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Assessment of Primary Outcome Measures for a Clinical Trial of Pediatric Hemorrhagic Injuries

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Author Contribution:
DN, MG, HN, and NK conceived designed the study. DN and NK and obtained research funding. DN, MG, HN, and NK supervised the conduct of the trial and data collection. DN, DT, and NK provided statistical advice on study design and analyzed the data. DN drafted the manuscript, and all authors contributed substantially to its revision. DN takes responsibility for the paper as a whole.

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TIC-TOC Collaborators of the Pediatric Emergency Care Applied Research Network (PECARN)

Abstract

Objective—We evaluated the acceptability of the Pediatric Quality of Life Inventory (PedsQL) and other outcomes as the primary outcomes for a pediatric hemorrhagic trauma trial (TIC-TOC) among clinicians.

Methods—We conducted a mixed-methods study that included an electronic questionnaire followed by teleconference discussions. Participants confirmed or rejected the PedsQL as the primary outcome for the TIC-TOC trial and evaluated and proposed alternative primary outcomes. Responses were compiled and a list of themes and representative quotes was generated.

Results—73 of 91 (80%) participants completed the questionnaire. 61 (84%) participants agreed that the PedsQL is an appropriate primary outcome for children with hemorrhagic brain injuries. 32 (44%) participants agreed that the PedsQL is an acceptable primary outcome for children with hemorrhagic torso injuries, 27 (38%) participants were neutral, and 13 (18%) participants disagreed. Several themes were identified from responses, including that the PedsQL is an important and patient-centered outcome but may be affected by other factors, and that intracranial hemorrhage progression assessed by brain imaging (among patients with brain injuries) or blood product transfusion requirements (among patients with torso injuries) may be more objective outcomes than the PedsQL.

Conclusions—The PedsQL was a well-accepted proposed primary outcome for children with hemorrhagic brain injuries. Traumatic intracranial hemorrhage progression was favored by a subset of clinicians. A plurality of participants also considered the PedsQL an acceptable outcome

for selection for pediatric trauma clinical trial children with hemorrhagic torso injuries. Blood product transfusion requirement was favored by fewer participants.

Keywords

Children; trauma; tranexamic acid; outcome measure; consensus; Pediatric Quality of Life

BACKGROUND

Tranexamic acid (TXA) is an antifibrinolytic drug that blocks plasmin-mediated fibrin clot breakdown and attenuates bleeding. TXA is extensively used in adult and pediatric surgery to decrease blood loss and blood product transfusion requirements,[1–4] and has been shown to save lives in several other clinical settings, such as post-partum hemorrhage.[5] The success of TXA in the surgical setting led to the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) and CRASH-3 trials, two separate international randomized controlled trials of early administration of TXA to adults with hemorrhagic torso trauma (CRASH-2) and hemorrhagic brain injuries (CRASH-3).[6,7] In both trials, TXA reduced mortality with no increase in adverse events compared to placebo. In addition, a post-hoc analysis of the CRASH-2 trial demonstrated improved functional outcomes associated with TXA use.[8] TXA is now considered standard treatment in adults with traumatic hemorrhage and is estimated to save 112,000 lives each year worldwide.[9]

Given the compelling results of the CRASH-2 and CRASH-3 trials for severely injured adults, TXA has the potential to significantly improve outcomes for children with hemorrhagic injuries. The use of TXA in pediatric trauma, however, has not been systematically studied. To address this important knowledge gap, we designed the Traumatic Injury Clinical Trial Evaluating Tranexamic Acid in Children (TIC-TOC) study – a multicenter, randomized placebo-controlled trial that will evaluate the efficacy of TXA in children 0 to 18 years old with hemorrhagic brain and/or torso injuries. Children with these injuries will be randomized to either receive TXA or placebo within three hours of the time of injury. The study cohort will be stratified by the injury subtype and include the following strata: isolated hemorrhagic torso injuries, isolated hemorrhagic brain injuries, and mixed hemorrhagic brain and torso injuries.

Prior to this mixed-methods study, the proposed primary outcome measure for the TIC-TOC trial was the Pediatric Quality of Life Inventory (PedsQL). The PedsQL measures function and health-related quality of life in healthy children, as well as in children with acute and chronic health conditions, including trauma.[10] The PedsQL generic core scales include 23 questions that measure the core dimensions of health (physical, emotional, social, and school functioning) as delineated by the World Health Organization. More than 850 publications reporting research have used the PedsQL measure, including trauma.cohorts.[11] The PedsQL is recommended by the Common Data Elements (CDE) Traumatic Brain Injury (TBI) Outcomes Workgroup as a core quality-of-life measure post-TBI and a primary measure of global outcome.[12] The PedsQL is a continuous score that ranges from 0–100. A clinically meaningful difference occurs with a 4.5-point change on the PedsQL scale.[10] The PedsQL meets the requirements of an outcome instrument, including reliability (measurements are

made with minimum error), validity (measures what it is intended to measure), and responsiveness (sensitivity to change).[13] The PedsQL is practical (fewer than 4 minutes to complete and administer by telephone), developmentally appropriate (valid across the entire pediatric age spectrum), and has been translated into multiple languages.[14]

We conducted a mixed-methods study using a sequential explanatory design to determine if the PedsQL is an acceptable primary outcome measure in a study of pediatric hemorrhagic trauma to a disparate group of pediatric trauma clinicians, and that it meets the needs of patients and clinicians in the setting of pediatric trauma. We also explored other possible primary outcome measures. To achieve our goals, we used an electronic questionnaire and teleconference discussions to target pediatric trauma research collaborators.

METHODS

Study Design

We conducted a mixed-methods study that included an electronic questionnaire followed by teleconference discussions with participants. We used a sequential explanatory design, in which the quantitative data are collected first followed by the qualitative data.[15] The qualitative data was used to further explain and interpret the findings from the quantitative data collection phase. We designed the study for participants to either confirm or reject a proposed primary outcome measure (PedsQL) for the TIC-TOC trial, and then evaluate and propose alternative outcome measures. We chose this study design to gather informed responses rather than having participants select de novo from a list of potential primary outcome measures, which would require considerable time and effort from study participants to understand the various feasibility and statistical considerations for each potential primary outcome measure. This mixed-methods study was determined to be exempt by the Institutional Review Board at the lead site.

Participants

We recruited participants for quantitative and qualitative data collection from 24 potential TIC-TOC trial enrollment sites in the Pediatric Emergency Care Applied Research Network (PECARN).[16] At each site, recruitment was specific to participants who provide clinical care to pediatric trauma patients, including emergency/pediatric emergency medicine physicians, neurosurgeons, trauma surgeons, and pediatric critical care physicians. We asked each site PI to provide at least one name and email address for individuals from their sites from each of the above specialties. We invited 91 individuals to participate in the study to meet the goal of at least 40 study participants (see Analysis Section below for sample size calculation), with representation from each of the different specialties.

Questionnaire Development

We developed a confidential and anonymous electronic questionnaire based on prior published guidelines.[17] We designed the questionnaire with input from experts in mixed methods research and pediatric trauma clinician-investigator experts. Before distribution to the participants, we pilot-tested the questionnaire with non-study clinicians (Online Supplement).

The questionnaire consisted of an informational section, a series of closed-ended statements, and a series of open-ended questions. Statements and questions separately addressed children with hemorrhagic torso injuries and children with hemorrhagic brain injuries. The informational section included a background of the TIC-TOC trial and an overview of the PedsQL instrument, including information on the PedsQL components, the reliability, validity, and responsiveness of the PedsQL, the feasibility of the PedsQL as a primary outcome measure, and relevant references (Online Supplement). Similar overviews were provided for alternative outcome measures including all-cause mortality, injury-specific mortality, intracranial hemorrhage progression (for the hemorrhagic brain injury stratum), blood product transfusion (for the hemorrhagic torso injury stratum), coagulation biomarkers (such as d-dimer or thromboelastography [TEG]), and emergency surgery. We created closed-ended and open-ended questions to 1) assess the overall importance of the TIC-TOC trial, 2) assess the acceptability of the PedsQL as the primary outcome measure for the TIC-TOC trial, and 3) to present alternative primary outcome measures for discussion. Responses to closed-ended statements were based on a 5-point Likert scale (1-strongly agree, 2-agree, 3-neutral, 4-disagree, 5-strongly disagree). In open-ended questions, we asked participants to discuss the proposed alternative primary outcome measures and suggest other outcome measures for the TIC-TOC trial they deemed more appropriate and feasible than the PedsQL.

Study Procedures

The study consisted of an introductory webinar, a quantitative data collection phase (i.e., questionnaire), and a qualitative data collection phase (i.e., telephone discussions). We invited all participants to the 60-minute introductory webinar, which included a slide presentation describing the study objectives and procedures followed by a question and answer period. We distributed the slide presentation electronically to study participants and then emailed the electronic questionnaire regarding potential outcome measures for the TIC-TOC trial. We asked study participants to complete the electronic questionnaire within 2 weeks. The responses to the study questionnaire were analyzed and the results were distributed by email to participants. We then invited participants to attend teleconference discussions to confer the results of the electronic questionnaire. Each teleconference discussion included no more than 6 study participants. Participants in the teleconference discussions were randomly selected within clinical specialty groups to ensure relatively equal specialty representation in each teleconference discussion.

Study Questionnaire—We obtained informed consent before circulation of the electronic questionnaire. We sent weekly email reminders if the questionnaire remained uncompleted after two weeks. After four weeks, missing and incomplete questionnaires were considered as non-responsive. We summarized responses to the electronic questionnaire and provided these results to the participants before the teleconference discussion sessions.

Teleconference Discussions—We completed two 1-hour teleconference discussions with additional sessions planned if theme saturation was not met. Two independent facilitators, with expertise and experience in group facilitation and qualitative research, led

all sessions. The facilitators used a structured guide during teleconference discussions. We recorded teleconference discussions for analysis.

Statistical Analysis

We characterized the study population using descriptive statistics (Table 1). Non-normally distributed interval data were analyzed using non-parametric statistics and reported as medians and interquartile ranges. Proportions were presented with 95% confidence intervals (CIs). Responses to closed-ended questions were reported by each Likert scale response and also collapsed into “agree” (strongly agree and agree), “neutral” (neutral, or neither agree nor disagree), and “disagree” (disagree and strongly disagree) categories.

We estimated associations between dichotomized responses (agree vs. neutral or disagree) and participants’ specialty (emergency medicine, neurosurgery, trauma surgery, pediatric critical care), controlling for region (West, Midwest, East, South), using a logistic regression model. All statistical analyses were conducted using STATA 14.0 statistical software (STATA Corp, College Station, TX).

We compiled transcriptions from open-ended questions and notes from teleconference discussions into a list of participant responses. We developed coding criteria and applied the criteria to the formatted transcripts by “tagging” elements within the participant responses. “Tagged” elements were quantitatively assessed to generate a list of predominant themes. We then chose specific quotes from the participant responses that best represented these themes. Theme saturation was determined by consensus among four study authors (DN, MG, HN, and NK).

We chose a sample size of 48 participants because the lower bound of the 95% CI was greater than 60% (36/48, 75% [95% CI] 60 to 86%) if 75% of participants agreed that the PedsQL is an appropriate primary outcome measure (our hypothesis threshold). Our threshold of 75% was based on the median threshold to define consensus.[18]

RESULTS

Characteristics of the Study Participants

Among 91 invited participants, 73 (80%) completed the electronic questionnaire, including 31/34 (91%) emergency (or pediatric emergency) medicine physicians, 16/21 (76%) trauma surgeons, 14/18 (78%) neurosurgeons, and 12/18 (67%) pediatric critical care physicians. Twenty-eight (38%) participants were from the West region, 17 (23%) from the Midwest region, 17 (23%) from the East region, and 11 (15%) from the South region (Table 1).

We scheduled two teleconference discussions based on the availability of volunteer participants, inviting 6 participants (2 emergency or pediatric emergency medicine physicians, 2 trauma surgeons, and 2 neurosurgeons) for the first telephone discussion and 6 participants (2 emergency or pediatric emergency medicine physicians, 1 trauma surgeon, 1 neurosurgeon, and 1 pediatric critical care surgeon) for the second discussion. For the first discussion 3/6 participants attended (1 pediatric emergency medicine physician, 1 trauma

surgeon, and 1 neurosurgeon) and 2/6 participants attended the second discussion (1 pediatric emergency medicine physician and 1 neurosurgeon).

Main Results

Hemorrhagic brain injuries—The electronic questionnaire showed that the PedsQL was well-accepted as a primary outcome measure for children with hemorrhagic brain injuries. Sixty-one (84%) participants agreed that the PedsQL is an appropriate primary outcome measure for children with hemorrhagic brain injuries, including 12 of 14 (86%) neurosurgeons (Tables 2, 3, and eTable). Fewer pediatric critical care physicians agreed that the PedsQL was an appropriate outcome measure (8/12, 67%; Table 3).

Only 14 (19%) participants felt that intracranial hemorrhage progression should be the primary outcome measure instead of PedsQL and 9 (13%) participants thought that a coagulation biomarker should be the primary outcome measure. Suggested alternative primary outcome measures included the Pediatric Glasgow Outcome Scale Score Extended, [19] need for surgery, thromboembolism, a drop in hemoglobin level, transfusion requirements, mortality, and neurocognitive function.

We identified several themes from responses to open-ended questions and teleconference discussions regarding hemorrhagic brain injuries (Box 1). Participants felt that the PedsQL was an important and patient-centered outcome measure, but some felt it may be impacted by other factors such as orthopedic injuries and family or societal factors. Other concerns included the subjectivity, validity, and reliability of the PedsQL. Some participants felt that alternative outcome measures such as intracranial hemorrhage progression and coagulation biomarkers would serve as better primary outcomes than the PedsQL for hemorrhagic brain injuries, because they were more objective measures. Other participants felt intracranial hemorrhage progression and coagulation biomarkers were not meaningful outcomes to patients and were unlikely to change practice.

Hemorrhagic torso injuries—Thirty-two (45%) participants agreed that the PedsQL is an acceptable primary outcome measure for children with hemorrhagic torso injuries, 27 (38%) participants were neutral, and 13 (18%) participants disagreed that the PedsQL is an accepted primary outcome measure (Table 1). Fewer trauma surgeons (3/16, 20%) and pediatric critical care physicians (3/12, 25%) agreed that the PedsQL is an appropriate outcome measure (Table 3). We did not observe substantial agreement on a better alternative primary outcome measure. Sixty-six (88%) participants agreed that the PedsQL was an important outcome measure to children and their families. Forty-eight (67%) participants agreed an improvement in PedsQL with TXA use would change their practice with regard to hemorrhagic torso injuries.

A subset of participants (26 participants, 36%) felt that total blood product transfusion requirements and a coagulation biomarker (13 participants, 18%) should be the primary outcome measure for hemorrhagic torso injuries instead of PedsQL. Other alternative outcome measures included total transfusion requirements (3 participants), a drop in hemoglobin level, mortality, death due to bleeding, need for surgery, and the Stein-Jessup

Functional Status II (Revised), a scale that measures the functional status of a child with ongoing health problems.[20]

The primary theme identified from responses to open-ended questions and teleconference discussions was that the PedsQL could potentially be impacted by other factors other than the study intervention (Box 2). Some participants felt that the PedsQL is less intuitive and a less responsive outcome measure for hemorrhagic torso injuries compared to hemorrhagic brain injuries. Some participants felt that blood product transfusion requirement is a more direct and objective outcome measure compared to PedsQL. Other participants had concerns with blood product transfusion requirement as a primary outcome measure, noting the variation and subjectivity of transfusion decisions and its feasibility as an outcome measure.

DISCUSSION

Our study has several key findings. First, the PedsQL was the most frequently accepted primary outcome measure for children with hemorrhagic brain injuries. Second, the PedsQL was less accepted as the primary outcome measure for children with hemorrhagic torso injuries. Third, some participants favored outcomes such as intracranial hemorrhage progression, blood product transfusion, and/or coagulation biomarkers that are objective and more directly related to the intervention.

Appropriate selection of the primary outcome measure is fundamental to the success of clinical trials, and for adoption of their findings.[13] Poorly chosen primary outcome measures may lead to underpowered trials, type II errors,[21] or results that are not interpretable or relevant to patients or clinicians.[22] Inappropriate or non-feasible outcome measures may also be inadequate for detecting the true effect of an intervention.[23]

Based on the results of the questionnaire and the subsequent teleconference discussions, we observed no perfect outcome measure for the TIC-TOC trial. The ideal outcome measure is patient-centered, objective and easily measured, and sensitive to detecting the efficacy of the intervention with a meaningful effect size to be feasible in the context of a clinical trial. We saw a consensus with the PedsQL as the primary outcome measure for children with hemorrhagic brain injuries, however, it was more controversial for children with hemorrhagic torso injuries. Participants equally preferred the PedsQL and blood transfusion requirement as the primary outcome measure for children with hemorrhagic torso injuries. Disadvantages with blood product transfusion requirement as a primary outcome measure include different transfusion thresholds at different sites, susceptibility to survivor bias (those who survive will receive more blood project transfusions), and it is not uniformly considered a patient-centered outcome measure. The most important limitation is that blood product transfusion is not an easily feasible primary outcome measure. Based on preliminary data, only approximately 20% of children with significant hemorrhagic torso injuries require blood product transfusions.[24] We estimate a sample size of 3790 children with hemorrhagic torso injuries will be required to detect a difference of 10 ml/kg of total blood product requirements.

Previous clinical trials of children with traumatic brain injuries have also focused on patient-centered, functional outcomes including the Glasgow Outcome Score[25] and the Pediatric Cerebral Performance Category,[26] and other trials used mortality as the primary outcome measure.[27,28] The PED-TRAX study was a retrospective study evaluating TXA use in children 18 years old and younger admitted to a combat hospital in Afghanistan.[29] Patients receiving TXA had lower mortality rates compared to those not receiving TXA. In adults with hemorrhagic trauma of the torso and brain, the use of TXA had a 1.5% absolute mortality reduction compared to placebo in the CRASH-2 (14.5% vs. 16.0%) and CRASH-3 trials (12.5% vs. 14.0%).[6,7] Mortality is not an easily feasible primary outcome measure for the TIC-TOC trial. We estimate that it would require 14,000 children with hemorrhagic brain injuries to detect a 2% mortality difference.

LIMITATIONS

Our study has several limitations. Selecting the ideal primary outcome measure for a clinical trial is complex. Study participants may not have had sufficient background information or time to respond to the questionnaire or participate in teleconference discussions. We provided a detailed background table that participants could reference while completing the questionnaire (Online Supplement). We considered including patient advocates in our study but preliminary feedback from several patient advocates suggested that the various outcomes were complex and difficult to understand. The participation rate of teleconference discussions was low. Most participants were scheduled but did not attend teleconference discussions attributed their absence to changes in their clinical schedules. Because we invited all respondents to the questionnaire to participate in the teleconference discussions, those volunteering may have been biased towards a particular outcome measure. Finally, although we had adequate representation across disciplines and geographic regions, participants were from large, academic medical centers and primarily freestanding children's hospitals. The responses from clinicians from general or community hospitals may differ.

CONCLUSION

Across a multidisciplinary cohort of clinicians caring for injured children, the PedsQL was a well-accepted primary outcome measure in a clinical trial of severely injured children with hemorrhagic brain injuries. Traumatic intracranial hemorrhage progression was favored by a smaller subset of clinicians. For children with hemorrhagic torso injuries, a plurality, but not a majority of study participants also considered the PedsQL an appropriate outcome measure. Blood product transfusion requirement was favored by about half of the participants for the hemorrhagic torso injury stratum. The primary concern about the PedsQL as a primary outcome measure was that it was potentially impacted by other factors outside of the study intervention. In addition to the primary outcome measure, it was suggested that we collect several other outcome measures, to ensure important effects are captured in this trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1.

Summative themes based on open-ended questions and the telephone discussions

Hemorrhagic brain injuries
PedsQL is impacted by multiple other factors
"I am concerned that there are multiple factors that will impact QOL to a greater degree than bleeding including arrest, hypoxic injury, family/societal factors."
"[Peds]QL is most important but may be too blunt and influenced by too many factors. A meaningful incremental benefit may be washed out."
"Quality of life/cognitive function would be the most impactful but is a multifactorial, extrapolated outcome so I feel it is a poor choice for primary endpoint (clinically meaningful but confounded by other factors and much lower likelihood of demonstrating impact)."
Intracranial hemorrhage progression would be a better outcome measure
"A radiographic outcome (e.g., increased hematoma size) would be far more sensitive and responsive. "
"Progression of cranial hemorrhage may be a good marker for TXA outcome. If we can minimize bleeding perhaps, we can also prevent the ICP that follows it."
Importance of a patient-centered outcome measure
"Given the information provided, I feel PedsQL is the most appropriate primary outcome variable."
"Clinical and functional outcome is a more important marker than progression on CT as patients may have clinical progression of an intracranial injury but still do well."
"A biomarker outcome might be insufficient to change practice. Progression will be subject to missing data/ practice variation - particularly in the sickest patients."
"Progression of hemorrhage is important but not primarily; how this factors into overall recovery and quality of living regardless of hemorrhage and re-bleed is ultimately more meaningful for all involved."
"Neither [intracranial hemorrhage progression nor coagulation biomarkers] reflect long term neurologic outcome."

Box 2.

Summative themes based on open-ended questions and the telephone discussions

Hemorrhagic torso injuries
PedsQL is impacted by multiple other factors
"Too many other factors impacting PedsQL."
"The correlation between TXA use and mitigating torso bleeding and long term PedQL is much less intuitive/biologically plausible than in TBI."
"There are multiple other variables which will influence outcomes rather than TXA."
"I think the Peds QL results will be much more dependent on associated injuries such as orthopedic injuries than earlier hemorrhage control."
Quality of life/cognitive function would be the most impactful but is a multifactorial, extrapolated outcome so I feel it is a poor choice for primary endpoint (clinically meaningful but confounded by other factors and much lower likelihood of demonstrating impact)."
Blood transfusion requirements would be a better outcome measure
"Total blood transfusion is a more objective measure."
[Blood transfusion] is biologically plausible, immediate, cheap outcome compared with PedQL but if requires 9 years of recruitment, then no…"
"Understand feasibility issues with blood transfusion, but I do feel that it is a patient-centric outcome, as most parents would like to avoid/minimize blood transfusions in their children if possible and may be more likely to show effect in torso trauma."
"Transfusion requirement would be the ideal primary endpoint and has been used in various other TXA studies. It is directly related to the intervention (thus plausible causality), and clinically meaningful. If there is a difference between TXA and placebo, this would be a meaningful, clinically-relevant demonstration of the difference (more so than coagulation labs), and likely detectable (more so than QL)."
Concerns about blood transfusion requirement as an outcome measure
"This is a struggle. Transfusion practices are variable and subjective."
"Total transfusion volume is important because of the relationship between the risk of adverse outcomes and the administration of blood per unit; however, there are many important confounding factors that may be difficult to account for - threshold tolerance; hospital policies; etc…"
"Am worried about the number of patients who will receive blood transfusions, and can we be exact enough to find a difference."

Highlights

- Across a multidisciplinary cohort of clinicians caring for injured children, the PedsQL was a well-accepted primary outcome measure in a clinical trial of severely injured children with hemorrhagic injuries
- Traumatic intracranial hemorrhage progression and blood transfusion requirement was favored by a smaller subset of clinicians
- The primary concern about the PedsQL as a primary outcome measure was that it was potentially impacted by other factors outside of the study intervention

Table 1.

Characteristics of study participants, n=73

Characteristic	n (%)
Specialty	
Pediatric emergency medicine	31 (42)
Trauma surgery	16 (22)
Pediatric neurosurgery	14 (19)
Pediatric critical care	12 (16)
Patient advocate	
Geographic region	
West	28 (38)
Midwest	17 (23)
East	17 (23)
South	11 (15)

Table 2.

Responses to questionnaire, n=73

Question/statement[a]	Agree	Neutral	Disagree
Hemorrhagic brain injuries			
1. The PedsQL is an appropriate primary outcome for children with hemorrhagic brain injuries.	61 (84)	6 (8)	6 (8)
2. The PedsQL is an outcome that is important to children and their families.	67 (92)	6 (8)	0 (0)
3. If the TIC-TOC trial showed improved PedQL with the use of TXA, this would change my practice in the management of children with hemorrhagic brain injuries.	62 (85)	9 (12)	2 (3)
4. Intracranial hemorrhage progression on cranial CT scan should be the primary outcome instead of PedsQL.	23 (32)	20 (27)	30 (41)
5. A coagulation biomarker such as d-dimer or thromboelastography (TEG) should be the primary outcome instead of PedsQL.	9 (12)	17 (23)	47 (64)
6. Should another outcome, not listed above, be the primary outcome instead of PedsQL? (Yes, Don't know, No)[b]	7 (10)	24 (33)	42 (58)
Hemorrhagic torso injuries[c]			
1. The PedsQL is an appropriate primary outcome for children with hemorrhagic torso injuries.	32 (44)	27 (38)	13 (18)
2. The PedsQL is an outcome that is important to children and their families.	63 (88)	9 (13)	0 (0)
3. If the TIC-TOC trial showed improved PedQL with the use of TXA, this would change my practice in the management of children with hemorrhagic torso injuries.	48 (67)	20 (28)	4 (6)
4. Total blood transfusion requirements (ml/kg) should be the primary outcome instead of PedsQL.	26 (36)	27 (38)	19 (26)
5. A coagulation biomarker such as d-dimer or thromboelastography (TEG) should be the primary outcome instead of PedsQL.	13 (18)	19 (26)	40 (56)
6. Should another outcome, not listed above, be the primary outcome instead of PedsQL?[d]	8 (11)	28 (39)	36 (50)

[a] - Responses are reported as the compressed results of the Likert scale where "Agree" includes Agree and Strongly Agree responses and "Disagree" includes Disagree, and Strongly Disagree responses. Specific Likert scale responses are reported in eTable 1

[b] - Suggested alternative primary outcome measures: Peds GOS-E (1), drop in hemoglobin (1), transfusion requirements (1), mortality (1), neurocognitive function (1), thromboembolism (1), need for surgery (1)

[c] - n=72 (one participant did not complete torso injury questions)

[d] - Suggested alternative primary outcome measures: drop in hemoglobin (1), transfusion requirements (3), mortality (1), death due to bleeding (1), need for surgery (1), Stein-Jessup Functional Status II (Revised) (1)

Table 3.

Agreement to responses to questionnaire, n=73

Question/statement[a]	Emergency Medicine, n=31	Trauma Surgery, n=16	Neurological Surgery, n=14	Pediatric Critical Care, n=12
Hemorrhagic brain injuries				
1. The PedsQL is an appropriate primary outcome for children with hemorrhagic brain injuries.	29 (94)	12 (75)	12 (86)	8 (67)[c]
2. The PedsQL is an outcome that is important to children and their families.	30 (97)	14 (88)	12 (86)	11 (92)
3. If the TIC-TOC trial showed improved PedQL with the use of TXA, this would change my practice in the management of children with hemorrhagic brain injuries.	31 (100)	11 (69)	13 (93)	7 (58)
4. Intracranial hemorrhage progression on cranial CT scan should be the primary outcome instead of PedsQL.	10 (32)	3 (19)	6 (43)	4 (33)
5. A coagulation biomarker such as d-dimer or thromboelastography (TEG) should be the primary outcome instead of PedsQL.	3 (10)	4 (25)	1 (7)	1 (8)
Hemorrhagic torso injuries[b]				
1. The PedsQL is an appropriate primary outcome for children with hemorrhagic torso injuries.	18 (58)	3 (20)[c]	8 (57)	3 (25)[c]
2. The PedsQL is an outcome that is important to children and their families.	30 (97)	12 (80)	11 (79)	10 (83)
3. If the TIC-TOC trial showed improved PedQL with the use of TXA, this would change my practice in the management of children with hemorrhagic torso injuries.	29 (94)	7 (47)[c]	7 (50)[c]	5 (42)[c]
4. Total blood transfusion requirements (ml/kg) should be the primary outcome instead of PedsQL.	10 (32)	3 (21)	9 (60)	4 (33)
5. A coagulation biomarker such as d-dimer or thromboelastography (TEG) should be the primary outcome instead of PedsQL.	3 (10)	5 (33)	4 (29)	1 (8)

[a] - Responses are reported as the number and percentage of respondents who agreed to statement (Agree and Strongly Agree)

[b] - n=72 (one participant [trauma surgery] did not complete torso injury questions)

[c] - significant difference compared to emergency medicine reference on adjusted analysis