception of consideration for tension pneumothorax would be beyond the skills of EMTs.

1.d ii: Has the sponsor submitted adequate data to guide EMTs in their response to BP > 150 mmHg?

No. It appears that the only guidance is cessation of HBOC-201 infusion. This is prudent but still may leave some patients in an incompletely fluid repleted state. Given the uncertainties about assessing volume status with a vasoconstrictor volume expander, it would be premature to consider vasodilator use to bring the BP below 150 mmHg.

1.e i: Do the data support the sponsor's claim that the benefit to risk profile for HBOC-210 compared to standard of care in trauma patients is reasonable.

Yes. It is not clear that the high incidence of BP > 141 mmHg during the first infusion of HBOC-201 in the HEM-0115 study is applicable to the proposed target population of the RESUS trial, since these are patients with traumatic hemorrhagic shock.

1.e ii: What are the clinical implications of the statement "Vasopressors are contraindicated for the treatment of hemorrhagic shock" ?

HBOCs represent such a novel and unique resuscitative fluid strategy, that it is not clear that the above proscription is valid. No other resuscitative fluids have the added important aspect of increased O2 carrying and release capacity. Only research will be able to place HBOCs within or outside of this rule.

1.f i: With respect to tissue perfusion has the sponsor submitted adequate evidence to show that BP measurement by cuff techniques and titration of HBOC-201 use is reasonable?

No. There are at least two issues here. The first is whether the potential vasoconstrictor effect of HBOC-201 might be more potent on more distal sites of BP measurement such as extremity cuffs. The second goes back to the problem of the insensitivity and non-specificity of BP measurements to accurately assess volume status in HS. Thus it is not clear how accurate cuff measurement for titration of HBOC-201 infusion will be, and only careful observation and recording of data in a field study will permit an answer in practical terms.

Clinical Safety Profile

2.a.i: Are the imbalances in adverse events against the HBOC-201 arising from the pivotal HEM-0115 trial relevant for RESUS subjects?

Given the younger and likely healthier patients to be studied in the RESUS trial and the larger volume requirements, it seems reasonable to conclude that the adverse event rate will be lower in RESUS trial.

2.b: What is the clinical relevance of a higher CVA, TIA, cerebral ischemia/infarction rate noted in the sponsor's BLA ?

This is worrisome, since in non-head injured younger and healthier trauma victims, I don't think CVAs and TIAs are common. But again, if these results are from an older, less healthy population with a greater degree of asymptomatic CV disease, then it may not be as relevant for the RESUS trial.

2.c What relevance is there to the lack of adverse events in the porcine studies of HBOC-201?

Since these pigs were likely young and otherwise healthy, and likely not to have unrecognized vascular pathology, it is unlikely that the RESUS subjects will be as healthy or to escape some adverse effects of HBOC-201 use.

2.d What is the clinical importance of the 4% rate of hypertension with < 1 unit of HBOC-201 in the European PCI trial for RESUS subjects?

If this was not a traumatic hemorrhagic shock trial, then it very likely that hypertension with a single unit will be so common.

2.e Are the rates of cardiac ACs from the HEM-0115 trial of HBOC-201 in orthopedic patients relevant to the RESUS subjects?

Again, these results are from an older, less healthy population with a greater degree of asymptomatic or even known CAD disease, and they may not be as relevant for the RESUS trial.

Sample Size Estimate

3.a.i Are there additional limitations of the NTDB?

I am not aware of any.

3.a.ii: Can the information from the NTDB be used to estimate the control mortality rate, given the RESUS trial enrollment criteria?

Since several of the study centers are part of the NTDB and some of the others are institutions in the same metropolitan areas, it seems reasonable to use the NTDB data. The problem may be that the NTDB includes some catchment areas that are more rural, such as Vermont and has a non-US site. Additionally these are historic data which usually change over time, so direct comparison to a present-day study is problematic. However, this concern is somewhat mitigated by the inclusion of a LR control arm representing usual care.

3.b.i: Do the RESUS trial and these studies share the same, or nearly the same, enrollment criteria?

I was unable to find the section 9 referred to 'below' so I cannot comment.

3.c.i: Has the sponsor submitted adequate evidence to support the 25% reduction in mortality in the HBOC-201 arm of RESUS?

No. This appears to be simply the hypothesis they are testing and the value around which they project the needed numbers to enroll

3.c.ii.(1): Does the projected 34% mortality in the control arm vs. a recent much smaller study of another HBOC (Sloan et al. JAMA, 1999) that found a 17% mortality in the control arm comport with the exception of informed consent that participation holds out the prospect of direct benefit to the subjects?

It is rare that any treatment arm of a study will extend benefit to 100% of subjects. The issue is does it harm a subset? This is a real concern and should be considered in the final exception for informed consent based upon the JAMA study and its higher mortality in the treatment arm.

Exception from Informed Consent

4 a Overall, does the RESUS protocol contain adequate evidence to meet the clinical requirements for exception from informed consent?

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Yes, I believe the investigators have addressed all of the relevant items in 21CFR50.24.

Respectfully submitted,

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