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Missingness matters: a secondary analysis of thromboelastography measurements from a recent prehospital randomized tranexamic acid clinical trial

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ABSTRACT

Background Tranexamic acid (TXA) has been hypothesized to mitigate coagulopathy in patients after traumatic injury. Despite previous prehospital clinical trials demonstrating a TXA survival benefit, none have demonstrated correlated changes in thromboelastography (TEG) parameters. We sought to analyze if missing TEG data contributed to this paucity of findings.

Methods We performed a secondary analysis of the Study of Tranexamic Acid During Air Medical and Ground Prehospital Transport Trial. We compared patients that received TEG (YES-TEG) and patients unable to be sampled (NO-TEG) to analyze subgroups in which to investigate TEG differences. TEG parameter differences across TXA intervention arms were assessed within subgroups disproportionately present in the NO-TEG relative to the YES-TEG cohort. Generalized linear models controlling for potential confounders were applied to findings with p<0.10 on univariate analysis.

Results NO-TEG patients had lower prehospital systolic blood pressure (SBP) (100 (78, 140) vs 125 (88, 147), p<0.01), lower prehospital Glascow Coma Score (14 (3, 15) vs 15 (12, 15), p<0.01), greater rates of prehospital intubation (39.4% vs 24.4%, p<0.01) and greater mortality at 30 days (36.4% vs 6.8%, p<0.01). NO-TEG patients had a greater international normalized ratio relative to the YES-TEG subgroup (1.2 (1.1, 1.5) vs 1.1 (1.0, 1.2), p=0.04). Within a severe prehospital shock cohort (SBP<70), TXA was associated with a significant decrease in clot lysis at 30 min on multivariate analysis (β=−27.6, 95% CI (−51.3 to −3.9), p=0.02).

Conclusions Missing data, due to the logistical challenges of sampling certain severely injured patients, may be associated with a lack of TEG parameter changes on TXA administration in the primary analysis. Previous demonstration of TXA's survival benefit in patients with severe prehospital shock in tandem with the current findings supports the notion that TXA acts at least partially by improving clot integrity.

Level of evidence Level II.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Tranexamic acid (TXA) is hypothesized to mitigate hyperfibrinolysis and reduce bleeding.
⇒ However, previous prehospital clinical trials have not concomitantly demonstrated a TXA survival benefit and reduction in clot lysis at 30 min (LY30).

WHAT THIS STUDY ADDS

⇒ In a secondary analysis of a prehospital clinical trial, we demonstrate that prehospital TXA administration is associated with a significant reduction of LY30 in the same cohort (severe prehospital shock patients) in which a survival benefit was found in the primary trial analysis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Importantly, we analyzed that missing TEG measurements may play a role in the paucity of previous findings.

INTRODUCTION

Resuscitation after severe traumatic injury has transformed during the past decade, with the use of early blood products and adjunctive strategies to prevent coagulopathy, improve hemostasis and modulate the downstream immune response that complicates traumatic injury.[1–5] Concomitantly, there has been an increasing number of randomized clinical trials characterizing early resuscitation adjuncts to reduce coagulopathy and mortality attributable to traumatic injury.[6–9]

Tranexamic acid (TXA) improves survival in patients with traumatic injury[7 9–12] and is hypothesized to mitigate hyperfibrinolysis and the ensuing coagulopathy induced by shock and traumatic hemorrhage.[13] Despite previous clinical trials demonstrating TXA is associated with a survival benefit and an improvement in endothelial cell damage markers,[9 12] none have demonstrated improvement in thromboelastography (TEG) parameters.[7 11] The underlying mechanisms responsible for the benefits of prehospital TXA must be better characterized.

Abnormal TEG parameters are clinically relevant and predict coagulopathy and mortality in patients with traumatic injury.[14 15] A significant proportion of patients enrolled in TXA clinical trials could not be sampled for TEG analysis resulting in substantial missing data.[7 11] Little is known regarding the characteristics of patients with missing TEG measurements and how this missingness relates to the lack of TEG parameter differences found across TXA intervention arms.

Table 1 Demographic and clinical characteristics of the STAAMP cohort with TEG samples stratified by TXA

Variable	Overall (n=837)	Placebo (n=430)	TXA (n=407)	P value
Age	38.0 (26.0–55.0)	39.0 (26.0–56.0)	38.0 (26.0–51.0)	0.20
Male	624 (74.6%)	322 (74.9%)	302 (74.2%)	0.82
Blunt Injury	702 (83.9%)	366 (85.1%)	336 (82.6%)	0.31
TBI	196 (23.4%)	100 (23.3%)	96 (23.6%)	0.92
ISS	12.0 (5.0–22.0)	11.0 (4.0–22.0)	12.0 (5.0–22.0)	0.39
Prehospital GCS	15.0 (12.0–15.0)	14.0 (11.0–15.0)	15.0 (12.0–15.0)	0.25
Transfer	113 (13.7%)	57 (13.4%)	56 (14.0%)	0.78
Prehospital Intubation	204 (24.4%)	109 (25.3%)	95 (23.3%)	0.50
Prehospital SBP	125.0 (88.0–147.0)	126.0 (88.0–148.0)	124.0 (88.0–144.0)	0.89
24-hour whole blood	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.64
24-hour PRBC	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.50
24-hour plasma	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.11
24-hour platelets	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.85
INR	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	0.77
Lactate	2.7 (1.8–3.9)	2.6 (1.8–4.1)	2.8 (1.8–3.8)	0.97
30-day mortality	57 (6.8%)	35 (8.1%)	22 (5.4%)	0.12
MOF	69 (8.2%)	37 (8.6%)	32 (7.9%)	0.70
VTE	35 (4.2%)	13 (3.0%)	22 (5.4%)	0.09

Values are represented by numbers (percentages) and means (IQR). TXA refers to patients who received prehospital tranexamic acid (TXA).
GCS, Glasgow Coma Scale; INR, international normalized ratio; ISS, Injury Severity Score; MOF, multiple organ failure; PRBC, packed red blood cells; SBP, systolic blood pressure; STAAMP, Study of Tranexamic Acid During Air Medical and Ground Prehospital Transport; TBI, traumatic brain injury; TEG, thromboelastography; transfer, transferred from another hospital; VTE, venous thromboembolism.

Our objectives were to identify specific subgroups of patients unable to be sampled for TEG measurements and analyze whether TXA is associated with TEG parameter changes within subgroups highly correlated with missing TEG in the Study of Tranexamic Acid During Air Medical and Ground Prehospital Transport (STAAMP) Trial. These objectives may provide insight into TXA and its mechanism of action. We hypothesized that injury characteristics attributable to missingness may be responsible for the absence of TEG differences found across TXA intervention arms.

METHODS

Trial design and study population

We performed a secondary analysis of the STAAMP Trial.[7] The STAAMP Trial (NCT02086500) was a prospective prehospital phase III multicenter double-blind randomized placebo-controlled trial. The study included patients from the scene or transferred from an outside emergency department to one of four participating trauma centers within 2 hours of injury with either hypotension (systolic blood pressure (SBP) <90 mm Hg) or tachycardia (heart rate >110 beats per minute). Patients were randomized to receive TXA (1 gram bolus during 10 min en route to hospital) or placebo in the prehospital phase. This was followed by an in-hospital phase in which patients were randomized to an abbreviated (1 g total TXA), standard (2 g total TXA), or repeat bolus (3 g total TXA) dose at trauma center arrival. All in-hospital doses of TXA were administered within the first 8 hours of hospital admission. TEG was a principal secondary outcome and a required measurement specified in the protocol.

The STAAMP Trial enrolled subjects through the Emergency Exception From Informed Consent protocol, after a period of community consultation and public notification. Informed consent for continuing participation was obtained from all subjects enrolled in the trial. All study methods were performed in accordance with relevant guidelines and regulations.

Sample collection and measurement

Patients who met all the inclusion and no exclusion criteria of STAAMP en route via emergency medical transport received point of care rapid TEG performed for coagulation parameter measurements within 6 hours of arrival at definitive trauma care. TEG analysis was performed on a TEG 5000 Thromboelastograph Hemostasis Analyzer. Activated clotting time (ACT; sec), kinetic time (K; min), alpha angle (degrees), maximum amplitude (MA; mm) and clot lysis at 30 min (LY30; %) were analyzed. Standard international normalized ratio (INR) was drawn and measured at each institution within 6 hours of arrival.

Statistical analysis

We first compared patients that received TEG analysis (YES-TEG) and patients who did not (NO-TEG) to characterize injury-related differences and identify subgroups with a significant amount of missing TEG data. Kaplan Meier analysis was also performed to assess 24-hour survival differences between the NO-TEG and YES-TEG groups to further investigate the relative injury severity of NO-TEG patients. In an attempt to assess whether TXA administration was associated with TEG parameter differences within subgroups correlated with missing TEG data, TEG measurement differences were compared between the TXA and placebo arms in subgroups disproportionately present in the NO-TEG cohort relative to the YES-TEG cohort.

Finally, for associations approaching significance ($p<0.10$) we employed a generalized linear model to analyze the independent effect of prehospital TXA administration on TEG parameters. We modeled the relationship between intervention and TEG parameters using regression analysis controlling for Injury Severity Score (ISS), a known confounder in this trauma population. We analyzed ACT, K, alpha angle, MA and LY30 at admission as a function of prehospital TXA controlling for arrival Glascow Coma Score (GCS) and ISS. We evaluated variance

Table 2 Demographic and clinical characteristics of the STAAMP cohort stratified by TEG sampling

Variable	Overall (n=903)	YES-TEG (n=837)	NO-TEG (n=66)	P value
Age	39.0 (26.0–55.0)	38.0 (26.0–55.0)	39.5 (25.0–61.0)	0.57
Male	668 (74.0%)	624 (74.6%)	44 (66.7%)	0.16
Blunt Injury	755 (83.6%)	702 (83.9%)	53 (80.3%)	0.45
TBI	212 (23.6%)	196 (23.4%)	16 (25.4%)	0.72
ISS	12.0 (5.0–22.0)	12.0 (5.0–22.0)	14.0 (5.0–29.0)	0.13
Prehospital GCS	15.0 (11.0–15.0)	15.0 (12.0–15.0)	14.0 (3.0–15.0)	<0.01
Transfer	127 (14.3%)	113 (13.7%)	14 (21.5%)	0.08
Prehospital Intubation	230 (25.5%)	204 (24.4%)	26 (39.4%)	<0.01
Prehospital SBP	124 (88–146)	125 (88–147)	100 (78–140)	<0.01
24-hour whole blood	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.05
24-hour PRBC	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–4.0)	<0.01
24-hour plasma	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–1.0)	<0.01
24-hour platelets	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.03
INR	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.2 (1.1–1.5)	0.04
Lactate	2.8 (1.8–4.0)	2.7 (1.8–3.9)	3.9 (2.3–5.8)	<0.01
30-day mortality	81 (9.0%)	57 (6.8%)	24 (36.4%)	<0.01
MOF	72 (8.0%)	69 (8.2%)	3 (4.5%)	0.29
VTE	36 (4.0%)	35 (4.2%)	1 (1.5%)	0.29

Values are represented by numbers (percentages) and means (IQR).
GCS, Glascow Coma Score; INR, international normalized ratio; ISS, Injury Severity Score; MOF, multiple organ failure; NO-TEG, patients unable to be sampled; SBP, systolic blood pressure; STAAMP, Study of Tranexamic Acid During Air Medical and Ground Prehospital Transport; TBI, traumatic brain injury; TEG, thromboelastography; VTE, venous thromboembolism; YES-TEG, patients that received TEG.

inflation factors to ensure that the variance of our regression coefficients was not due to multicollinearity.

Descriptive statistics characterized the demographics and injuries of the patients and outcomes of interest. A Shapiro-Wilk test was conducted on all continuous variables to test for normality. Categorical variables were presented as frequencies and percentages and tested using the χ^2 test. Continuous variables were expressed as medians with IQRs and were tested using Wilcoxon rank-sum. Statistical significance was analyzed at the $p<0.05$ level (two-sided). All data were analyzed using STATA V.17.0 (College Station, Texas, USA).

RESULTS

The STAAMP Trial assessed 30-day mortality in 903 patients who were randomized to prehospital TXA (n=447) or placebo (n=456). This cohort was moderately injured with a median (IQR) ISS of 12 (5, 22) and 30-day mortality of 9.0%. There were no significant differences in TEG parameters between patients that received TXA and those that received placebo in the overall study cohort. In the overall study cohort, there were 66 (7.3%) NO-TEG patients and this missingness was similar across the TXA and placebo arms (9.0% vs 5.7%, p=0.06).

The subset of YES-TEG patients (n=837) was similar to those patients included in the primary STAAMP Trial analysis regarding injury severity and demographics. In the YES-TEG cohort patients were predominantly male (75%) patients with median ages of 38 (26, 55) years who sustained blunt injuries (84%) with a median ISS of 12 (5, 22). This subgroup of patients had a 30-day mortality rate of 6.8%, which was lower than that of the overall STAAMP Trial cohort. There were no significant differences between the TXA and placebo arms within the YES-TEG subgroup (table 1).

In a comparison of YES-TEG (n=837) and NO-TEG (n=66) patients, NO-TEG patients were similar in terms of demographics but were more severely injured. Specifically, NO-TEG patients had lower prehospital SBP (100 (78, 140) vs 125 (88, 147), p<0.01), lower prehospital GCS (14 (3, 15) vs 15 (12, 15), p<0.01), higher rates of prehospital intubation (39.4% vs 24.4%, p<0.01) and significantly greater mortality at 30 days (36.4% vs 6.8%, p<0.01; table 2). Importantly, NO-TEG patients had a significantly higher INR relative to the YES-TEG subgroup. However, 32 (48.5%) of the NO-TEG patients were also missing INR analysis. Kaplan-Meier survival analysis demonstrated a significant higher mortality for the NO-TEG subgroup with early separation of the survival curves that persisted out to 30 days (log rank p<001; figure 1).

Based on these missingness related injury characteristics we further analyzed the severe shock subgroup (SBP <70 mm Hg, n=58), low prehospital GCS (GCS<8, n=196), and those patients that required prehospital intubation (n=230). We next compared TEG measurements ACT, K, alpha, MA and LY30 at hospital admission stratified by prehospital TXA administration using univariate analysis within each missingness informed subgroup. On univariate analysis, there were no significant differences in TEG parameters between patients that received TXA and those that received placebo in the prehospital GCS <8 subgroup, patients that required prehospital intubation subgroup and in the severe prehospital shock subgroup (table 3). However, within the severe prehospital shock cohort, TXA trended towards an association with lower LY30 relative to placebo (2.7% vs 40.0%, p=0.07). After controlling for ISS, within the severe prehospital shock cohort, TXA was associated with a significant decrease in LY30 (β=−27.6, 95% CI −51.3 to −3.9, p=0.02; table 4) without significant associations for other TEG parameters.

DISCUSSION

In prior randomized prehospital clinical trials after injury, TXA administration has not been associated with changes in TEG parameters,[7 11] despite the proposed antifibrinolytic mechanism of action of TXA treatment.[13] Missing data may contribute to a lack of observed difference in TEG parameters due to the

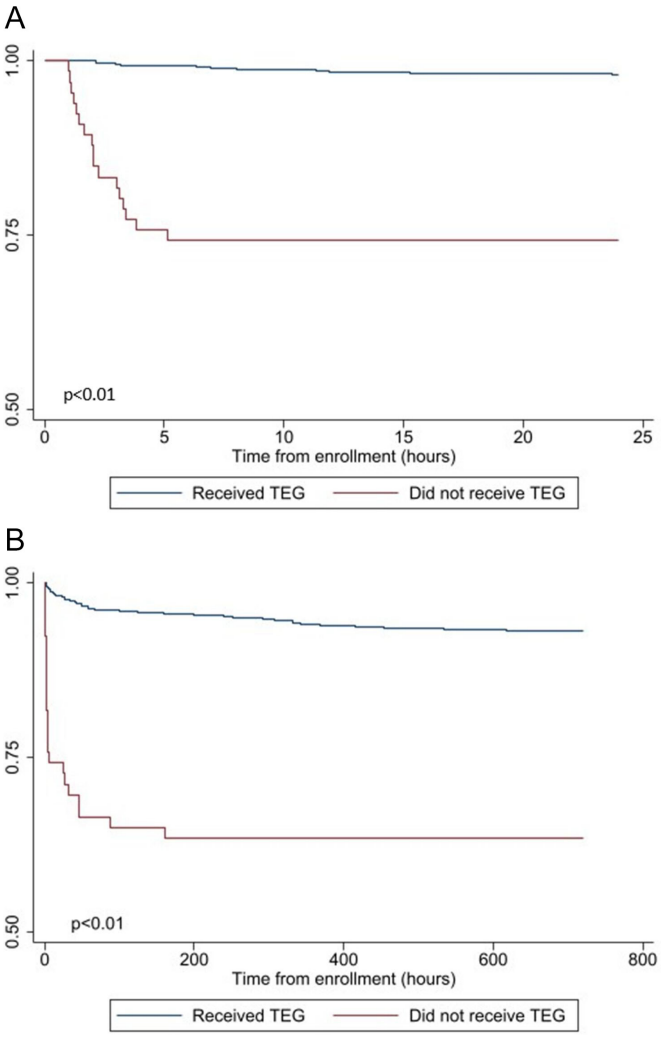

Figure 1 (A) Kaplan-Meier survival analysis comparing patients that received thromboelastography (TEG) measurements and those unable to be sampled at 24 hours. (B) Kaplan-Meier survival analysis comparing patients that received TEG measurements and those unable to be sampled at 30 days.

logistics of sampling severely injured patients and the time sensitive nature of trauma treatment.[16 17] The results from the current secondary analysis demonstrate that TXA administration in patients with severe shock is independently associated with a lower LY30. Importantly, the reduction in LY30 found is consistent with TXA's hypothesized mechanism of action.

TXA prevents the conversion of plasminogen to plasmin. As a result, inhibition of plasminogen activation stabilizes the preformed fibrin meshwork produced by secondary hemostasis and ultimately reducing bleeding.[13 18 19] Alternate hypotheses for TXA's mechanism of action have been explored, particularly as a pro-endothelial therapeutic agent to reduce glycocalyx shedding.[20] Our results add to the existing literature and our TEG findings correspond to the historic TXA mechanism of action.

NO-TEG patients were significantly more injured than YES-TEG patients supporting the likelihood that these patients were unable to undergo sampling due to the logistical difficulties associated with the management of the severely injured patient. In addition, approximately half of these patients had INR values calculated, indicating that this challenge may be unique to TEG. It has been previously demonstrated that severely injured patients

Table 3 TEG measurements stratified by TXA administration in specified subgroups

Variable	Placebo (n=96)	TXA (n=76)	P value
Prehospital GCS <8 subgroup			
ACT	121.0 (105.0–136.0)	113.0 (105.0–128.0)	0.40
K	1.8 (1.4–2.6)	1.8 (1.4–2.5)	0.83
Alpha	69.8 (64.8–74.5)	70.5 (66.1–74.2)	0.63
MA	59.8 (53.5–64.9)	60.1 (55.2–64.1)	1.00
LY30	20.0 (1.8–70.0)	12.3 (1.8–60.0)	0.99
Prehospital intubation subgroup			
CT	121.0 (105.0–136.0)	113.0 (105.0–128.0)	0.46
K	1.8 (1.2–2.6)	1.8 (1.4–2.6)	0.57
Alpha	70.8 (65.1–74.9)	70.1 (65.5–73.9)	0.80
MA	59.6 (53.6–65.2)	58.7 (53.4–63.2)	0.18
LY30	20.0 (1.8–70.0)	10.0 (1.75–60.0)	0.57
Severe prehospital shock subgroup			
ACT	121.0 (101.0–132.0)	121.0 (105.0–136.0)	0.65
K	1.7 (1.2–3.1)	1.6 (1.1–2.3)	0.27
Alpha	69.8 (61.9–74.3)	72.2 (64.5–75.6)	0.58
MA	60.7 (51.4–66.2)	60.2 (55.7–67.5)	0.62
LY30	40.0 (2.2–60.0)	2.7 (1.6–10.0)	0.07

ACT, activated clotting time; GCS, Glascow Coma Score; LY30, lysis at 30 min; MA, maximum amplitude; TEG, thromboelastography; TXA, tranexamic acid.

at higher risk of mortality consistently demonstrate TEG parameter abnormalities relative to those less severely injured.[14 15] Importantly, it is in the severe prehospital shock subgroup where TEG improvements were demonstrated and TXA treatment was associated with a significant reduction in 30-day mortality in the primary STAAMP analysis.[7] The concomitant demonstration of a TXA survival benefit and a reduction of LY30 is novel in the setting of traumatic injury.

However, it is critical to note that TXA administration, in the other subgroups disproportionately present in NO-TEG patients, was not associated with TEG parameter differences relative to placebo. In addition, the primary STAAMP analysis[7] did not demonstrate a survival benefit in these subgroups. This finding suggests that the administration of TXA and its impact on TEG parameters and survival is dependent on specific characteristics of traumatic injury. It's plausible that missing TEG data from the severe prehospital shock cohort, as opposed to severely injured patients in general, may underlie the importance of missing TEG data.

Limitations

There are limitations to this analysis. First, this is a post hoc secondary analysis with the potential for confounding and is hypothesis generating in nature. Second, although our models

Table 4 Adjusted coefficients of TEG measurements by TXA administration in severe prehospital shock cohort

Variable	Adjusted coefficient (95% CI)	P value
ACT	93.0 (–52.9 to 238.9)	0.21
K	–7.5 (–19.2 to 4.0)	0.20
Alpha	–1.8 (–10.1 to 6.6)	0.68
MA	–0.5 (–9.0 to 8.0)	0.90
LY30	–27.6 (–51.3 to 3.9)	0.02

ACT, activated clotting time; LY30, lysis at 30 min; MA, maximum amplitude; TEG, thromboelastography; TXA, tranexamic acid.

were statistically robust, the small sample size limits our ability to include additional variables for adjustment and there may be unknown and unaccounted confounding factors missing in our models. Third, this analysis is limited by the times at which we were able to sample blood from injured trauma patients. Specifically, TEG was only sampled at hospital admission, which may mask delayed effects of prehospital TXA on TEG parameters. Of equal importance, the early sampling that was accomplished may vary significantly from the time of injury. Fourth, the number of patients with severe prehospital shock was relatively low in this cohort which may limit the generalizability of our findings. Lastly, patients in the missingness defined subgroups were not randomized relative to the overall trial cohort. We attempted to minimize the impact of this by using a generalized linear model accounting for potential confounding variables.

CONCLUSIONS

In conclusion, the logistical difficulties of sampling patients with severe shock and the attributable missingness may be responsible for the paucity of TEG differences found in previous prehospital TXA trials. TXA is associated with TEG parameter improvement in patients with severe prehospital shock, a subgroup disproportionately present in patients unable to be sampled for TEG. Importantly, TXA's associated decrease in LY30 corresponds to its historical mechanism of action and the subgroup in which this decrease was found is the same subgroup in which TXA was associated with a survival benefit. Further translational and basic science research is crucial to investigating the proposed mechanism of TXA in traumatic injury.

Contributors JBB, FG, BE, RN, GV, TO, BJ, MN, JLS designed and executed the trials. FG, JBB, JLS collected the trial data. JKD designed the study, harmonized data sets, analyzed data and drafted the article. JLS designed the study, analyzed data and drafted the article. NI and JML interpreted data. All authors performed critical revision and approved the final article for submission. JLS is the guarantor for this manuscript.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the University of Pittsburgh Institutional Review Board (STUDY19060072) and at all other study sites. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available upon reasonable request. After publication of the primary and all secondary analyses detailed in study protocols, individual de-identified data will be available upon request and approval of the proposed use of the data after 3 years of the close of the trial. The trial protocol, statistical analysis plan embedded in the protocol, and the trial publications are available online. Requests should be sent to the corresponding author.

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