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Enrollment with and without Exception from Informed Consent in a Pilot Trial of Tranexamic Acid in Children with Hemorrhagic Injuries

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Abstract

Background: Federal exception from informed consent (EFIC) procedures allow studies to enroll patients with time-sensitive, life-threatening conditions when written consent is not feasible. Our objective was to compare enrollment rates with and without EFIC in a trial of tranexamic acid (TXA) for children with hemorrhagic injuries.

Methods: We conducted a four-center randomized controlled pilot and feasibility trial evaluating TXA in children with severe hemorrhagic brain and/or torso injuries. We initiated the trial

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DKN and NK conceptualized and designed the initial study and obtained funding. SWL drafted the initial manuscript. DKN, RMS, NK, HH, SM, JV, TCC, MB, SG, and WOS provided substantive feedback on the initial draft. All authors provided substantive feedback on one or more drafts of the manuscript.

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enrolling patients without EFIC. After 3 months of enrollment, we met our a priori futility threshold and paused the trial to incorporate EFIC procedures and obtain regulatory approval. We then restarted the trial allowing EFIC if the guardian was unable to provide timely written consent. We used descriptive statistics to compare characteristics of eligible patients approached with and without EFIC procedures. We also calculated the time delay to restart the trial using EFIC.

Results: We enrolled 1 of 15 (6.7%) eligible patients (0.17 per site per month) prior to using EFIC procedures. Of the 14 missed eligible patients, 7 (50%) were not enrolled because guardians were not present or were injured and unable to provide written consent. After obtaining approval for EFIC, we enrolled 30 of 48 (62.5%) eligible patients (1.34 per site per month). Of these 30 patients, 22 (73.3%) were enrolled with EFIC. Of the 22, no guardians refused written consent after randomization. There were no significant differences in the eligibility rate and patient characteristics enrolled with and without EFIC procedures. Across all sites, the mean delay to restart the trial using EFIC procedures was 12 months.

Conclusions: In a multicenter trial of severely injured children, the use of EFIC procedures greatly increased the enrollment rate and was well accepted by guardians. Initiating the trial without EFIC procedures led to a significant delay in enrollment.

Keywords

pediatric trauma; exception from informed consent (EFIC); tranexamic acid

INTRODUCTION

In 1996, the FDA established 21 CFR 50.24, which created a pathway to perform clinical research under an exception from informed consent (EFIC).[1] EFIC was primarily introduced as a response to the difficulty of obtaining informed consent from patients or their proxies in the setting of immediately life-threatening injuries or illnesses, especially in the case of incapacity of the patient. While there has been considerable debate over the ethical implications of EFIC, several studies have demonstrated that there is a high level of community support and trust for trials conducted under these procedures.[2–5]

The use of EFIC has played an important role in trials that have substantially changed the standard of care in life-threatening situations. Perhaps the most notable example of this was the Public Access Defibrillation (PAD) trial published in 2004.[6] This study demonstrated a marked improvement in survival for patients with out-of-hospital cardiac arrest who received cardiopulmonary resuscitation (CPR) and an automated external defibrillator (AED) compared to those who received CPR alone (relative risk 2.0, 95% confidence intervals [CI] 1.07–3.77). The results of this trial helped lead to widespread deployment of AEDs in public areas throughout the United States.

EFIC has been more widely applied in adults than in children. One review found that from 1996 to 2016, there were 28 completed trials that used either EFIC (n=24) or waiver of informed consent (n=4). Of these, 21 were conducted exclusively in adults, 4 included patients as young as 15 years, and only three were studies enrolling only children (one of which was a pilot study of 10 patients).[7] One pediatric clinical trial that used EFIC

procedures was conducted in the Pediatric Emergency Care Applied Research Network (PECARN) in 2014 to study the relative effectiveness and safety of lorazepam vs diazepam for pediatric status epilepticus.[8] This trial demonstrated that research in acutely ill children could be effectively conducted with EFIC.

We conducted the Traumatic Injury Clinical Trial Evaluating Tranexamic Acid in Children (TIC-TOC) pilot study to evaluate the feasibility of performing a large-scale randomized, double-blinded, placebo-controlled trial of tranexamic acid (TXA) for children with severe hemorrhagic brain and/or torso injuries. The trial was regulated by the United States Food and Drug Administration (FDA) and began enrollment without EFIC procedures but was later revised to include EFIC. The objective of this study was to compare the enrollment rates and considerations before and after the implementation of EFIC procedures.

METHODS

Study Design

We conducted a four-center, double-blind, randomized controlled trial of TXA in children with severe hemorrhagic brain and/or torso injuries as a pilot to test feasibility. The trial was approved using a single IRB at the University of Utah. Details of the pilot trial have been previously described.[9]

Study Setting and Population

The trial was conducted at four Level I pediatric trauma centers. Children with severe hemorrhagic brain and/or torso injuries were enrolled only if study drug could be administered within 3 hours from the time of injury. Inclusion and exclusion criteria have been described previously.[9] Enrolled patients were block-randomized (in blocks of 3, 6, and 9 with a ratio of 1:1:1) into one of three groups: TXA 15 mg/kg bolus dose followed by a 2 mg/kg/hr infusion over 8 hours, TXA 30 mg/kg bolus dose followed by a 4 mg/kg/hr infusion over 8 hours, or a placebo (saline) bolus and infusion.

Study Procedures

After consultation with the FDA, we conducted the initial phase of the pilot study without EFIC. A patient was enrolled only if written informed consent was obtained from the patient's guardian. This phase lasted approximately three months. After it became evident that this enrollment strategy was not feasible (using an *a priori* futility threshold described below), we revised the protocol to include EFIC procedures. This second phase of the trial introduced the possibility of enrolling under EFIC and completing consent with a guardian at the earliest possible opportunity after enrollment. The FDA and the single IRB approved of these new consent procedures (Figure 1).

EFIC was used in two scenarios. If the guardian was not present or was unable to provide written informed consent (e.g., parent was also seriously injured), we provided any family member, if present, the opportunity to object to the enrollment. In this scenario, the family member was provided a brief overview of the study and an explanation on why we were unable to obtain written informed consent (i.e., the guardian was absent during the narrow

therapeutic time window). If the family member present objected to the patient's enrollment, the patient was not enrolled. If no objections were made, the patient was enrolled using EFIC (eFigure 1). In the second scenario, if the guardian was present but there was not sufficient time to obtain informed consent, the guardian was provided the opportunity to decline enrollment using the same procedures described above (eFigure 2). However, if the on-site research team believed that the guardian was too emotionally distraught to process presented information, the patient was enrolled under EFIC and consent was obtained later.

Prior to implementing EFIC procedures for enrollment, the four sites developed site-specific plans for community consultations and public disclosures. This was done to increase awareness of the trial in the broader communities regarding its potential risks and benefits as well as use of EFIC procedures. After completion of community consultation activities, sites were approved by the single IRB to restart the trial using EFIC procedures.

Analysis

Our target enrollment rate for the pilot trial was 1.25 patients per site per month or 40 patients total over 8 months at the 4 participating sites. We determined that an enrollment rate of 1.25 patients per site per month would demonstrate the feasibility of conducting a large-scale, phase 3 trial at approximately 40 sites over a 5-year period.[9]

Prior to the start of the trial, we set a priori thresholds for recruitment futility to consider conversion to the use of EFIC study procedures. To do this, we calculated 95% confidence intervals around the monthly enrollment rate, assuming a Poisson distribution. We assumed the higher end of the confidence interval to be the most optimistic enrollment rate and calculated the probability of enrolling 40 patients by the end of 8 months. If that probability was less than 50%, the current enrollment strategy would be deemed futile and we would convert to the use of EFIC study procedures. Assuming all 4 sites were enrolling patients, this futility threshold translated to 0 enrollments at 1 month, 4 enrollments or fewer at 2 months, 9 enrollments or fewer at 3 months, and 14 enrollments or fewer at 4 months.

We calculated the number of eligible and enrolled patients per month by site and overall, with and without EFIC, and compared enrollment rates between these two time periods using chi-squared test. Patients who met inclusion criteria and did not fall under exclusion criteria were considered eligible for enrollment. Missed patients were those patients who would have been eligible but were not enrolled. Frequencies and percentages were used to summarize categorical variables and medians and quartiles were used to summarize continuous variables. These observations were strictly exploratory; we did not specify any analyses *a priori.* We reported the time the trial was paused to obtain regulatory approval and complete community consultations across sites. We also summarized the days of the week and the ED arrival times of eligible patients, stratified by enrollment status, to explore the relationship between day of the week and ED arrival time and successful enrollment. All calculations were made using Stata statistical software (Stata 14, College Station, TX).

RESULTS

We enrolled patients without EFIC procedures from June 2018 to September 2018 (Figure 2). After meeting the a priori enrollment futility threshold, we then paused the trial for FDA and IRB review, approval of incorporation of EFIC procedures and completion of site-specific community consultations. Completion of these activities required 6 months for site 1, 13 months for sites 2 and 3, and 17 months for site 4. The trial was restarted using EFIC procedures from March 2019 until March 2020.

Overall, there were 63 eligible patients, of whom 32 (51%) were approached for enrollment. Of the 32 patients, 31 (97%) were successfully enrolled (one patient had verbal objection from family), with 22 (71%) enrolled with EFIC procedures and 9 (29%) enrolled with written informed consent (see Figure 3 for CONSORT diagram). Enrollment was stopped in March 2020 prior to the 40-patient goal after research activities were suspended by all participating institutions as a result of the COVID-19 pandemic.

The median age of eligible patients was 11.7 years (interquartile range 5.0 to 14.7) and 40 of 62 (64.5%) were male. There were 27 eligible patients (43.5%) with hemorrhagic brain injuries only, 34 patients (54.8%) with hemorrhagic torso injuries only, and 1 patient (1.6%) with both hemorrhagic brain and torso injuries. Overall, eligible patient characteristics were similar before and after EFIC procedures were initiated (Table 1).

Main Results

During the phase of the trial before EFIC, there were a total of 15 eligible patients at three enrolling sites (one site had not yet opened for enrollment; 2.6 eligible patients per site per month) (Table 2). Of these eligible patients, one (6.7%) was successfully enrolled (0.2 enrollments per site per month). Even adjusting for one unanticipated non-enrolling site, these numbers met the a priori futility threshold.

During the phase of the trial after EFIC procedures were initiated, there were 48 eligible patients encountered among the four participating sites (2.14 eligible patients per site per month) (Table 2). Of these 48 eligible patients, 30 were enrolled (63%; 1.3 enrollments per site per month), demonstrating a significant difference between the pre- and post-EFIC groups ($p<0.001$).

The most frequent reason eligible patients were not enrolled before the initiation of EFIC was because the guardians were either not present or severely injured (7/14 missed eligible patients, 50%) (Table 3). The most frequent reason eligible patients were not enrolled after the initiation of EFIC was because the ED staff did not alert research staff of eligible patients within the 3-hour enrollment window after injury (7/17, 41.2%).

Most eligible patients arrived at the ED between 1 and 10 PM for all days of the week (eFigure 3). There was no clear association between day of the week or time of ED arrival and enrollment of eligible patients.

DISCUSSION

In our randomized controlled pilot trial of children with hemorrhagic brain and/or torso injuries, our results demonstrated a significant increase in enrollment after revising the initial written informed consent protocol to include EFIC procedures. Use of EFIC procedures was also well-accepted, as no guardian refused consent when approached after enrollment with EFIC. We met our enrollment futility threshold after 3 months of enrolling only with written informed consent (enrolling only 1 of 15 eligible patients [6.7%]). Pausing the trial, obtaining regulatory approvals, and completing community consultations led to a mean 12-month delay before restarting the trial across sites.

Prior to the start of the trial, we requested the use of EFIC procedures from the FDA as we anticipated that a significant proportion of guardians would not be present in the ED to provide written informed consent within 3 hours from the time of injury. In prior studies, half of injured children did not have a guardian present during their initial evaluation and nearly 40% of guardians arrived in the ED 2 or more hours after the initial injury (over 25% arrived 3 or more hours after injury), making it difficult to obtain written informed consent for time-sensitive experimental interventions.[10,11] The FDA, however, advised that we begin the trial enrolling only with written informed consent and would consider EFIC procedures if we demonstrated futility. During approximately 3 months of enrollment without EFIC, half of the missed eligible patients were not enrolled because the guardians were absent or injured and unable to provide informed consent.

After the initial period of enrollment without EFIC, once it had been demonstrated that enrollment was meeting the designated futility threshold, the trial was paused to lay the groundwork for restarting with EFIC in place. This included retraining research staff at each institution as well as the design, execution, and approval of community consultation at all sites. This delayed the trial by a mean of 12 months among the four sites.

The potential benefit of EFIC is the ability to enroll critically ill or injured patients in time-sensitive studies for which it is impractical or impossible to obtain written informed consent prior to the initiation of intervention. This is demonstrated by the nearly tenfold increase in enrollment rate in our study - from 6.7% without EFIC to 62.5% once we initiated EFIC procedures. Given the low enrollment rate without EFIC (0.2 patients per site per month), it would be extremely difficult to enroll enough patients for an adequately powered trial in a reasonable timeframe. However, using EFIC, we were able to enroll nearly 2 patients per site per month, which would allow us to generate clinically impactful results well within the five-year course of the proposed definitive large-scale trial.

EFIC has been used in a relatively sparing fashion in clinical trials. In the first 20 years after its creation, there were 24 trials completed using EFIC.[7] Trials using EFIC have always had to address two primary concerns: first, that they do not adversely impact the care or the rights of the patient being enrolled; and second, that they do not result in loss of public trust. However, studies examining these potential pitfalls have largely demonstrated that the public approves of trials being conducted using EFIC and express that they would participate (or allow a family member to participate) in such trials.[2–4,12–15]

There are few studies examining enrollment of patients into studies using or not using EFIC procedures. One study compared actual time required to enroll adult patients with traumatic brain injuries with proxy consent versus the estimated time needed had EFIC been used.[15] The authors concluded that EFIC would have allowed for study initiation approximately 4 hours earlier (on average) than with the use of proxy consent. Another study indicated that patients with severe trauma were frequently unable to consent to participate and, in a high proportion of cases, patient representatives could not be reached to provide consent in a timely fashion.[16]

LIMITATIONS

Our results should be interpreted in the context of several limitations. The eligible and enrolled patient rates may differ at different sites. Seasonal variation may also have influenced enrollment rates during study periods before and after the use of EFIC. However, the study phase before EFIC was primarily conducted during the summer which traditionally has more traumatic injuries among children and the eligibility rates were similar before and after EFIC procedures were initiated. There may also be differences in the characteristics of the eligible patients evaluated before and after EFIC procedures were initiated that influenced the enrollment rate. However, we did not identify patient characteristic differences between the cohorts. Finally, although the excellent consent rate suggests a high level of confidence in and acceptance of the EFIC process, there may be other contributing factors. Specifically, the unavoidable power differential may result in guardians feeling obliged to continue the study despite preferring to withdraw their children. It is also possible that the consent rate was in part a product of the small sample size of this feasibility trial and may decrease somewhat in a larger definitive trial.

CONCLUSIONS

In a multicenter trial of children with hemorrhagic injuries, the use of EFIC procedures greatly increased the enrollment rate compared to without the use of EFIC and was well accepted by guardians. Initiating the trial without EFIC procedures led to a significant delay in enrollment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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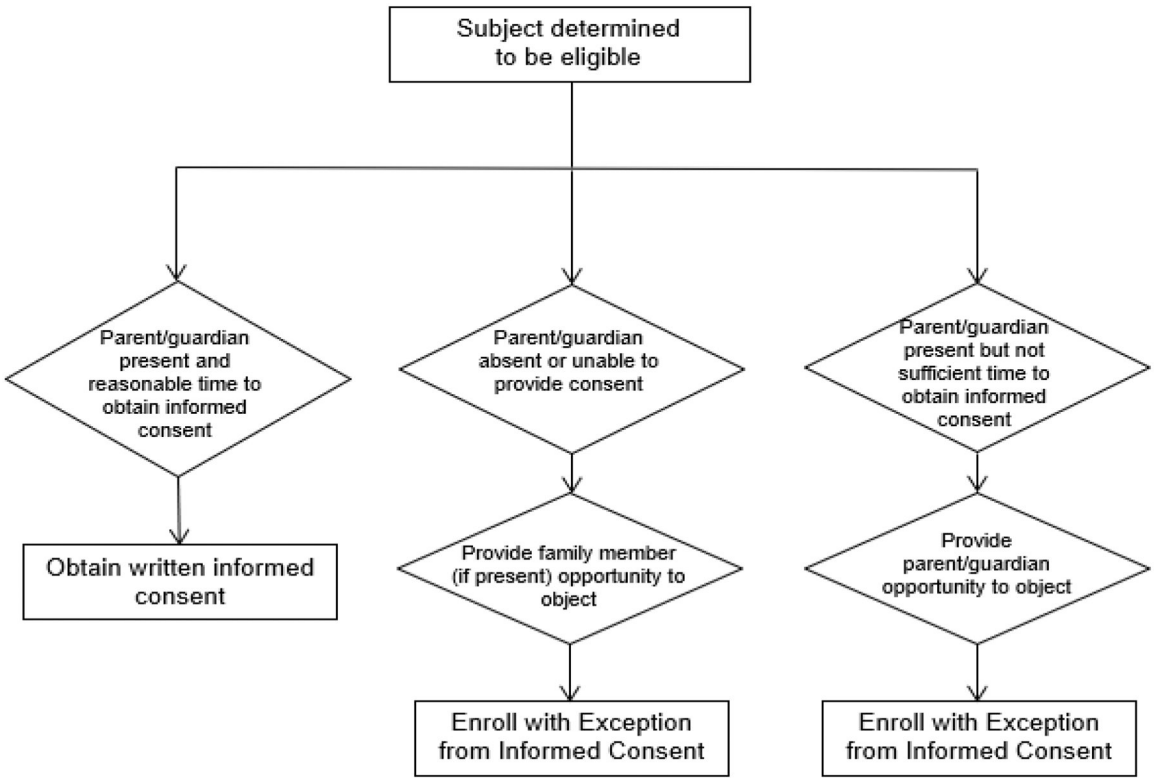

Figure 1:
Consent procedures during the post-EFIC phase of the TIC-TOC trial

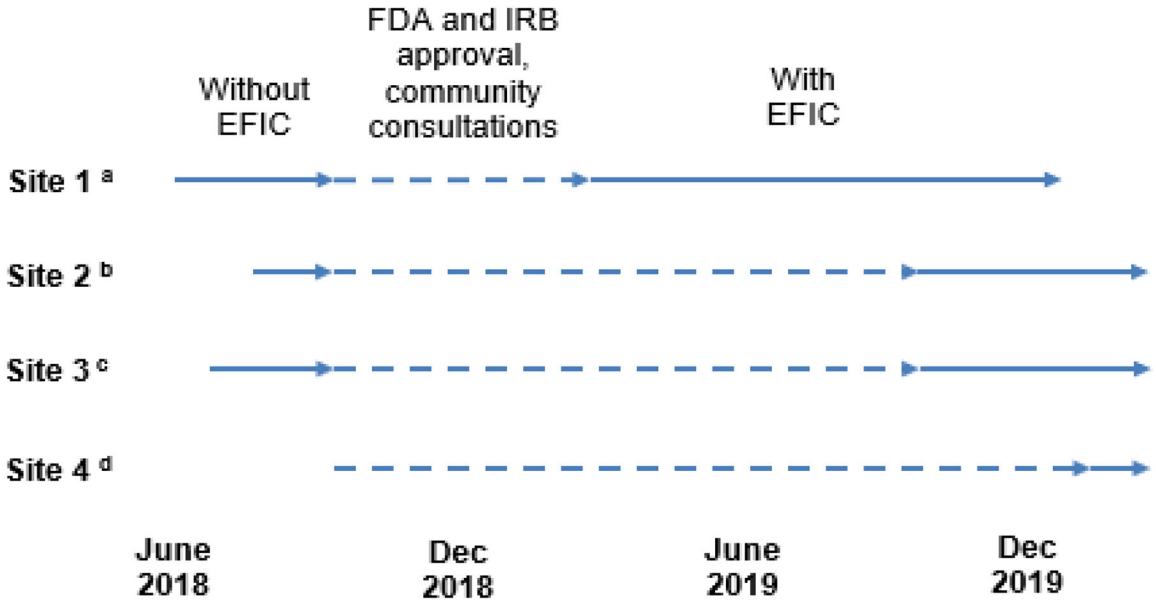

Figure 2:

Duration of trial without exception from informed consent (EFIC), paused for regulatory approval and community consultations (dashed lines), and with EFIC

[a]– Pre-EFIC, enrolled 6/12/18 to 9/10/18; Post-EFIC 3/4/19 to 1/5/20 (community consultations were completed as part of separate study thus shorter time to restarting enrollment)

[b]– Pre-EFIC, enrolled 8/15/18 to 9/10/18; Post-EFIC 10/4/19 to 3/13/20

[c]– Pre-EFIC, enrolled 7/17/18 to 9/10/18; Post-EFIC 10/8/19 to 3/25/20

[d]– Pre-EFIC (did not open for enrollment); Post-EFIC 2/10/20 to 3/13/20

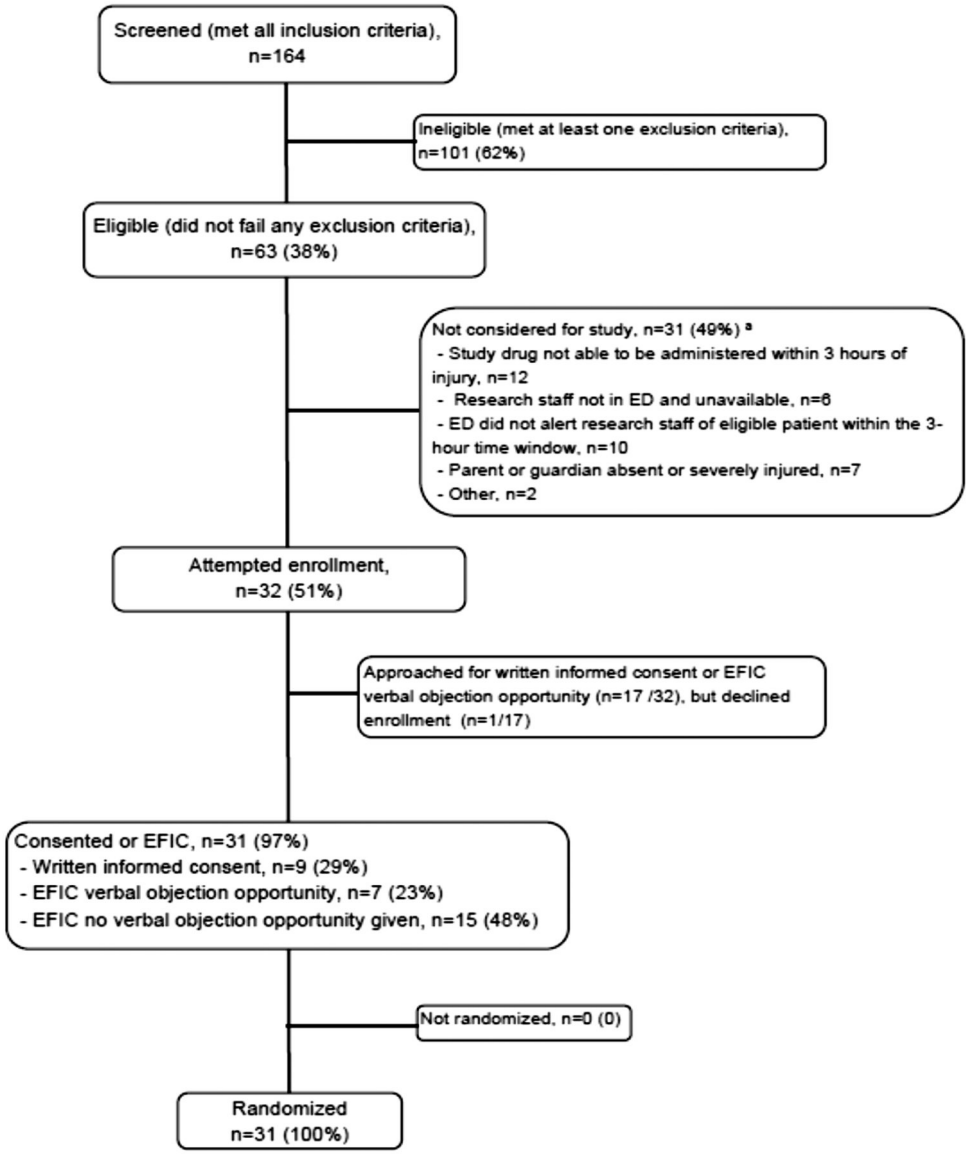

Figure 3:
CONSORT diagram
[a] - not mutually exclusive

Table 1.

Patient characteristics among eligible patients with and without use of federal exception from informed consent[a]

		Screening Phase	
	Overall, N=62 (%)	**Before EFIC, n=15 (%)**	**After EFIC, n=47 (%)**
Demographics			
Age, years, median (IQR)	11.7 (5.0,14.7)	11.4 (6.8, 14.3)	12.0 (4.6, 14.7)
Age, years			
< 2 years	6 (9.7)	1 (6.7)	5 (10.6)
2–9 years	19 (30.6)	5 (33.3)	14 (29.8)
>= 10 years	37 (59.7)	9 (60.0)	28 (59.6)
Sex			
Male	40 (64.5)	7 (46.7)	33 (70.2)
Female	22 (35.5)	8 (53.3)	14 (29.8)
Race[b]			
Asian	1 (1.6)	0 (0)	1 (2.1)
Black or African American	12 (19.4)	2 (13.3)	10 (21.3)
White	36 (58.1)	8 (53.3)	28 (59.6)
Multiple	2 (3.2)	0 (0.0)	2 (4.3)
Unknown or not reported	11 (17.7)	5 (33.3)	6 (12.8)
Hispanic or Latino	11 (17.7)	5 (33.3)	6 (12.8)
Study Site			
Site 1	42 (67.7)	12 (80.0)	30 (63.8)
Site 2	11 (17.7)	0 (0.0)	11 (23.4)
Site 3	7 (11.3)	3 (20.0)	4 (8.5)
Site 4	2 (3.2)	0 (0.0)	2 (4.3)
Injury Characteristics			
Actual injury location			
Head	27 (43.5)	8 (53.3)	19 (40.4)
Torso	34 (54.8)	6 (40.0)	28 (59.6)
Both	1 (1.6)	1 (6.7)	0 (0.0)
Method of transport to ED			
EMS air	22 (35.5)	6 (40.0)	16 (34.0)
EMS ground	32 (51.6)	8 (53.3)	24 (51.1)
Private vehicle/walk-in	2 (3.2)	0 (0.0)	2 (4.3)
Interfacility transfer	4 (6.5)	1 (6.7)	3 (6.4)
Multiple methods of transportation	2 (3.2)	0 (0.0)	2 (4.3)
Time from injury to ED arrival, hours, median (IQR)	1.0 (0.6, 1.7)	1.0 (0.6, 1.7)	1.0 (0.6, 1.8)
Time from ED arrival to randomization, hours, median (IQR)[c]	1.4 (1.0, 1.8)	2.0 (2.0, 2.0)	1.3 (1.0, 1.8)
Time from injury to randomization, hours, median (IQR)	2.6 (2.1, 2.9)	2.9 (2.9, 2.9)	2.6 (2.1, 2.9)
Primary mechanism of injury			

		Screening Phase	
	Overall, N=62 (%)	**Before EFIC, n=15 (%)**	**After EFIC, n=47 (%)**
Fall from standing height or less	1 (1.6)	0 (0)	1 (2.1)
Fall from greater than standing height	11 (17.7)	3 (20.0)	8 (17.0)
Motor vehicle collision	21 (33.9)	7 (46.7)	14 (29.8)
Pedestrian/bicyclist hit by moving vehicle	5 (8.1)	0 (0)	5 (10.6)
Gun-shot wound	7 (11.3)	2 (13.3)	5 (10.6)
Stab wound	1 (1.6)	0 (0)	1 (2.1)
Recreational vehicle injury	4 (6.5)	1 (6.7)	3 (6.4)
Sports-related injury	9 (14.5)	2 (13.3)	7 (14.9)
Other	3 (4.8)	0 (0)	3 (6.4)
Craniotomy or craniectomy	9 (14.5)	4 (26.7)	5 (10.6)
Intracranial pressure monitor	7 (11.3)	3 (20.0)	4 (8.5)
Other neurosurgical procedure	2 (3.2)	2 (13.3)	0 (0)
Laparotomy	13 (21.0)	4 (26.7)	9 (19.1)
Thoracotomy	3 (4.8)	0 (0)	3 (6.4)
Initial GCS total score			
Head/Both	8.0 (3.5, 13.0)	8.0 (4.0, 12.0)	8.0 (3.0, 13.0)
Torso	15 (14.0, 15.0)	15.0 (14.0, 15.0)	15.0 (13.5, 15.0)

[a] - One subject refused enrollment and is not included in this table

[b] - Not mutually exclusive

[c] - Study drug is started at the time of randomization

IQR – Interquartile Range

Table 2.

Enrollment pre- and post-EFIC

Study Site	Months open	Eligible patients[a]	Missed eligible[b]	Enrolled patients	Eligible rate per site per month	Enrollment rate per site per month
Pre-EFIC						
Site 1	3.0	12	11	1	4.0	0.3
Site 2	0.9	0	0	0	0	0
Site 3	1.9	3	3	0	1.6	0
Total	*5.8*	*15*	*14*	*1*	*2.6*	*0.2*
Post-EFIC						
Site 1	10.3	30	11	19	2.9	1.9
Site 2	5.4	12[a]	4	7	2.2	1.3
Site 3	5.7	4	1	3	0.7	0.5
Site 4	1.1	2	1	1	1.8	0.9
Total	*22.5*	*48*	*17*	*30*	*2.1*	*1.3*

a - included patients who met inclusion and exclusion criteria

b - see Table 3 for reasons for missed enrollment

c - one patient was approached but refused enrollment

Table 3.

Reasons eligible patients were not enrolled, with and without use of federal exception from informed consent (EFIC)

		Screening Phase	
	Overall, N = 31 (%)	**Without EFIC, n = 14 (%)**	**With EFIC, n = 17 (%)**
Reasons not approached [a]			
Study drug not able to be administered within 3 hours of injury	12 (38.7)	4 (28.6)	8 (47.1)
Research staff not in ED and unavailable (e.g., after hours or between shifts)	6 (19.4)	4 (28.6)	2 (11.8)
ED staff did not alert research staff of eligible patient within the 3-hour window	10 (32.3)	3 (21.4)	7 (41.2)
Parent or guardian not present or severely injured	7 (22.6)	7 (50.0)	0 (0)
Other	2 (6.4)	1 (7.1)	1 (5.9)

[a] -Reasons not approached are not mutually exclusive