# Title page

## Title {1}

Effects of Advanced Trauma Life Support® Training Compared with Standard Care on Adult Trauma Patient Outcomes (ADVANCE TRAUMA): Study Protocol for a Stepped-Wedge Cluster Randomised Trial

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### Roles and contributions

SR, SF and PK prepared the protocol for publication, and drafted the first and subsequent manuscript versions. SR lead the preparation of this manuscript, under the supervision of MGW. AB, GB, DB, JB, SC, LFT, KH, VJ, MK, AM, RS, KDS and MGW designed the trial. MGW drafted the first and subsequent versions of the protocol. AB, GB, DB, JB, SC, LFT, KH, VJ, MK, AM, AO, RS and KDS provided input on the first and subsequent versions of the protocol. JK and JM provided input on later versions of the protocol and this manuscript, specifically related to the nested staircase design and the randomisation procedure respectively. All authors reviewed the manuscript.

# Abstract

## Background

Advanced Trauma Life Support® (ATLS®) is the most widely adopted trauma life support training worldwide, but there is no high-quality evidence that it improves patient outcomes. This trial aims to compare the effects of ATLS® training with standard care on outcomes in adult trauma patients.

## Methods

ADVANCE TRAUMA is a batched stepped-wedge cluster randomised controlled trial in India, where ATLS® is not routinely taught. The trial will be conducted in 30 clusters over six batches in secondary or tertiary hospitals. There will be five clusters in each batch, which will be randomised to one of five implementation sequences. One hospital will be randomised to each implementation sequence. All clusters will transition through three phases: first, a standard care phase; second, a one-month transition phase, during which the training is delivered; and finally, an intervention phase, for a total of 13 months. The implementation sequence will determine the duration of the standard care and intervention phases. The participants will be adult trauma patients above 15 years of age who presents to the emergency department of participating hospitals and are admitted or transferred to another hospital for admission. At least 4320 participants will be included in this trial.

## Discussion

This will be the first large-scale trial to provide robust evidence of the effectiveness of ATLS® since the programme was initiated in 1978. Regardless of the findings, this study will have important implications for trauma life support training globally. If ATLS® training improves patient outcomes, ways to promote its use and optimise its implementation, especially in low- and middle income countries such as India, should be explored. If patient outcomes do not improve, trauma life support training needs to change.

## Trial registration

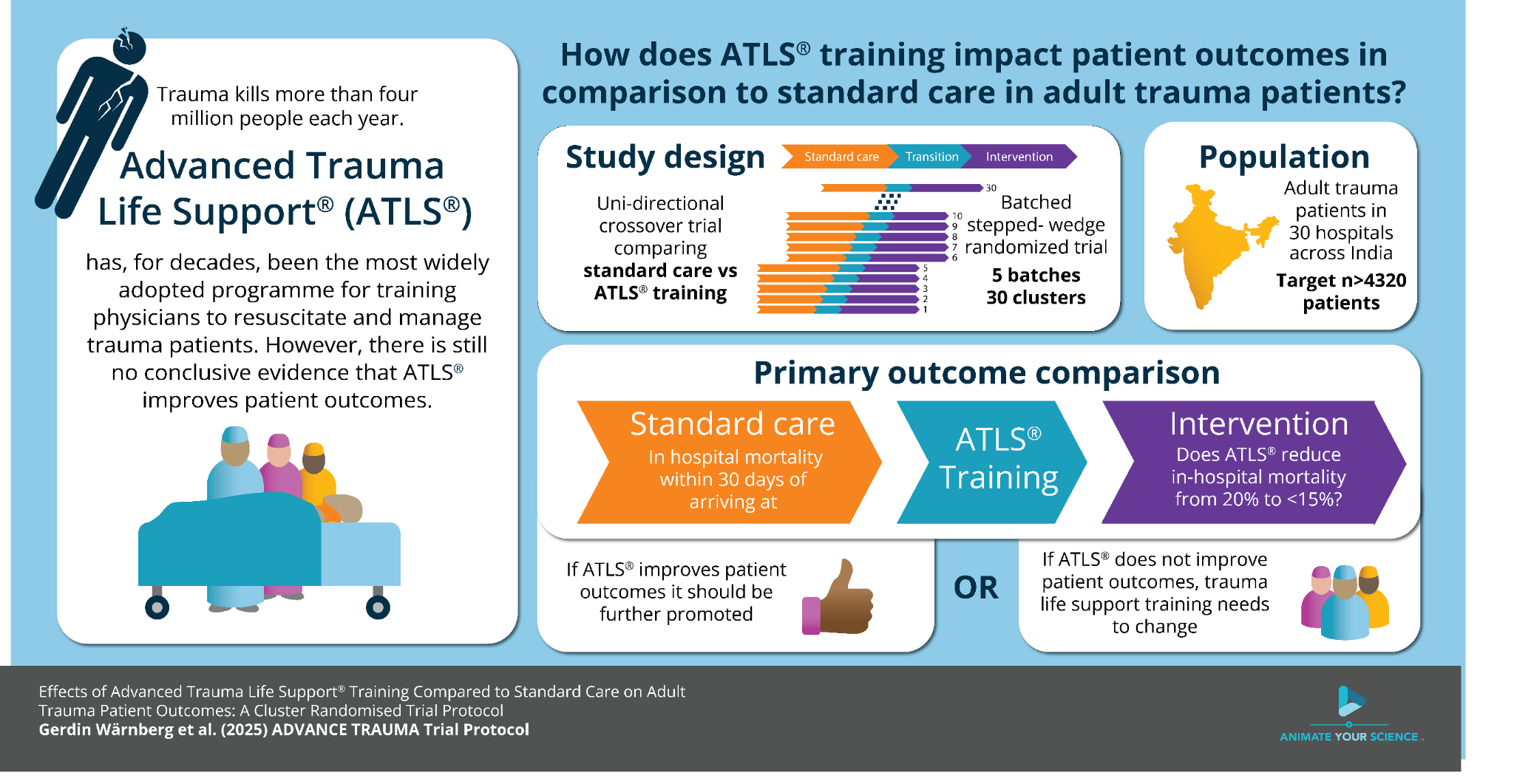
{2a} Clinical Trials Registry - India identifier: CTRI/2024/07/071336 (<https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=MTAwMzM1&Enc=44478&userName=>)

{2b} ClinicalTrials.gov identifier: NCT06321419 (<https://clinicaltrials.gov/study/NCT06321419>)

# Keywords

Advanced Trauma Life Support, [Traumatology,](https://meshb.nlm.nih.gov/record/ui?ui=D014194) [Life Support Care](https://meshb.nlm.nih.gov/record/ui?ui=D008020)

# Visual abstract



# Introduction

## Background and rationale {6a}

Each year, 4.3 million people die from trauma (1). Trauma is the largest cause of disability adjusted life years among people aged 10-24- and 25-49-years (2), and most deaths from trauma occur within the first 24-48 hours (3). Traumatic brain injury and exsanguination are the most common causes of trauma related deaths (4,5). Most preventable trauma deaths from trauma are caused by errors in clinical judgement during initial resuscitation or early care, including airway management and haemorrhage control, even when the deaths occur later during the hospital stay (4,6).

Several trauma life support training programmes have been developed to improve the early management of patients in hospitals by providing a structured framework for assessment and treatment (7–11). 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 (12). In the US and many other countries training in ATLS® is virtually mandatory for trauma care physicians (13). However, uptake in low- and middle-income countries (LMICs) has been slow, potentially due to high costs (9).

Three randomised studies show that ATLS® improves knowledge and clinical skills (14–16), but no randomised controlled trials or high-quality quasi-experimental trials indicate that ATLS® improves patient outcomes (7,8,10,11,17). We conducted an updated systematic review (unpublished), and estimated a pooled risk ratio of 0.76 (95% CI 0.57; 1.01) from 12 heterogeneous (I2 0.9) observational studies on the effect of ATLS on mortality (18–29). We also conducted a pilot cluster randomised controlled trial that showed that a full scale trial should be feasible (30,31), as well as semi-structured interviews that indicated high acceptability of our research and helped to identify important outcomes (32).

## Objectives {7}

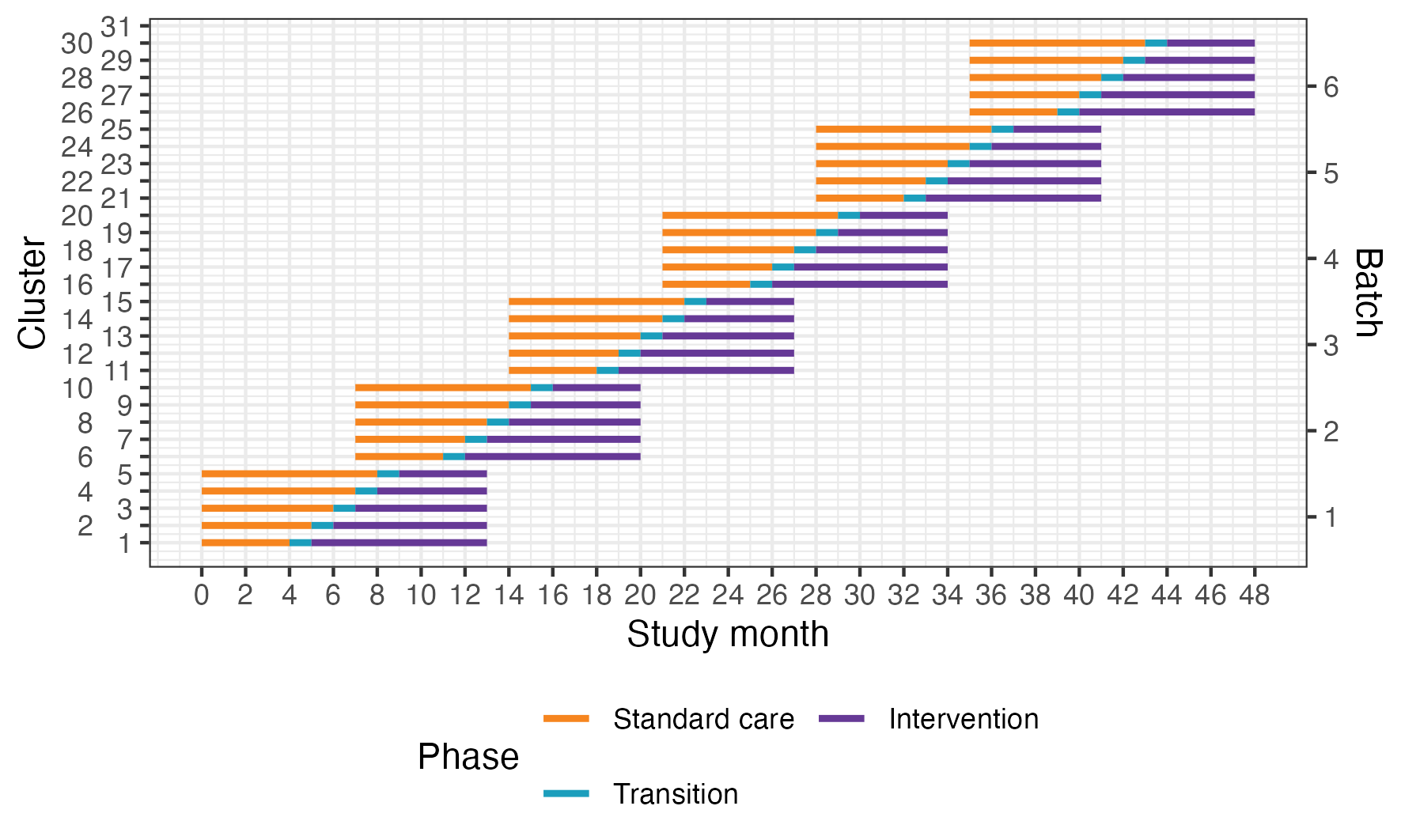
The aim of this trial is to compare the effects of ATLS® training with standard care on outcomes in adult trauma patients.

## Trial design {8}

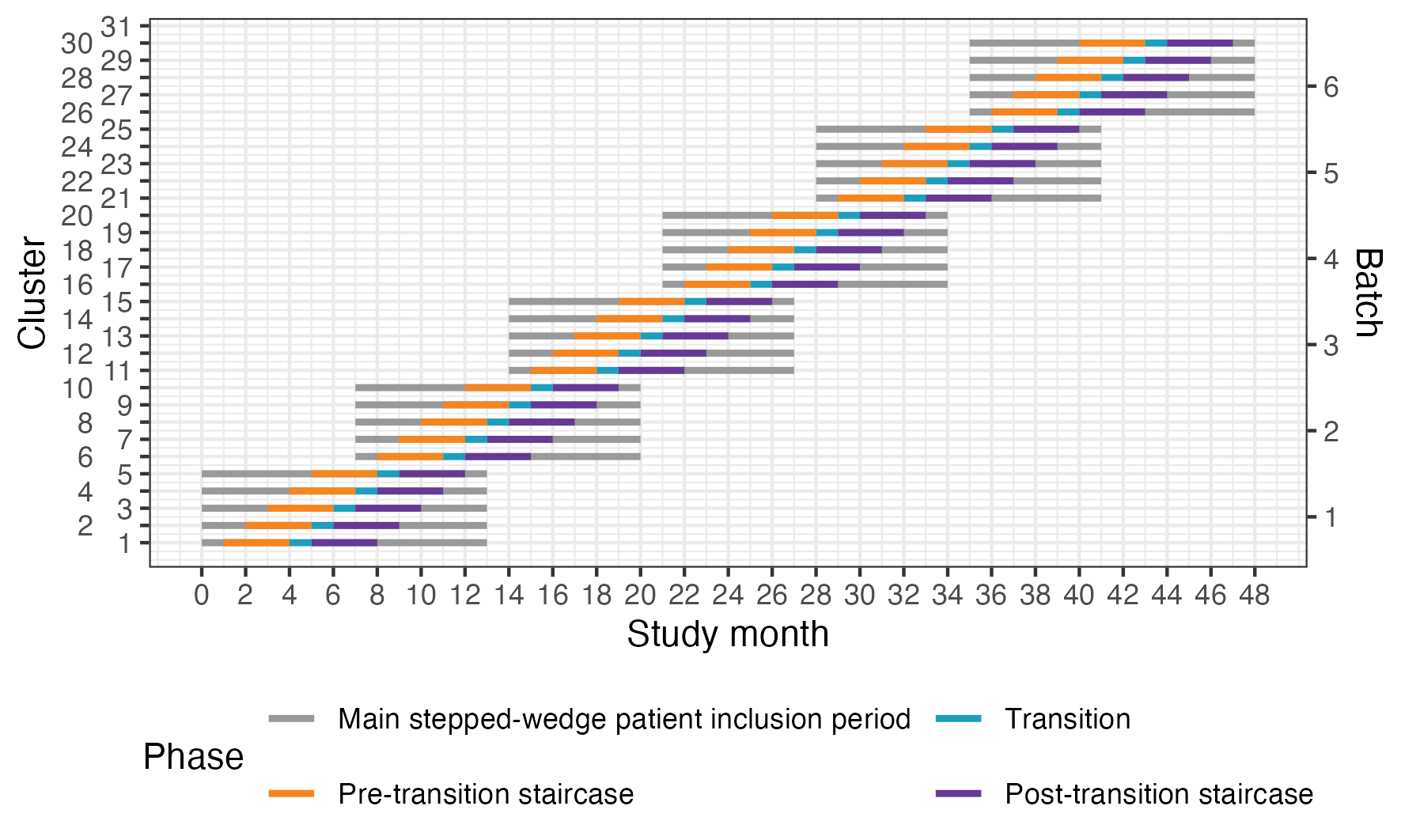
This is a batched stepped-wedge cluster randomised controlled trial in India (see Figure 1). The stepped-wedge trial is a unidirectional crossover trial, with a randomised time point when clusters cross-over from standard care to the intervention (33). In this trial, the unit of randomisation is the hospital: that is, the “clusters” randomised to the sequences of the stepped wedge design are the hospitals. Within each hospital, one or more units of physicians performing initial resuscitation of trauma patients in the emergency department may be trained. The number of units that will be trained in each hospital will depend on the sizes of these units and the volumes of patients the physicians attend. If more than one unit is trained in the same hospital, these are all considered to be part of the same cluster (i.e. hospital) for the purpose of randomisation.

We will include a total of 30 clusters in six batches, with five clusters in each batch. The clusters in each batch will be randomised to one of five implementation sequences, with one cluster randomised to each implementation sequence. All clusters will transition through three phases: first, a standard care phase; second, a transition phase lasting one month during which the ATLS® training will be delivered to the physicians; and finally, the intervention phase. The period of participant inclusion (within any cluster) will last for a total of 13 months. The duration of the standard care and intervention phases will be determined by the implementation sequence.

We will nest a staircase design within the main stepped-wedge design to measure a range of secondary outcomes (see Figure 2) (34). The staircase design will include a random subset of patients who present during the three months preceding and the three months following the transition phase.



**Figure 1:** 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.



**Figure 2:** Nested staircase design. The design includes a random subset of patients presenting during the three months preceding the transition phase, and the three months following the transition phase.

## Design justification

We use a cluster randomised design because the intervention cannot be randomised at the individual patient level. We use a 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 (35). 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 increase 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 (36). We nest a staircase design within the main design because some of the secondary outcomes will be considerably more labour intensive to collect than the primary outcome, and collecting these secondary outcomes for all patient participants would be unfeasible.

# Methods: participants, interventions, and outcomes

## Study setting {9}

The study setting includes 30 secondary or tertiary hospitals distributed across India. These hospitals will be divided into six batches, with each batch including five hospitals. Each hospital will include one or more units of physicians providing initial trauma care in the emergency department of tertiary hospitals in India. Included hospitals will include patient participants for 13 months.

## Eligibility criteria {10}

The eligibility criteria for this trial are on the cluster and patient participant levels.

### Cluster

We will compile a list of potentially eligible hospitals and then screen these by completing an initial hospital screening call, followed by an in-depth interview with hospitals fulfilling the eligibility criteria.

The inclusion criteria for participating hospitals are as follows::

* Admit or refer/transfer for admission at least 400 patients with trauma per year or 35 patients with trauma per month for at least the last six months;
* Provide surgical and orthopaedic emergency services around the clock;
* Have at most 25% of physicians providing initial trauma care trained in a formalised trauma life support training programme, like ATLS® or Primary Trauma Care (PTC).

The exclusion criteria for participating hospitals are as follows:

* Implement a formalised trauma life support training programme during the trial period.
* Plan to implement or implement other major interventions that affects trauma care during the trial period.

Within each included hospital, we will include one or more units of physicians providing initial trauma care in the emergency department. These units already exist in the hospitals and rotate through the emergency department on specific days of the week. The units must meet the following criteria:

* Admits or refers/transfers for admission at least 12 patients with trauma per month for at least the last six months;
* No more than 25% of physicians providing initial trauma care trained in a formalised trauma life support training programme.

### Patient participants

The inclusion criteria for the patient are as follows:

* At least 15 years of age;
* Trauma occuring less than 48 hours before arrival at the hospital;
* Presenting to the emergency department of the participating hospitals, with a history of trauma defined as any of the reasons listed in the International Classification of Diseases chapter 20 as the reason for presenting;
* Admitted, or died between arrival at the hospital and admission, or referred/ transferred from the emergency department of a participating hospital to another hospital for admission; and
* Managed by a participating unit in the emergency department.

The exclusion criteria for the patient participants are as follows:

* Presenting with isolated closed extremity fracture;
* Admitted directly to a ward without being seen by a physician in the emergency department.

## Who will obtain informed consent or assent? {26a, 26b}

The ATLS ® intervention will be given to the physicians at the cluster level. It is unreasonable to expect these physicians to temporarily disregard their training. Therefore, for this study, consent will refer to consent for data collection as the patient participants cannot opt out of the intervention.

Participants will be included in this trial with the following modes of consent:

1. Opt-out consent for routinely recorded data and measurement of adherence to ATLS® principles. Consent for the collection of routinely recorded data, either through interviews or by extracting information from medical records, as well as for the measurement of adherence to ATLS® principles, will be presumed unless explicitly declined. This approach is justified because the trial is considered to pose minimal risk and because data collection will be noninvasive. Additionally, obtaining consent specifically for the measurement of adherence to ATLS® principles could interfere with the provision of care and cause undue stress for patients and their representatives. Participants, or their legally authorised representatives, will be provided with written information about the study upon their arrival at the hospital.
2. Opt-in consent and assent for nonroutinely recorded data. Informed consent for nonroutinely recorded data will be actively sought from participants or their legally authorised representative. For participants who are between 15 and 18 years of age we will obtain both the assent of the participant as well as the consent of their guardian or legally authorized representative. Participants and their representatives will be approached after admission. Consent and assent will be written for participants who are admitted to the hospital and verbal for participants who are transferred or discharged before the clinical research coordinators have had an opportunity to approach them. Verbal consent will be audio recorded.
3. Waiver of informed consent for participants who are unconscious or otherwise unable to provide consent and who do not have a legally authorised representative. This group represents the most severely injured participants, who must be included to make the trial representative of the entire population of trauma participants. Participants who regain consciousness will be informed about the study and asked to consent to the collection of nonroutinely recorded data.

# Intervention

## Explanation of the choice of comparators {6b}

The control will be standard care, meaning no formal trauma life support training. Standard care varies across hospitals in India, but trauma patients are initially managed by casualty medical oﬀicers, surgical residents, or emergency medicine residents. Thee are mainly first- or second-year residents who resuscitate patients, perform interventions and refer patients for imaging or other investigations.

## Intervention description {11a}

The intervention in this study is the ATLS® training, which is a proprietary 2.5-day course that teaches 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 initial treatment and resuscitation, triage and interfacility transfers. Learning is based on practical scenario-driven skill stations and lectures and includes a final performance proficiency evaluation (12).

We will train physicians who 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. Physicians will be trained in an accredited ATLS® training facility in India. The training will occur during the transition phase in each cluster. Our experience from the pilot study is that study sites adhere to the training slot allotted to them through the trial; therefore, we judge the risk of clusters implementing ATLS ® before their randomised implementation sequence to be very low.

We will train the number of units of physicians needed to reach the required patient sample size. We estimate that this will require training an average of ten physicians per hospital, which should be mean that we can train one to two units per hospital on average. This is possible because many hospitals in India organise physician staﬀing of their emergency departments in units, and physicians in the same unit work together in the emergency department on the same days of the week. These physicians’ duties may change into another department as per the residency programme. Therefore, we will collect data only on the days when these units work. The units selected from each hospital will be a convenience sample of all eligible units in those hospitals. We will also assess adherence to ATLS principles before and after implementing ATLS training.

## Procedures to monitor adherence to intervention {11c}

Adherence to ATLS is one of the secondary outcomes and will be monitored using a checklist that covers the key steps of the ATLS® primary survey (see Table 1).

## Concomitant care and interventions {11d}

Other than the implementation of another formalised trauma life support training programme or other major interventions to change the care of trauma patients as specified in the exclusion criteria, concomitant use of other medications and treatments may be provided at the discretion of the investigators and will not be considered an exclusion criterion.

## Provisions for posttrial care {30}

Provisions for posttrial care are not relevant in this study as the intervention is provided to the trauma physicians.

# Outcomes {12}

The primary outcome will be in-hospital mortality within 30 days of arrival at the emergency department. There are several secondary outcomes (**see Table 1.**)

**Table 1**. Primary and secondary outcomes.

|  |  |  |
| --- | --- | --- |
| Outcome | Source of data | Mode of collection |
| Primary outcome | |  |
| In-hospital mortality within 30 days of arrival at the emergency department. | Patient hospital records. If the patient has been transferred to another hospital, the clinical research coordinators will collect data on this outcome by calling the patient or the patient’s representative, or by contacting the hospital to which the patient was transferred. Data on this outcome will be collected continuously during the trial. | Main stepped-wedge design. Collected for all patients. |
| Secondary outcome | |  |
| All-cause mortality within 24 hours, 30 days and 3 months after arrival at the emergency department. | Patient hospital records or telephone follow up. If the patient has been transferred to another hospital or discharged, the clinical research coordinators will collect data on this outcome by calling the patient or a patient representative, or by contacting the hospital to which the patient was transferred. Data on this outcome will be collected continuously during the trial. | Main stepped-wedge design. Collected for all patients. |
| Length of emergency department stay | Data on this outcome will be collected from patient hospital records. | Main stepped-wedge design. Collected for all patients. |
| Length of hospital stay. | Data on this outcome will be collected from patient hospital records. | Main stepped-wedge design. Collected for all patients. |
| Intensive care unit admission. | Data on this outcome will be collected from patient hospital records. | Main stepped-wedge design. Collected for all patients. |
| Length of intensive care unit stay. | Data on this outcome will be collected from patient hospital records. | Main stepped-wedge design. Collected for all patients. |
| 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. | Main stepped-wedge design. Collected for all patients. |
| Adherence to ATLS® principles during initial patient resuscitation, up to one hour after the physician has first seen the patient. | This assessment will be performed using a 14-item checklist covering the key steps of the ATLS® primary survey, based on previous work on ATLS® adherence (31). We will consider completion of all 14 steps as 100% adherence. The clinical research coordinators will collect this data by observe the care being delivered to patients and will be trained by the trial team to do this, prior to the start of the trial. | Nested staircase design. Collected for a random subset of patients. |
| 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. | Nested staircase design. Collected for a random subset of patients. |
| Disability within seven days of discharge, and at 30 days and three months of arrival at the emergency department, assessed using the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0). | 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. | Nested staircase design. Collected for a random subset of patients. |

# Participant timeline {13}

The patient participants will be adult trauma patients who present to the emergency departments of the participating hospitals and are admitted or transferred for admission. Participants are screened by the clinical research coordinators and all participants who meet the eligibility criteria will be included in the study. The participant’s baseline and subsequent data will be collected as per Table 2.

**Table 2: Schedule of assessment**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Procedures | Screening | Consenting | Initial assessment | In-hospital care |
| Eligibility criteria | √ |  |  |  |
| Study information 1 |  | √ |  |  |
| Informed consent1 |  | √ |  |  |
| Baseline data collection |  |  | √ |  |
| Prehospital data collection |  |  | √ |  |
| ATLS adherence2 |  |  | √ |  |
| ED data collection3 |  |  | √ |  |
| Hospital data collection |  |  |  | √ |
| Surgery data collection |  |  |  | √ |
| Imaging data collection |  |  |  | √ |
| Transfusion data collection |  |  |  | √ |
| Injury data collection |  |  |  | √ |
| Mortality data collection |  |  |  | √ |
| Assessment of safety events |  |  |  | √ |

1Clinical research coordinators will inform patient participants about the study, including their right to withdraw their data from the study at any time, and will approach them in person or by telephone for informed consent for the collection of non-routinely recorded.

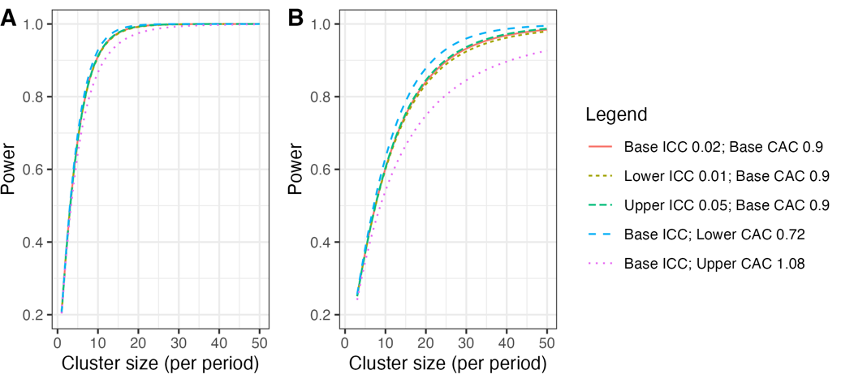
2ATLS adherence will be assessed by observing the care provided to a random sample of patient participants.

3Emergency department

# Sample size {14}

## Main stepped wedge design and primary outcome

With 30 clusters across 6 batches and a total participant sample size of 4320, our study has ~90% power across different combinations of cluster autocorrelations (CACs) and intracluster correlations (ICCs) 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 3) (37). This effect is a conservative estimate. The reduction equals a risk ratio of 0.75, which would be clinically important as well as consistent with our pilot study and updated systematic review. We allow for the clustered design, incorporated the one month transition period, and assumed: a discrete time decay correlation structure, an ICC of 0.02 (but considered sensitivity across the 0.01-0.05 range) and a CAC of 0.9 (but considered sensitivity across the 0.8-1.0 range), based on our pilot study and current guidance (38–41). 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, but allowed for substantial variations in cluster sizes, on the basis of our previous work.



**Figure 3:** Power curves for different combinations of cluster autocorrelations (CACs) and intra-cluster correlations (ICCs). A) 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) 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 approximately 30 observations to achieve 90% power under most combinations of CACs and ICCs.

## Nested staircase design and secondary outcomes

The secondary outcomes that will be measured using the nested staircase design are adherence to ATLS® principles during initial patient resuscitation, quality of life, and disability. We will not include any multiplicity adjustment as these are intended to be hypothesis driving only. The expecteds effect of the intervention on each of these outcomes are an improvement in adherence from 50% during standard care to 70% after training (42), an increase in EQ5D5L health status from 70 during care to 75 after training (43), and a decrease in disability from a baseline value of 25 during standard care to 22.5 after training (44). For quality of life and disability, these effects correspond to standardised effect sizes, expressed as Cohen's d of 0.5. With a total of 30 clusters, six per sequence, for a discrete time decay correlation structure, with ICCs of 0.01 to 0.15 and a CAC of 0.8, there is >80% power to detect these effects by including four patients in each cluster in each period. To account for loss to follow-up, we will include at least six patients per cluster per month. These patients constitute a random subset of patients included during the staircase months. The random subset will be selected using simple random sampling at the shift level, meaning that the timing of the clinical research coordinator's shift will be randomised to cover approximately eight hours during the morning, afternoon, or night shift. Adherence to ATLS® principles, quality of life, and disability will be measured for all patients included during these shifts. In each hospital, the number of shifts that will be randomised will be determined by the volume of patients included during the months preceding the staircase months.

# Recruitment {15}

Participant data collection will include all participants who meets the eligibility criteria. These participants will be adult trauma patients who present to the emergency department of a participating hospital. Participants cannot opt out of the intervention because it is implemented at the cluster level and involves training physicians in ATLS®, and it is unreasonable to expect these physicians to temporarily disregard their training. However, patient participants can choose to withdraw their consent for the collection of non-routinely recorded data at any time before the final analysis. If patients withdraw their consent for the data collection no further data collection will be performed, including follow-up data. Participants can also choose to remove the previously collected data in the trial at any time before the final analysis of the data. Withdrawal of consent or removal of data from the trial will not affect patients’ care in any way. If a participant withdraws consent, follow-up will be performed according to the participating hospital’s routine. We will document and report total numbers of withdrawals (by cluster and period).

# Assignment of interventions: allocation

## Sequence generation {16a}

Clusters will be assigned to batches as they are found to be eligible and receive ethical approval. We will randomise the clusters within each batch to the different intervention implementation sequences within that batch (36). The randomisation will be balanced within each batch on cluster size, defined as the monthly volume of eligible patient participants, using covariate constrained randomisation. Cluster sizes are expected to vary from 12 and to 20 patients per month, based on our previous experiences.

## Allocation concealment mechanism {16b}

The randomisation will be concealed for as long as it is logistically possible, considering that arrangements for sending physicians to ATLS® training must be made in advance.

# Assignment of interventions: blinding

## Blinding (masking) {17a}

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

## Procedure for unblinding if needed {17b}

This is an open label trial hence, unblinding procedures are not required.

# Data collection and management

## Data collection methods {18a, 18b}

Data collection will be performed via a paper based case record form (CRF), which will then be transferred to an electronic CRF (eCRF) on REDCap (45,46). Site investigators will 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) will be included in the Investigator Site File (ISF). Data will be registered, managed, and stored in a manner that enables correct reporting, interpretation, and verification. All documentation will be stored securely and retained according to regulatory requirements. The complete Trial Master File, as well as source documents, will be archived for at least 10 years after the trial is completed. Source data in the medical records system are stored and archived in accordance with Indian national regulations. Metadata will be publicly accessible via a persistent DOI, and anonymized data will be released upon project completion.

## Data management {19}

Data entry will be performed in REDCap. The George Institute India will be the coordinating center in India. It will be the responsibility of the George Institute to train site investigators and site staff before the trial about the documentation requirements and data collection procedures. Data management will be performed through ongoing quality metrics assessment, review of missing data and outliers, and documentation in the investigator site file. Study-related documents will be stored securely and retained according to regulatory requirements. Data management will strictly follow ICH GCP principles and Indian regulations. 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 will also be granted in the context of regulatory inspections.

## Confidentiality {27}

All data will be handled according to the Indian Council of Medical Research’s guidelines and standard operating procedures of the George Institute for Global Health India on data security and protection. Trial data will be stored and shared via the trial electronic CRF (eCRF) throughout the trial. The eCRF will be accessible via two-factor authentication, and the data will be held on a secure server. All investigators and trial site staff involved in this trial must comply with the requirements of the ICMR guidelines on data security and protection.

# Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

No biological specimens will be collected in this trial.

# Statistical methods

## Statistical methods for primary and secondary outcomes {20a}

The primary analysis set will include all observations within clusters with available data and irrespective of the receipt of the intervention. Clusters and observations within clusters will be considered exposed to the intervention after the date at which the cluster was scheduled for 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 the way all are affected by the intervention without undue emphasis on a single outcome that might be statistically significant when all others appear to have remained unchanged.

We have several requirements for the analysis model. First, all analyses will consider the clustered nature of the design. Second, as the trial has only 30 clusters, it will be essential for the model to allow for correction due to the small number of clusters. Third, as the design is a stepped-wedge study, we will adjust for temporal confounding using categorical effects for the period of the study (one month) (47).

In the case of binary outcomes, a mixed effects binomial regression with a logit link will be used to estimate the odds ratio, and a binomial model with identity link will be used to estimate the risk difference. These models will be fitted using residual pseudo-likelihood estimation based on linearisation with subject-specific expansion (RSPL). If the binomial model with the identity link does not converge then only an 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 as a random cluster and random cluster by period effect. To correct potential inflation of the type I error rate due to the small number of clusters, a correction for a small number of clusters will be applied. The correction that will be selected will be based on the best evidence that is available closer to the time, which may differ for the outcomes collected via the complete and incomplete designs. We will use a two-sided significance level of 5% and estimate 95% confidence intervals.

## Interim analyses {21b}

There will be one interim analysis after half of the batches have completed the trial. The interim analysis will be assessed by the joint Trial Steering and Data Monitoring Committee. The purposes of this interim analysis will be to assess the trial's feasibility and recommend that the trial be stopped if it is not feasible (e.g. if hospitals fail to adhere to the randomisation schedule or if there are substantial missing data in outcomes), and to compare characteristics across intervention conditions to monitor for differential recruitment/ascertainment between the intervention and control groups.

## Method for additional analyses (e.g., subgroup and adjusted analyses) {20b}

### Sensitivity analyses

We will conduct a sensitivity analysis to explore whether models with more complicated correlation structures are better fits to the data. These models are not our primary analysis models as there is limited understanding of when such models will converge and how to choose between the various correlation structures that may be plausible. To this end we will additionally fit generalised linear mixed models (with the same link functions and fixed effects described above) to include a discrete time decay correlation structure that includes a random cluster effect with an auto-regressive structure (AR (1)).

To explore whether 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 whether the results are sensitive to the assumption of no intervention by cluster interaction. A fully adjusted covariate analysis will adjust for a set of prespecified individual-level covariates of known prognostic importance.

### Additional analyses including subgroup analyses

The primary subgroup analyses will be based on geographical region because demonstrating the consistency of any effect across multiple regions will improve the generalisability of the results (4). The number of regions will depend on how clusters are distributed across states in India. Additional subgroup analyses will include age across the groups such as older adolescents (15-19 years), young adults (20-24 years), adults (25-59 years), and older adults (60 years and older) (48); sex; and the clinical cohorts blunt multisystem trauma, penetrating trauma, and severe isolated traumatic brain injury (49).

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 consider different lag effects (i.e., 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 (i.e., the effect of the intervention starts to decrease – or fade). This type of analysis attempts to disentangle the effect of having differing lengths of exposure to the intervention.

## Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

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%, we will perform a complete case analysis. If the percentage of missing data for the primary outcome is 10% or more, we will handle missing data depending on the missing data mechanism. If the data are missing at random (MAR), we will perform multiple imputation 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. If there is evidence that the data are missing not at random (MNAR), we will explore the impact of this assumption using a sensitivity analysis (e.g., pattern mixture models or selection models) to assess how robust our findings are to different assumptions about the missing data mechanism. Additionally, we will perform diagnostic checks after multiple imputation to ensure the quality of the imputation process, including comparing distributions of observed and imputed data and checking convergence.

## Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The full protocol and statistical code will be publicly available. A deidentified anonymous dataset will also be publicly available.

# Oversight and monitoring

## Composition of the coordinating centre and trial steering committee {5d}

The trial management and oversight are governed by three trial committees and groups: the Trial Team (TT), the Trial Management Group (TMG), the joint Trial Steering and Data Monitoring Committee (SDMC). The TT is responsible for running the trial operations on a day-to-day basis, maintaining trial databases, randomising clusters, ensuring complete and correct data, and preparing reports for meetings (including those of the TMG, and the SDMC). The TT will also address research governance and regulatory matters wherever needed. The TMG will be responsible for managing the trial, including its clinical and practical aspects as well as technical aspects and any safety issues related to the trial participants. In addition, the TMG will be also responsible for providing inputs to the SDMC meetings.

## Composition of the data monitoring committee, its role, and reporting structure {21a}

In this trial a SDMC will be used. The SDMC’s responsibility is to oversee and safeguard the trial and the trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall progress of the trial. The SDMC also receives and reviews information on the accruing data of this trial and provides advice on the trial to the TMG. The relationship between the groups is briefly described in Figure 4. Details of the composition, roles, and meeting frequency of TT, TMG and SDMC are tabulated in the Table 3.



**Figure 4:** Trial organisation overview.

## Adverse event reporting and harms {22}

In line with other current trials that include critically ill patients (50), we will not collect adverse events or serious adverse events, because many of these events are expected in this patient population. We already collect many of these events, such as mortality, 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. It is difficult to predefine a comprehensive list of events that can be considered safety events, but we will actively assess the presence of the following safety events:

* Prolonged mechanical ventilation (> 7 days)
* Initiation of renal replacement therapy
* Prolonged (> 2 days) or renewed (restarting after at least 2 days) use of vasopressors such as norepinephrine or vasopressin

These are considered safety events because they may suggest pulmonary, renal, septic or bleeding complications, and an increase in their occurrence following ATLS® training may indicate that the intervention is harmful. These events must therefore be tracked during the standard care phase as well as the intervention phase. However, these events will be considered indicative of harm related to the intervention only if they occurr more often during the intervention phase than during the standard care phase. In addition, safety reports other than those mentioned above will be collected. These events will be identified during the trial, and the reporting of these safety events will be based on the clinical judgement of the site investigators. Examples of safety events may include missed injuries or missed investigations, which may be suspected if certain injuries or investigations were identified or conducted more often during the standard care phase than during the intervention phase.

All 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 reporting. Events that are probably related will be reported immediately to the joint SDMC. All safety events will be followed up by the local investigator until they are fully evaluated. In addition, site investigators will report safety events based on the local ethics committee as per the Indian guidelines.

## Frequency and plans for auditing trial conduct {23}

Authorised representatives for the sponsor and Competent Authorities (CA) may conduct 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 audit or inspection will ensure that all study-related activities are performed, registered, analysed and reported correctly and according to the protocol, ICH-GCP and national regulations. These audits will be perfomed to systematically and independently review all trial-related activities and documents.

## Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

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

## Dissemination plans {31a}

The trial will be reported to the funders within a year of completion. The results of the trial will also be prepared as manuscripts for publication. The authorship of the trial manuscripts will be based on the International Committee of Medical Journal Editors (ICMJE) criteria (51):

* Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
* Drafting the work or reviewing it critically for important intellectual content; AND
* Final approval of the version to be published; AND
* Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work completed, an author should be able to identify which coauthors are responsible for other specific parts of the work. In addition, authors should have confidence in the integrity of the contributions of their coauthors. The most recent version of the ICMJE criteria will be followed. We will also use the ICMJE criteria for nonauthor contributorship. Before work on a trial manuscript is initiated, a writing group will be formed and first and last authors will be designated. This writing group will be formed by discussion in the TMG.

# Discussion

This will be the first large scale trial to provide robust evidence of the effectiveness of ATLS® since the programme was initiated in 1978. Regardless of the findings, this study will have important implications for trauma life support training globally. If ATLS® training improves patient outcomes, ways to promote its use and optimise its implementation, especially in low- and middle income countries such as India, should be explored. If patient outcomes do not improve, then trauma life support training needs to change.

# Trial status

The most updated protocol version is Version 1.4.0, 2025-04-30.

Necessary approvals have been obtained. The trial and the first batch of five hospitals began including patient participants in February 2025. The second batch of five hospitals will begin in September 2025.

**Table 4: The composition, roles and responsibilities and the meeting frequencies of the Advance Trauma Study.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Composition** | **Roles & Responsibilities** | **Meeting Frequency** |
| The George Institute of Global Health | * Prof Vivekanand Jha * Nobhojit Roy * Abhinav Bassi * Samriddhi Ranjan * Prashant Kharat | As the coordinating center in India, the George Institute, India will ensure proper conduct of the trial through quality control measures including on-site training of personnel, standard operating procedures, assessment of ongoing quality metrics, and review of missing data and outliers. This will also include maintenance of the Trial Master File (TMF) and Investigator Site File (ISF) at the site level.  The institute will be responsible for data security and protection. The institute will also be responsible for appropriate insurance for the duration of the study to cover claims for compensation by participants arising from their participation in the trial in India. |  |
| Trial Team (TT) | * Martin Gerdin Wärnberg * Monty Khajanchi * Abhinav Bassi * Prashant Kharat * Samriddhi Ranjan * Bijini Bahuleyan * Manoj Soni | Run the trial on a day-to-day basis, maintains trial databases, randomises clusters and ensures complete and correct data, prepares reports for meetings (including those of the TMG and SDMC) and deals with research governance and, if needed, regulatory matters. | Weekly |
| Trial Management Goup (TMG) | * Anurag Alok * Li Felländer-Tsai * Debojit Basak * Shamita Chatterjee * G D Bakhshi * Karla Hemming * K D Soni * Nobhojit Roy * Vivekanand Jha * Rajdeep Singh * Martin Gerdin Wärnberg * Johanna Berg * Monty Khajanchi * Abhinav Bassi * Prashant Kharat * Samriddhi Ranjan | Manages the trial, including its clinical and practical aspects. Includes members with broad expertise appropriate to the trial. The TMG is chaired by the principal investigator. | Monthly to every six months. |
| Trial Steering  and Data Monitoring Committee (SDMC) | * Ganesan Karthikeyan: Chair, Independent Member * Richard Hooper: Independent Member, Statistician Kathryn Chu (Independent Member, Clinical expert) * Elamurugan TP: Independent Member, Clinical expert * Sai Kulkarni: Independent Member, Lay-person representative) | The SDMC’s responsibility is to oversee and safeguard the trial and the trial participants, monitor the main outcome measures including safety and eﬀicacy, and monitor the overall process of the trial. The SDMC also receives and reviews information on the progress and accruing data of this trial and provide advice on the trial to the Trial Management Group (TMG). The specific roles of the SDMC are detailed below:  **Expert supervision and monitoring**  • Providing expert supervision of the trial.  • Monitoring recruitment figures, follow-up rates, and losses to follow-up.  • Monitoring compliance with the protocol by investigators.  • Assessing data quality, including completeness, and encouraging the collection of  high-quality data.  • Overseeing the completion of CRFs and advising on TMG’s future strategies for  satisfactory completion.  • Reviewing interim analyses including main outcomes and safety data.  • Assessing the impact and relevance of external evidence.  • Monitoring sample size assumptions, preferably with regards to:  – a priori assumptions about the control arm outcome; and/or  – emerging differences in clinically relevant subgroups.  **Advising and approving changes**  • Sanctioning any changes to the protocol proposed by the TMG (e.g., to design,  inclusion criteria, trial endpoints, or sample size).  • Approving TMG’s proposals for new sub studies.  • Suggesting additional data analyses if necessary.  **Decision making on trial continuation**  • Deciding whether to recommend that the trial continues to recruit participants or  whether recruitment should be terminated for everyone or for some treatment  groups and/or some participant subgroups.  • Deciding whether trial follow-up should be stopped earlier.  **Oversight of trial completion and findings**  • Supervising the prompt disclosure of trial findings.  • Providing input on the policy for publication.  • Approving and giving feedback on the main trial manuscript.  **Confidentiality and appropriateness**  • Maintaining confidentiality of all trial information that is not in the public domain.  • Monitoring the continuing appropriateness of patient information. |  |

# List of abbreviations

***ATLS:*** Advance Trauma Life Support

***CRF:*** Case Record Form

***ISF:*** Investigator Site File

***SAE:*** Serious adverse event

***TMF:*** Trial Master File

***TMG:*** Trial management group

***TT:*** Trial team

***SDMC:*** Trial Steering and Data Monitoring Committee

# Declarations

## Ethics approval and consent to participate {24}

Ethics approval has been obtained from The George Institute Ethics Committee (ECR/272/Indt/DL/2017), all hospitals in the first batch, and the Swedish Ethical Review Authority (2024-07547-01)

## Consent for publication {32}

This manuscript does not contain individual personal data from patients.

## Competing interests {28}

Several of the contributors are active instructors of ATLS® and/or other trauma life support training programmes.

## Availability of data and materials {29}

The full protocol and statistical code will be publicly available. A deidentified anonymous dataset will also be publicly available.

## Funding {4}

The study is funded by the Swedish Research Council (reg. no. 2023-03128) and Laerdal Foundation (reg. no. 2023-0297). However, the funding for this study is partial, and additional funding will be secured during the course of the study. If funding is not secured, the study will be stopped, which will likely result in an underpowered study. However, the intervention in this case is the standard of care in many countries and data collection is considered to carry minimal risk. The risk of harm to participants is minimal and there is potentially a direct benefit to the participants who receive the intervention. Therefore, the benefit-risk ratio is considered favourable, even if the study is underpowered.

## Authors' contributions

SR, SF and PK prepared the protocol for publication, and drafted the first and subsequent manuscript versions. SR lead the preparation of this manuscript, under the supervision of MGW. AB, GB, DB, JB, SC, LFT, KH, VJ, MK, AM, RS, KDS and MGW designed the trial. MGW drafted the first and subsequent versions of the protocol. AB, GB, DB, JB, SC, LFT, KH, VJ, MK, AM, AO, RS and KDS provided input on the first and subsequent versions of the protocol. JK and JM provided input on later versions of the protocol and this manuscript, specifically related to the nested staircase design and the randomisation procedure respectively. All authors reviewed the manuscript.

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