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[1]. 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[2].

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[3].

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: mixed effects binomial model with logit link

We will use a mixed effects binomial model with a logit link to estimate the OR. 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. The full model is specified in Equation 1. 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[4]. This model will be fitted using residual pseudo-likelihood estimation based on linearization with subject-specific expansion (RSPL).

$$\text{logit}(\Pr(Y_{bkti} = 1)) = \beta_{bt} + \theta X_{bkt} + \alpha_{bk} + \gamma_{bkt} \tag{1}$$

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_{bk} is the random effect of cluster k in batch b, i.e. the random effect of cluster.
- γ_{bkt} is the random effect of cluster k in period t in batch b, i.e. the random effect of cluster by period.

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.

4.7 Sensitivity analyses

The sensitivity analyses will be conducted to assess the robustness of the main analysis results to different model specifications. We will first model the primary outcome using an identity link function to estimate the risk difference instead of the OR. We will also explore more complex correlation structures and model time using a spline function. Finally, we will conduct a fully adjusted covariate analysis.

4.7.1 Model with identify link

We will use an identity link used to estimate the risk difference. This model is specified in Equation 2 and will also be fitted using RSPL. If the binomial model with the identity link does not converge then only a odds ratio will be reported.

$$\Pr(Y_{bkti} = 1) = \beta_{bt} + \theta X_{bkt} + \alpha_{bk} + \gamma_{bkt} \tag{2}$$

4.7.2 Model with logit link and different correlation structure

We will explore if models with more complicated correlation structures are a better fit to the data. These models are not being used as our primary analysis models as there is limited understanding as to when such models will converge and how to choose between the various different correlation structures which might be plausible. First, we will include a discrete time decay correlation structure including a random cluster effect with auto-regressive structure (AR(1)), described in Equation 3.

$$\alpha_{bk,t} = \rho\alpha_{bk,t-1} + \epsilon_t, \quad \epsilon_t \sim N(0, \sigma^2_\alpha) \tag{3}$$

Where:

- $\alpha_{bk,t}$ is the random effect of cluster k in period t in batch b.
- ρ is the correlation between the random effects of two consecutive periods, the period t and the period $t-1$.
- ϵ_t is the error term for period t, which is assumed to be normally distributed with mean 0 and variance σ^2_α.

Second, we will also include a different secular trend for each batch as an interaction term between batch and period. This model is specified in Equation 4.

$$\text{logit}(\Pr(Y_{bkti} = 1)) = \beta_{bt} + \theta X_{bkt} + \alpha_{bk,t} + \gamma_{bkt} \tag{4}$$

To this end we will fit generalised linear mixed models using the same link functions and fixed effects as described above to include . To allow for the randomisation by batches, a different secular trend will be included for each batch as an interaction term between batch and period.

4.7.3 Model with identity link and different correlation structure

4.7.4 Model with spline function

To additionally explore if the fixed period effect is both parsimonious and adequate to represent the extent of any underlying secular trend, we will model the time effect using a spline function. Models will also be extended to include random cluster by intervention effects (with a non-zero covariance term) to examine if results are sensitive to the assumption of no intervention by cluster interaction. Models will also be extended to include an interaction between treatment and number of periods since first treated, to examine if there is any indication of a relationship between duration of exposure to the intervention and outcomes.

This will allow us to different lag effects (whereby it takes time for the intervention to become embedded within the culture before its impact can properly start to be realised); as well as weaning effects (whereby the effect of the intervention starts to decrease – or fade). This type of analysis attempts to disentangle how some clusters end up having a long exposure to the intervention and others have a much shorter exposure time.

4.7.5 Adjusted analyses

A fully adjusted covariate analysis will additionally adjust for a set of pre-specified individual-level covariates of known prognostic importance.

4.7.6 Subgroup analyses

We will use a two-sided significance level of 5% and estimate 95% confidence intervals. The primary subgroup analyses will be based on geographical region because demonstrating the consistency of any effect across multiple regions will enhance the generalisibility of the results[ˆquestion:batch-region]. Additional subgroup analyses will include age across the groups older adolescents (15-19 years), young adults (20-24 years), adults (25-59 years), and older adults (60 years and older)[5]; sex; and the clinical cohorts blunt multisytem trauma, penetrating trauma, and severe isolated traumatic brain injury.

4.7.7 Treatment of missing data

4.8 Analysis of secondary outcomes

For continuous, count and prevalence outcomes similar model-based approaches will be used but with appropriate links and distribution functions, using transformations where appropriate.

1. Kasza, J. *et al.* The batched stepped wedge design: A design robust to delays in cluster recruitment. *Stat Med* **41**, 3627–3641 (2022).
2. R Core Team. *R: A language and environment for statistical computing.* (R Foundation for Statistical Computing, 2023).
3. Hemming, K. *et al.* Reporting of stepped wedge cluster randomised trials: Extension of the CONSORT 2010 statement with explanation and elaboration. *BMJ* k1614 (2018).
4. Kenward, M. G. *et al.* Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood. *Biometrics* **53**, 983–997 (1997).
5. Diaz, T. *et al.* A call for standardised age-disaggregated health data. *The Lancet Healthy Longevity* **2**, e436–e443 (2021).