Pre-hospital freeze-dried plasma for critical bleeding after trauma:

A pilot randomised controlled trial

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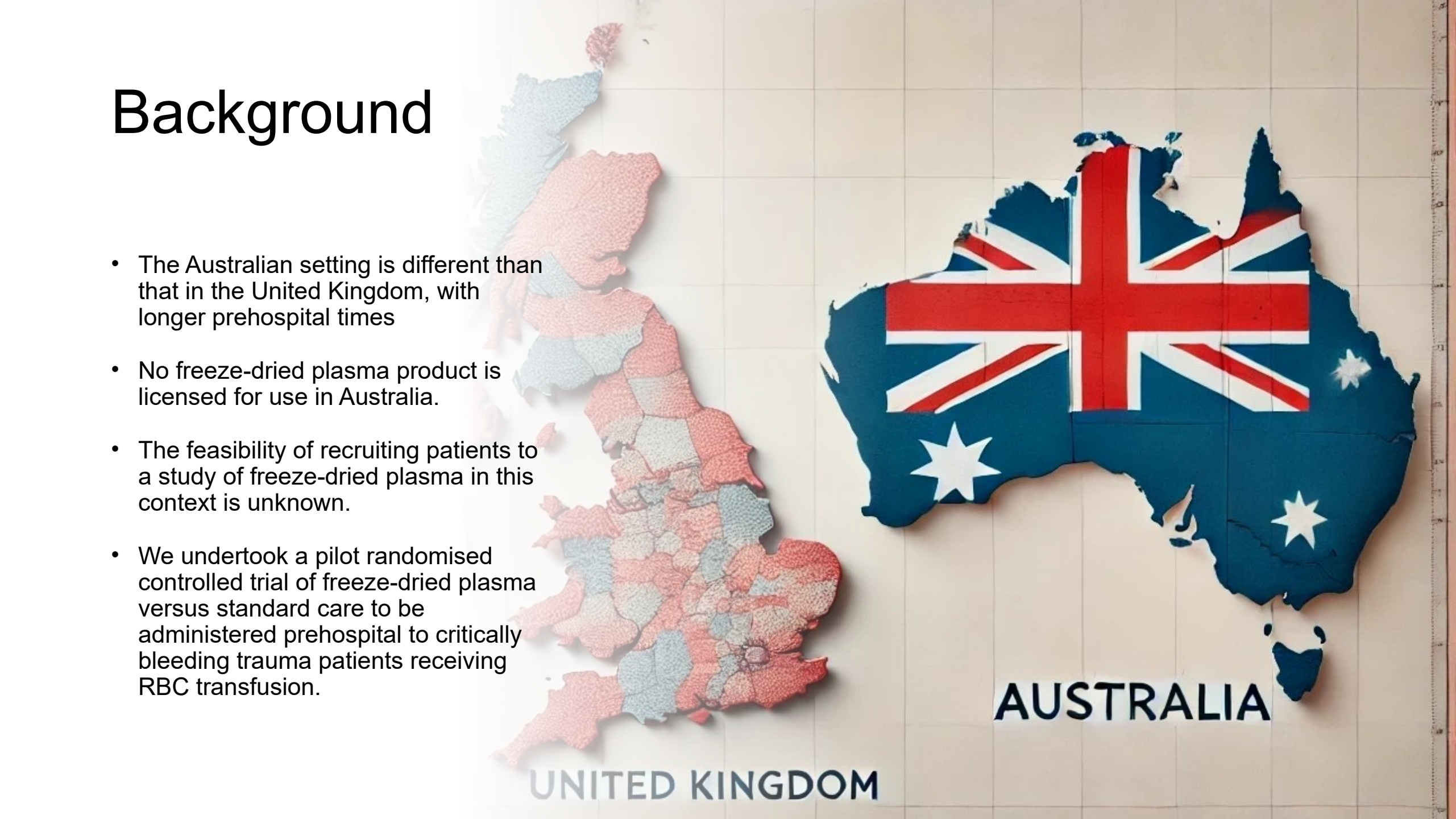
Background

- One treatment of ATC is the infusion of fresh-frozen plasma(FFP).
- There is limited evidence to support the resource investment necessary to provide FFP in the prehospital environment.
- The two randomised controlled trials using prehospital FFP differed in their conclusions.
- An alternative to FFP that is suitable for prehospital use is freeze-dried plasma, but a recent United Kingdom trial of freeze-dried plasma and RBCs compared to crystalloid in the prehospital setting did not demonstrate a difference in outcomes

Background

- The Australian setting is different than that in the United Kingdom, with longer prehospital times
- No freeze-dried plasma product is licensed for use in Australia.
- The feasibility of recruiting patients to a study of freeze-dried plasma in this context is unknown.
- We undertook a pilot randomised controlled trial of freeze-dried plasma versus standard care to be administered prehospital to critically bleeding trauma patients receiving RBC transfusion.



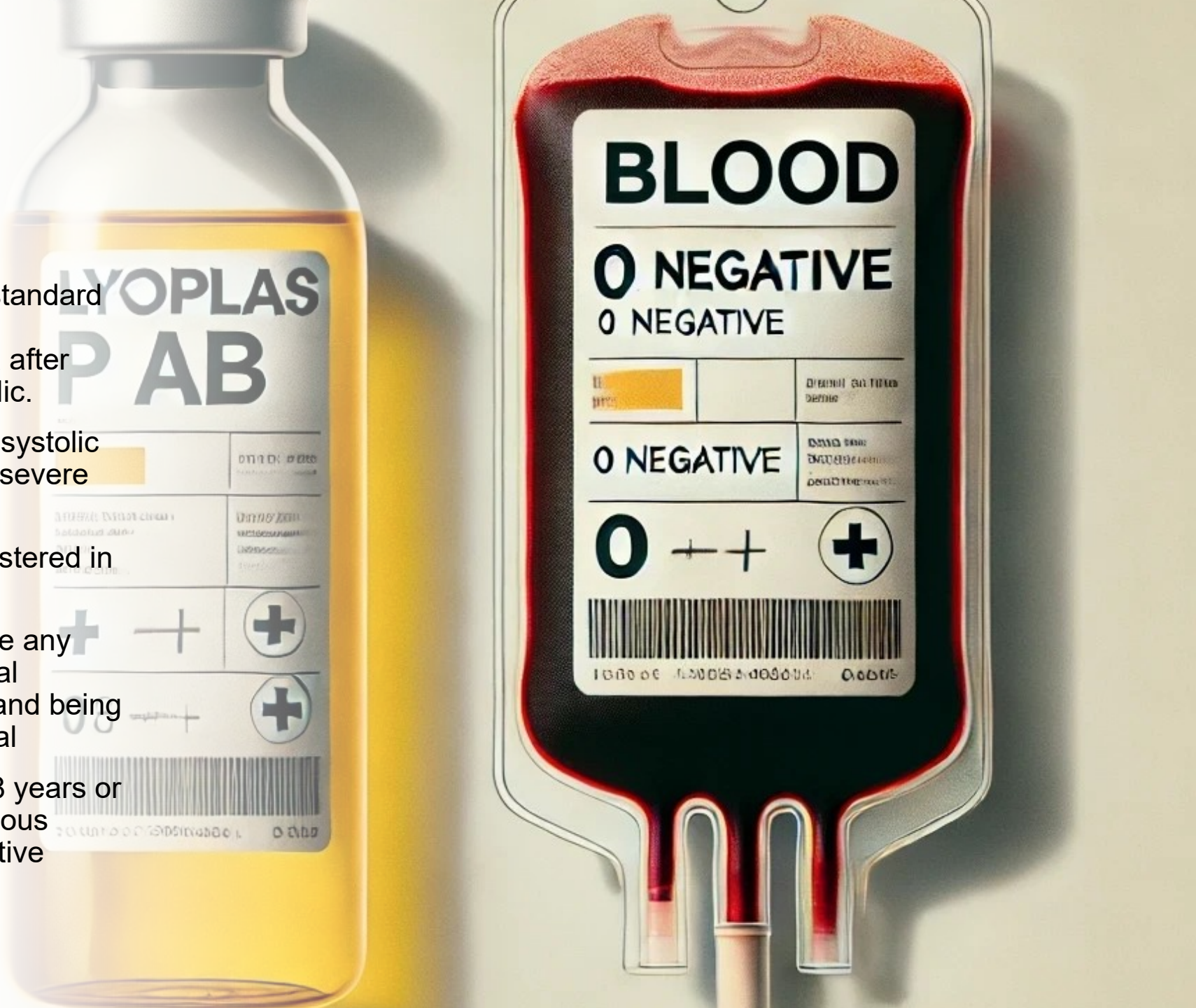
Aims and hypothesis

- The aim was to determine feasibility for a definitive trial of prehospital freeze-dried plasma, assessing prehospital times, numbers of eligible patients, and the proportion able to be recruited to the trial in this context

- Further, we evaluated the clinically relevant effectiveness outcomes that might be employed in a subsequent study

Methods

- Patients eligible for RBCs (i.e., standard care) are those with suspected haemorrhage and hypovolaemia after clinical judgment of the paramedic.
- RBCs are transfused to a target systolic blood pressure ≥70 mm Hg or if severe TBI, ≥ 120 mm Hg.
- Tranexamic acid was not administered in this service during the study.
- Eligibility criteria for this trial were any adult patient receiving prehospital transfusion of RBCs for trauma and being transported to The Alfred Hospital
- Patients at extremes of age (<18 years or >90 years), who had no intravenous access, known pregnancy, or active palliative care, were not eligible



Methods

- The primary outcome of successful enrolment was reported using proportion with 95% confidence intervals (95% CIs).
- Secondary outcomes were reported by intention-to-treat subgroup using odds ratios (ORs) with 95% CIs.
- Count variables were compared with the unadjusted Chi-square test for equal proportions, with results reported as frequency (percentage) per treatment group with a relative risk (RR), accompanied by 95% CI.
- As a feasibility study, a sample size of 20 patients was chosen and not adequately powered for statistical hypothesis testing.

Results

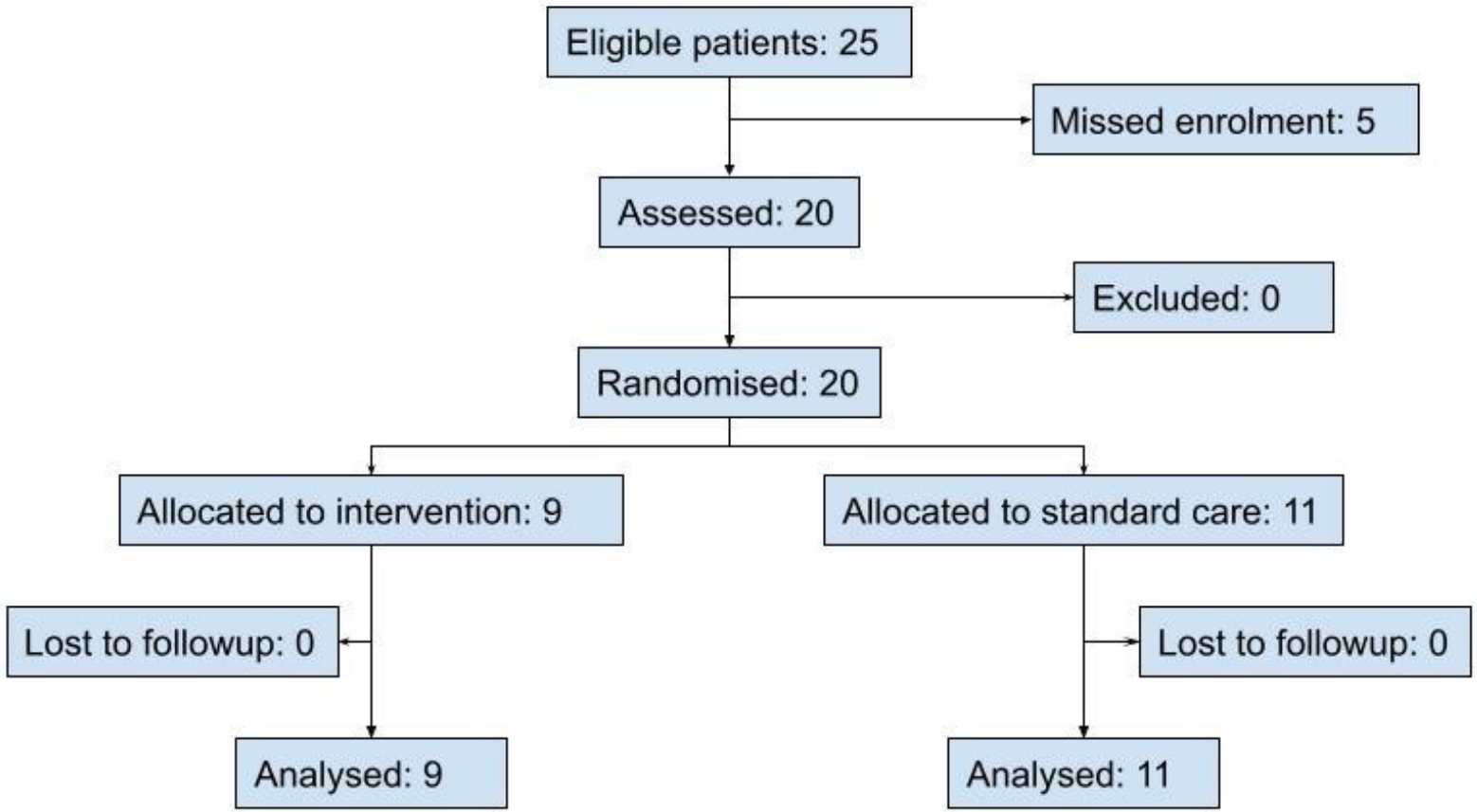

Eligible patients: 25
Missed enrolment: 5
Assessed: 20
Excluded: 0
Randomised: 20
Allocated to intervention: 9
Allocated to standard care: 11
Lost to followup: 0
Lost to followup: 0
Analysed: 9
Analysed: 11

TABLE 1 Baseline characteristics of patients.

	Freeze-dried plasma ($n=9$)	Standard care ($n=11$)
Age (years)	48 (40–51)	34 (19–54)
Sex		
Male	7 (77.8)	7 (63.6)
Female	2 (22.2)	4 (36.4)
Mechanism of injury		
Motor vehicle crash	4 (44.4)	6 (54.5)
Motorcycle crash	2 (22.2)	1 (9.1)
Pedestrian	1 (11.1)	1 (9.1)
Bicycle crash	1 (11.1)	1 (9.1)
Fall	0	1 (9.1)
Stabbing	1 (11.1)	0
Crushed by object	0	1 (9.1)
Injury severity score		
≤25	1 (11.1)	2 (18.2)
26–50	3 (33.3)	2 (18.2)
>50	5 (55.6)	7 (63.6)
Prehospital vital signs		
Heart rate (beats/min)	112 (92–134)	123 (110–133)
Systolic blood pressure (mm Hg)	81 (60–100)	79 (0–86)
Prehospital GCS		
3–8	6 (66.7)	10 (90.9)
9–12	1 (11.1)	1 (9.1)
13–15	2 (22.2)	0
Time to ED (min)		
From initial call	183.5 (154–196.5)	149.5 (123.5–149.5)
From randomization	95.5 (65–109)	90 (72.5–98)

Note: Data are reported as median (IQR) or *n* (%).

Abbreviations: GCS, Glasgow Coma Scale; IQR, interquartile range.

TABLE 2 Secondary outcomes.

	Freeze-dried plasma ($n=9$)[a]	Standard care ($n=11$)[a]	Relative risk or median difference (95% CI)
Mortality (censored at 24 h)	1 (11.1)	5 (45.4)	0.24 (0.03 to 1.73)
Mortality (censored at hospital discharge)	3 (33.3)	5 (45.4)	0.73 (0.24 to 2.27)
ICU admission	6 (66.7)	6 (54.5)	1.2 (0.6 to 2.5)
Hemoglobin[b] (g/L)	101.5 (83 to 125)	142.5 (126 to 155)	−41.0 (−82.0 to 6.0)
Platelet count[b] ($\times 10^9$/L)	206 (148.5 to 295.5)	210.5 (156 to 296)	−4.5 (−318.1 to 300.1)
Fibrinogen[b] (g/L)	2.0 (1.8 to 2.6)	2.3 (1.9 to 2.3)	−0.3 (−2.6 to 2.4)
INR[b]	1.3 (1.2 to 1.4)	1.3 (1.2 to 1.5)	0 (−62.9 to 62.9)
≤1.3	5 (62.5)	5 (62.5)	1.0 (0.28 to 3.54)
>1.3	3 (37.5)	3 (37.5)	
aPTT[b] (s)	30.5 (24.8 to 34.2)	32 (28.4 to 48.2)	−1.5 (−38.6 to 31.8)
Lactate[b] (mmol/L)	2.8 (1.7 to 4.5)	2.8 (1.8 to 6.5)	0 (−5.0 to 4.6)
RBC units in 24 h[b]	8 (2 to 8)	6.5 (1 to 8.5)	1.5 (−5.8 to 9.8)
FFP units in 24 h[b]	4 (0 to 7)	4 (0 to 5.5)	0 (−5.6 to 5.6)
Platelets units in 4 h[b,c]	1 (0 to 5)	1 (0 to 1)	0 (− 5.2 to 5.2)
Cryoprecipitate in 4 h	0 (0 to 0)	0 (0 to 0)	0 (−6.9 to 6.9)
Hospital length of stay (days)	19 (13 to 21)	9 (0 to 30)	10 (−14.3 to 34.3)
Thromboembolism	1 (11.1)	2 (18.2)	0.61 (0.07 to 5.70)

Abbreviations: aPTT, activated partial thromboplastin time; FFP, fresh-frozen plasma; ICU, intensive care unit; INR, international normalized ratio; RBC, red blood cell.

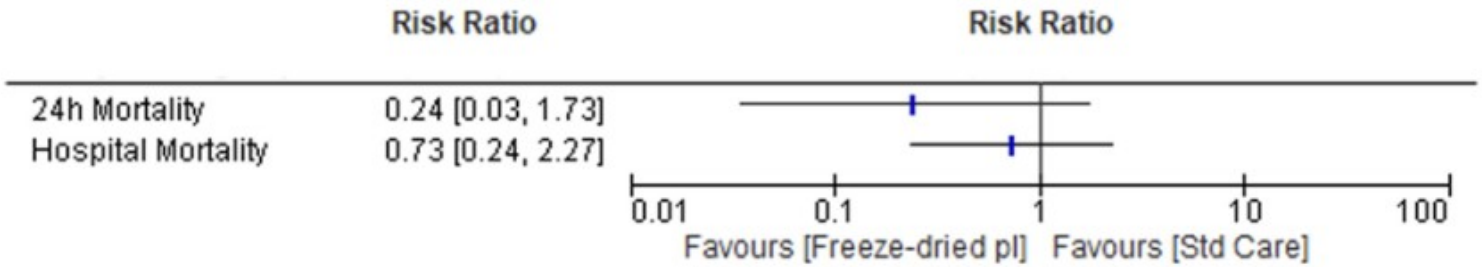
[a]Data are reported as median (IQR) or *n* (%).

[b]Among 16 patients who arrived at the hospital.

[c]One adult dose is either a platelet unit produced from a pool of buffy coats collected from four whole-blood donors or an apheresis platelet unit.

Results

FIGURE 2 Mortality outcomes.



Results

- During the study period of June 1 to October 31, 2022, there were 25 eligible patients, of whom 20 (80%) were enrolled in the trial and 19 (76%) received the allocated intervention.
- Median time from randomization to hospital arrival was 92.5 min(IQR 68–101.5 min).
- Mortality may have been lower in the freeze-dried plasma group at 24 h (RR 0.24, 95% CI 0.03–1.73) and at hospital discharge (RR 0.73, 95% CI 0.24–2.27).
- No serious adverse events related to the trial interventions were reported.

Discussion

- A key difference between this and the RePHILL trial was prehospital time.
- Overall time from initial call to hospital arrival in the United Kingdom was around 90 min, compared to 166 min in Victoria.
- Time from randomisation to hospital arrival in the United Kingdom was 36 min, compared to 92 min in Victoria.
- The hypothesis that prehospital RBCs and plasma may improve outcomes for critically bleeding trauma patients in the Australian context remains plausible.

Limitations

- Uncertainty that consistent rates of enrolment, without trial fatigue, can be achieved in a longer term.
- Eligibility for the trial was the pragmatic administration of RBCs, but not based on objective criteria.
- There was potential for imbalance between the two groups, particularly regarding a higher rate of traumatic brain injury in the standard care arm
- The point estimates for secondary outcomes are limited by wide CIs, but the observed mortality difference was consistent with the only prior randomised controlled trial of prehospital plasma during aeromedical transport.

Conclusions

- Prehospital transfusion of freeze-dried plasma with red blood cells was feasible in the setting of a randomised trial.
- In Australia, where prehospital times are long, the potential benefits could be similar to those experienced by aeromedical services in the United States using fresh-frozen plasma.
- These results provide strong support for a definitive trial of prehospital freeze-dried plasma for patients who have critical bleeding after trauma.

Acknowledgements

Commonwealth Government of Australia

National Blood Authority

Alfred Hospital clinicians

Ambulance Victoria paramedics

Emergency Research Unit, Monash University School of Public Health and Preventive Medicine

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DOI: 10.1111/acem.14745

ORIGINAL ARTICLE

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