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Characterization of adverse events in injured patients at risk of hemorrhagic shock: a secondary analysis of three harmonized prehospital randomized clinical trials

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ABSTRACT

Background The reporting of adverse events (AEs) is required and well defined in the execution of clinical trials, but is poorly characterized particularly in prehospital trials focusing on traumatic injury. In the setting of prehospital traumatic injury trials, no literature currently exists analyzing the clinical implications of AEs and their associations with mortality and morbidity. We sought to analyze AEs from three prehospital hemorrhagic shock trials and characterize their time course, incidence, severity, associated clinical outcomes, and relatedness.

Methods We performed a secondary analysis of three prehospital randomized clinical trials. We analyzed AEs at both the patient level as well as the individual AE level. We categorized patients who had no AEs, a single documented AE and those with multiple events (>1 AE). We characterized AE timing, severity, relatedness and attributable mortality outcomes.

Results We included 1490 patients from the three harmonized clinical trials, with 299 (20.1%) individual patients having at least a single AE documented with 529 AEs documented overall as a proportion of patients had multiple events. Over 44% of patients had a death-related misclassified AE. Patients with at least a single documented AE had a significantly higher 28-day mortality (log-rank χ^2=81.27, p<0.001) compared with those without an AE documented. Patients with a single AE had a significant higher mortality than those with multiple AEs, potentially due to survival bias (log-rank χ^2=11.80, p=0.006). When relatedness of each individual AE was characterized, over 97% of AEs were classified as 'definitely not related' or 'probably not related' to the intervention.

Conclusions AEs in hemorrhagic shock trials are common, occur early and are associated with mortality and survival bias. The potential for inaccurate reporting exists, and education and training remain essential for appropriate treatment arm comparison. The current results have important relevance to injury-related clinical trials.

Trial registration numbers NCT01818427, NCT02086500 and NCT03477006.

Level of evidence II.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Adverse events (AEs) are required and well defined in the execution of clinical trials. However, there is a paucity of literature regarding AEs and their respective clinical associations in hemorrhagic shock trials after traumatic injury.

WHAT THIS STUDY ADDS

⇒ In a secondary analysis of three prehospital clinical trials, we demonstrate that AEs in prehospital hemorrhagic shock trials are associated with increased mortality, occur early, and are commonly mislabeled.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The current results highlight the need for possible traumatic injury-specific AE guidelines.

INTRODUCTION

Hemorrhage remains a leading cause of preventable mortality after traumatic injury.[1–4] An increasing number of clinical trials focusing on interventions in the prehospital and early resuscitation phase of care have been recently completed or are currently underway.[5–10] These randomized trials are studying interventions aimed to mitigate the morbidity and mortality attributable to severe injury while simultaneously minimizing complications and adverse events (AEs).[11 12]

The recording of AEs is required during the execution of clinical trials. AEs after injury can be intervention specific, or more general such as venous thromboembolism or organ dysfunction. The definitions and classification of AEs including expectedness, grades of severity and relatedness to the study intervention are well described.[13 14] Despite these trial requirements, the collection, reporting and analysis of AEs have been shown to be inconsistent across multiple fields of study.[15–17] There is even less information regarding AEs in trials focusing on traumatic injury and hemorrhage.[18]

The significance of AEs has not been adequately studied in trauma trials that focus on hemorrhage and severe injury.[5 9 10] The objectives of the current analysis are to analyze documented AEs in severely injured patients in completed prehospital interventional trials and characterize their time course, clinical implications and their association with morbidity and mortality. We hypothesize that the timing, incidence, and severity of documented AEs in enrolled patients will be associated with outcome differences. These associations may inform AE documentation and reporting in future trials which focus on severe injury.

METHODS

We performed a secondary analysis of the documented AEs from three randomized prehospital, phase-III clinical trials which focused on patients at risk of hemorrhagic shock: the Prehospital Air Medical Plasma (PAMPer) trial,[5] the Study of Tranexamic Acid During Air Medical and Ground Prehospital Transport (STAAMP) trial[9] and the Pragmatic Prehospital Type O Whole Blood Early Resuscitation (PPOWER) trial.[10]

The PAMPer trial[5] (NCT01818427) was a multicenter trial designed to test the effect of administering plasma to severely injured trauma patients on air ambulances before arrival to definitive trauma care. Inclusion criteria were met if patients had at least one episode of hypotension (systolic blood pressure <90 mm Hg) and tachycardia (heart rate >108 beats per minute) or if they had any severe hypotension (systolic blood pressure <70 mm Hg). Patients were randomized to receive either standard care fluid resuscitation or 2 units of thawed plasma followed by standard care fluid resuscitation.

The STAAMP trial[9] (NCT02086500) was a multicenter trial that examined outcomes in severely injured trauma patients who received prehospital tranexamic acid (TXA) during air medical or ground transport. The study included patients within 2 hours of injury with either hypotension (systolic blood pressure <90 mm Hg) or tachycardia (heart rate >110 beats per minute). Patients were double-blind randomized to receive TXA (1 g bolus over 10 minutes en route to hospital) or placebo in the prehospital phase. Those in the treatment arm were then randomized to in-hospital TXA dosing regimens.

The PPOWER trial[10] (NCT03477006) was a single-center pilot trial designed to test the effect of administering low-titer group O whole blood to severely injured trauma patients on air ambulances before arrival to definitive trauma care. Inclusion criteria were identical to that of the PAMPer trial. Patients were randomized to receive whole blood resuscitation or standard prehospital care fluid resuscitation (red cell transfusion and crystalloids).

All three trials employed exception from informed consent enrollment through the Emergency Exception from Informed Consent protocol, after a period of community consultation and public notification. All study methods were performed in accordance with relevant guidelines and regulations. Due to similarities in inclusion criteria and clinical outcomes, we harmonized the datasets from these three trials to take advantage of the combined number of AEs and appropriately characterize their significance. AEs from individual trials required significant reformatting for proper analysis.

Our primary outcome was 28-day mortality. Secondary outcomes included the development of morbidity including multiple organ failure (MOF) and nosocomial infection (NI) in those patients who survived beyond 24 hours. Time-to-event survival comparisons were performed using Kaplan-Meier analyses and log-rank comparison. Time of enrollment for all trials occurred when patients met vital sign inclusion criteria and no exclusion criteria, determined by prehospital providers. We first assessed the incidence of reported AEs across enrolling sites. We then characterized the timing (first occurring AE) and number of AEs for individual enrolled trauma patients and their attributable mortality outcomes (categorized as no AE, single AE and >1 AE). We stratified analyses by adjudicated cause of death (hemorrhage, traumatic brain injury (TBI), other) and associated timing of the AE documented. Finally, we assessed expectedness of the individual AE, AE severity and relatedness of each AE relative to the respective clinical trial intervention. Expectedness was a dichotomous variable and the incidence was reported as a percentage. We analyzed severity of AEs first by characterizing their severity grade and by determining the highest graded event for an individual patient, as some enrolled patients had multiple AEs with different severity classification. Classification of severity was grade 1—mild, grade 2—moderate, grade 3—severe, grade 4—life threatening, and grade 5—death related to AE, following Common Terminology Criteria for Adverse Events (CTCAE).[14] Importantly, for the determination of relatedness, the intervention status was unknown to event assessors. Relatedness was similarly categorized using National Cancer Institute AE reporting definitions across five variables including 'definitely not related', 'probably not related', 'possibly related', 'probably related' and 'definitively related'.[14 19]

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 determined at the $p<0.05$ level (two sided). All data were analyzed using Stata V.18.0 (College Station, TX).

RESULTS

The harmonized cohort consisted of 1490 patients enrolled in the three clinical trials. Overall mortality rate was 16.4% with median Injury Severity Score (ISS) of 16 (IQR 6, 26). The harmonized cohort was injured via a blunt mechanism of injury 83.6% of the time, with the remaining 16.4% suffering penetrating injury with 52% of penetrating injuries being firearm related. Enrolled patients received the trial-specific study intervention 48.1% of time with the remaining receiving standard care or blinded placebo treatment. For the study cohort, 299 (20.1%) individual patients had at least a single AE documented and categorized with 529 AEs documented overall as a proportion of patients had multiple events. The rate of reported AEs relative to enrollment numbers was similar across enrolling sites with a single outlier (online supplemental figure 1).

Patients who had at least a single AE as compared with those enrolled without a documented AE were older, more severely injured with higher ISS, more commonly had a blunt mechanism of injury, had lower systolic blood pressures, had lower Glasgow Coma Scale scores, required prehospital interventions including intubation, and more commonly had TBI (table 1). Patients with at least a single documented AE had a significantly higher 24-hour and 28-day mortality.

We first characterized the specific individual AEs recorded and categorized them via CTCAE classification that occurred at any time throughout the study. We found that AEs recorded were death not otherwise specified (NOS) or cardiac arrest in 44.8% (n=134) of patients, with mortality occurring simultaneously

Table 1 Baseline characteristics for harmonized study cohort stratified by occurrence of at least one adverse event

Variable	No AE (n=1191)	Had AE (n=299)	P value
Age, median (IQR)	39 (27–56)	47 (28–65)	<0.001
Male, n (%)	876 (73.6)	210 (70.2)	0.25
Race, n (%)			
White	973 (81.7)	253 (84.6)	0.074
African American	115 (9.7)	23 (7.7)	
Asian	7 (0.6)	0 (0.0)	
Other	8 (0.7)	6 (2.0)	
Unknown	88 (7.4)	17 (5.7)	
Classification of blunt injury, n (%)			
Fall	130 (13.2)	26 (9.9)	0.002
Machinery	9 (0.9)	2 (0.8)	
MVC—occupant	493 (50.2)	148 (56.3)	
MVC—motorcyclist	155 (15.8)	61 (23.2)	
MVC—cyclist	28 (2.8)	3 (1.1)	
MVC—pedestrian	40 (4.1)	8 (3.0)	
MVC—unknown	9 (0.9)	1 (0.4)	
Struck by or against	31 (3.2)	5 (1.9)	
Crush	32 (3.3)	7 (2.7)	
Other	56 (5.7)	2 (0.8)	
Classification of penetrating injury, n (%)			
Firearm	109 (48.9)	28 (75.7)	0.026
Impalement	15 (6.7)	1 (2.7)	
Stabbing	80 (35.9)	7 (18.9)	
Other	19 (8.5)	1 (2.7)	
Prehospital crystalloid (mL), median (IQR)	500 (0–1000)	600 (0–1500)	0.24
Initial GCS score <8, n (%)	350 (29.4)	201 (67.2)	<0.001
Initial GCS, median (IQR)	15 (3–15)	3 (3–14)	<0.001
Received prehospital intervention, n (%)	583 (49.0)	134 (44.8)	0.20
Prehospital intubation, n (%)	327 (27.5)	190 (63.5)	<0.001
Prehospital systolic blood pressure, median (IQR)	89 (75–136)	75 (62–88)	<0.001
Prehospital heart rate, median (IQR)	117 (111–126)	118 (97.5–129)	0.48
Abbreviated Injury Scale, n (%)			
Head >2	341 (28.6)	144 (48.2)	<0.001
Face >2	94 (7.9)	16 (5.4)	0.13
Chest >2	448 (37.6)	164 (54.8)	<0.001
Abdomen >2	244 (20.5)	82 (27.4)	0.009
Extremity >2	325 (27.3)	86 (28.8)	0.61
External >2	52 (4.4)	7 (2.3)	0.11
ISS, median (IQR)	14 (5–22)	24.5 (16–34)	<0.001
Traumatic brain injury, n (%)	276 (23.3)	133 (44.6)	<0.001
24 h mortality, n (%)	31 (2.6)	108 (36.1)	<0.001
28-day mortality, n (%)	70 (5.9)	175 (58.5)	<0.001

AE, adverse event; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; MVC, motor vehicle collision.

with the timing of the event in all cases. For all subsequent analyses, we excluded these death-specific AEs and respective patients. This reduced the overall number of AE patients (n=165), with individual AEs for the harmonized cohort being 381 in total.

When we characterized the timing of the first recorded AE for each patient (n=165, figure 1), the majority of AEs were documented within the first 6 hours of arrival with the incidence

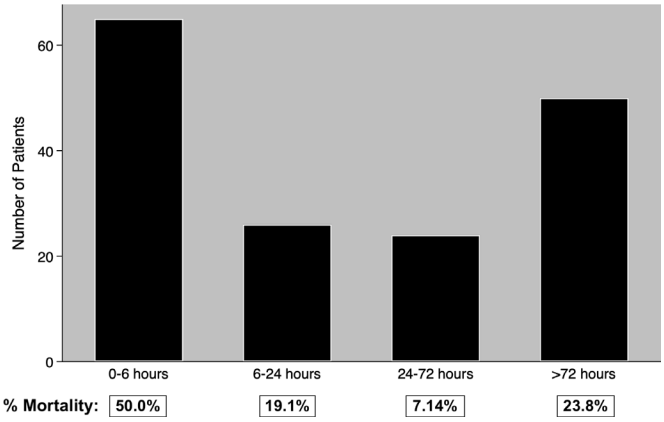

Figure 1 Timing of first recorded adverse event (AE) and attributable mortality rate.

of AEs decreasing during the subsequent time periods. The timing of the first AE in the initial 6 hours corresponded to the highest overall mortality rate (50.0%) occurring at any time during the patient's hospital stay. When we performed Kaplan-Meier survival analysis and compared those patients with any AE relative to those patients without a documented AE, the highest mortality rate occurred early in the first 6 hours for those patients with a recorded AE (figure 2). When those who suffered mortality were further analyzed, the adjudicated cause of death (hemorrhage, TBI, other) varied with the timing of the first AE recorded (online supplemental figure 2). Death during the hospital admission due to hemorrhage demonstrated a significantly lower time to first recorded AE relative to TBI or other adjudicated causes of mortality (online supplemental figure 3). Importantly, those AEs which were specifically death or cardiac arrest were not included in this significant relationship.

We next characterized the number of AEs an individual patient had during their hospital stay. Patients most commonly (61%) had a single AE (median 1, IQR (1–2)) with the remaining having multiple, and the highest being a single patient having 11 documented AEs. When we compared injury characteristics of those patients with a single AE versus multiple AEs, patients had similar demographics with the AE >1 group trending toward higher injury severity and significantly higher manifestations of shock (online supplemental table 1). Despite these differences, when we performed Kaplan-Meier survival analysis comparing

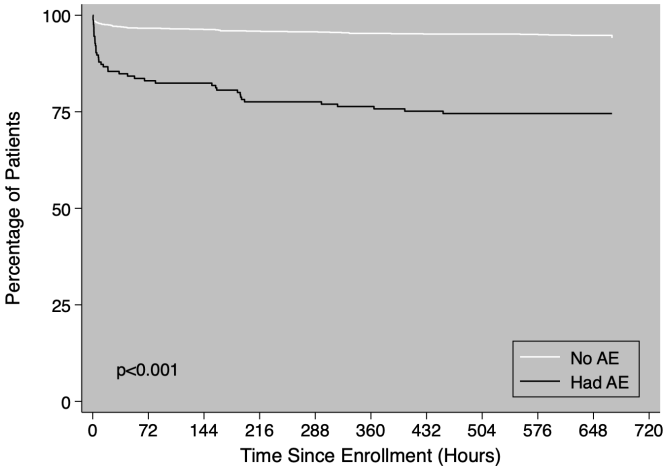

Figure 2 Kaplan-Meier survival analysis comparing patients with any adverse event (AE) versus those patients without a documented AE.

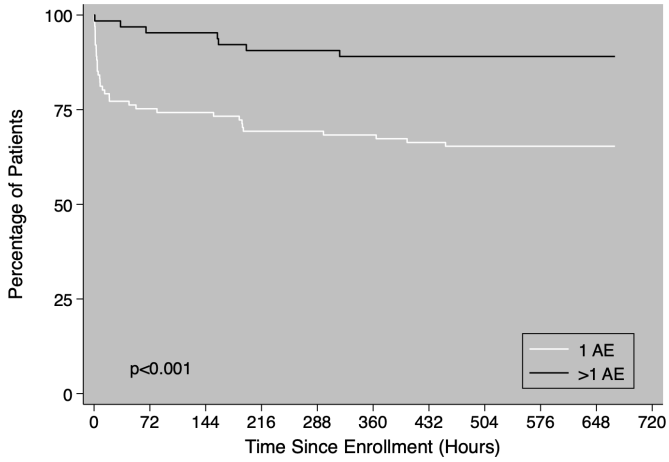

Figure 3 Kaplan-Meier survival analysis comparing patients with one adverse event (AE) versus those with multiple AEs (>1 AE).

those patients with a single AE (n=101) as compared with those with >1 AE (n=64), those patients with only a single AE suffered a significantly higher mortality (figure 3). When we focused on the development of MOF, NI and intensive care unit (ICU) days in those patients who survived beyond 24 hours, patients with >1 AE versus a single AE had a significantly higher rate of MOF (79.7% vs. 31.7%, p<0.01), NI (54.7% vs. 21.8%, p<0.01) and greater ICU days (median 8 days (14–21) vs. 2 days (0–9), p<0.01), highlighting the potential for survival bias.

When we assessed the expectedness of all the AEs (n=381), 71.1% of events were deemed expected with the remaining 28.9% designated as unexpected.

When the severity classification for each individual AE was characterized, AEs were more commonly distributed among the lower severity categories (table 2A). When the highest AE severity classification for an individual patient was assessed (n=165), the distribution shifted with 18.8% of highest severity AEs being classified as 'death related to AE' (table 2B).

When relatedness of each individual AE was characterized, over 97% of AEs were classified as 'definitely not related' or 'probably not related' to the study intervention (table 3). When we characterized the relatedness of each individual AE to the randomized intervention received (receiving prehospital plasma, TXA, or whole blood vs. standard care/placebo), AEs were documented equally across standard care arms and intervention arms in the lower relatedness categories, with the 'possibly related' (n=6) and 'probably related' (n=2) being more often in patients who received the randomized study intervention. These relatedness patterns remained irrespective of whether the intervention was blinded or open label in the prehospital environment.

Table 2 (A) Severity classification of AEs at the individual AE level; (B) Maximum severity classification of AEs at the patient level

Variable	Frequency	%	Cumulative %
A. Individual AE severity			
1	117	30.7	30.7
2	123	32.3	63.0
3	72	18.9	81.9
4	34	8.9	90.8
5	35	9.2	100
Total	381	100	
B. Maximum AE severity per patient			
1	23	13.9	13.9
2	48	29.1	43.0
3	41	24.9	67.9
4	22	13.3	81.2
5	31	18.8	100
Total	165	100	

AE, adverse event.

Table 3 Classification of AE relatedness

Variable	Frequency	%	% received intervention
AE relatedness			
Definitely not	342	89.8	47.6
Probably not	31	8.1	25.8
Possible	6	1.6	66.7
Probably	2	0.5	100
Definitely	0	0	N/A
Total	381	100	

AE, adverse event.

DISCUSSION

Evidence has accumulated regarding the beneficial effects of early interventions in patients with traumatic injury and hemorrhage.[1 5–7 9] The clinical trials leading to this growing evidence are required to document AEs during the enrollment periods of the trials. Although AEs are well defined in the literature, their presentation is commonly limited to descriptive differences across the randomized/comparison arms in the primary trial publication.[20–22] The appropriate characterization of trial AEs and their attributable clinical outcomes remains inadequately described in the literature, particularly for hemorrhagic shock trials.

Patients with severe injury at risk of hemorrhage are a unique patient population for clinical trials. Severely injured patients continue to suffer high morality, with the leading causes of death being TBI, hemorrhage, recalcitrant shock and organ dysfunction. These deaths occur in the first few hours from arrival most commonly due to hemorrhage, and out to 48 hours and beyond for brain injury, shock and organ dysfunction.[23] This early mortality and the time-sensitive treatments required for the care of the severely injured, in both the prehospital and early in-hospital phases of care, may complicate the ability to accurately document and categorize AEs.[23–25] Any AE reporting difficulties could be additionally affected by the unpredictable hours when the majority of traumatic injury occurs and the difficulties of obtaining AE information from medical record review. The results of the current analysis suggest that AEs in hemorrhagic shock trials are common, are influenced by the timing and cause of death, and are associated with clinical outcome differences including a significant higher rate of mortality. Importantly, the analysis highlights the importance of appropriate research staff training, particularly for accurate AE reporting in the severely injured population. A possible focus for further training would be differentiating AEs that may be associated with an outcome rather than an outcome itself. A prespecified list of pertinent intervention-specific AEs can similarly be provided which may minimize variability of reporting across different sites in multicenter trials.

The primary outcome for most injury-related clinical trials is mortality.[1 23 24] AE training for hemorrhagic shock trials includes instruction for the documentation of specific AEs that are

considered untoward occurrences during the execution of a trial. The current harmonized data demonstrated that over 44% of patients had an AE documented that was specifically death NOS or cardiac arrest by CTCAE[14] definitions, with the time of death being simultaneous. These events occurred soon after arrival, with the majority having no additional AEs documented. Due to the early mortality inherent with hemorrhagic shock trials, differentiating AE reporting versus trial outcome documentation can be challenging.[23 24] Detrimental outcomes are expected occurrences after severe traumatic injury with 71% of the AEs being categorized as expected in the current harmonized cohort.

Enrolled patients without a documented AE demonstrated significantly higher survival. It is interesting that those patients with multiple AEs documented also had a higher rate of survival. This potential survival bias with patients living to have multiple documented AEs may be specific to trauma and hemorrhagic shock trials.[26] This relationship may be different in trials where mortality is not the primary outcome and where mortality may not occur within hours of arrival. When the highest severity documented AE a patient had was characterized, over 18% were grade 5, defined as 'death related to an AE'. It may be that specific AEs and mortality are temporally related, with a limited ability to actually determine causality. When the relatedness of documented AEs was appropriately assessed, over 97% were designated 'definitely not related' or 'probably not related'. This highlights the potential for over-reporting of AEs in hemorrhagic shock trials and may provide an impetus to streamline the reporting of such events. Importantly, the relatedness overall was not more commonly associated with a specific treatment arm (intervention vs. standard care/placebo).

The current analysis does have limitations. The results are a post hoc secondary analysis limited to AEs that were recorded for three different clinical trials with similar but not identical inclusion criteria. The three trials had different interventions and randomization procedures employing different trauma centers across the country. Individual AE characteristics such as expectedness were unable to be appropriately characterized as a significant portion of patients had multiple AEs. The potential for bias and confounding exists. The trials were executed during different time periods but used the same clinical coordinating center and principal investigators. Education for AE reporting was consistent across the three trials; however, staff turnover occurred at participating sites and may have limited training retention. We attempted to remove death-specific AEs which more likely should have been documented as a clinical outcome. The potential exists that misclassification of additional AEs occurred that was unable to be accounted for. Although the harmonization process was robust, the potential for missingness and data inaccuracy exist.

CONCLUSIONS

In conclusion, AEs in hemorrhagic shock trials are common, occur early and are associated with mortality and potential survival bias. The potential for inaccurate reporting exists and education and training remain essential for appropriate treatment arm comparison. Prior AE literature focuses on clinical trials that do not involve traumatic injury. The current results have important relevance to future clinical trials and AE reporting for hemorrhagic shock. This highlights the need for possible traumatic injury-specific AE guidelines. As hemorrhagic shock trials become even more prevalent, further research is essential to appropriately characterize untoward events for those who suffer traumatic injury.

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Contributors JBB, FG, BD, BE, RSM, RN, BGH, JC, HAP, GV, TO'K, BJ, MN, and JLS designed and executed the trials. FG, JBB, and JLS collected the trial data. JML designed the study, harmonized the datasets, analyzed the data and drafted the article. JLS designed the study, analyzed the data, and drafted the article. NI and JKD interpreted the data. All authors performed critical revision and approved the final article for submission. JLS is the guarantor of the article.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the three clinical trials (PAMPer, STAAMP, PPOWER) in this secondary analysis were all approved by the University of Pittsburgh Institutional Review Board (IRB) and at all other study sites. No IRB approval was required for this secondary analysis, as the data were in existence. 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. Following publication of the primary and all secondary analyses detailed in study protocols, individual deidentified 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, the 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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