NETT Clinical Trial Proposal Summary

Project Description: Assessment and early 4 factor PCC treatment of TBI or ICH on anticoagulant therapy (warfarin)

Target Disease:
Traumatic or Spontaneous Intracranial Hemorrhage (ICH) on anticoagulant therapy

Primary Objective:

1) Assessment of Traumatic or Spontaneous ICH on anticoagulant therapy (and feasibility /outcomes of early treatment protocols in decentralized, non-trauma facilities), including clinical laboratory* and biomarker study values.
2) Comparison of SOC treatment at trauma center Hubs to protocolized PCC treatment at community hospitals/non-trauma centers prior to referral /transfer to a trauma center.

*Obtain TEG & TT values for all subjects using blood draws on arrival, before (if > 1hr from arrival) and after reversal therapy initiation with plasma or PCC. Compare TEG/platelet mapping to other, more broadly available, tests for coagulation for TBI or ICH patients.

Briefly describe the scientific rationale for the study:
There is very little known about the physiologic and serologic characteristics of anticoagulated Traumatic or Spontaneous ICH patients. The impact of protocolized treatment by community hospital sites with PCC, prior to transfer to a trauma center, has also not been evaluated in patients receiving this medication. Treatment protocols based on TEG results have been (in small samples) linked to reduced blood product usage (by 58.8%) and trend toward improved short-term outcomes. The TEG and TT lab tests are not widely available and take a longer time to produce at most sites than the more standard PT/PTT/INR tests but offer a greater depth of information about the capacity for hemostasis in anticoagulated patients.

Community hospitals/non-trauma centers may often receive elderly patients on anticoagulants with ICH. They have no capacity to reverse with plasma so looking at PCC at these facilities as a reversal agent prior to transfer would be very informative to healthcare system delivery practices.

Briefly describe the study design and indicate, in general terms, how the design will fulfill the intent of the study:

Prospective, Hub/site-randomized, study of early (referring community hospital-initiated) reversal treatment of anticoagulation therapy in Traumatic or Spontaneous ICH. 1:1 ration of Hubs assigned to either referral center recruitment for protocolized PCC administration vs standard of care (PCC treatment at trauma facility/Hub).

Study would consist of putting dedicated PCC at trauma centers as well as outlying community hospitals/non-trauma centers at assigned Hub/spoke sites, and initiating a treatment protocol in order to administer early treatment of reversal therapy in anticoagulated (warfarin) ICH cases.

Indicate the need, relevance and priority of doing the trial in the NETT network and its expected impact on current medical care:
A trial of a condition with this low an incidence rate requires, even for an exploratory hypothesis, a large multi-site network in order to enroll a useful sample size. The NETT involves both top-tier trauma centers with all available reversal treatments available and community hospitals who could adopt early treatment protocols (prior to transfer) with PCC.

Patient selection criteria:

1. **List Inclusion Criteria**

- Prior treatment with anticoagulant within 48 hrs (VKA: warfarin)
- Traumatic or Spontaneous ICH (blunt trauma only)

2. **List Exclusion Criteria**

- Poor prognosis (GCS =3, bilateral pupil dilation, etc.)
- Penetrating trauma
- Non-accidental trauma

Describe method for identifying and recruiting subjects for the trial:

Screening for trauma cases (TBI), non-contrast head CT orders, with home medication entries for warfarin. Targeted anticoagulant reversal order sets at both trauma centers and community hospitals/ non-trauma centers linked by electronic ordering systems could be used to trigger screening efforts as well.

Describe the informed consent process:

The study would require collection of delayed consent, given the critical nature of these injuries, neurologic status of the subjects, and time-sensitivity of enrollment. However, the approved-label use of the treatment in this trial, the critical/life-threatening nature of the cases, and the systematic (non-randomized by site) implementation of a protocol should allow for a delayed consent for collection of study data, use of biospecimens from shed blood for research testing.

Describe how the intervention will be administered:

IV bolus

Describe plan for follow-up:

1 week phone call if no longer in-patient
30 day phone call if no longer in-patient
90 in person return visit for disability /recovery testing compared to baseline

Endpoints and Outcomes:

1. **Primary Outcome:**
   Global hemostatic efficacy assessment at 24 hours (at discharge?)

Length of stay
90 day disability status
Mortality
Clotting factor levels in samples collected
Time to successful reversal from point of first provider contact