EFFECTS OF ADVANCED TRAUMA LIFE SUPPORT® TRAINING COMPARED TO STANDARD CARE ON ADULT TRAUMA PATIENT OUTCOMES: A CLUSTER RANDOMISED TRIAL

Statistical Analysis Plan
Version 0.0.0, 2024-04-30

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1 Administrative information

1.1 Study identifiers

- Protocol version 1.0.0 dated 2024-03-28
- ClinicalTrials.gov ID NCT06321419
- Clinical Trial Registry - India

1.2 Changelog

Once version 1.0.0 is finalised, this section will be updated with a changelog.

1.3 Contributors

Name and ORCID	Affiliation	Role
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2 Trial synopsis

Title Effects of Advanced Trauma Life Support® Training Compared to Standard Care on Adult Trauma Patient Outcomes: A Cluster Randomised Trial

Rationale Trauma is a massive global health issue. Many training programmes have been developed to help physicians in the initial management of trauma patients. Among these programmes, Advanced Trauma Life Support® (ATLS®) is the most popular, having trained over one million physicians worldwide. Despite its widespread use, there are no controlled trials showing that ATLS® improves patient outcomes. Multiple systematic reviews emphasise the need for such trials.

Aim To compare the effects of ATLS® training with standard care on outcomes in adult trauma patients.

Primary Outcome All-cause mortality within 30 days of arrival at the emergency department.

Trial Design Batched stepped-wedge cluster randomised trial in India.

Trial Population Adult trauma patients presenting to the emergency department of a participating hospital.

Sample Size 30 clusters and 4320 patients.

Eligibility Criteria

Hospitals are secondary or tertiary hospitals in India that admit or refer/transfer for admission at least 400 patients with trauma per year.

Clusters are one or more units of physicians providing initial trauma care in the emergency department of tertiary hospitals in India.

Patients participants are adult trauma patients who presents to the emergency department of participating hospitals and are admitted or transferred for admission.

Intervention The intervention will be ATLS® training, a proprietary 2.5 day course teaching a standardised approach to trauma patient care using the concepts of a primary and secondary survey. Physicians will be trained in an accredited ATLS® training facility in India.

Ethical Considerations We will use an opt-out consent approach for collection of routinely recorded data. We will obtain informed consent for collection of non-routinely recorded data, such as quality of life and disability outcomes. Patients who are unconscious or lack a legally authorized representative will be included under a waiver of informed consent. Note that consent here refers to consent to data collection.

Trial Period October 1, 2024, to September 30, 2029

3 Special considerations

3.1 Funding

This trial is not yet fully funded. The Trial Management Group has decided to proceed with the trial with the expectation that additional funding will be secured. The Trial Steering Committee will be informed of the funding status at each meeting. If funding is not secured, the trial will be stopped. This will likely result in an underpowered trial. The justification for this decision is that the intervention is considered standard of care in many countries and the data collection is considered minimal risk. There is therefore a very small risk of harm to patient participants, but a potential direct benefit to those patient participants who receive the intervention. The benefit-risk ratio is therefore considered to be favourable, even in the case of an underpowered trial.

3.2 Potential amendments

There are ongoing discussions about re-framing the trial as a hybrid effectiveness-implementation trial and include a cost-effectiveness analysis. This would involve adding additional data collection to assess the implementation and costs of the intervention. This would involve additional funding and amended ethical approvals.

4 Statistical analysis

4.1 Design

This is a batched stepped-wedge cluster randomised trial, composed of 6 batches of identical 12-period 5-sequence design, with one cluster being assigned to each sequence of each batch. Each period is one month, and each cluster will be in the trial for a total of 13 months. The intervention will be implemented during a one-month transition period, which will be excluded from the analysis. There will be an overlap of 6 months between successive batches.

4.2 Statistical hypotheses

Our primary statistical hypotheses are:

- **Null hypothesis**: There is no difference in the primary outcome of 30-day in-hospital mortality between those randomised to ATLS® and standard care, meaning that the odds ratio (OR) for ATLS® vs standard care would be 1.
- **Alternative hypothesis**: There is a difference in the primary outcome of 30-day in-hospital mortality between those randomised to ATLS® and standard care, meaning that the OR for ATLS® vs standard care would be different from 1. Our expectation, based on our pilot study and review of the literature, is that the OR will be less than 1, indicating lower odds of 30-day in-hospital mortality among those randomised to ATLS® group compared to those randomised to the standard care group.

4.3 Statistical principles

4.3.1 Statistical software

We will use the R Statistical Software for all analyses[1].

4.3.2 Levels of statistical significance and confidence

We will not perform any formal hypothesis testing as part of our planned interim analyses. We will use a two-sided significance level of 0.05 for all analyses, and we will report 95% confidence intervals (CI) for all estimates. We will not adjust for multiple testing because no secondary outcome is regarded as singularly more important.

4.4 Analysis populations

The unit of randomisation is the hospital, but the unit of analysis is the individual patient. The group allocation for a patient depends on the period in which the patient was admitted to the hospital, and patients will be considered exposed to the intervention if they were admitted to the hospital at any time point following the transition period. We will use an intention-to-treat approach for all analyses. We will use a CONSORT diagram to display the flow of hospitals, clusters and patients through the trial. We will report the study according to the CONSORT guidelines for stepped-wedge randomised trials[2].

4.5 Baseline analyses

4.5.1 Cluster characteristics

We will describe cluster characteristics including location and size using frequencies and percentages for discrete variables and means, standard deviations, medians and interquartile ranges (Q1-Q3) for continuous variables.

4.5.2 Patient characteristics

We will describe patient characteristics at baseline per treatment group and overall using frequencies and percentages for discrete variables and means, standard deviations, medians and interquartile ranges (Q1-Q3) for continuous variables. We will not adjust for clustering when presenting baseline characteristics.

4.6 Analysis of the primary outcome

The primary outcomes is 30-day in-hospital mortality and will be analysed as a dichotomous variable. We will estimate the primary intervention effect as the OR of death between the ATLS® and standard care arms, with an OR < 1 indicating lower odds of death in the ATLS® arm compared to the standard care arm and vice versa.

4.6.1 Main analysis

We will use a mixed effects binomial model (Equation 1) with a logit link to estimate the OR. We will also use an identity link used to estimate the risk difference. These models will be fitted using residual pseudo-likelihood estimation based on linearization with subject-specific expansion (RSPL). If the binomial model with the identity link does not converge then only a odds ratio will be reported. We will include fixed effects for period and a fixed effect for intervention exposure. The primary analysis will allow

for clustering by as a random cluster and random cluster by period effect. To correct the potential inflation of the type I error rate due to small number of clusters, the Kenward and Roger small sample correction will be used[3].

$$\Pr(Y_{bkti} = 1) = \beta_{bt} + \theta X_{bkt} + \alpha_{bkt} \quad (1)$$

Where:

- $\Pr(Y_{bkti} = 1)$ is the probability of death for patient $i = 1, \ldots, m$ in cluster $k = 1, \ldots, 30$ in period $t = 1, \ldots, 12$ in batch $b = 1, \ldots, 6$.
- β_{bt} is the fixed effect of period t in batch b, i.e. there is a separate period effect for each batch, so that there is a total of 72 period effects.
- θ is the fixed effect of intervention exposure, i.e. the effect of ATLS® exposure on the probability of death.
- X_{bkt} is the treatment arm for patient i in cluster k in period t, with $X_{bkt} = 1$ for ATLS® and $X_{bkt} = 0$ for standard care.
- α_{bkt} is the random effect of cluster k in period t in batch b, i.e. there is a separate cluster effect for each cluster in each period in each batch.

We will present the effect of ATLS® exposure as an OR of mortality with an associated 95% CI, using the standard care arm as the reference. We will also present the risk difference with a 95% CI. We will balance the randomization within each batch on cluster size, defined as expected monthly volume of eligible patient participants, and will therefore not adjust the main analysis for cluster size.

4.6.2 Adjusted analyses

4.6.3 Subgroup analyses

4.6.4 Treatment of missing data

Analysis of secondary outcomes

1. R Core Team. *R: A language and environment for statistical computing.* (R Foundation for Statistical Computing, 2023).
2. Hemming, K. *et al.* Reporting of stepped wedge cluster randomised trials: Extension of the CONSORT 2010 statement with explanation and elaboration. *BMJ* k1614 (2018).
3. Kenward, M. G. *et al.* Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood. *Biometrics* **53**, 983–997 (1997).