Perihematomal edema (PHE) complicates acute spontaneous intracerebral hemorrhage (ICH) and can increase mass effect, contributing to early neurological deterioration and poor outcome.1,2 The innate immune response within the brain is a key driver of PHE and is characterized by the activation of resident microglia by damage-associated molecular patterns, infiltration of peripheral immune cells, and the production of inflammatory mediators, all of which increase tissue damage and promote blood–brain barrier breakdown.3 Following the well-documented failure to translate treatments for ischemic stroke from experimental studies to clinical use, early-phase clinical trials to demonstrate proof-of-concept in clinical stroke have been recommended before definitive phase III trials.4 Edema has been widely used as the main outcome to test interventions in preclinical ICH,5 so has considerable appeal as an outcome measure for such early-phase clinical trials. PHE can be reliably and objectively measured using noncontrast computed tomography,6,7 so can be collected easily and cheaply from almost all patients with ICH. However, ICH and PHE volumes are closely correlated,2,6,8 so variation in hematoma volume introduces variation in PHE volume. Unlike experimental ICH (where hematoma volume is tightly controlled by the investigator), hematoma volumes in clinical ICH are highly variable, introducing variability in PHE volumes and increasing the sample size required to demonstrate a given treatment effect. The use of relative PHE volume (PHE volume/ICH volume) has been suggested as a solution to this, but tends to be disproportionately high for smaller hematomas and has thus been advised against.6 Here, we present a solution to this problem that will allow researchers to demonstrate a reduction in PHE with a much smaller sample size, thus potentially accelerating translational ICH research with reduced costs.

Description of the Solution

As the factors driving edema (eg, damage-associated molecular patterns) are derived from the hematoma and will passively diffuse into the brain parenchyma, they will tend to exert their proinflammatory effects along a similar distance from the hematoma border regardless of ICH volume. We thus hypothesized that for the same intensity of inflammatory response, edema will extend a fairly consistent mean linear distance from the hematoma border (which we have termed the edema extension distance [EED]) across a wide range of hematoma volumes. If this hypothesis is correct, EED would be largely influenced by the intensity of the inflammatory response and not the hematoma volume, thus representing an ideal measure for proof-of-concept trials of immune modulating treatments. We initially tested this hypothesis using a simple theoretical model and compared this with published data sets. Using individual patient data from the conservative arms of the Minimally Invasive Surgery Plus rt-PA for ICH Evacuation Phase II trial (MISTIE II) and the pilot phase Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT1), we then tested how EED compares with conventional measures (absolute PHE volume, relative PHE volume), in terms of the number of patients required to detect a treatment effect in a clinical trial.

Results of Pilot Testing

In developing our theoretical model, we assumed that PHE is contained within an ellipsoid which fully encapsulates a smaller ellipsoid representing the hematoma. We then calculated PHE volume and relative PHE volume across a range of hematoma volumes using 3 fixed EEDs of 0.5, 0.75, and 1.0 cm (Figure 1).9 Our model demonstrates a similar relationship between ICH and PHE volume as observed in previous clinical studies, with a clear tendency for relative PHE volume...
to increase with smaller ICH volumes, suggesting that EED may indeed be fairly consistent across a wide range of hematoma volumes in clinical ICH. To investigate this further, we pooled individual patient data describing PHE and hematoma volume in 39 patients from the conservative treatment arm of the MISTIE II trial\(^7\) and 139 patients from the conservative treatment arm of the INTERACT1 trial.\(^10\) For MISTIE II patients, a previously described, semiautomated, threshold-based approach\(^6\) was applied using computed tomographic scans to measure ICH and PHE volumes using an open source DICOM viewer (OsiriX v. 4.1, Pixmeo; Geneva, Switzerland). To define edema, a fixed lower Hounsfield unit (HU) value of 5 was used with the upper value adjusted by the reader to obtain the best delineation of edema and avoid artifact introduced by leukoaraiosis, with an absolute maximum of 33 HU allowed. For INTERACT1 patients, ICH and PHE volumes were calculated independently by 2 trained neurologists blind to clinical data, treatment, and date and sequence of scan, using computer-assisted multislice planimetric and voxel threshold techniques in MIStar software, version 3.2 (Apollo Medical Imaging Technology, Melbourne, Australia).\(^8\) Although a threshold-based method was also used for the INTERACT1 analysis, unlike the MISTIE II analysis, there was no pre-specified upper and lower threshold limit. EED (Figure 2) was calculated for each patient using the following formula:

\[
EED = \sqrt{\frac{\text{PHE vol} + \text{ICH vol}}{3\pi}} - \sqrt{\frac{\text{ICH vol}}{3\pi}}
\]

EED was found to be relatively independent of ICH volume (Figure 3), with a mean of 0.32 cm (SD=0.16 cm) at baseline and 0.51 cm (SD=0.23 cm) at day 3 to 4. We then used these data to calculate the sample size required for a trial using PHE at day 3 to 4 as the primary outcome and compared the 3 different edema measures (PHE volume, relative PHE, and EED) across a range of treatment effects (Table). Treatment effects ranging from 5% reduction to 30% reduction were considered for our analysis. Table demonstrates that using relative PHE as the outcome measure leads to a negligible reduction in sample size when compared with PHE volume, so relative PHE has no advantage as a clinical trial outcome measure. However, using EED instead of PHE volume reduces the required sample size by ≈75% across the range of treatment effects examined. As a diagnostic computed tomographic scan is readily available,
sample sizes can be reduced even further by also adjusting for PHE at baseline. This adjustment brings sample sizes down to a similar extent for all 3 PHE measures, thus maintaining relative performance.

We tested whether EED was associated with death or dependency at 90 days (according to scores 3–6 on the modified Rankin Scale) using the INTERACT1 data set (n=286), adjusting for age, log ICH volume at 72 hours, and randomized treatment in a multifactorial logistic regression model. EED was not associated with death or dependency at 90 days (odds ratio, 1.03; 95% confidence interval CI, 0.31–3.36; P=0.968). Limiting our analysis to patients with smaller ICH volume (<30 mL) produced similar results (odds ratio, 0.89; 95% CI, 0.24–3.33; P=0.858).

Conclusions, Limitations, and Next Steps

We describe a novel PHE measure that unlike existing measures is relatively independent of hematoma volume. We provide evidence from theoretical modeling and analyses of data from the MISTIE II and INTERACT1 conservative treatment arms to support our conclusions. These data sets demonstrate the use of the EED as an outcome measure in early phase clinical trials of treatments targeting PHE, showing that the use of EED as a primary outcome measure can reduce the sample size requirements by as much as 75%, when compared with absolute or relative PHE volume.

Brain water content is an outcome often used in preclinical ICH research, and a meta-analysis combining data from 78 comparisons in 867 animals found a pooled reduction of 34% (95% confidence interval, 25–43).5 In the clinical setting, the MISTIE II trial demonstrated a 33% reduction in PHE volume at day 3 (27.7 versus 41.7 mL),7 a proof-of-concept trial of fingolimod showed a 57% reduction in PHE volume (47 versus 108 mL) and a 61% reduction in relative PHE (2.5 versus 6.4) at day 7 post onset.11 A study with 80% power to detect a more modest 15% reduction in EED would require 142 patients in each arm, compared with >500 patients in each arm using PHE volume or relative PHE as the primary outcome.

In developing the EED, we made the assumption that ICH and PHE volumes approximate to an ellipsoid shape, but in a significant minority of ICH patients, this is not the case. A previous study of unselected ICH patients found that 70% had a round/ellipsoid hematoma and 24% had an irregular hematoma shape.12 Hematoma shape was not available in the trial data sets used for our analysis, but the participants in the MISTIE II and INTERACT1 trials would be expected to include some with irregularly shaped hematomas. However, even with the inclusion of such patients, we have found that using EED as the primary edema outcome measure leads to reduced sample size requirements to assessments of variable sized treatment effects, suggesting that hematoma shape is unlikely to have an

### Table. Clinical Trial Sample Size Calculations Using PHE as the Primary Outcome

<table>
<thead>
<tr>
<th>Reduction in Measure, %</th>
<th>80% Power</th>
<th>90% Power</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PHE Volume</td>
<td>Relative PHE</td>
</tr>
<tr>
<td>5</td>
<td>5020</td>
<td>4775</td>
</tr>
<tr>
<td>10</td>
<td>1266</td>
<td>1210</td>
</tr>
<tr>
<td>15</td>
<td>562</td>
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<td>194</td>
</tr>
<tr>
<td>30</td>
<td>142</td>
<td>136</td>
</tr>
</tbody>
</table>

Number of patients required in each arm of a clinical trial with PHE at day 3 to 4 as the primary outcome, assuming α=0.05 and either 80% or 90% power to detect a range of reductions in each measure. Calculations based on data from conservative arms of INTERACT 1 and MISTIE II. Mean (SD) for each measure were PHE volume, 25.12 mL (22.53 mL); relative PHE, 1.63 (1.43); EED, 0.51 cm (0.23 cm). EED indicates edema extension distance; INTERACT1, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial; MISTIE II, Minimally Invasive Surgery Plus rt-PA for ICH Evacuation Phase II trial; and PHE, perihematomal edema.
important impact on EED variability. We recognize, however, that this requires confirmation in further analysis.

Accurate calculation of the EED is dependent on the robust and accurate measurement of the absolute PHE and ICH volumes. To define PHE volume, we recommend the semiautomated threshold-based approach described by Volbers et al,6 using a HU range of 5 to 33. This technique has been validated against T2-weighted magnetic resonance imaging and shows an excellent intraclass correlation coefficient for interobserver reliability of 0.96 (95% CI, 0.93–0.99).6 Early phase trials would be well advised to use this or similarly robust methods with equivalent interobserver reliability.

In agreement with previous work, testing for associations between conventional measures of edema and clinical outcomes in INTERACT1 patients,8 we have found that EED was not an independent predictor of poor outcome. However, edema is only one component of the pathophysiology of the inflammatory response to ICH, and inflammation worsens injury via multiple parallel mechanisms.13 Thus, EED seems to provide a useful surrogate parameter in early phase proof-of-concept clinical trials of anti-inflammatory treatments. Although reduction in edema alone is unlikely to be the only factor that could improve clinical outcomes, it does provide an indication that a treatment can reduce the inflammatory response within the brain. This approach could allow early selection of the most promising treatments to take forward to larger and more expensive trials that test clinical efficacy. It is important to distinguish this approach from that of using reduction of edema (as measured by EED) as a surrogate measure for functional outcome, an approach that is dependent on an association of EED with clinical outcomes, which our findings do not support.

Regardless of its association with clinical outcomes, PHE is an ideal primary target for early-phase proof-of-concept clinical trials. Using EED as the preferred PHE measure could allow the necessary data to be acquired with around a quarter of the patients needed for assessments with conventional PHE measures, and thereby serve to accelerate translation of novel findings from the laboratory to the clinic.

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Disclosures
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