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

Clinical Trial Protocol
Version 0.2.0
2023-12-11

Table of contents

ATLS® vs Standard Care in Adult Trauma Patients

Clinical Trials Registry-India ID:

ClinicalTrials.gov ID:

Sponsor: Karolinska Institutet

Co-sponsor: The George Institute for Global Health, India

1 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[1,2]. Many training programmes have been developed to help physicians in the initial management of trauma patients[3–6]. Advanced Trauma Life Support® (ATLS®) is the most popular of these programmes and have been used to train over one million physicians worldwide[7]. Despite its widespread use, there are no controlled trials showing that ATLS® improves patient outcomes[3,4,6]. Multiple systematic reviews emphasise the need for such trials[3,4,6].

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

Cluster will be hospitals with a baseline admission rate of at least 400 patients with trauma per year or 35 patients with trauma per month for at least the last six months, that provide general surgery, imaging and blood banking services around the clock, and where no more than 25% of initial trauma care providers trained in any trauma life support training programme.

Patients will at least 15 years old, who present to the emergency department of participating hospitals with a history of trauma occuring less than 48 hours before arrival, and who are admitted or die between and admission, or who are transferred from the emergency department of a participating hospital to another hospital 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 In-hospital data collection will be conducted under a waiver of informed consent. Patients will be informed about the trial and their right to opt out of data collection. Patients will be informed that they can withdraw their data from the trial at any time.

Trial Period 2024-10-01 to 2029-10-01

2 Background and rationale

Each year, 4.3 million people die from trauma[1]. Among people aged 10-24 and 25-49 years trauma is the largest cause of disability adjusted life years[2]. Most deaths from trauma occur within the first 24-48 hours[8]. Traumatic brain injury and exsanguination are the most common causes of trauma deaths[9,10]. Most preventable trauma deaths are caused by clinical judgement errors during initial resuscitation or early care including airway management and haemorrhage control, even though the deaths occur later during the hospital stay[9,11].

Several trauma life support training programmes have been developed to improve the early management of patients in the hospital by providing a structured framework for assessment and treatment[3–6]. The proprietary Advanced Trauma Life Support® (ATLS®) is the most established trauma life support training programme and more than one million physicians in over 80 countries have been trained in the programme since the first course in 1978[7]. In the US and many other countries training in ATLS® is virtually mandatory for trauma care physicians[12]. Uptake in low- and middle income countries (LMIC) has been slow, potentially due to high costs[5].

There are three randomised controlled studies showing that ATLS® improves knowledge and clinical skills[13–15], but there are no randomised controlled trials or high-quality quasi-experimental trials indicating that ATLS® improves patient outcomes[3,4,6]. We conducted an updated systematic review for project (unpublished), and estimated a pooled risk ratio of 0.82 (95% CI 0.60; 1.11) from ten heterogeneous (I^2 0.91) retrospective or small studies on the effect of ATLS on mortality (see Figure 1)[16–25]. No study assessed functional outcomes.

We conducted a pilot cluster randomised controlled trial (ClinicalTrials.gov NCT05417243) that we conducted between April 2022 and February 2023 as part of our network grant to assess the feasibility of a full scale trial. We published the protocol for this pilot study[26]. Our pilot study enrolled 376 patients from seven hospitals across India (unpublished data) and shows that it is feasible to conduct the proposed trial with a high recruitment rate (78%), low loss to follow-up rate (1%), and low missingness in key variables (mean 0.8%).

To involve patients and the public in the planning of this trial we conducted 19 semi-structured interviews with trauma patients, caregivers, and community representatives (unpublished data). The aim of these interviews was to understand their views on the trial and important outcomes and the interviews showed high acceptability of our research and emphasised the importance of better recovery before discharge and functional outcomes at and after discharge, including pain, mobility and self-care activities. The interviews also highlighted return to work as an important outcome.

2.1 Updated systematic review

We performed a systematic literature search in the Medline, Embase, Cochrane, Web of Science, CINAHL and Google Scholar databases (PROSPERO ID CRD42022373977). The last search

was conducted on November 11, 2022. We developed the search strategy in Medline (Ovid) in collaboration with librarians at the Karolinska Institutet University Library. We limited the search to English language articles, searched all databases from inception, and screened a total of 7896 records. We used a random effects model to pool estimates across studies.

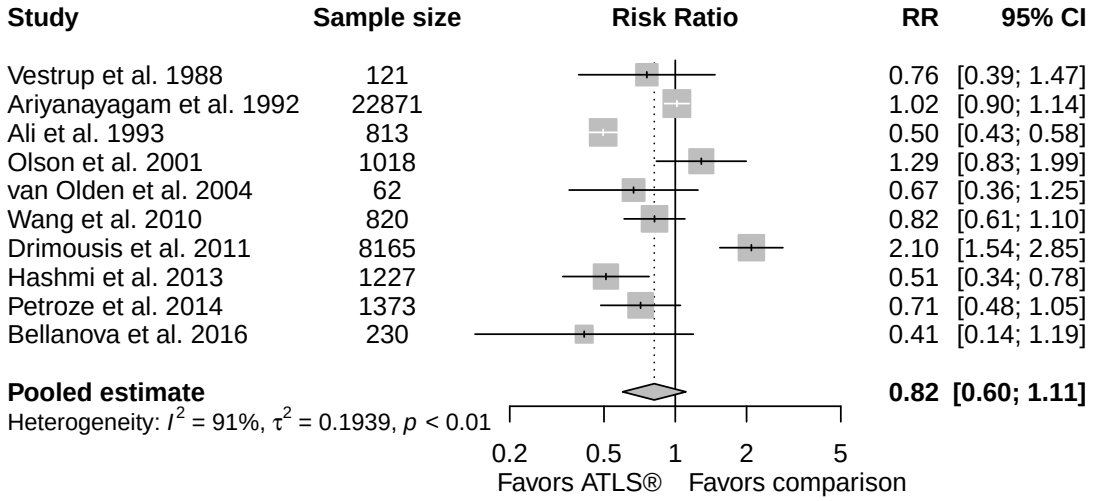

Figure 1: Summary of the updated system review. The forest plot shows the effect of ATLS on mortality. Abbreviations: RR, risk ratio; CI, confidence interval; ATLS, Advanced Trauma Life Support; I^2, heterogeneity.

3 Benefit-risk evaluation

The direct risks includes integrity violations and data leakage. We will mitigate these risks by employing rigorous data collection and storage mechanisms. The procedures that we will use to collect data will be direct observation of care, routine physical examinations, questionnaires, and extraction of already collected data from patient records, which are often seen as involving only minimal risk.

The long-term risks of the research and the risk that the research will be used in detrimental ways are minimal. Our trial will assess the effect of Advanced Trauma Life Support® (ATLS®) on patient outcomes. Training in ATLS® is standard in many health care systems and it is unlikely that training physicians in this programme induces any harm to participants.

We consider these risks weighed up by the potential direct benefit for the participants in the intervention phase, if ATLS® is found to improve patient outcomes, and by the potential for improved care for the trauma patient population.

4 Trial aim

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

5 Regulatory approvals and trial registration

This trial will be submitted to the Health Ministry Screening Committee at the Indian Council for Medical Research for their approval, and registered with Clinical Trials Registry-India and ClinicalTrials.gov.

6 Trial design and procedures

6.1 Overall trial design

We will conduct a batched stepped-wedge cluster randomised controlled trial (see Figure 2). The stepped-wedge trial is a uni-directional cross-over trial but the time point when clusters cross-over from standard care to the intervention is randomised[27]. Each cluster will be a tertiary hospital in India. We will conduct this trial in India because physicians providing initial trauma care in India are not routinely trained in ATLS® or similar programmes.

We will roll out the interventions to 30 clusters over six batches, so there will be five clusters in each batch. The clusters in each batch will be randomised to one of five implementation sequences, with one hospital randomised to each implementation sequence. All clusters will transition through three phases, first a standard care phase, then a transition phase during which the training is delivered, and finally an intervention phase, for a total of 13 months. The implementation sequence determines how long the phases of standard care and intervention are. Patient participants will be followed up for a total of three.

6.2 Design justification

We use the cluster randomised design because the intervention cannot be randomised at the individual patient level. We use the stepped-wedge design for two reasons. First, this design is statistically more efficient than the parallel cluster design when the number of clusters is limited[28]. In this trial, the number of clusters is limited because of the costs associated with ATLS® training and the available slots for ATLS® training in India. Second, the stepped-wedge design is likely to enhance participation and engagement because all clusters receive the intervention. The batched stepped-wedge design further improves feasibility as it does not require all clusters to start at the same time, and it is robust to potential delays in cluster recruitment[29].

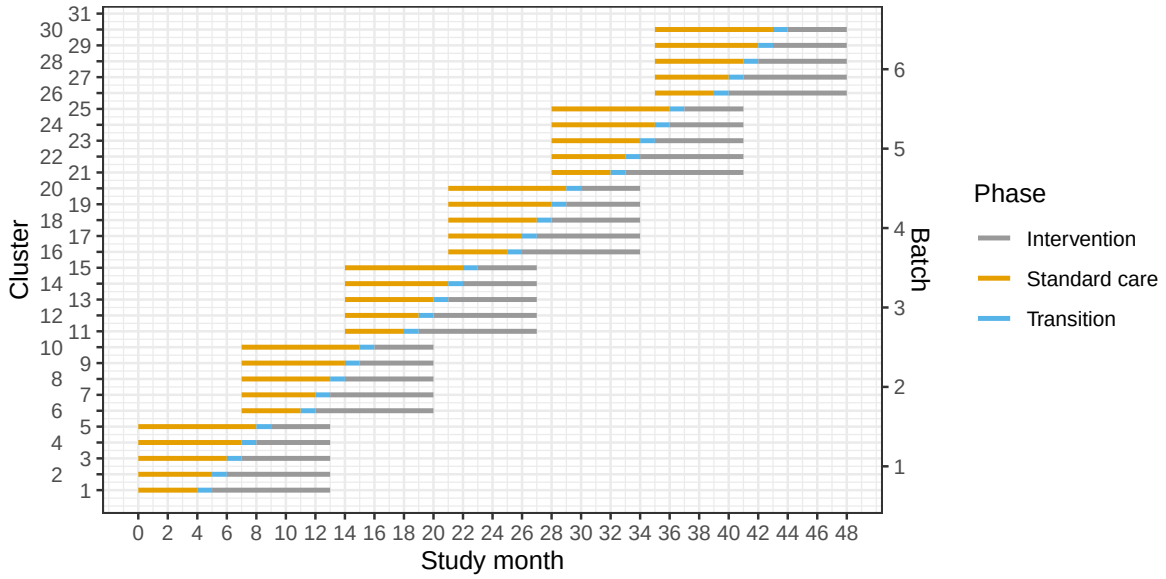

Figure 2: Trial design. Lines represent the duration of patient enrolment across clusters and phases. Clusters will be sequentially allocated to a batch based on when they enter the study. Within each batch clusters will then be randomised to an intervention implementation sequence.

6.3 Cluster selection

6.3.1 Eligibility criteria

Clusters must meet the following criteria:

- admits or refers/transfers for admission at least 400 patients with trauma per year or 35 patients with trauma per month for at least the last six months;
- receives no more than 25% of trauma patients as referrals/transfers from other hospitals;
- provides surgical and orthopaedic emergency services around the clock; and
- no more than 25% of physicians providing initial trauma care trained in any trauma life support programme.

6.3.2 Screening

The research team will compile a list of potentially eligible clusters and reach out to them to assess their interest in participating in the trial. We will then screen clusters for eligibility based on the criteria above. The data sources for screening will be hospital records and

interviews with hospital staff. The screening will be standardised using a cluster screening form[1] and logged in a cluster screening log[2].

6.4 Patient participants selection

6.4.1 Inclusion criteria

Patients participants must meet the following criteria:

- age of at least 15 years;
- present to the emergency department of participating hospitals, with a history of trauma defined as having any of the reasons listed in the International Classification of Diseases chapter XX as the reason for presenting;
- admitted or died between arrival at the hospital and admission;
- referred/transferred from the emergency department of a participating hospital to another hospital for admission; and
- trauma occurred less than 48 hours before arrival at the hospital.

6.4.2 Exclusion criteria

Patients participants are excluded if they meet the following criteria:

- present with isolated limb injuries; or
- are directly admitted to a ward without being seen by a physician in the emergency department.

6.4.3 Screening

Clinical research coordinators will screen patient participants either as they arrive to the emergency department or using emergency department registers. They will then approach eligible patients or their caregivers to provide study information and obtain informed consent for out of hospital data collection. They will also inform patients that they can opt out of in-hospital data collection. Patients who present during the clinical research coordinator's working hours will be approached in person. Patients who present outside of working hours will be approached by phone. Phone numbers will be extracted from the emergency department registers.

[1] **TODO** We need to create a form that we can use to screen clusters.
[2] **TODO** We need to create a log that we can use to log the screening process.

6.4.4 Withdrawal criteria

Patient participants can choose to withdraw their consent to out of hospital follow up at any time. If they withdraw their consent to out of hospital follow up the clinical research coordinator will not contact them for additional follow ups. They can also choose to have the data collected about them removed from the trial at any time. Withdrawal of consent to out of hospital follow up or removal of data from the trial will not affect their care in any way. If the patient participant withdraws consent, follow-up of this participant will be performed according to the participating hospitals routine.

6.5 Procedures

Table 1 shows an overview of trial procedures. Clinical research coordinators will follow up patients daily until discharge to capture injury information. They will also follow up patients at 24 hours, 30 days and 90 days after arrival to the emergency department to capture mortality outcomes, and at 30 days and 90 days after arrival to the emergency department to capture functional outcomes and return to work. If patient participants are discharged before any of these follow-up time points, clinical research coordinators will follow up patients by phone.

Table 1: Overview of trial procedures

		Follow up				
Procedure	Screening	Daily	24 hours	Discharge	Within 7 days of discharge	30
Eligibility criteria	√					
Study information[1]	√					
Informed consent for follow up[1]	√					
Baseline data collection	√					
Injury data collection	√	√				
Complications data collection		√				
Mortality data collection[2]	√	√	√	√		√
EQ-5D/WHODAS					√	√
Return to work						√
End of Trial						

[1]Clinical research coordinators will inform patient participants about the study, including that they are free to withdraw their data from the study at any time, and approach them for informed consent for follow up either in person or telephonically.
[2]Mortality data will be collected from the hospital records and from the patient participants or their caregivers by telephone.

6.6 Biological sampling procedures

This trial does not include biological sampling.

6.7 End of Trial

The trial ends when the last patient participant has completed the last follow-up. The trial may be prematurely terminated if it this is necessary for safety reasons affecting the risk-benefit balance or if the recruitment of subjects cannot be met within reasonable time limits. If the trial is prematurely terminated or suspended, the investigator should immediately inform the subjects about this and ensure appropriate treatment and follow-up. Decisions on premature termination are taken by the sponsor.

6.8 Intervention and control treatment

The intervention will be ATLS® training. The control will be standard care, meaning no formal trauma life support training. We will train the physicians that initially resuscitate and provide trauma care during the first hour after patient arrival at the emergency department. These physicians can be casualty medical officers, surgical residents, or emergency medicine residents, depending on the setup at each participating centre. The training will occur during the transition phase in each cluster. We will train the number of physicians needed to reach the required patient sample size.

Advanced Trauma Life Support® (ATLS®)[7] is a proprietary 2.5 day course teaching a standardised approach to trauma patient care using the concepts of a primary and secondary survey. The programme was developed by the Committee of Trauma of the American College of Surgeons. The course includes intial treatment and resuscitation, triage and interfacility transfers. Leaning is based on practical scenario-driven skill stations, lectures and includes a final performance proficiency evaluation. Physicians will be trained in an accredited ATLS® training facility in India.

Standard care varies across hospitals in India, but trauma patients are initially managed by casualty medical officers, surgical residents, or emergency medicine residents. They are mainly first- or second-year residents who resuscitate patients, perform interventions and refer patients for imaging or other investigations. Compared with other settings where a trauma team approach is adopted, nurses and other healthcare professionals are only involved to a limited extent during the initial management.

6.8.1 Description of investigational medicinal products

This trial does not include any investigational medicinal products.

6.8.2 Auxiliary medicinal products

This trial does not include any auxiliary medicinal products.

6.8.3 Concomitant use of other medications or treatments

Medications or treatments considered necessary for the safety and well-being of the subject may be provided at the discretion of the investigators, unless otherwise specified in the exclusion criteria.

6.9 Randomization

We will assign clusters to batches as they are found to be eligible and receive ethical approval, and will randomise the clusters to intervention implementation sequences within batches[3]. Randomisation will be stratified by geographical region and anticipated cluster size[4]. Randomisation will be conducted by an independent statistician, with the order concealed from study investigators until one month before the start of the transition date.[5]

6.10 Blinding

It is not possible to blind a stepped-wedge trial, because all clusters receive the intervention.

6.11 Treatment after trial end

When the trial ends, the intervention will have been implemented in all clusters.

6.12 Outcomes

6.12.1 Primary outcome

The primary outcome will be in-hospital mortality within 30 days of arrival at the emergency department. Clinical research coordinators will extract information on death from patient hospital records or by calling the patient or a patient representative. Data on this outcome will be collected continuously during the trial. We chose this outcome as the primary outcome

[3] **TODO** Add details on software used to randomise clusters.

[4] **Question:** Is it still relevant to stratify by geographical region and anticipated cluster size in the stepped-wedge design?

[5] **Question:** Is it logistically feasible to conceal the randomisation order until one month before the start of the transition date? We need to book ATLS training slots in advance.

because it is an outcome of clinical and patient importance with very low missing data rates (1%) in our pilot study. We will also be able to compare our findings with previous research.

6.12.2 Secondary outcomes

- All cause mortality within 24 hours, 30 days, and three months of arrival at the emergency department. Data on this outcome will be collected from patient hospital records or by calling the patient or a patient representative.
- Quality of life within seven days of discharge, and at 30 days and three months of arrival at the emergency department, measured by the official and validated translations of the EQ5D3L. Data on this outcome will be collected in person if the patient is still in hospital, or by phone if the patient has been discharged.
- Poor functional outcome within seven days of discharge, and at 30 days and three months of arrival at the emergency department, assessed using the EQ5D3L domains of mobility, self-care, usual activities, and pain/discomfort, with poor functional outcome defined as being confined to bed, unable to bath or dress oneself, unable to perform usual activities, or having extreme pain or discomfort [^question:whodas];
- Return to work at 30 days and three months after arrival at the emergency department. Data on this outcome will be collected in person if the patient is still in hospital, or by phone if the patient has been discharged.
- Length of emergency department stay. Data on this outcome will be collected from patient hospital records.
- Length of hospital stay. Data on this outcome will be collected from patient hospital records.
- Intensive care unit admission. Data on this outcome will be collected from patient hospital records.
- Length of intensive care unit stay. Data on this outcome will be collected from patient hospital records.
- In-hospital pulmonary, septic, or renal complications [^question:complications].

[^question:whodas] **Question:** Should we measure functional outcome/disability with WHO-DAS instead?

[^question:complications] **Question:** Should we remove complications because they are too difficult to measure?

6.13 Handling of Adverse and Safety Events

6.13.1 Definitions

6.13.1.1 Adverse Event

Any untoward medical occurrence in a clinical trial subject and, which does not necessarily have a causal relationship with the treatment, can be an unfavorable and unintended sign (including an abnormal laboratory discovery), symptom or disease temporally associated with the inclusion in the trial, whether or not related to the trial.

6.13.1.2 Serious Adverse Event

Any untoward medical occurrence in a trial subject that:

- leads to death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- results in a congenital anomaly/malformation

6.13.1.3 Safety Event

Any unexpected serious complication that might occur as a consequence of the trial and that are not part of the natural history of trauma.

6.13.2 Reporting and Assessment of Adverse and Safety Events

In alignment with other current trials including critically ill patients[30], we will not collect adverse events or serious adverse events, because many of these events are expected in this patient population and we already collect many of these events, for example mortality and complications, outcomes as part of our outcomes.

We will only report safety events, if they are life-threatening, prolong hospitalisation or result in meaningful harm to the participant. We cannot pre-define a comprehensive list of events that can be considered safety events, but the reporting of such will have to be based on the intuition of the clinical research coordinators and local investigators. Examples of safety events could include missed injuries or missed investigations, which could be expected if certain injuries or investigations were identified or conducted more often during the standard care phase than during the intervention phase.

All potential safety events will be recorded in the CRF and reported to the trial management team within 24 hours of its occurrence. The trial management team will then assess if the event can be considered related to the trial or the intervention within 24 hours of it being reported. Events that are considered probably related will be reported immediately to the Data Safety Monitoring Board.

6.13.3 Follow up of Safety Events

All safety events should be followed up by the local investigator until they are fully evaluated.

6.14 Independent Data Safety Monitoring Committee

An independent Data Safety Monitoring Committee, comprising four external members, will review trial data for each batch, assessing data quality, completeness, cluster performance in recruitment and loss to follow-up rates, and external factors affecting trial validity, safety, or ethics. They will also review the results of interim analyses and review safety events reported by the trial management group. The Data Safety Monitoring Committee can at any time, based on its reviews, recommend to terminate the trial.[6]

6.15 Statistics

6.15.1 General principles

We will conduct all analysis by modified intention to treat. Clusters and observations within clusters will be considered exposed to the intervention after the date at which the cluster was scheduled to transition. All data will be included with the exception of the transition phases. We will not adjust for multiplicity of analyses because none of the secondary outcomes will be singularly more important. However, all secondary outcomes will be interpreted with due consideration for how all are affected by the intervention without putting any undue emphasis on a single outcome that might be statistically significant but where all others appear to have remained unchanged.

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[7]. Additional subgroup analyses will include age, sex, and clinical cohorts with blunt multisytem trauma, penetrating trauma, and severe isolated traumatic brain injury.

6.15.2 Analysis models

There are a number of requirements for the analysis model. Firstly, all analysis will consider the clustered nature of the design. Secondly, as the trial has only 30 clusters, it will be essential that the model allows for a correction due to the small number of clusters. Thirdly, as the design is a stepped-wedge study, we will adjust for temporal confounding using categorical

[6] **TODO** Identify four members of the independent Data Safety Monitoring committee.

[7] **Note:** Batches will not be based on regions because it will be logistically more feasible to include clusters from different regions in each batch.

effects for period of the study (month). Full details on how each of these will be undertaken, with justification is provided below[31].

For binary outcomes, a mixed effects binomial regression with a log-link will be used to estimate the relative risk; and a binomial model with identity link used to estimate the risk difference, with estimation using REML. In the case of non-convergence of the binomial model with a log-link, a Poisson model with robust standard errors will be fitted. If the binomial model with the identity link does not converge then only a relative risk will be reported. If neither the log or identify link converge we will use the logistic link and report odds ratios.

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. In a sensitivity analysis 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.

To this end we will additionally fit generalised linear mixed models (with same link functions and fixed effects as described above) to include a discrete time decay correlation structure including a random cluster effect with auto-regressive structure (AR(1)). To allow for the randomisation by batches, a different secular trend will be included for each batch (interaction between batch and period). For continuous, count and prevalence outcomes similar model-based approaches will be used.

6.15.3 Additional sensitivity analyses

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

6.15.4 Estimation and reporting of within cluster correlations

We will report time adjusted within-cluster correlations for all outcomes with 95% confidence intervals. We will report correlations from the different assumed correlation structures (so we will report intra-cluster correlations (ICC); within and between-period correlations; and within-period correlations and exponential decay). As well as reporting correlations we will additionally report all variance components. For all outcomes we will report correlations on the latent scale (i.e. proportions scale for binary outcomes) as is appropriate to inform future sample size calculations.

6.15.5 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 from 20% under standard care to 15% after ATLS® training. 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[32,33], and a CAC of 0.9 but considered sensitivity across the range 0.8-1.0, based on our pilot study and current guidance[34–36]. 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.

6.15.6 Interim analysis

There will be two interim analyses, one after the first batch has completed the trial and one after half of the batches have completed the trial. The primary purpose of the interim analyses will be to assess the safety of the intervention, and assess if there is a significant increase in the primary outcome after ATLS® training. The interim analyses will be conducted by the independent Data Safety Monitoring committee. The independent Data Safety Monitoring committee will use the Haybittle-Peto boundary to assess statistical significance, and will recommend stopping the trial if the p-value is less than 0.001. The secondary purpose of the interim analyses will be to assess the trial's feasibility and recommend stopping the trial if the trial is not feasible, for example if clusters fail to adhere to the randomisation schedule or if there are substantial missing data in outcomes. The final purpose of the interim analysis will be to assess if sample size calculations should be revised. The independent Data Safety Monitoring committee will not have access to the trial's data before the interim analyses.

6.16 Quality Control and Quality Assurance

There may be less stringent rules for low-intervention clinical trials (see cover page), e.g. limited monitoring requirements.[8]

6.17 Quality Assurance and Sponsor oversight

In this section, describe which quality assurance systems the trial will have to ensure and control the quality as well as the sponsor's methods for having oversight of the trial's quality. For example, communication plan, training of trial personnel, working manuals, meetings, central/local monitoring, audits, etc.

The sponsor's quality-related work must be based on a risk analysis of the trial as a whole: design, conduct, data collection, evaluation, reporting and archiving.

To enable monitoring and auditing, the protocol or other written agreement must specify that the investigators allow trial-related monitoring, auditing, and regulatory inspections by providing direct access to the CRF, subject's medical record and other source data and other trial-specific documentation. Similarly, this also must be apparent to the subjects in the Subject Information and Informed Consent Form.

The sponsor is responsible for the trial's monitoring plan, which should be based on the identified risks, follow-up of risks during the trial and timeliness of the monitoring plan.[9]

6.18 Monitoring

The minimum level for quality control is that the following can be verified:

- *that subjects exist*
- *that informed consent has been signed prior to execution of any trial-specific actions*
- *that subjects are included according to the protocol's inclusion and exclusion criteria*
- *that the trial's main parameters and safety reporting are handled correctly*

Other tasks for a monitor include verifying that the trial's essential documents are complete (according to chapter 8, ICH-GCP (E6(R2)).[10]

[8] **TODO TGI** Add a section on quality control.
[9] **TODO TGI** Add a section on quality assurance.
[10] **TODO TGI** Add a section on monitoring.

7 Deviations, serious breaches and other reporting obligations

The responsible investigator shall, without delay, report to the sponsor any serious breaches and deviations from the trial protocol, ICH-GCP and other regulations that significantly and directly affect, or with high likelihood could affect, the subjects' safety and integrity or the reliability and robustness of the data generated in the trial. The sponsor should assess the suspected serious breach and the consequences of deviations that have occurred. Minor deviations that do not affect subjects' integrity or safety, nor significantly affect the trial's scientific value, are documented in the trial documentation of the principal investigator and the sponsor and appropriate measures shall be taken. The deviations must be recorded in the clinical trial report.

8 Audits and inspections

Authorized representatives for the sponsor and Competent Authorities (CA) may carry out audits or inspections at the trial site, including source data verification. The investigator must ensure that all source documents are available for audits and inspections. The purpose of an audit or inspection is to systematically and independently review all trial-related activities and documents, to determine whether these activities were performed, registered, analyzed and reported correctly according to protocol, ICH- GCP and applicable regulations.

9 Ethics

9.1 Compliance to the protocol, ICH-GCP and regulations

The trial will be performed in compliance with this clinical trial protocol, the Declaration of Helsinki, ICH-GCP (Good Clinical Practice), and current national regulations governing this clinical trial. This is to ensure the safety and integrity of the trial subjects as well as the quality of the data collected.

9.2 Ethical review of the trial

The final protocol will be submitted for ethical review at all participating hospitals, where possible, as well as the Swedish Ethical Review Atuhortiy.

9.3 Procedure for obtaining informed consent

We will apply for a waiver of informed consent from the ethical review boards at the participating hospitals for collection of in-hospital data including outcomes that are considered routinly collected data. We do this because it will not be possible for patients to opt out from being subjected to the intervention, as the intervention is delivered at the cluster level and involves training physicians in trauma life support, and these physicians cannot be expected to temporarily forget their training. All patients will however be informed about the study and will be given the opportunity have their data deleted.

Clinical research coordinators will obtain informed consent from patients or a patient representative for out of hospital follow up and collection of data on quality of life, functional outcome, and return to work. The clinical research coordinators will approach patients or patient representatives for consent in person if a patient is screened during the clinical research coordinators working hours. For patients arriving outside of the clinical research coordinators working hours, the clinical research coordinators will approach patients or patient representatives for consent by phone.

9.4 Data protection

We will ensure that appropriate agreements and/or other appropriate protective measures are taken to ensure that the data processing is performed in accordance with the provisions of the relevant legislation, before any data transfer takes place.

In the study information provided to patient participants, they will be fully informed about how their trial data will be collected, used and disclosed. The study information and the informed consent form will explain how trial data are stored to maintain confidentiality in accordance with national data legislation[11]. All information processed by the sponsor will be pseudonymized.

The study information will also explain that for verification of the data, representatives delegated by the sponsor, as well as relevant authorities, may require access to parts of medical records or trial records that are relevant to the trial, including the patient participant's medical history.

10 Insurances

Here it should be explained how subjects are insured throughout the trial.[12]

[11] **TODO:** Describe data protection mechanisms, or cross-reference the section on "Collection, handling and archiving of data"

[12] **TODO TGI:** Please add information about insurance.

11 Substantial changes to the trial

Substantial changes to the signed clinical trial protocol are only possible through approved protocol amendments and by agreement between the sponsor and the principal investigator.

12 Collection, handling, and archiving of data

Clinical research coordinators will collect data using a paper based Case Record Form (CRF)[13], which is then transferred to an electronic CRF (eCRF). Paper-based CRFs will be securely stored on-site and archived for as long as required by local regulations, but at least 10 years. Access to the eCRF is provided using a Virtual Private Network with two-factor authentication[14]. Access is granted by the project PI or authorized delegates. Metadata will be publicly accessible via a persistent DOI, and anonymised data will be released upon project completion. The data management plan is published (https://doi.org/10.5281/zenodo.7748764).

12.1 Source data

The source data for each variable is given in Section 12.2. Whenever medical records are the source data, this includes imaging and lab reports. Whenever an interview is given as the source, the CRF will constitute the source data, as this is where the responses to questions will be recorded.

The local investigator must keep source documents for each patient participant in the trial. A document describing what has been classified as source data in the trial (source data reference document) should be included in the Investigator Site File (ISF)[15]. The investigator must ensure that all source documents are accessible for monitoring and other quality control activities.

Source data is further defined before trial start at each individual site and can, in cases where source data is not registered in another document, consist of the CRF. This should be decided in consultation with the monitor and clearly stated in the source data reference document.

Access to trial-related documentation, such as patient participants' medical records, CRFs, other source data and other trial documentation will be provided for monitoring and auditing purposes. Access to patient participants' medical records will require a confidentiality agreement to be signed by the person in charge of the medical records at the trial site and by the monitor and auditor, if applicable. Access will also be granted in the context of regulatory inspections.[16]

[13] **TODO:** Create a CRF template and attach.
[14] **TODO TGI:** Please check that this is correct.
[15] **TODO:** Create an ISF template.
[16] **TODO TGI:** Please check that this applies.

12.2 Variables

12.2.1 Baseline

- **Inclusion and exclusion criteria**, *Source:* Medical records
- **Age in years**, *Source:* Medical records/interview
- **Sex**, *Source:* Medical records/interview
- **Mechanism of injury** (Coded using the external causes codes in Chapter XX (20) of International Classification of Diseases - 10th Revision (ICD-10)), *Source:* Medical records/interview
- **Comorbidities** (Coded using Charlson Comorbidity Index), *Source:* Medical records/interview
- **Phone numbers to patient and patient representative**, *Source:* Medical records/interview

12.2.2 Pre-Hospital Data

- **Date and time of injury**, *Source:* Medical records/interview
- **Mode of transport to the participating centre**, *Source:* Medical records/interview
- **Referred to the participating centre from another centre**, *Source:* Medical records/interview

12.2.3 Emergency Department Data

- **Date and time of arrival to emergency department at the participating centre**, *Source:* Medical records/interview
- **First recorded systolic blood pressure**, *Source:* Medical records
- **First recorded diastolic blood pressure**, *Source:* Medical records
- **First recorded heart rate**, *Source:* Medical records
- **First recorded respiratory rate**, *Source:* Medical records
- **First recorded Glasgow Coma Scale score**, *Source:* Medical records
- **First recorded temperature**, *Source:* Medical records
- **First recorded oxygen saturation**, *Source:* Medical records
- **First creatinine**, *Source:* Medical records
- **Emergency department disposition**, *Source:* Medical records
- **Date and time of discharge from emergency department at the participating centre**, *Source:* Medical records/interview
- **Date and time of referral or transfer for admission at a higher level centre**, *Source:* Medical records/interview

12.2.4 Hospital Data

- **Date and time of admission to the participating centre**, *Source:* Medical records/interview
- **Type of admitting ward**, *Source:* Medical records
- **Date, time and type of any surgical procedure** (A surgical procedure is defined as any procedure performed in the operating room, interventional radiology suite, or at the bedside, requiring general or regional anesthesia, coded using), *Source:* Medical records
- **Date and time of any transfusion, type of blood product, and number of units transfused**, *Source:* Medical records
- **Date and time of intensive care unit admission and discharge**, *Source:* Medical records
- **Date and time of discharge from the participating centre, and the discharge destination**, *Source:* Medical records

12.2.5 Injury Data

- **Injury, the modality used to diagnose the injury, and the date and time when the injury was first registered** (Coded using the International Classification of Diseases - 10th Revision (ICD-10)), *Source:* Medical records

12.2.6 Outcomes

- **Pulmonary complication** (**Definition needed**), *Source:* Medical records
- **Septic complication** (**Definition needed**), *Source:* Medical records
- **Renal complication** (An increase in serum creatinine of at least 1.5 times compared to the first recorded creatinine, within 7 days of arrival to the participating centre, or the need for renal replacement theraphy), *Source:* Medical records
- **Date and time of death**, *Source:* Medical records/interview
- **Quality of life** (The EuroQol 5 Dimensions 3 Levels (EQ-5D-3L) questionnaire will be used to assess quality of life within 7 days of discharge, and at 30 and 90 days after arrival to the participating centre), *Source:* Interview
- **Disability** (The World Health Organization Disability Assessment Schedule (WHODAS) questionnaire will be used to assess disability within 7 days of discharge, and at 30 and 90 days after arrival to the participating centre), *Source:* Interview
- **Return to work** (Assessed at 30 and 90 days after arrival to the participating centre), *Source:* Interview

13 Trial Organization

More information will be added here

14 Funding

- Swedish Research Council (reg. no. 2023-03128)

15 Notification of trial completion, reporting, and publication

More information will be added here

16 References

1. GBD 2019 Diseases and Injuries Collaborators. Injuries—level 1 cause. *The Lancet* **396**, (2020).
2. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the global burden of disease study 2019. *The Lancet* **396**, 1204–1222 (2020).
3. Mohammad, A. *et al.* Educational and clinical impact of advanced trauma life support (ATLS) courses: A systematic review. *World J. Surg.* **38**, 322–329 (2013).
4. Jayaraman, S. *et al.* Advanced trauma life support training for hospital staff. *Cochrane Database Syst Rev* (2014).
5. Kadhum, M. *et al.* Are primary trauma care (PTC) courses beneficial in low- and middle-income countries - a systematic review. *Injury* **51**, 136–141 (2020).
6. Jin, J. *et al.* Effectiveness of quality improvement processes, interventions, and structure in trauma systems in low- and middle-income countries: A systematic review and meta-analysis. *World J. Surg.* **45**, 1982–1998 (2021).
7. Committee on Trauma. *Advanced trauma life support® student course manual.* (American College of Surgeons, 2018).
8. Rauf, R. *et al.* Changes in the temporal distribution of in-hospital mortality in severely injured patients—an analysis of the TraumaRegister DGU. *PLOS ONE* **14**, e0212095 (2019).
9. Roy, N. *et al.* Learning from 2523 trauma deaths in india- opportunities to prevent in-hospital deaths. *BMC Health Serv Res* **17**, (2017).

10. Callcut, R. A. *et al.* The why and how our trauma patients die: A prospective multicenter western trauma association study. *J Trauma.* **86**, 864–870 (2019).

11. Ghorbani, P. *et al.* Analysis of preventable deaths and errors in trauma care in a scandinavian trauma level-i centre. *Acta Anaesthesiol Scand* **62**, 1146–1153 (2018).

12. American College of Surgeons. *Resources for optimal care of the injured patient.* (American College of Surgeons, 2022).

13. Ali, J. *et al.* Demonstration of acquisition of trauma management skills by senior medical students completing the ATLS program. *J Trauma.* **38**, 687–691 (1995).

14. Ali, J. *et al.* Teaching effectiveness of the advanced trauma life support program as demonstrated by an objective structured clinical examination for practicing physicians. *World J. Surg.* **20**, 1121–1126 (1996).

15. Ali, J. *et al.* Comparison of performance of interns completing the old (1993) and new interactive (1997) advanced trauma life support courses. *J Trauma.* **46**, 80–86 (1999).

16. Vestrup, J. A. *et al.* Impact of advanced trauma life support training on early trauma management. *Am J Surg* **155**, 704–707 (1988).

17. Ariyanayagam, D. C. *et al.* The impact of the ATLS course on traffic accident mortality in trinidad and tobago. *West Indian Med J* **41**, 72–74 (1992).

18. Ali, J. *et al.* Trauma outcome improves following the advanced trauma life support program in a developing country. *J Trauma* **34**, 890–899 (1993).

19. Olson, C. J. *et al.* Influence of trauma system implementation on process of care delivered to seriously injured patients in rural trauma centers. *Surgery* **130**, 273–279 (2001).

20. Olden, G. D. J. van *et al.* Clinical impact of advanced trauma life support. *Am J Emerg Med* **22**, 522–525 (2004).

21. Wang, P. *et al.* Comparison of severe trauma care effect before and after advanced trauma life support training. *Chin J Traumatol* **13**, 341–344 (2010).

22. Drimousis, P. G. *et al.* Advanced trauma life support certified physicians in a non trauma system setting: Is it enough? *Resuscitation* **82**, 180–184 (2011).

23. Hashmi, Z. G. *et al.* Hospital-based trauma quality improvement initiatives. *J Trauma* **75**, 60–68 (2013).

24. Petroze, R. T. *et al.* Can focused trauma education initiatives reduce mortality or improve resource utilization in a low-resource setting? *World J. Surg.* **39**, 926–933 (2014).

25. Giovanni Bellanova, R. B., Francesco Buccelletti. How formative courses about damage control surgery and non-operative management improved outcome and survival in unstable politrauma patients in a mountain trauma center. *Annali italiani di chirurgia* **87**, 68–74 (2016).

26. Gerdin Wärnberg, M. *et al.* A pilot multicentre cluster randomised trial to compare the effect of trauma life support training programmes on patient and provider outcomes. *BMJ Open* **12**, e057504 (2022).

27. Hemming, K. *et al.* The stepped wedge cluster randomised trial: Rationale, design, analysis, and reporting. *BMJ* **350**, h391–h391 (2015).

28. Hemming, K. *et al.* Reflection on modern methods: When is a stepped-wedge cluster randomized trial a good study design choice? *Int J Epidemiol* **49**, 1043–1052 (2020).

29. Kasza, J. *et al.* The batched stepped wedge design: A design robust to delays in cluster recruitment. *Stat Med* **41**, 3627–3641 (2022).

30. Nielsen, Niklas. Sedation, Temperature and Pressure after Cardiac Arrest and Resuscitation – the STEPCARE trial. (2023).

31. Li, F. *et al.* Mixed-effects models for the design and analysis of stepped wedge cluster randomized trials: An overview. *Stat Methods Med Res* **30**, 612–639 (2020).

32. 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).

33. 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).

34. 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).

35. 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).

36. 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).