

Clinical Trial Protocol

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

Table of contents

1	Roles and Contact information	4
2	List of used acronyms and abbreviations	5
3	Synopsis	7
4	Background and rationale	8
4.1	Updated systematic review	9
5	Benefit-risk evaluation	9
6	Trial aim	10
7	Trial design and procedures	10
7.1	Overall trial design	10
7.2	Design justification	10
7.3	Cluster selection	11
7.3.1	Eligibility criteria	11
7.3.2	Screening	11
7.4	Patient participants selection	12
7.4.1	Eligibility criteria	12
7.4.2	Screening	12
7.4.3	Withdrawal criteria	12
7.5	Procedures	13
7.6	Biological sampling procedures	13
7.7	End of Trial	13
7.7.1	Intervention and control treatment	14
7.8	Description of investigational medicinal products	14

7.9	Randomization	14
7.10	Blinding	14
7.11	Auxiliary medicinal products	15
7.12	Concomitant use of other medications or treatments	15
7.13	Treatment after trial end	15
7.14	Outcomes	15
7.14.1	Primary outcome	15
7.14.2	Secondary outcomes	15
7.15	Independent Data Monitoring Committee	16
7.16	Statistics	16
7.16.1	Analysis population	16
7.16.2	Statistical analyses	17
7.16.3	Adjustment of significance and confidence interval	17
7.16.4	Sample size calculations	17
7.16.5	Interim analysis (if relevant)	18
7.17	Quality Control and Quality Assurance	18
7.18	Quality Assurance and Sponsor oversight	18
7.19	Monitoring	19
7.20	Source data	19
7.21	Deviations, serious breaches and other reporting obligations	20
7.22	Audits and inspections	20
7.23	Ethics	21
7.23.1	Compliance to the protocol, ICH-GCP and regulations	21
7.23.2	Ethical review of the trial	21
7.23.3	Procedure for obtaining informed consent	22
7.23.4	Data protection	22
7.23.5	Insurances	23
8	Substantial changes to the trial	23
9	Collection, handling, and archiving of data	24
10	Case Report Form	25
11	Notification of trial completion, reporting, and publication	26
12	References	27
13	Attachments	27

ATLS® vs Standard Care in Adult Trauma Patients

Clinical Trials Registry-India ID:

ClinicalTrials.gov ID:

Version number: 0.9

Date: 2023-12-04

Sponsor: Karolinska Institutet

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

Principal Investigator: Martin Gerdin Wärnberg

1 Roles and Contact information

List the name, role in the trial, contact address, telephone number, and email for all involved in the trial (Sponsor, eventual Co-sponsor, Coordinating Investigator/Principal Investigator, clinical monitoring organization if appointed, etc.). Add rows if needed for the trial.

Contact details must be provided for the sponsor; name and address and the name and responsibilities of the sponsor's representative and any co-sponsors authorised to sign the clinical trial protocol or any eventual amendments of this.

In order to avoid liability issues in clinical trials with multiple sponsors, all sponsors shall be subject to the liability of one sponsor unless they otherwise agree in a written agreement.

Responsibility in the clinical trial	
Sponsor	«Name, title»
Responsibility:	«Site/Institution»
	«Contact address»
• X	«Telephone number»
• Y	«Email»
Co-sponsor	
Responsibility:	
• X	
• Y	
Coordinating Investigator / Principal Investigator	
Responsibility:	
• X	
• Y	
Specify others involved:	
Clinical monitoring organization, project management, statistics or data management.	

2 List of used acronyms and abbreviations

List all abbreviations used in the protocol. Each term should be written out fully the first time it is used in the protocol, with the abbreviation in parentheses. Examples of common abbreviations are shown below but this list should be adapted to your trial; add and/or remove rows as needed.

Abbreviation	Term/Explanation
Adverse Event (AE)	Any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.
Serious Adverse Event (SAE)	Any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death
AR	Adverse Reaction = any unfavorable and unexpected reaction to an investigational medicinal product, regardless of dose
ASR	Annual Safety Report = the annual safety report for reporting to authorities. In Sweden this is the Swedish Medical Products Agency.
CRF	Case Report Form
CTIS	Clinical Trial Information System = Centralized EU database/portal for application and communication with authorities concerning clinical trials. In Sweden this includes the Swedish Medical Products Agency and the Swedish Ethical Review Authority.
CTR	EU Regulation 536/2014, also called CTR, Clinical Trials Regulation
DSUR	Development Safety Update Report = the standard which should be used for annual safety reporting to authorities
EPM	Etikprövningsmyndigheten (English: Swedish Ethical Review Authority)
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Council for Harmonization
ITT	Intention-to-treat = including all data from all subjects who have participated in the trial
PP	Per Protocol analysis = including only data from subjects who have completed the trial completely in accordance with the protocol, with no deviations from the protocol

Abbreviation	Term/Explanation
RSI	Reference safety information. A list of all known adverse reactions for the investigational medicinal product, including severity and frequency of the adverse reaction. The RSI is contained in the Summary of Product Characteristics or IB and is used to determine which new adverse reactions should be reported as suspected unexpected serious adverse reactions (SUSARs).
SPC or SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction. This is an event that is likely related to the investigational medicinal product but with unexpected occurrence. An adverse reaction is unexpected if its nature or seriousness is not consistent with the information on the product in the RSI.

3 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 patients³⁻⁶. Advanced Trauma Life Support® (ATLS®) is the most popular of these programmes and have been used to train over one million physicians worldwide⁷. 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 occurring 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

4 Background and rationale

Each year, 4.3 million people die from trauma¹. Among people aged 10-24 and 25-49 years trauma is the largest cause of disability adjusted life years². Most deaths from trauma occur within the first 24-48 hours⁸. 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 treatment³⁻⁶. 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 1978⁷. In the US and many other countries training in ATLS® is virtually mandatory for trauma care physicians¹². Uptake in low- and middle income countries (LMIC) has been slow, potentially due to high costs⁵.

There are three randomised controlled studies showing that ATLS® improves knowledge and clinical skills¹³⁻¹⁵, 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 (Figure @ref(fig:forest-plot))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 study²⁶. 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.

4.1 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.

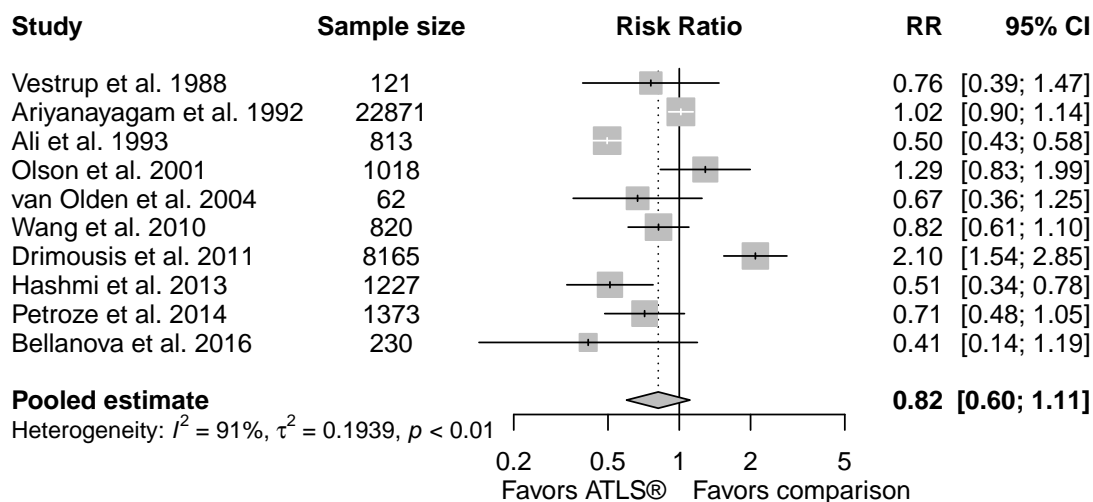


Figure 1: Summary of the updated system review. The forest plot shows the effect of ATLS on mortality. Abbreviations: RR, risk ratio; CI, confidence interval; ATLS, Advanced Trauma Life Support; I^2 , heterogeneity.

5 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.

6 Trial aim

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

7 Trial design and procedures

7.1 Overall trial design

We will conduct a batched stepped-wedge cluster randomised controlled trial (see Figure @ref(fig:trial-design)). 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 randomised²⁷. 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.

7.2 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 limited²⁸. 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 recruitment²⁹.

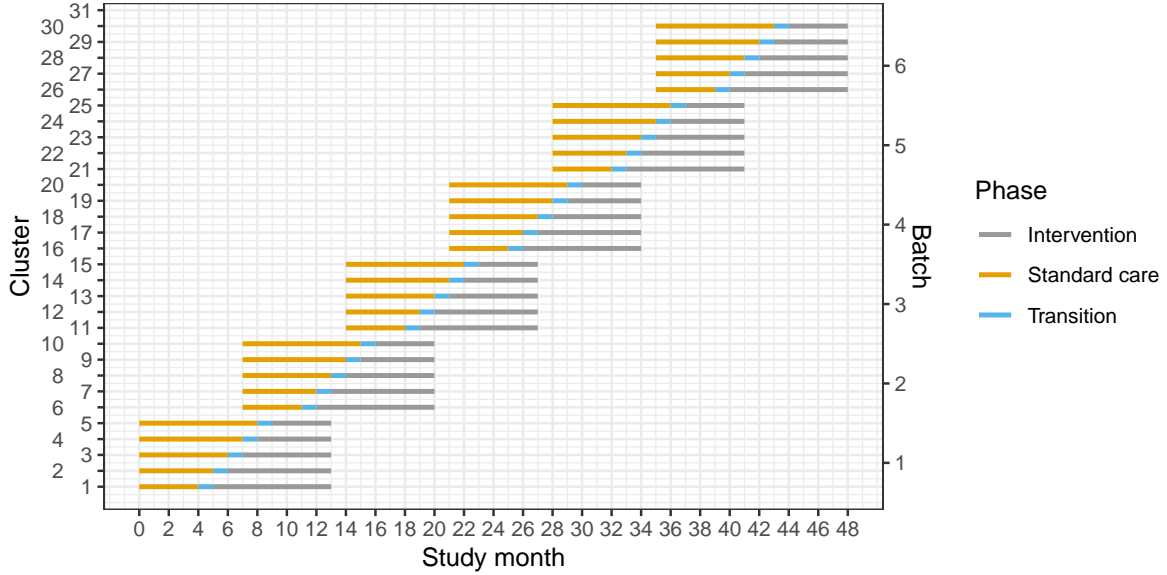


Figure 2: Trial design. Lines represent the duration of patient enrolment across clusters and phases. Clusters will be sequentially allocated to a batch based on when they enter the study. Within each batch clusters will then be randomised to an intervention implementation sequence.

7.3 Cluster selection

7.3.1 Eligibility criteria

Clusters must meet the following criteria:

- 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;
- provides general surgery, imaging and blood banking services around the clock; and
- no more than 25% of physicians providing initial trauma care trained in any trauma life support programme.

7.3.2 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 form¹ and logged in a cluster screening log².

7.4 Patient participants selection

7.4.1 Eligibility 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;
- 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.

7.4.2 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.

7.4.3 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.

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.

7.5 Procedures

Table 3 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 3: Overview of trial procedures

Procedure	Screening	Follow up					Within 7 days
		Daily	24 hours	Discharge	30 days	90 days	
Eligibility criteria	✓						
Study information ¹	✓						
Informed consent for follow up ¹	✓						
Baseline data collection	✓						
Injury data collection	✓	✓					
Mortality data collection ²	✓	✓	✓	✓	✓	✓	
EQ-5D/WHODAS					✓	✓	✓
Return to work					✓	✓	
End of Trial						✓	

¹Clinical 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.

²Mortality data will be collected from the hospital records and from the patient participants or their caregivers by telephone.

7.6 Biological sampling procedures

This trial does not include biological sampling.

7.7 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 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.

7.7.1 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 initial treatment and resuscitation, triage and interfacility transfers. Learning 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.

7.8 Description of investigational medicinal products

This trial does not include any investigational medicinal products.

7.9 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 batches³. Randomisation will be stratified by geographical region and anticipated cluster size.

7.10 Blinding

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

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

7.11 Auxiliary medicinal products

This trial does not include any auxiliary medicinal products.

7.12 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.

7.13 Treatment after trial end

Describe any continued treatment of subjects after the trial end, e.g., if the subject returns to previous treatments, if the subject receives no further treatment, if the subject continues treatment with the investigational medicinal product (note that this may require approval by the Swedish Medical Products Agency).

7.14 Outcomes

7.14.1 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 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.

7.14.2 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.
- 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?

7.15 Independent Data Monitoring Committee

If the clinical trial involves an extended risk or if the trial is performed over a long time period and is divided into different blinded treatment groups, an external independent (of the sponsor and investigator) data monitoring committee should evaluate the decoded results.

Remove this section if not applicable.

7.16 Statistics

This statistics section provides general guidelines, i.e. not everything is applicable to all trials. It is not necessary to use all sub-sections and some sub-sections can be deleted and/or new ones added.

7.16.1 Analysis population

- *Define the subjects that will be included in the analyses, e.g., state if the analyses will apply intention-to-treat (ITT) or per protocol (PP).*
- *Specify whether sensitivity analyses of the main analyses will be performed, i.e. examining the sensitivity of an ITT analysis with help of a complementary PP analysis.*

7.16.2 Statistical analyses

7.16.2.1 Statistical methods

- *Provide a general description of the descriptive/summary statistics.*
- *Describe the statistical methods that will be used to answer the primary and secondary objectives and clarify the underlying statistical models. State which covariates (and any stratifications) will be adjusted for in the analyses. Any subgroup analyses must be specified.*
- *State any transformations of variables and justification for this.*
- *State how the trial results will be reported, e.g., a relative treatment effect with associated 95% confidence interval and p-value.*
- *State if one- or two-sided tests of statistical significance will be used. Justify the use of one-sided tests in particular.*
- *If hypothesis testing is not appropriate, an alternative process for arriving at statistical conclusions should be provided.*

7.16.2.2 Drop-outs

- *Specify how drop-outs and missing values will be handled. For planned imputation of missing values, the method for this must be stated.*
- *State how any deviations from the original statistical analysis plan will be reported.*

7.16.3 Adjustment of significance and confidence interval

- *Indicate possible tests for multiple comparisons. Adjustment should always be considered for multiple primary outcomes. Specify details of any adjustment procedures or provide an explanation for why adjustment is not considered necessary.*

7.16.4 Sample size calculations

- *State the total number of subjects needed for the trial. Sample size calculations should be performed for all primary outcome variables (in the case of several). In the case of multicentre trials, the number of subjects at each site should be stated.*
- *State and motivate the effect size (e.g., group differences, standard deviations) that sample size calculation builds upon, usually the smallest clinically relevant effect.*
- *Specify in detail the assumptions on which the sample size is based. Specify in particular:*

- *method by which the sample size is calculated*
- *significance level*
- *desired power*
- *compensation for expected drop-outs*
- *handling of any corrections for multiple comparisons*

7.16.5 Interim analysis (if relevant)

- *A description of the statistical methods to be applied.*
- *Time points for interim analyses.*
- *Criteria for trial termination.*
- *Potential need for recalculation of sample size.*

7.17 Quality Control and Quality Assurance

In a clinical trial for medicinal products the sponsor is responsible for Quality Control (monitoring) and Quality Assurance (auditing). An independent review (monitoring) should be carried out for all clinical trials for medicinal products. The sponsor is responsible for appointing a monitor and for the quality throughout the trial; design, conduct, data collection, evaluation, reporting, and archiving. Methods used should be proportionate in relation to the trial's risks.

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

7.18 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.

7.19 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))).⁴

7.20 Source data

Refer to, and indicate in the site-specific source data reference document of the trial site, the location of the source data for each variable. The CRF may in specific cases be defined as the source data for specific endpoints (variables) that are not recorded elsewhere, in which case the data are recorded directly in the CRF.

Also describe that the monitor has access to medical records and source data after secrecy agreements have been signed by the responsible party at the site and by the monitor. Subjects have provided consent by signing the Subject Information and Informed Consent Form where this is specified.

Text suggestion: The investigator must keep source documents for each subject 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). The investigator must ensure that all source documents are accessible for monitoring and other quality control activities.

Source data is 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 subjects' medical records, CRFs, other source data and other trial documentation will be provided for monitoring and auditing purposes. Access to subjects' 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.

⁴**TODO TGI** Add a section on monitoring.

7.21 Deviations, serious breaches and other reporting obligations

The protocol should describe how deviations or serious breaches from Clinical Trials Regulation, the approved trial protocol, ICH-GCP and other regulations, directly affect, or with high likelihood could affect, the safety of subjects and their rights or the reliability and robustness of the data generated in the trial. In addition, the protocol needs to describe how the investigators should report suspected serious breaches to the sponsor.

Serious breaches should be assessed by the sponsor and without undue delay but at the latest within 7 days be reported by the sponsor to the Swedish Medical Products Agency via CTIS. See also section 13, Substantial changes to the trial.

Link to Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-notification-serious-breaches-regulation-eu-no-536/2014-clinical-trial-protocol_en.pdf

The sponsor should notify the relevant Member States, via CTIS, of any unexpected events that may affect the benefit/risk relationship of a trial but are not suspected unexpected serious adverse reactions. This should be done without undue delay, but no later than 15 days after the sponsor becomes aware of the event.

Text suggestion: 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, and, without undue delay but no later than 7 days (from knowledge) report these to the Swedish Medical Products Agency via CTIS.

Other unexpected events that may affect the benefit/risk relationship must be reported via CTIS without undue delay, but no later than 15 days after the sponsor becomes aware of the event.

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.

7.22 Audits and inspections

Text suggestion: 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.

7.23 Ethics

7.23.1 Compliance to the protocol, ICH-GCP and regulations

Text suggestion: The trial will be performed in compliance with this clinical trial protocol, the EU regulation on clinical trials on medicinal products for human use (536/2014), 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.

7.23.2 Ethical review of the trial

It will not be possible for patients to opt out from being subjected to the intervention, because 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. - We will apply for a waiver of informed consent from the ethical review boards at the participating hospitals. We do this because the target population will often have reduced decisional capacity at the time of data collection and the nature of the intervention is such that they can not refuse receiving it.

Our research measure up to these issues for the following reasons. First, it cannot be conducted using informed consent because the cohort of patients with severe trauma is the group most likely to benefit from improvements in early management and it is therefore crucial to include this population.

Describe the procedure for approval of the final clinical trial protocol and informed consent form. Application for permission for a clinical trial on medicinal products from the Swedish Medical Products Agency and the Swedish Ethical Review Authority is made via CTIS. The Swedish Medical Products Agency has an obligation to forward the application documents to the Swedish Ethical Review Authority. The Swedish Ethical Review Authority submits its opinion on the application back to the Swedish Medical Products Agency.

Text suggestion: The final protocol for clinical trials on medicinal products must be approved, as a part of the application for a permit for clinical trials via CTIS, by both the Swedish Ethical Review Authority and the Swedish Medical Products Agency before the trial can be conducted. The final version of the informed consent form and other information provided to subjects, must be approved or given a written positive opinion by the Swedish Ethical Review Authority. The authority must be informed via CTIS of any changes in the trial protocol in accordance with current requirements. *See also section 13, Substantial changes to the trial.*

7.23.3 Procedure for obtaining informed consent

Describe the procedure for how information is given to trial subjects and how consent is obtained. For vulnerable groups see information on the Swedish Medical Products Agency website ([link](#)) and Chapter V of the [CTR](#).

Remember to adapt and describe the procedure based on whether the subject is a child. In trials where minors participate, the consent of both parents (legal representatives of the minor) must be obtained. According to the Medicines Act, a minor who has reached the age of 15 must also give his or her informed consent to participate in the clinical trial of a medicinal product, provided that the minor understands the implications of the trial for him or her. In Sweden, a minor means a person younger than 18 years of age.

The principal investigator (or the person to whom the task has been delegated) must provide both oral and written information to the intended subject regarding what participation in the trial entails. Keep in mind that in a clinical trial for investigational medicinal products, informed consent must be obtained by a licensed physician.

A copy of the subject information as well as the signed informed consent form shall be provided to the subject.

If the subject information changes during the trial execution, the subject has the right to once again decide whether he/she would like to continue their participation. This occurs by allowing the subject to sign a revised subject information and informed consent form.

Text suggestion: The principal investigator at each site shall ensure that the subject is given full and adequate oral and written information about the trial, its purpose, any risks and benefits as well as inclusion and exclusion criteria. Subjects must also be informed that they are free to discontinue their participation in the trial at any time without having to provide a reason. Subjects should be given the opportunity to ask questions and be allowed time to consider the provided information. If the person chooses to participate, both the subject and the investigator shall sign the informed consent form. A copy of the subject information as well as the informed consent form shall be provided to the subject. The subject's signed and dated informed consent must be obtained before any trial-specific activity is performed. Each subject who participates in the trial will be identified by a subject number on a subject identification list. The subject agrees that monitors, auditors, and inspectors may have access to their medical records and other source data. If new information is added to the trial, the subject has the right to reconsider whether he/she will continue their participation.

7.23.4 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 information provided to subjects, subjects will be fully informed about how their trial data will be collected, used and disclosed. The content of the informed consent form complies with relevant integrity and data protection legislation. The subject information and the informed consent form will explain how trial data are stored to maintain confidentiality in accordance with national data legislation (*please describe how data is stored and which data security measures are taken*). 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 subject's medical history.

7.23.5 Insurances

*Here it should be explained how subjects are insured throughout the trial.*⁵

8 Substantial changes to the trial

This section describes how to handle substantial changes in the trial. Substantial changes include changes that:

- *may affect the safety or rights of the subjects,*
- *can change the reliability and robustness of the data generated in the clinical trial, or*
- *are significant for any other reason, such as the addition of a trial site or a change of the principal investigator*

Substantial changes to the clinical trial protocol may not be implemented before authorisation has been granted by the relevant authority via CTIS. It is the responsibility of the sponsor to assess whether a change is substantial or not. For examples of what are considered substantial and non-substantial amendments, see the European Commission's CTR Questions and Answers document ([link](#), Chapter V, EudraLex - Volume 10 - Clinical trials guidelines).

The investigator must not make any deviation from or change of the protocol, except when it is necessary to eliminate an immediate risk to the trial subjects, or where the changes only include logistical or administrative aspects of the trial (e.g., change of telephone number). Other deviations/changes besides the abovementioned required agreement with the sponsor and documented authoritative opinion regarding the amendment from relevant authorities. See also section 11.4, Deviations or serious breaches.

⁵**TODO: TGI** Please add information about insurance.

Text suggestion: 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.

In the event that substantial changes to the protocol which may affect the safety, rights of subjects or the reliability and robustness of data generated need to be implemented during the course of the trial, permission from the relevant authority via application in CTIS should be obtained before implementing the change. This includes the addition of a new trial site or a change of the principal investigator at the trial site.

Non-substantial changes should be continuously recorded and entered in CTIS.

9 Collection, handling, and archiving of data

Clinical research coordinators will collect data, screen patients using emergency department records, and obtain informed consent for post-discharge follow-up. Paper-based CRFs will be securely stored on-site and uploaded to project servers using a VPN with two-factor authentication. 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 and was reviewed by Karolinska Institutet (<https://doi.org/10.5281/zenodo.7748764>).

From the protocol it must be clear how the data will be collected. Describe which other types of data collection documents, in addition to the CRF, are used, e.g.: diaries, quality of life questionnaires, health economics, different patient-reported outcomes measures, etc. Describe how corrections will occur and by whom, that there will be an independent copy of the CRF with the investigator when the trial is completed, and how other trial documentation is stored and who has access to it. The sponsor and investigator must archive the information in the Trial Master File for at least 25 years after the end of the clinical trial, providing that a longer archiving period follows from other parts of the law. The sponsor and investigator can also agree that the documents shall be archived for a longer period. The Swedish Archives Act (Arkivlagen) applies to archiving of research material. For clinical trials in ATMP (Advanced Therapy Medicinal Product), the archiving period is 30 years according to GCP specific for ATMP.

The sponsor and the investigator shall keep a Clinical trial master file with documentation for the whole trial. The clinical trial master file shall at all times contain the essential documents relating to that clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated, taking into account all characteristics of the clinical trial, including in particular whether the clinical trial is a low-intervention clinical trial. It shall be readily available, and directly accessible upon request, to the Member States.

The clinical trial master file kept by the investigator and that kept by the sponsor may have a different content if this is justified by the different nature of the responsibilities of the investigator and the sponsor. The principal investigator shall keep an Investigator Site File (part of the Clinical Trial Master File) with all trial documentation for the site. The files should have relevant content according to the trial and follow ICH-GCP chapter 8 “Essential documents”. The principal investigator will store the trial site’s data, subject identification list, original of the subject information sheet and obtained trial consent inaccessible to unauthorized persons, but such that trial subjects can be identified by those responsible for the trial. This information must not be stored at the sponsor.

For information about data protection see section 12.4, Data protection.

Text suggestion:

Subjects who participate in the trial are coded with a trial-specific identification number. All subjects are registered in a subject identification list (subject enrolment and identification list) that connects the subject’s name and personal number with a subject number/trial identification number.

All data will be registered, managed, and stored in a manner that enables correct reporting, interpretation, and verification. The complete Trial Master File, as well as source documents, will be archived for at least 25 years after the trial is completed. Source data in the medical records system are stored and archived in accordance with national regulations.

10 Case Report Form

All information related to the clinical trial should be recorded, processed, handled and stored by the sponsor or investigator, as appropriate, so that it can be accurately reported, interpreted and controlled, while protecting the subjects’ medical records and personal data in accordance with applicable personal data protection law.

Text suggestion:

A Case Report Form (CRF) is used for data collection. *Describe which type of CRF will be used (eCRF or paper CRF).* The investigator must ensure that data is registered and any corrections in the CRF are made as stated in the clinical trial protocol and in accordance with the instructions. The investigator must ensure that the registered data is correct, complete, and that reporting takes place according to the timelines that have been predefined and agreed. The investigator signs the completed CRF. A copy of the completed CRF will be archived at the study site.

11 Notification of trial completion, reporting, and publication

The sponsor must notify, via CTIS, each concerned Member State that a clinical trial involving that Member State has been terminated. Notification must also be made when a trial has been terminated in all participating EU countries and also when termination has occurred in all participating third countries. The notification must be made within 15 days.

Within one year of the completion of the clinical trial in all Member States, the sponsor must submit a summary of the results of the clinical trial to CTIS, regardless of the outcome of the trial.

Guidance on content can be found in the CTR ([Link](#)), Annex IV. It should be accompanied by a summary written in a way that is understandable to lay people. The content of the summary is given in CTR ([Link](#)), Annex V.

For clinical trials involving children, the above summaries must be submitted within six months of the end of the trial. This shortened deadline of six months applies to sponsors who are marketing authorisation holders for the medicinal product.

If the trial is submitted for marketing authorization of an investigational medicinal product, the applicant for marketing authorisation must also, in addition to the summary of results, submit the full clinical trial report to CTIS within 30 days of the decision being taken.

In addition to submitting a summary of the results to CTIS a complete report with individual data shall be available from the sponsor on request or for any inspections by the Swedish Medical Products Agency throughout the entire retention period. A published article is not to be equated with a summary of a report. The report must contain sufficient information so that the Swedish Medical Products Agency can make an evaluation.

In addition to submitting a summary of the results to CTIS, a full clinical trial report with individual data shall be completed by the sponsor and provided to Principal investigators. The clinical trial report shall be archived in the Trial Master File by the sponsor and by the principal investigator at each site, in their Investigator Site Files, throughout the entire retention period, and available on request for inspections by the authorities. The clinical trial report must contain sufficient information so that the Swedish Medical Products Agency or other authorities can make a complete evaluation of the trial conduct and the results. A published article is not to be equated with the summary report to CTIS or the full clinical trial report.

The sponsor is responsible for the compilation of statistical analyses and their presentation to involved principal investigators. These analyses may be the basis for a manuscript for publication.

If the results are summarized in a manuscript with the purpose to publish in a scientific journal, it is recommended that the EU trial number is stated at the end of the abstract. This clearly documents that the trial has been published in advance and meets the requirements from ICMJE

(International Committee for Medical Journal Editors) that are set for publications in medical science journals.

If a clinical trial is suspended or prematurely terminated due to a change in the risk-benefit balance, for reasons of subject safety, this must be notified to the Member States concerned through CTIS. The notification should be made as soon as possible, but not later than 15 days after the clinical trial was suspended or terminated prematurely. The reasons for such action and follow-up measures must be provided. The resumption of a clinical trial after its temporary interruption due to a change in the benefit/risk balance is considered a substantial modification.

Interruptions that do not affect the benefit/risk relationship must be notified, via CTIS, within 15 days, stating the reason for the interruption. Notification of restart shall be made, via CTIS, within 15 days. See also section 5.4, End of Trial, as well as section 6.4, Withdrawal criteria.

Text suggestion:

End of the trial is reported in CTIS at the latest 15 days after completion.

Within one year of trial completion, a clinical study report is completed, and a summary of the clinical trial results must be reported in CTIS, including a summary for lay people.

12 References

Literature referenced in the text is listed here. The list should be sorted in the order in which it is referred to in the protocol. For example, the Vancouver system can be used.

13 Attachments

These could include, for example, validated self-report scales, questionnaires, diaries, etc. All attachments should have a version number and be dated.

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 multi-center 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).