Consensus Statement | Neurology

Recommended Primary Outcomes for Clinical Trials Evaluating Hemostatic Agents in Patients With Intracranial Hemorrhage
A Consensus Statement

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Abstract

IMPORTANCE In patients with acute spontaneous or traumatic intracranial hemorrhage, early hemostasis is thought to be critical to minimize ongoing bleeding. However, research evaluating hemostatic therapies has been hampered by a lack of standardized clinical trial outcome measures.

OBJECTIVE To identify appropriate primary outcomes for phase 2 and 3 clinical trials of therapies aimed at reducing acute intracranial bleeding.

EVIDENCE REVIEW A comprehensive review of all previous clinical trials of hemostatic therapy for intracranial bleeding was performed, and studies measuring the frequency, risk factors, and association of intracranial bleeding with outcome of hemorrhage growth were included.

FINDINGS A hierarchy of 3 outcome measures is recommended, with the first choice being a global patient-centered clinical outcome scale measured 30 to 180 days after the event; the second, a combined clinical and radiographic end point associating hemorrhage expansion with a poor patient-centered outcome at 24 hours or later; and the third, a radiographic measure of hemorrhage expansion at 24 hours alone. Additional recommendations stress the importance of separating various subtypes of bleeding when possible, early treatment within a standardized treatment window, and the routine use of computerized planimetry comparing continuous measures of absolute and relative hemorrhage growth as either a primary or secondary end point.

CONCLUSIONS AND RELEVANCE Standardization of outcome measures in studies of intracranial bleeding and hemostatic therapy will support comparative effectiveness research and meta-analysis, with the goal of accelerating the translation of research into clinical practice. The 3 outcome measures proposed in this consensus statement could help this process.

Key Points

Question What is the ideal primary outcome for clinical trials of hemostatic agents for acute intracranial hemorrhage?

Findings In this consensus statement, the recommended optimal primary outcome was a score on a global patient-centered clinical outcome scale measured between 30 and 180 days after the event. For studies without sufficient power for this end point, a combined clinical and radiographic outcome would be an acceptable second choice.

Meaning Clinical trials of hemostatic therapy in intracranial hemorrhage should ideally demonstrate improved clinical outcome as well as hemostasis.

Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Due to the exquisite sensitivity of the brain to the effects of tissue damage, intracranial hemorrhage is the most dangerous form of bleeding that can occur in the human body, with the highest rate of mortality and residual disability.1 Hemostatic agents, including those that enhance normal coagulation, inhibit fibrinolysis, or reverse anticoagulation, are increasingly available for use in the acute phase of intracranial bleeding. Clinical trials have been performed to test the efficacy of these interventions, but optimal methods for evaluating the efficacy of these agents have yet to be established.
Research evaluating hemostatic agents across a variety of clinical scenarios has been hampered by a lack of standardized primary clinical trial outcome measures. To address this unmet need, an international panel of experts was convened by the National Heart Lung and Blood Institute (NHLBI) and the US Department of Defense in 2019. This panel was divided into 6 subgroups focused on different organ systems, with each group tasked to create a hierarchy of preferred primary outcome measures based on literature review, consideration of clinical relevance, feasibility, and biological rationale.

In this consensus statement, we report our recommendations on preferred outcome measures for pivotal trials evaluating hemostatic therapies for acute intracranial bleeding. These guidelines primarily refer to outcomes for hemostatic therapies applied to coagulopathic or noncoagulopathic spontaneous intracerebral hemorrhage (ICH) or traumatic intracranial hemorrhage (intraparenchymal, extra-axial, or both). At the conclusion, we address specific issues related to the treatment of less common forms of intracranial bleeding.

Methods

In January 2019, an international working group of experts in the clinical treatment of bleeding, hemostasis research, and clinical research methods was assembled. The Hemostasis Trials Outcomes Working Group steering committee invited 2 cochairs to lead each subgroup based on their experience and leadership skills. Additional panelists for each subgroup were identified by both the workshop steering committee and the subgroup cochairs based on current and prior research activities, clinical expertise, and roles within relevant organizations to ensure diversity of perspectives across clinical and scientific domains. In the case of the Central Nervous System (CNS) Bleeding subgroup, membership was balanced to include members from diverse specialties, including neurology, neurosurgery, neurocritical care, emergency medicine, and hematology. We also took care to include members with expertise in translational research, clinical trials, and epidemiology or statistics. Experts employed by industry were not included in any of the subgroups. The members of the CNS Bleeding subgroup are listed in the Supplement.

Each working group was tasked with developing a hierarchy of preferred primary and secondary outcome measures for phase 2 and 3 human trials evaluating hemostatic interventions with the goal of supporting alignment between investigators, sponsors, and regulators. A comprehensive search of the literature was performed by cross-linking search terms related to various forms of intracranial bleeding, hemorrhage growth or expansion, hemostasis, hemostatic therapy, and anticoagulation in 4 electronic databases (PubMed, Ovid Medline/Embase, and Google Scholar). Studies published as of March 1, 2021, were included. The references from each article were examined, and additional relevant articles were retrieved. As we did not perform a formal systematic review or rate the quality of the evidence, our search and reporting methodology conformed with some but not all Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.

We developed and evaluated a comprehensive list of potential outcome metrics to consider based on literature review in a series of teleconferences over a period of 12 months. We refined and ranked these recommendations based on clinical relevance, biologic rationale, and feasibility. In September 2019, the entire working group met in a 2-day open conference in Bethesda, Maryland, along with representatives of funding and regulatory agencies, industry, and the general public to present, discuss, further refine, and finalize the recommendations. Following general discussion, modifications to the proposals occurred in subgroup breakout sessions. Consensus was achieved using a modified Delphi approach in which formal electronic polling or quick votes were conducted before or after each round of discussion. The final report was prepared according to the Standards for Quality Improvement Reporting Excellence (SQUIRE) 2.0 reporting guideline for quality improvement reporting excellence.
Results

Categories of Intracranial Hemorrhage

The term **intracranial hemorrhage** is used for any form of spontaneous or traumatic bleeding within the intracranial vault (Box). The term **ICH** refers to a subtype of intracranial hemorrhage in which spontaneous bleeding is confined to the brain parenchyma or ventricles, most commonly due to hypertension. The suggested hierarchy of trial end points presented in this document are meant to apply to the 4 most common categories of CNS bleeding: (1) noncoagulopathic spontaneous ICH; (2) coagulopathic spontaneous ICH; (3) noncoagulopathic traumatic intracranial hemorrhage; and (4) coagulopathic traumatic intracranial hemorrhage.

Because the tempo and pathobiology of traumatic and spontaneous bleeding into the brain is different and because anticoagulation can dramatically affect the risk, magnitude, and mechanism of bleeding, we recommend that hemostatic therapies be assessed for the 4 subgroups separately when possible. In the case of spontaneous ICH, the window for active bleeding is hyperacute, and the risk varies by location; hematoma growth occurs in 38% of patients initially scanned within 3 hours of onset and occurs more frequently with deep than lobar location. By contrast, approximately half of patients presenting with traumatic cerebral contusions experience hemorrhagic progression over a much more prolonged time window; bleeding typically occurs within the first 12 hours but may occur as late as 3 or 4 days after injury. The risk of significant expansion of acute subdural hematoma requiring rescue craniotomy is lower, ranging from 6% to 22%, within an intermediate time window of 12 to 24 hours. Regardless, the risk of progressive bleeding is greater for all forms of intracranial hemorrhage the earlier the baseline computed tomography (CT) scan is performed and when coagulopathy is present.

Despite our recommendation that studies evaluating hemostatic therapy separate spontaneous from traumatic intracranial bleeding and coagulopathic from noncoagulopathic bleeding when possible, we do recognize that combining categories may be appropriate and justifiable when evaluating reversal agents for specific forms of anticoagulation, such as vitamin K antagonists and antiplatelet, antithrombin, fibrinolytic, or anti–factor Xa agents. Investigators may also wish to combine or focus on various etiologic or anatomic subgroups of intracranial hemorrhage, eg, deep hypertensive as opposed to presumably amyloid-related lobar ICH or intraparenchymal contusional bleeding as opposed to extra-axial subdural hemorrhage.

Hemorrhage Volume Measurement Techniques

Accurate calculation of hemorrhage volume is critical, both as a prognostic feature and an outcome measure. Numerous methods for calculating volume have been proposed, with the most commonly used techniques being the ABC/2 method, planimetric measurement, and, more recently, automated hemorrhage segmentation and volume calculation.

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**Box. Main Anatomic Subtypes of Intracranial Bleeding**

<table>
<thead>
<tr>
<th>Spontaneous Intracerebral Hemorrhage (ICH)</th>
<th>Spontaneous Subarachnoid Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology: hypertensive vs nonhypertensive</td>
<td>Etiology: aneurysmal vs nonaneurysmal</td>
</tr>
<tr>
<td>Location: supratentorial, infratentorial,</td>
<td></td>
</tr>
<tr>
<td>intraventricular</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Traumatic Intracranial Hemorrhage</th>
<th>Secondary Intracranial Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location: intraparenchymal (contusion, ICH), extra-axial (subdural, epidural), subarachnoid</td>
<td>Hemorrhagic transformation of infarct</td>
</tr>
<tr>
<td></td>
<td>Arteriovenous malformation</td>
</tr>
<tr>
<td></td>
<td>Tumor-related hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Perioperative Intracranial Hemorrhage</td>
</tr>
</tbody>
</table>

All anatomic subtypes listed may occur in the presence of anticoagulation, antiplatelet, or fibrinolytic therapy. The guidelines presented in this article apply specifically to spontaneous ICH and traumatic intracranial hemorrhage, with or without anticoagulation.
For the purposes of phase 2 and 3 clinical trials, we consider manual computerized planimetric measurement to be the reference standard for measuring intracranial hemorrhage volume. This technique consists of tracing the perimeter of contiguous blood elements to calculate the total area of hemorrhage on each slice and converting each slice to a volume by multiplying the area by the slice thickness. The volume of hemorrhage on each slice is then summed to arrive at a final volume (in milliliters) estimate. Interrater reliability using this technique is excellent: the intraclass correlation coefficient of hand-drawn (manual) planimeteric volume measurements ranges from 0.96 to 0.99. In 1 study, the mean SD of the difference between volumes measured by 2 independent readers was 1.9 mL, with 82% of paired measurements falling within 2 mL of each other. It has been shown that a minimum detectable difference of greater than 6 mL of hematoma growth can be detected with extremely high reliability using this method.

In semi-automated threshold-guided planimetry, the slice area measurement is performed using computerized image segmentation based on assigned Hounsfield unit thresholds, with subsequent adjustments performed by a trained image analyst to adjust for artifacts when present. Automated segmentation has recently become available using algorithms derived from artificial intelligence techniques applied to large data sets. A recent study of 300 CT scans with ICH demonstrated excellent accuracy ($R^2 = 0.98$) between the fully automated algorithm vs manual segmentation or semi-automated segmentation. Image segmentation algorithms have also been shown to accurately measure complex multicompartmental intracranial hemorrhage due to trauma. Given the fast speed (ie, <20 seconds) and high accuracy of this technique, it is likely that high-reliability fully automated segmentation will eventually replace the need for manual and semi-automated estimates of intracranial hemorrhage volume in the near future.

The simplified ABC/2 method of hemorrhage volume estimation consists of identifying the slice with the largest cross-sectional area, measuring the largest diameter on that slice (A), identifying and measuring the largest perpendicular diameter (B), then calculating the diameter of the hemorrhage in the rostrocaudal plane by multiplying the number of involved slices by the CT slice thickness. The product of these 3 dimensions is then divided by 2, which approximates the hemorrhage volume, given that a perfect sphere occupies half the volume of a surrounding cube. Although the ABC/2 method is simple, rapid, and appropriate for clinical use, it is not as reliable and accurate as computerized planimetry with segmentation, particularly in the case of larger, more irregular and complex subarachnoid and intraventricular hemorrhages. The ABC/2 method may be sufficient for use in observational cohort studies and can be very useful for screening patients for eligibility in trials, but should not be used as an end point for clinical trials.

Definitions of Hemorrhage Expansion

Expansion of ICH is defined as a change in volume between initial and follow-up neuroimaging. In most studies of ICH volume growth, the baseline scan is performed within an appropriate early period (ie, <3 hours) and the follow-up scan is performed approximately 24 hours later. When measured accurately, this radiographic outcome (or biomarker) should be considered an accurate measure of clinically relevant hemostasis. ICH volume growth has been shown to contribute to poor outcome even after accounting for baseline hematoma volume. In studies evaluating hemostatic agents, hematoma growth is the most relevant biomarker of therapeutic efficacy and hence is preferred over final hemorrhage volume as the primary radiological outcome. Whether effective hemostasis leads to improved clinical outcome is an important but separate question, affected by both the extent of hemorrhage prevented, baseline hemorrhage volume and location, and a wide range of nonhemostatic factors that can affect recovery after brain injury.

The high degree of correlation between final hemorrhage volume, mortality, and functional outcome makes hemorrhage volume growth a reasonable and compelling end point for phase 2 trials of hemostatic therapies when there is insufficient power to use patient-centered outcomes as primary end points. Fortunately, intracranial bleeding is easy to quantify with extreme precision using CT scanning, allowing for accurate and valid measurement of blood volume to the nearest
This represents an unparalleled metric or biomarker for clinical trial development. More importantly, there is a high degree of correlation between volume of blood in the brain and clinical outcome.\textsuperscript{9,21,22} In the case of spontaneous ICH, the volume of hemorrhage is associated with outcome and mortality.\textsuperscript{9} Similar findings have been found with aneurysmal subarachnoid hemorrhage and traumatic intracranial hemorrhage.\textsuperscript{23,24}

Varied definitions and cut points have been used to define clinically relevant ICH volume growth. The relative benefits of using absolute vs percentage change as a primary outcome measure for intracranial bleeding remains uncertain. The best evidence to examine this issue comes from a study relating various hematoma expansion definitions to 3-month outcome assessed using the modified Rankin Scale (mRS), in which absolute changes in ICH volume (in milliliters) had a stronger association with outcome than relative (ie, percentage) changes.\textsuperscript{25} Note that smaller cutoffs will improve sensitivity with lower specificity regarding clinical impact, while higher cutoffs can optimize specificity while losing sensitivity. Data are limited regarding the optimal cutoff for absolute changes in hemorrhage volume. The highest proposed cut point of 12.5 mL may be optimal for identifying patients whose clinical outcome will be positively affected by hemostatic therapy, at the cost of low sensitivity.\textsuperscript{25} On the other hand, in a post hoc analysis of the Factor VIIa for Acute Hemorrhagic Stroke Trial,\textsuperscript{26} a 7 mL reduction in absolute ICH growth between active treatment and placebo was associated with significantly improved 3-month mRS scores in a shift analysis. The most appropriate dichotomized definition or statistical approach may depend on the patient population. For instance, it may make more sense to use percentage rather than absolute change in ICH volume in children, since baseline brain volume varies with age.\textsuperscript{27}

Regardless of any dichotomized end point for hemorrhage expansion, in clinical trials statistical comparison of a continuous absolute or percentage change measurement should always be performed as either a primary or secondary end point because arbitrary dichotomized end points result in loss of information. Also note that if percentage change is to be used as a measure of hematoma growth, consideration should be given to excluding patients with very small baseline hemorrhage volumes, since small absolute changes of low clinical relevance can lead to large proportional changes.

### CNS Hemostasis Clinical Trials

Several clinical trials have examined hemostatic therapies in patients with acute traumatic or spontaneous intracranial hemorrhage, using a range of radiographic (Table 1) and clinical (Table 2) end points.\textsuperscript{11,28-36} A number of important lessons have been learned from these trials. First, there are many determinants of clinical outcome after ICH other than hemorrhage expansion, including baseline ICH volume and level of consciousness, presence of intraventricular hemorrhage, age, and medical comorbidities. Second, a systematic review and meta-analysis of individual patient data\textsuperscript{37} demonstrated that the highest risk of hematoma expansion occurs within 3 hours of the onset of hemorrhage.

### Table 1. Treatment or Prognostic Studies Using Hemorrhage Volume Growth as the Primary Outcome Measure

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Year</th>
<th>Study population</th>
<th>Intervention or factor</th>
<th>Imaging end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>rFVIIa phase 2B</td>
<td>2005</td>
<td>Noncoagulopathic spontaneous ICH</td>
<td>rFVIIa vs placebo</td>
<td>Percentage change in hematoma volume at 24 h</td>
</tr>
<tr>
<td>rFVIIa for TBI\textsuperscript{28}</td>
<td>2008</td>
<td>Traumatic brain contusion</td>
<td>rFVIIa vs placebo</td>
<td>Absolute change (in mL) in hemorrhage volume</td>
</tr>
<tr>
<td>INTERACT-1\textsuperscript{29}</td>
<td>2008</td>
<td>Noncoagulopathic spontaneous ICH</td>
<td>Systolic blood pressure &lt;140 mm Hg vs &lt;180 mm Hg</td>
<td>Percentage change in hematoma volume at 24 h</td>
</tr>
<tr>
<td>PREDICT\textsuperscript{30}</td>
<td>2012</td>
<td>Noncoagulopathic spontaneous ICH</td>
<td>Presence or absence of CTA spot sign</td>
<td>Hematoma expansion, defined as an increase of ≥6 mL or 33%</td>
</tr>
<tr>
<td>SPOTLIGHT and STOP-IT\textsuperscript{31}</td>
<td>2019</td>
<td>Spot sign with noncoagulopathic ICH</td>
<td>rFVIIa vs placebo in patients with CTA spot sign</td>
<td>Absolute change in ICH volume (in mL)</td>
</tr>
<tr>
<td>STOP-AUST\textsuperscript{32}</td>
<td>2020</td>
<td>Spot sign with noncoagulopathic ICH</td>
<td>TXA vs placebo</td>
<td>Hematoma expansion, defined as an increase of ≥6 mL or 33%</td>
</tr>
</tbody>
</table>

Abbreviations: CTA, computed tomography angiography; ICH, intracerebral hemorrhage; rFVIIa, recombinant activated factor VIIa; TBI, traumatic brain injury; TXA, tranexamic acid.
bleeding. Trials of hemostatic therapy for intracranial bleeding are more likely to be successful when treatment is given earlier. The same study revealed that the probability of hematoma expansion increases with hematoma volume at baseline. Ultra-early hematoma growth, calculated by dividing baseline ICH volume by the onset-to-CT interval, accounts for these predictors of active bleeding (shorter onset-to-CT time and larger baseline ICH volume) and may serve as a useful variable for risk stratification in future trials.

Among trials that have used radiographic evidence of hematoma expansion as their primary end point, both absolute and percentage change have been used (Table 1). Most studies adjusted the statistical analysis for baseline covariates that might influence hematoma expansion. We recommend that trials comparing changes in CNS hemorrhage volume as a primary or secondary end point adjust for onset-to-CT time and baseline ICH volume in the statistical analysis because these variables can affect the risk and extent of subsequent bleeding. Investigators may also wish to adjust for other covariates, such as CT-to-treatment time, use of antiplatelet or antithrombotic agents, hemorrhage location, presence of intraventricular hemorrhage, presence of spot sign, or other variables, as needed.

Prior studies have compared both continuous and dichotomized measures of absolute (in milliliters) or relative (as a percentage) change in hemorrhage volume. The most commonly used cut points have been 6.0, 7.0, 10.0, and 12.5 mL for absolute increases in hemorrhage volume and 15%, 20%, 25%, and 33% for relative changes. As stated previously, higher cut points trade reduced sensitivity to change with increased specificity regarding clinical impact, with no clear indication of the superiority of any particular cut point within these ranges. Finally, exceeding a given threshold of absolute or relative hemorrhage volume growth, as a combined end point, can be used to define expansion. For example, either a 33% or greater or 12.5 mL or greater increase in size was used to denote significant ICH expansion in the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial, whereas either a 33% or greater or a 6 mL or greater increase was used to define expansion in the Prediction of Hematoma Growth and Outcome in Patients with ICH Using the CT-Angiography Spot Sign Study.

Among the phase 3 trials of hemostatic therapy for CNS bleeding that have used 90-day clinical outcome as the primary end point (Table 2), most have used the mRS, although the extended Glasgow Outcome Scale is a valid alternative. The exception was the CRASH-3 trial of tranexamic acid for severe traumatic brain injury (TBI), which used 28-day TBI-related mortality as the primary end point. As is the case with trials of ischemic stroke, shift analysis is generally preferred over dichotomized outcome measures because it has greater sensitivity to change and less loss of information. For example, the primary endpoint of the INTERACT-2 trial of intensive blood pressure lowering (mRS 4-6) did not meet the prespecified dichotomized outcome ($P = .06$), whereas the ordinal shift analysis of mRS outcomes did ($P = .04$). Although most stroke trials have historically evaluated outcome at 90 days, there are some indications that recovery is more protracted after ICH and that long-term assessment of outcome at 180 days or longer is required to capture the full extent of functional recovery.

### Table 2. Trials of Hemostatic Therapy With Clinical Outcome as the Primary End Point

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Year</th>
<th>Study population</th>
<th>Intervention or factor</th>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAST33</td>
<td>2008</td>
<td>Noncoagulopathic spontaneous ICH</td>
<td>rFVIIa vs placebo</td>
<td>90-d mRS of 4-6</td>
</tr>
<tr>
<td>PATCH34</td>
<td>2016</td>
<td>Patients with spontaneous ICH receiving antiplatelet agents</td>
<td>Platelet transfusion vs no platelet transfusion</td>
<td>90-d mRS shift analysis</td>
</tr>
<tr>
<td>TICH-235</td>
<td>2018</td>
<td>Noncoagulopathic spontaneous ICH</td>
<td>TXA vs placebo</td>
<td>90-d mRS shift analysis</td>
</tr>
<tr>
<td>CRASH-336</td>
<td>2019</td>
<td>TBI</td>
<td>TXA vs placebo</td>
<td>TBI-related death within 28 d</td>
</tr>
</tbody>
</table>

*For the purposes of this analysis, trials of blood pressure lowering for ICH were not considered hemostatic interventions.

Abbreviations: ICH, intracerebral hemorrhage; mRS, modified Rankin score; rFVIIa, recombinant activated factor VIIa; TBI, traumatic brain injury; TXA, tranexamic acid.
Recommended Trial Outcome Measures

We propose a hierarchy of 3 different end points for trials of hemostatic therapy for CNS bleeding, in order of preference. In general, end points that involve a patient-centered outcome are superior to pure radiographic outcomes. That said, the goal of a hemostatic therapy is to reduce bleeding, and neuroimaging can accurately measure the success or failure of this goal. For this reason, many (but not all) of our authors consider imaging-based measurements of bleeding to be a valid primary end point; all consider this a reasonable biomarker for phase 2 studies.

Best Option: A Global Patient-Centered Clinical Outcome Scale at 30 to 180 Days

This outcome is patient centered and captures a meaningful clinical benefit of any therapy to a patient. The most commonly used scales include the mRS, utility-weighted mRS, and Extended Glasgow Outcome Scale, but any similar relevant patient-centered outcome measure would be appropriate.

Second Option: A Combined Clinical and Radiographic End Point Linking Hemorrhage Expansion With a Poor Outcome at 24 Hours

This could come in 1 of 2 broad categories: (1) symptomatic hemorrhage expansion at 24 hours and (2) hemorrhage expansion at 24 hours combined with a poor outcome at 30 days or later. For the first end point, the patient would need to experience both hemorrhage expansion and concurrent symptomatic worsening. Commonly used definitions for symptomatic worsening (typically at 24 hours) include a 4-point or greater increase in the National Institutes of Health Stroke Scale or a 2-point or greater decrease in the Glasgow Coma Scale, but a change in any clinically relevant, valid, and reproducible scale could be used. The second end point, ie, hemorrhage expansion at 24 hours combined with a poor outcome at 30 days or later, would be broadly analogous to the use of bleeding-related adverse events related to cardiovascular surgery or head injury-related mortality at 28 days (as used in the CRASH-3 trial of tranexamic acid). As another example, the International Normalized Ratio Normalization in Coumadin Associated Intracerebral Haemorrhage (INCH) Trial, which compared prothrombin complex concentrate to plasma for reversing vitamin K antagonists, used death at 90 days and relative hematoma expansion (>15%) as a secondary end point. Such an outcome can potentially isolate an effect of improved coagulation from those poor outcomes unrelated to hemostasis.

Third Option: A Radiographic Measure of Hemorrhage Expansion at 24 Hours Alone

This end point accurately measures clinical hemostasis and can determine whether a hemostatic therapy successfully accomplished its goal. Hemorrhage should be measured using planimetric methods and may evaluate any combination of intraparenchymal, intraventricular, subarachnoid, extra-axial, or total intracranial blood. A rationale should be provided for justifying which components are analyzed. Based on the literature, if a dichotomized outcome is used, we recommend definitions of intracranial hemorrhage expansion in absolute terms, ranging from 6.0 mL to 12.5 mL, and in relative terms from 20% to 33%. In all cases, a continuous measure of hemorrhage volume growth should also be measured as a primary or secondary end point.

Special Circumstances

Neurosurgical Intraoperative Bleeding and Subarachnoid Hemorrhage

These guidelines do not apply to intra-operative or perioperative neurosurgical bleeding, aneurysmal subarachnoid hemorrhage (SAH), or aneurysm rerupture. These specific situations differ substantially from hemorrhage associated with spontaneous ICH or traumatic intracranial hemorrhage. First, they are rarely studied in the same trials. Second, spontaneous and traumatic ICH are confined to a fixed space, are usually compact volumes, and are easily measured on simple radiographic studies with high resolution, speed, and reproducibility. Aneurysmal SAH, rerupture, or bleeding after aneurysm treatment are generally low frequency and register as all-or-none events.
As such, extremely large sample sizes would be required to demonstrate any significant reduction of either form of bleeding. Furthermore, SAH is often diffuse and difficult to measure, although automated segmentation is making this easier.44 Regarding operative bleeding, it can be difficult to quantify given that actionable behaviors (ie, direct hematoma evacuation, suctioning, cerebrospinal fluid drainage, lavage) can affect measured hemorrhage volumes. Efforts aimed at quantification of intra-operative blood loss and improved volumetric measurements of blood in the subarachnoid space are ongoing.

**Pediatric Considerations**

In children, measuring intracranial hemorrhage and changes in hemorrhage over time should account for differences in total brain volume by age. The same volume of intracranial hemorrhage represents a substantially different proportion of brain volume in infants than it does in older children. An infant with a smaller brain volume may be affected more severely than an adolescent with a larger brain volume given the same volume of intracranial hemorrhage. Measuring intracranial hemorrhage volume as a percentage of total brain volume standardizes intracranial hemorrhage across different ages and brain volumes.27,45 Regarding long-term global outcome scales, a reasonable option is the Pediatric Quality of Life score, which evaluates physical, emotional, social, and school functioning on a scale from 0 to 100,46 although alternatives exist. Finally, the neurocognitive impact may be largely dependent on the location of the intracranial hemorrhage.45 Researchers and clinicians must be cognizant of the area of the brain impacted by the hemorrhage, as this could be at least as important as the absolute volume of hemorrhage.

**Discussion**

The suggested hierarchy of hemostatic trial outcomes that we have recommended are meant to apply to 4 main categories of CNS bleeding: (1) noncoagulopathic spontaneous ICH, (2) coagulopathic ICH, (3) noncoagulopathic traumatic intracranial hemorrhage, and (4) coagulopathic traumatic intracranial hemorrhage. As the tempo of traumatic and spontaneous bleeding are different and since anticoagulation can dramatically affect both the rate and mechanism of bleeding,39 we recommend that hemostatic therapies be assessed for these 4 subtypes separately when possible. However, we recognize that combining spontaneous ICH and traumatic bleeding may be justifiable when they are related to a specific form of anticoagulation.47 For trials including a range of intracranial hemorrhage categories, total intracranial blood may be most relevant, whereas for studies focused on a specific disease (eg, hypertensive spontaneous ICH), it might be reasonable to limit enrollment to intraparenchymal bleeding in the basal ganglia, pons, or cerebellum. A clear justification based on pathophysiology should be used for the proposed measurement.

If a radiographic end point alone is selected as the primary end point, a close correlation between final hemorrhage volume and a relevant patient-centered outcome should be established. If possible, a strong association between hematoma growth and outcome is desirable as well. These associations may be stronger for spontaneous ICH than traumatic intracranial hemorrhage,8 for which outcomes are often affected by variables other than bleeding, such as axonal shearing injury and multisystem organ failure. Of note, many participants in the panel did not feel that a purely radiographic end point would be acceptable for a definitive trial of hemostatic therapy. Others countered that hemorrhage growth precisely measures the relevant pathological process and is well correlated with outcome.9,19 If the primary end point includes a radiographic measure, patients who undergo primary or salvage neurosurgical hematoma evacuation need to be excluded, as this will affect the measurement of hemorrhage volumes, unless expansion is determined prior to neurosurgical intervention.

It is worth noting that panel groups examining hemostasis in other organ systems recommended primary outcomes that focused on bleeding (analogous to a pure radiographic outcome) rather than all-cause clinical outcomes. For example, the cardiac surgery subgroup...
considered perioperative blood products transfused to be a definitive, clinically relevant primary outcome. The gastrointestinal bleeding subgroup recommended a composite end point of further bleeding events or bleeding-specific mortality (rather than all-cause mortality or overall clinical outcome). The trauma subgroup recommended a primary outcome of mortality at 3 to 6 hours to focus on bleeding-related mortality. A common theme in this workshop was to highlight the value of primary end points that best capture the outcomes of improved hemostasis.

The interval from symptom onset to baseline CT should be standardized, given that the risk of progressive bleeding is always higher the earlier the baseline CT is obtained. A rationale for how to define the inclusion time window should be provided, recognizing that the risk period for progressive bleeding is generally longer when patients are receiving anticoagulation. Investigators may choose between measuring hemorrhage expansion in terms of absolute (in milliliters) or relative (as a percentage) change from baseline to follow-up, which should be at 24 hours. Earlier points may fail to capture relevant delayed bleeding, whereas later points will be increasingly affected by clot retraction. In addition, use of 24 hours as a universal time will facilitate meta-analyses, and most studies of hemostatic therapy for CNS bleeding have used this imaging follow-up interval.

Varied definitions exist to determine the most appropriate cut point for clinically relevant change in hematoma volume. Statistically, there is more power to detect an effect comparing continuous or absolute volume change; however, dichotomized outcomes may offer the opportunity to compare clinically relevant ICH expansion if a large enough threshold is used. After review of the existing literature, we recommend that volume growth in absolute terms be defined between 6.0 mL and 12.5 mL and in relative terms between 20% and 33%. There is no indication that any particular cut point within these ranges is superior to another. Absolute rather than relative changes in hemorrhage volume may be preferable in ICH, given that they are more predictive of 3-month outcome. Smaller cutoffs (as low as 7 mL) can improve sensitivity with lower specificity regarding clinical impact, while higher cutoffs (as high as 12.5 mL) can optimize specificity while losing sensitivity; both of these cut points have been validated as meaningfully related to outcomes at 3 months. If percentage change is to be used, consideration should be given to excluding patients with very small baseline hemorrhage volumes, since small absolute changes of low clinical relevance can lead to large proportional changes. Since dichotomization results in loss of information, the panel recommends that continuous measurements of absolute and percentage change always be included as either a primary or secondary end point. The most appropriate approach may depend on the patient population. For instance, it may make more sense to use percentage rather than absolute change in ICH volume in children as opposed to adults, since much smaller amounts of incremental bleeding are needed to lead to clinical worsening.

Two radiological safety outcomes unique to trials of hemostatic therapy for ICH may deserve special attention. Given that thrombin is associated with secondary brain injury and inflammation, standardized measurement of perihematomal edema volume (easily measured using planimetric techniques and expressed as an edema-to-ICH volume ratio) should be strongly considered. Similarly, if magnetic resonance imaging is included in the study protocol, remote punctate lesions on diffusion weighted imaging, which occur in approximately 20% of cases normally, should be assessed to evaluate for ischemic injury.

It is important to note that while the link between final intracranial hemorrhage volume and outcome is well established, clinical trials have not consistently linked the reduction of active bleeding with improved clinical outcomes. Observational studies and clinical trials have shown that greater ICH expansion is clearly associated with worse clinical outcome. The phase 2B NovoSeven ICH trial showed a dose-related reduction in hematoma growth and improved outcome, but these findings were not replicated in the phase 3 trial. The INCH trial of anticoagulation reversal and Tranexamic Acid for Hyperacute Primary ICH Trial similarly found small reductions in ICH growth, but the effect on clinical outcome was not statistically significant. There is a need to better understand the clinical significance of various thresholds of ICH volume expansion, which may vary based on the initial location of hemorrhage. There is also a need to better understand the
association between hemorrhage location and overall global functional outcome. Since there is new data indicating that the risk of early hematoma expansion is higher in deep vs lobar bleeds, consideration should be given to standardization or stratification by location. Trials should exclude patients who present with such large hemorrhages that reduction of further bleeding would have little chance of improving outcome. Inclusion criteria should emphasize tight time periods, since treatment as early as possible provides the greatest opportunity to prevent bleeding. Finally, more research is needed to develop automated segmentation techniques to improve the accuracy of measuring multifocal, multicompartamental intracranial bleeding from amyloid angiopathy or traumatic brain injury.

Future studies evaluating hemostatic agents in patients with and without extrinsic coagulopathy are ongoing. For example, the Treatment of Intracerebral Hemorrhage in Patients on Non–Vitamin K Antagonist trial (NCT02866838) is investigating the use of tranexamic acid in direct thrombin or factor Xa inhibitor–related ICH, and a randomized trial of andexanet for factor Xa inhibitor–related ICH is ongoing (NCT03661528). The Stopping Haemorrhage With Tranexamic Acid for Hyperacute Onset Presentation Including Mobile Stroke Units Trial (NCT03385928) evaluates tranexamic acid in the hyperacute time frame of ICH using mobile stroke units. The Desmopressin for Reversal of Antiplatelet Drugs in Stroke Due to Haemorrhage Trial (NCT03696121) is evaluating desmopressin in antiplatelet–associated ICH, and the Recombinant Factor VIIa (rFVIIa) for Hemorrhagic Stroke Trial (NCT03496883) will examine rFVIIa in a select group of patients with ICH treated within 2 hours of symptom onset. Our hope is that with further study, using the right hemostatic agent in the right population, the link between prevention of hemorrhage growth and clinical outcome will be better established.

Limitations
This consensus statement has limitations. We did not perform a formal systematic review according to PRISMA guidelines and did not grade the quality of evidence that we reviewed. Consensus was obtained using a modified Delphi approach that included both formal quantitative and informal conversational voting, rather than a completely structured and quantitative approach. Finally, the proposed third option for an end point in studies of CNS hemostasis was felt to be acceptable for drug development and phase 2 studies, but the panel was split on whether a purely radiographic end point alone is suitable for definitive phase 3 trials.

Conclusions
This consensus statement found that clinical trials of hemostatic therapy in intracranial hemorrhage should ideally demonstrate improved clinical outcome as well as hemostasis. Therefore, we proposed 3 end points for clinical trials in order of preference: (1) a global patient-centered clinical outcome scale at 30 to 180 days, (2) a combined clinical and radiographic end point associating hemorrhage expansion with a poor patient-centered outcome at 24 hours or later, and (3) a radiographic measure of hemorrhage expansion at 24 hours alone. Standardization of outcome measures in clinical trials will support comparative effectiveness research and meta-analysis, with the goal of accelerating the translation of research into clinical practice.
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Author Contributions: Drs Mayer and Goldstein had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Administrative, technical, or material support: Jankowitz, Naik, Steiner, Goldstein.

Supervision: Mayer, Frontera.

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SUPPLEMENT.
Nonauthor Collaborators