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

Statistical Analysis Plan
Version 0.2.0, 2024-06-04

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1 Administrative information

1.1 Study identifiers

- Protocol version 1.2.0 dated 2024-08-26
- 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

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 In-hospital 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, including a total of 30. The trial will be 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 an absolute difference in the primary outcome of 30-day in-hospital mortality between those randomised to ATLS® and standard care of at least 5% units, 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 Sample size calculations

With 30 clusters and a total sample size of 4320 our study has ~90% power across different combinations of cluster autocorrelations (CAC) and intra-cluster correlations (ICC) to detect a reduction in the primary outcome of in-hospital mortality within 30 days from 20% under standard care to 15% after ATLS® training (see Figure 1). This effect is a conservative estimate and the reduction equals a risk ratio of 0.75, which would be clinically important while also being consistent with our pilot study and updated systematic review. We allowed for the clustered design and assumed an ICC of 0.02, but considered sensitivity across the range 0.01-0.05[2,3], and a CAC of 0.9 but considered sensitivity across the range 0.8-1.0, based on our pilot study and current guidance[4–6]. We included the CAC to allow for variation in clustering over time. We assume that each cluster will contribute approximately 12 observations per month to the analysis, based on our previous work.

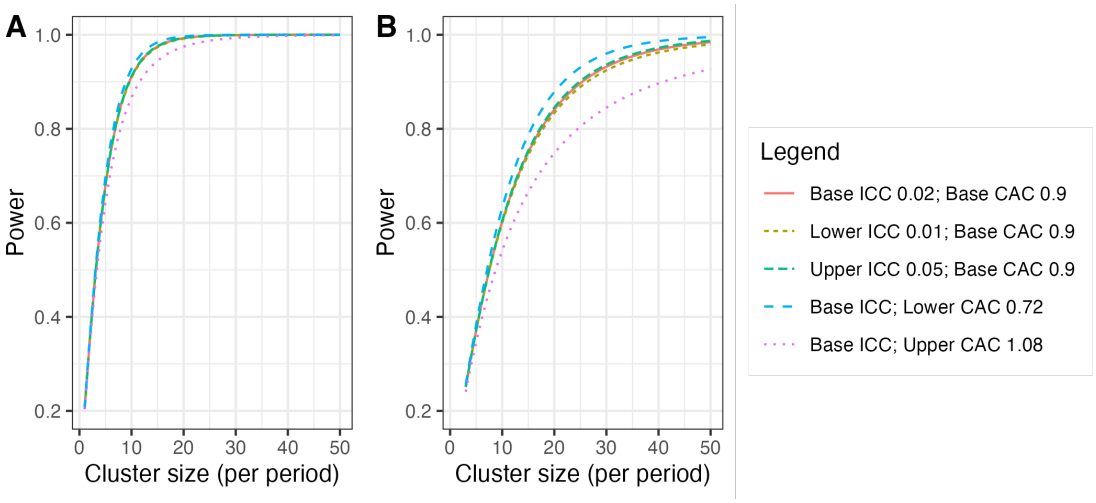

Figure 1: Power curves for different combinations of cluster autocorrelations (CAC) and intra-cluster correlations (ICC). **A)** Shows power curves assuming a reduction in the primary outcome of in-hospital mortality within 30 days from 20% under standard care to 15% after ATLS® training. **B)** Shows power curves assuming a reduction in the primary outcome from 10% under standard care to 7.5% after ATLS® training. Under this scenario, we would need to increase the sample size per month to around 30 observations to achieve 90% powere under most combinations of CAC and ICC.

4.4 Statistical principles

4.4.1 Statistical software

We will use the R Statistical Software for all analyses[7].

4.4.2 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.

4.5 Analysis populations

The unit of randomisation is the hospital, because all units trained in the same hospital will be treated as one cluster, 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 not do a per protocol or safety analysis. We will use a CONSORT diagram to display the flow of hospitals, clusters and patients through the trial. We will present cluster level summaries of the intervention effect. We will report the study according to the CONSORT guidelines for stepped-wedge randomised trials[8].

4.6 Baseline analyses

4.6.1 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.

4.6.2 Patient characteristics

We will describe patient characteristics at baseline, meaning all pre-training periods, 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.

4.7 Analysis of the primary outcome

The primary outcomes is in-hospital mortality within 30 days of arrival at the emergency department 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.

4.7.1 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 as a categorical variable and a fixed effect for intervention exposure[1]. The primary analysis will allow for clustering as a random cluster and random cluster by period effect, both assumed to follow a normal distribution. 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[9]. This model will be fitted using residual pseudo-likelihood estimation based on linearization with subject-specific expansion (RSPL).

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

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 $b = 1, \ldots, 6$.
- μ is the intercept, representing the baseline log-odds of the outcome when all predictors are 1.
- 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.[2]
- 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.

[1] **Question:** Should we adjust for calendar time because the last batch will be two years later than the first batch?

[2] **Question:** The model will estimate some 78 parameters. Is this a problem considering the low number of participants per 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.

4.7.2 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. Henceforth, each additional sensitivity analyses will be operationalised using two separate models, one with the logit link and one with the identity link. We will first explore more complex correlation structures. We will then model time using a spline function. Finally, we will conduct a fully adjusted covariate analysis.

Model with identify link

We will use an identity link used to estimate the risk difference, meaning that the coefficient will be interpreted as the difference in the probability of death between the ATLS® and standard care arms. We will present the risk difference with a 95% CI. 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.

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

Where:

- μ is the intercept, representing the baseline probability of the outcome when all predictors are zero.

Models with 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:

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

To allow for the randomisation by batches, we will also include a different secular trend for each batch as a random effect interaction term between batch and period. The full model is specified in Equation 4.

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

Where:

- $g(\cdot)$ is the link function.
- $\alpha_{bk,t}$ is the is the updated random effect of cluster k in batch b in period t with the AR(1) correlation structure.
- δ_{bt} is the random effect of batch b in period t.

Models with random cluster by intervention effects

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. The model is specified in Equation 5.

$$g(\Pr(Y_{bkti}=1)) = \mu + \beta_{bt} + \theta X_{bkt} + \alpha_{bk} + \gamma_{bkt} + u_{bk} \times X_{bkt} \tag{5}$$

Where:

- u_{bk} is the random effect of cluster k by intervention interaction.

Models with time modelled with a spline function

We will further explore the potential for a time-varying treatment effect[10]. To 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 natural cubic splines with knots at the equally spaced time points 3, 6 and 9. This will result in five spline basis functions, because the natural cubic splines are modelled with three degrees of freedom but are constrained to be linear before the first and after the last knot. The model is specified in Equation 6.

$$g(\Pr(Y_{bkti} = 1)) = \mu + \sum_{j=1}^{5} \beta_j S_j(t, \{3, 6, 9\}) + \theta X_{bkt} + \alpha_{bk} + \gamma_{bkt} \tag{6}$$

Where:

- $S_j(t, \{3, 6, 9\})$ is the natural cubic spline basis functions with knots placed at times 3, 6 and 9.
- β_j is the coefficient for the j-th spline basis function.

Models exploring lag and weaning effects

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 model 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. The model is specified in Equation 7.

$$g(\Pr(Y_{bkti} = 1)) = \mu + \beta_{bt} + \theta X_{bkt} + \theta_{\text{int}} X_{bkt} \times T_{bkt} + \alpha_{bk} + \gamma_{bkt} \tag{7}$$

Where:

- θ_{int} is the coefficient for the interaction between treatment and time since first treated.
- T_{bkt} is the number of periods since first treated.

4.7.3 Adjusted analyses

Fully adjusted covariate analysis will additionally adjust for:

- Age
- Sex
- Systolic blood pressure
- Glasgow Coma Scale
- Injury Severity Score
- Mechanism of injury

These are known individual-level prognostic factors for the primary outcome. These covariates will be included in the models specified in Equation 1 and Equation 2 as fixed effects.

4.7.4 Subgroup analyses

We will perform the following subgroup analyses[3]:

- geographical region, defined using the state in which the participating hospital is located. Demonstrating the consistency of any effect across multiple regions will enhance the generalisibility of the results;
- age groups, defined as older adolescents (15-19 years), young adults (20-24 years), adults (25-59 years), and older adults (60 years and older) [[11];
- sex, using the levels male and female;
- clinical cohorts, defined as blunt multisystem trauma, penetrating trauma, and severe isolated traumatic brain injury, with modification to avoid overlap between the cohorts; and
- cluster size.

These subgroup analyses will be conducted by adding the subgroup variable and the interaction between the subgroup variable and the intervention exposure variable as fixed effects to the models specified in Equation 1 and Equation 2.

4.7.5 Treatment of missing data

We will present the frequency and percentage of missing data for all variables. If the percentage of missing data for the primary outcome is less than 10% then we will perform a complete case analysis. If the percentage of missing data for the primary outcome is 10% or more, then we will handle missing data using multiple imputation by chained equations (MICE), imputing data for the primary outcome as well as all covariates included in the fully adjusted model. The number of imputations will be determined by the percentage of missing data, with a minimum of 20 imputations.

4.8 Analysis of secondary outcomes

4.8.1 All cause mortality within 24 hours, 30 days and three months of arrival at the emergency department

We will use the model with the logit link specified in Equation 1 and the model with the identity link specified in Equation 2 to estimate the OR and risk difference for these mortality outcomes.

[3] **Question:** Are we exploring too many subgroups?

4.8.2 Quality of life within seven days of discharge, and at 30 days and three months of arrival at the emergency department

Quality of life will be measured by the official and validated translations of the EQ5D5L. This tool assesses five dimensions of health-related quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a likert scale from 1 to 5. There is also a visual analogue scale (VAS) for self-rated quality of life, ranging from 0 to 100. For each of the five dimensions we will use a mixed effects ordinal model as specified in Equation 8.

$$\text{logit}(\Pr(Y_{bkti} \leq j)) = \mu_j + \beta_{bt} + \theta X_{bkt} + \alpha_{bk} + \gamma_{bkt} \tag{8}$$

Where:

- μ_j is the intercept for the j-th category of the EQ5D dimension ($j = 1, 2, 3, 4, 5$).

The VAS will be analysed using a linear mixed effects model as specified in Equation 9.

$$\text{VAS}_{bkti} = \mu + \beta_{bt} + \theta X_{bkt} + \alpha_{bk} + \gamma_{bkt} + \epsilon_{bkti}, \quad \epsilon_{bkti} \sim N(0, \sigma^2) \tag{9}$$

Where:

- ϵ_{bkti} is the error term for patient i in cluster k in period t in batch b, assumed to be normally distributed with mean 0 and variance σ^2.

4.8.3 Disability within seven days of discharge, and at 30 days and three months of arrival at the emergency department

We will measure disability using the WHO Disability Assessment Schedule 2.0 (WHO-DAS 2.0)[12]. This tool assesses six domains of functioning: cognition, mobility, self-care, getting along, life activities, and participation. Each domain is rated on a likert scale from 1 to 5, with 1 indicating no difficulties and 5 indicating extreme difficulties. We will analyse each domain separately using a mixed effects ordinal model as specified in Equation 8. We will also calculate a WHODAS 2.0 summary score using the method referred to as the "complex scoring" method. This method involves summing the item scores within each of the six domains, then summing the scores of all domains, and finally transforming the total score to a 0-100 scale. We will analyse the summary score using a linear mixed effects model as specified in Equation 9.

4.8.4 Return to work at 30 days and three months after arrival at the emergency department

We will analyse return to work as a dichotomous variable using a mixed effects binomial model with a logit link as specified in Equation 1.

4.8.5 Length of emergency department stay

We will analyse length of emergency department stay as a continuous variable using a linear mixed effects model as specified in Equation 9.

4.8.6 Length of hospital stay

We will analyse length of hospital stay as a continuous variable using a linear mixed effects model as specified in Equation 9.

4.8.7 Intensive care unit admission

We will analyse intensive care unit admission as a dichotomous variable using a mixed effects binomial model with a logit link as specified in Equation 1.

4.8.8 Length of intensive care unit stay

We will analyse length of intensive care unit stay as a continuous variable using a linear mixed effects model as specified in Equation 9.

References

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. Campbell, M. K. *et al.* Determinants of the intracluster correlation coefficient in cluster randomized trials: The case of implementation research. *Clinical Trials* **2**, 99–107 (2005).
3. Eldridge, S. M. *et al.* How big should the pilot study for my cluster randomised trial be? *Stat Methods Med Res* **25**, 1039–1056 (2015).
4. Hemming, K. *et al.* A tutorial on sample size calculation for multiple-period cluster randomized parallel, cross-over and stepped-wedge trials using the shiny CRT calculator. *Int J Epidemiol* **49**, 979–995 (2020).

5. Martin, J. *et al.* Intra-cluster and inter-period correlation coefficients for cross-sectional cluster randomised controlled trials for type-2 diabetes in UK primary care. *Trials* **17**, (2016).

6. Korevaar, E. *et al.* Intra-cluster correlations from the CLustered OUtcome dataset bank to inform the design of longitudinal cluster trials. *Clinical Trials* **18**, 529–540 (2021).

7. R Core Team. *R: A language and environment for statistical computing.* (R Foundation for Statistical Computing, 2023).

8. Hemming, K. *et al.* Reporting of stepped wedge cluster randomised trials: Extension of the CONSORT 2010 statement with explanation and elaboration. *BMJ* k1614 (2018).

9. Kenward, M. G. *et al.* Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood. *Biometrics* **53**, 983–997 (1997).

10. Kenny, A. *et al.* Analysis of stepped wedge cluster randomized trials in the presence of a time-varying treatment effect. *Statistics in medicine* 10.1002/sim.9511 (2022).

11. Diaz, T. *et al.* A call for standardised age-disaggregated health data. *The Lancet Healthy Longevity* **2**, e436–e443 (2021).

12. Ustun, T. B. *et al. Measuring Health and Disability: Manual for WHO Disability Assessment Schedule (WHODAS 2.0).* (World Health Organization, 2010).