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 **5**

2 List of used acronyms and abbreviations **6**

3 Synopsis **8**

4 Background and rationale **9**
4.1 Updated systematic review 10

5 Benefit-risk evaluation **10**

6 Trial aim **11**

7 Trial design and procedures **11**
7.1 Overall trial design 11
7.2 Design justification 11
7.3 Procedures 12
7.4 Biological sampling procedures 13
7.5 End of Trial 13
7.6 Subject selection 14
7.6.1 Inclusion criteria 14
7.6.2 Exclusion criteria 15
7.6.3 Screening 15
7.6.4 Withdrawal criteria 16
7.7 Trial treatments 16
7.8 Description of investigational medicinal product(s) 16
7.9 Randomization 17
7.10 Blinding 17

7.11 Code breaking . . . 17
7.12 Auxiliary medicinal products . . . 17
7.13 Concomitant use of other medicinal products and treatments . . . 17
7.14 Treatment after trial end . . . 18
7.15 Methods for measurement of endpoints for clinical efficacy and safety . . . 18
7.15.1 Methods for measurement of endpoints for clinical efficacy . . . 18
7.15.2 Methods for measurement of endpoints for clinical safety . . . 19
7.16 Handling of Adverse Events . . . 19
7.16.1 Definitions . . . 20
7.16.2 Assessment of Adverse Events (AE) . . . 21
7.16.3 Reporting and registration of Adverse Events . . . 22
7.16.4 Follow-up of Adverse Events . . . 25
7.16.5 Independent Data Monitoring Committee . . . 25
7.16.6 Annual Safety Report (ASR) . . . 25
7.16.7 Procedures in case of emergencies, overdose or pregnancy . . . 26
7.17 Statistics . . . 26
7.17.1 Analysis population . . . 26
7.17.2 Statistical analyses . . . 27
7.17.3 Adjustment of significance and confidence interval . . . 27
7.17.4 Sample size calculations . . . 27
7.17.5 Interim analysis (if relevant) . . . 28
7.18 Quality Control and Quality Assurance . . . 28
7.19 Quality Assurance and Sponsor oversight . . . 28
7.20 Monitoring . . . 29
7.21 Source data . . . 30
7.22 Deviations, serious breaches and other reporting obligations . . . 30
7.23 Audits and inspections . . . 31
7.24 Ethics . . . 31
7.24.1 Compliance to the protocol, ICH-GCP and regulations . . . 31
7.24.2 Ethical review of the trial . . . 32
7.24.3 Procedure for obtaining informed consent . . . 32
7.24.4 Data protection . . . 33
7.24.5 Insurances . . . 34

8 Substantial changes to the trial 34

9 Collection, handling, and archiving of data 35

10 Case Report Form 36

11 Notification of trial completion, reporting, and publication 37

12 References 38

13 Attachments **38**

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 Responsibility: • X • Y	«Name, title» «Site/Institution» «Contact address» «Telephone number» «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 patients[3–6]. Advanced Trauma Life Support® (ATLS®) is the most popular of these programmes and have been used to train over one million physicians worldwide[7]. Despite its widespread use, there are no controlled trials showing that ATLS® improves patient outcomes[3,4,6]. Multiple systematic reviews emphasise the need for such trials[3,4,6].

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

Primary Outcome In-hospital mortality within 30 days of arrival at the emergency department.

Trial Design Batched stepped-wedge cluster randomised trial in India.

Trial Population Adult trauma patients presenting to the emergency department of a participating hospital.

Sample Size 30 clusters and 4320 patients.

Eligibility Criteria

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

Patients will at least 15 years old, who present to the emergency department of participating hospitals with a history of trauma occuring less than 48 hours before arrival, and who are admitted or die between and admission, or who are transferred from the emergency department of a participating hospital to another hospital for admission.

Intervention The intervention will be ATLS® training, a proprietary 2.5 day course teaching a standardised approach to trauma patient care using the concepts of a primary and secondary survey. Physicians will be trained in an accredited ATLS® training facility in India.

Ethical Considerations In-hospital data collection will be conducted under a waiver of informed consent. Patients will be informed about the trial and their right to opt out of data collection. Patients will be informed that they can withdraw their data from the trial at any time.

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

4 Background and rationale

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

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

There are three randomised controlled studies showing that ATLS® improves knowledge and clinical skills[13–15], but there are no randomised controlled trials or high-quality quasi-experimental trials indicating that ATLS® improves patient outcomes[3,4,6]. We conducted an updated systematic review for project (unpublished), and estimated a pooled risk ratio of 0.82 (95% CI 0.60; 1.11) from ten heterogeneous (I^2 0.91) retrospective or small studies on the effect of ATLS on mortality (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 study[26]. Our pilot study enrolled 376 patients from seven hospitals across India (unpublished data) and shows that it is feasible to conduct the proposed trial with a high recruitment rate (78%), low loss to follow-up rate (1%), and low missingness in key variables (mean 0.8%).

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

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.

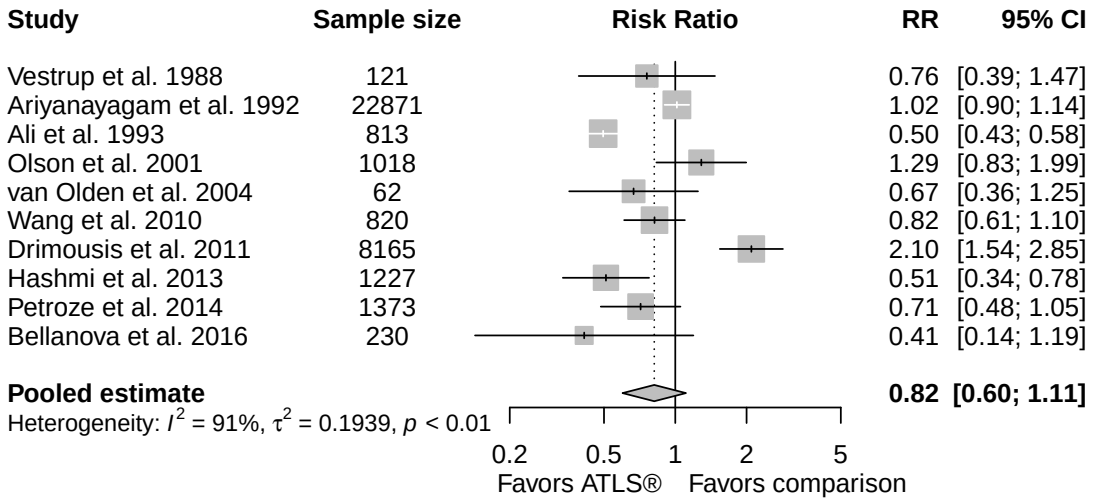

Figure 1: Summary of the updated system review. The forest plot shows the effect of ATLS on mortality. Abbreviations: RR, risk ratio; CI, confidence interval; ATLS, Advanced Trauma Life Support; I^2, heterogeneity.

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 randomised[27]. Each cluster will be a tertiary hospital in India. We will conduct this trial in India because physicians providing initial trauma care in India are not routinely trained in ATLS® or similar programmes.

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

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 limited[28]. In this trial, the number of clusters is limited because of the costs associated with ATLS® training and the available slots for ATLS® training in India. Second, the stepped-wedge design is likely to enhance participation and engagement because all clusters receive the intervention. The batched stepped-wedge design further improves feasibility as it does not

require all clusters to start at the same time, and it is robust to potential delays in cluster recruitment[29].

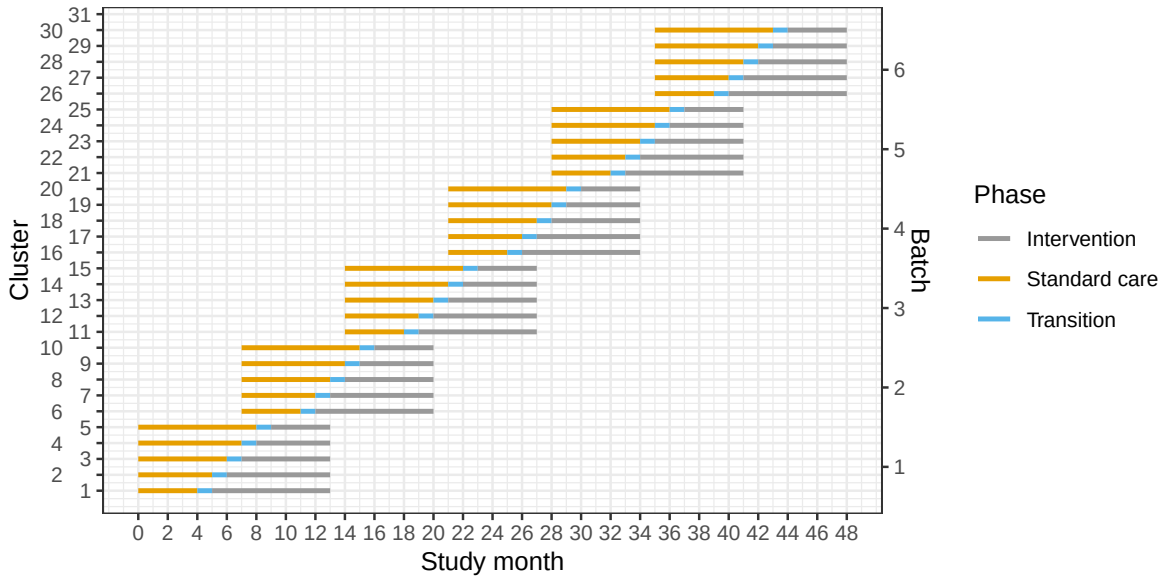

Figure 2: Trial design. Lines represent the duration of patient enrolment across clusters and phases. Clusters will be sequentially allocated to a batch based on when they enter the study. Within each batch clusters will then be randomised to an intervention implementation sequence.

7.3 Procedures

Table 3 shows an overview of trial procedures. 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. 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

	Follow up

Procedure	Screening	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						√

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

7.4 Biological sampling procedures

This trial does not include biological sampling.

7.5 End of Trial

Provide a clear and unambiguous indication of what constitutes the end of the trial and, if it is not the date of the last visit of the last subject, a specification of the estimated end date of the trial.

If treatment of the subjects who completed the trial differs from normal clinical practice, this should be stated. This can, for example, mean that the trial subjects should receive the investigational medicinal product after the trial ends – if so, describe how this will be done (see section 7.10, Treatment after trial end).

See also section 6.4, Withdrawal criteria, and section 15, Notification of trial completion, reporting, and publication.

If a clinical trial is suspended or terminated prematurely due to a change in the benefit/risk balance, for reasons of subject safety, this should be notified to the concerned Member States via CTIS. The notification should be made as soon as possible, but no later than 15 days after the clinical trial was suspended or terminated prematurely. The reasons for such action and follow-up measures should be provided. The resumption of a clinical trial after it has

been temporarily suspended due to a change in the benefit/risk balance is considered to be a substantial modification.

Text suggestion:

The trial ends when the last subject has completed the last follow-up (or if this is not relevant give the estimate completion date instead).

The trial may be prematurely terminated if it this is necessary for safety reasons affecting the risk-benefit balance or if the recruitment of subjects cannot be met within reasonable time limits. If the trial is prematurely terminated or suspended, the investigator should immediately inform the subjects about this and ensure appropriate treatment and follow-up. The Swedish Medical Products Agency should be informed as soon as possible via CTIS, but no later than 15 days after trial suspension.

Decisions on premature termination are taken by the sponsor.

7.6 Subject selection

A description of the groups and subgroups of subjects to be enrolled in the clinical trial, including, where applicable, groups of subjects with special needs (e.g. age, gender, healthy volunteers, subjects with rare or very rare diseases). A justification of the gender and age distribution of the subjects if a certain gender or age group is not enrolled or is underrepresented in the clinical trial, an explanation of the reasons and a justification of these exclusion criteria.

7.6.1 Inclusion criteria

Only pre-defined inclusion, exclusion, and withdrawal criteria can be used in the trial. Inclusion criteria often include signed informed consent, age, disease, symptoms, possibly requirements for negative pregnancy test, contraception use during the trial. If fertile women are to be included, see document,"Antikonceptionsrekommendationer" (in Swedish), on the Swedish Medical Product Agency's website.

Note that all inclusion criteria are written so that they can be answered with a" Yes".

Text suggestion: To be included in the trial, subjects must meet the following criteria:

- The subject has given their written consent to participate in the trial.
- *For female subjects of fertile age, adequate contraception should be used, specify which methods. A negative pregnancy test can eventually be a requirement, specify requirement/type of pregnancy test. Contraceptive requirements may also apply to male subjects.*

7.6.2 Exclusion criteria

State the criteria that the subject cannot meet in order to be included in the trial, with respect to the subject's safety or something that may interfere with the trial results.

Check that all contraindications for the investigational medicinal product in the SPC/IB are included.

The following exclusion criteria are commonly included in trials:

- *Contraindications*
- *Concomitant medications*
- *Known or suspected allergies against any product included in the trial*
- *Pregnancy, breastfeeding, or planned pregnancy*
- *Mental inability, reluctance or language difficulties that result in difficulty understanding the meaning of participation in the trial*
- *Treatment or disease which, according to the investigator, can affect treatment or trial results*
- *Participation or recent participation in a clinical trial with a investigational medicinal product (specify how recently, usually 30 days). Previous participation in this trial.*

Text suggestion: Subjects must not be included in this trial if any of the following criteria are met:

- .
- .
- .

7.6.3 Screening

Describe the process for screening and inclusion. Also provide information about whether and when re-screening is allowed.

Text suggestion: Subject eligibility (that subjects fulfill all inclusion criteria and do not meet any exclusion criteria) is established before inclusion, treatment, or randomization.

7.6.4 Withdrawal criteria

Specify criteria for when and how subjects can/must be prematurely taken out of the trial.

- *The subject may choose to discontinue the trial at any time*
- *The principal investigator or safety committee can terminate a subject's participation (due to, e.g., non-tolerable adverse events/adverse reactions, pregnancy, etc.)*
- *A concerned Competent Authority can terminate the trial.*

Describe the care of trial subjects who prematurely discontinue the trial (e.g., continued treatment, examinations).

Describe how data will be handled for subjects who discontinue the trial prematurely. Specify if a closing visit will be performed or if other follow-up is planned (e.g., overall survival).

It should also be clarified whether a subject who has discontinued the trial will/can be replaced to achieve the desired number of included subjects and, if so, in which case/how this will be done.

If an exclusion criterion applies throughout the trial, this should also be stated.

See also section 5.4, End of Trial, and section 15, Notification of trial completion, reporting, and publication.

Example text:
Subjects can discontinue their participation in the trial at any time without any consequence to his/her continued treatment. The investigator/sponsor can at any time terminate the trial for a subject due to, e.g., unacceptable adverse events/adverse reactions or because the subject does not follow procedures in the clinical trial protocol. If the subject discontinues the trial, follow-up of this subject will be performed according to the clinic's routine.

7.7 Trial treatments

The term investigational medicinal product includes medicinal products used as comparators (placebo or active medicinal product). The same requirements apply to comparator medicinal products as to the medicinal products under investigation. Comparator medicinal products should therefore be described in a similar way in this section, i.e. when the instruction text below states investigational medicinal products, the corresponding information also needs to be provided for any comparator medicinal products.

7.8 Description of investigational medicinal product(s)

This trial does not include any investigational medicinal products.

7.9 Randomization

Describe in detail how randomization will be performed and how subjects receive a randomization number. Also include information according to the example text below.

Text suggestion: Subjects are included/randomized consecutively as they are found to be eligible for inclusion in the trial. If a subject discontinues their participation, the subject's trial-specific code will not be reused and the subject will not be allowed to re-enter the trial again.

7.10 Blinding

Describe the process for blinding. If this is not a blinded trial, this section can be removed.

7.11 Code breaking

The protocol must describe how the code is broken in emergency situations and who should be informed in connection with this. A clear definition of situations where the code may need to be broken helps prevent unnecessary unblinding. It is important that the code in emergency situations can be broken by the investigator, without the involvement of the sponsor. Describe how possible code break envelopes are stored and who will have access to this as well as how these persons can be reached in case of an emergency.

If an electronic system is used, it must be clear how to break the code if the system does not work.

If this is not relevant, remove this section.

Text suggestion: The list for breaking the code can be found at…

7.12 Auxiliary medicinal products

This trial does not include any auxiliary medicinal products.

7.13 Concomitant use of other medicinal products and treatments

For other concomitant medications (non-investigational medicinal products or auxiliary medicinal products and other treatments), justify and describe permitted and unauthorised treatments and medicinal product use before starting the trial, during the trial and after the end of the trial. Assess whether anything should be listed as an exclusion criterion and add this to section 6.2, Exclusion criteria.

Indicate what should be documented in the CRF regarding other concomitant medications (name, dose, start and stop dates, indication, etc.) The following text suggestion can be a part of the text under this heading.

Text suggestion: Medications 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. Concomitant medication should be recorded in the Case Report Form (CRF).

7.14 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).

7.15 Methods for measurement of endpoints for clinical efficacy and safety

7.15.1 Methods for measurement of endpoints for clinical efficacy

This section describes measurements and endpoints (variables) associated with primary and secondary objectives to demonstrate the effect of treatment through, e.g., different types of analyses and measurements such as X-ray, analysis of blood samples, measurements of tumor size, and questionnaires. Describe methods as well as approaches to sample collection and when the different measurements will be performed. State where any analyses will be performed. State whether biological material will be stored in the biobank and routines for this. See also section 5.3.3, Biobank.

7.15.1.1 Primary outcome

Describe the primary endpoint (variable) as precisely as possible. Include information about how the primary variable will be measured: e.g. type of sample, method used and eventual responsible laboratory. State whether the analysis will be performed continuously during the trial or after completion of subject enrollment.

7.15.1.2 Secondary outcomes

- Should we measure functional outcome/disability with WHODAS instead? - Should we remove complications because they are too difficult to measure?

- all cause mortality within 24 hours, 30 days, and three months of arrival at the emergency department;

- 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;
- 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;
- return to work at 30 days and three months after arrival at the emergency department; and
- in-hospital pulmonary, septic, or renal complications.

Describe the secondary endpoints (variables) as precisely as possible. Include information about how the secondary endpoints (variables) will be measured: e.g. type of sample, method used and eventual responsible laboratory. State whether the analysis will be performed continuously during the trial or after completion of subject enrollment.

7.15.2 Methods for measurement of endpoints for clinical safety

This paragraph may be included as part of the other paragraphs under 8.1. Describe the endpoint(s) (variables) for clinical safety as precisely as possible. Include information about how the endpoint(s) will be measured: e.g. type of sample, method used and eventual responsible laboratory. State whether the analysis will be performed continuously during the trial or after completion of subject enrollment.

Describe any measures for handling deviations in section 9.3, Reporting and registration of Adverse Events.

7.16 Handling of Adverse Events

Explain which adverse events (AE) and serious adverse events (SAE) will be reported during the trial (compare with the Investigator's Brochure for non-approved investigational medicinal products or SPC for approved medications used according to the approved indication). Carefully consider what should and should not be reported, and under which time period of the trial that AE/SAE shall be reported. If the disease itself causes certain symptoms, hospitalization, etc., these conditions can be given as exceptions for what shall ***not*** *be reported as an AE, SAE, or SUSAR.*

AE and SAE are followed up until they are fully evaluated or no longer considered clinically non-significant by the principal investigator (described in section 9.2.1, Assessment of causal relationship, and section 9.4, Follow-up of Adverse Events). Note that persistent adverse events are classified as serious.

7.16.1 Definitions

7.16.1.1 Adverse Event (AE)

Text suggestion: Adverse Event (AE): Any untoward medical occurrence in a clinical trial subject administered a medicinal product and, which does not necessarily have a causal relationship with the treatment, can be an unfavorable and unintended sign (including an abnormal laboratory discovery), symptom or disease temporally associated with the use of the investigational medicinal product, whether or not related to the investigational medicinal product.

7.16.1.2 Adverse Reaction (AR)

Keep relevant selections and delete other sections.

Text suggestion: In the pre-approval clinical experience with a new medicinal product or new use of a medicinal product, and particularly as the therapeutic dose(s) may not be established, all noxious and unintended reactions to the medicinal product related to any dose should be considered an adverse reaction (AR). The phrase "reaction" to a medicinal product means that the causal relationship between the medical product and an adverse event is at least a reasonable possibility, that is the relationship cannot be ruled out.

7.16.1.3 Serious Adverse Event (SAE)

Serious adverse event (SAE): Any untoward medical occurrence that at any dose:

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

Medical and scientific assessment will be made to determine if an event is "serious" and whether it would prompt reporting in other situations, for example important medical events that may not be directly life-threatening or result in death or hospitalization but may compromise the study subject or may require intervention to prevent one of the other results set forth in the definitions above. These should also normally be considered as SAEs.

7.16.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SUSAR: A reaction/event that is unexpected, serious, and suspected to be caused by the treatment, i.e. adverse reactions that are not included in the Investigator's Brochure (IB) or SPC.

7.16.2 Assessment of Adverse Events (AE)

7.16.2.1 Assessment of causal relationship

Text suggestion: The investigator is responsible for determining whether there is a causal relationship between the AE/SAE and use of the investigational medicinal product.

Consideration should be given to whether there is a reasonable possibility of establishing a causal relationship between the adverse event and the investigational medicinal product based on the analysis of the available evidence.

All AE can be categorized as either likely related, possibly related, unlikely related or not related, in accordance with the definitions below:

Likely related: Clinical event, including abnormal results from laboratory analyses, occurring within a reasonable time after administration of the intervention/investigational medicinal product. It is unlikely that the event can be attributed to underlying disease or other medications but is most likely caused by the investigational medicinal product and its emergence is reasonable in relationship with use of the investigational medicinal product.

Possibly related: Clinical event, including abnormal results from laboratory analyses, occurring within a reasonable time after administration of the intervention/investigational medicinal product. The event could be explained by the investigational medicinal product and its emergence is reasonable in relationship with use of the investigational medicinal product, but there is insufficient information to determine the relationship. The event could be explained by an underlying disease or other medications.

Unlikely related: Clinical event, including abnormal responses from laboratory tests, unlikely to be related to the intervention/investigational medicinal product and can be reasonably explained by other medication or underlying disease.

Not related: Clinical event, including abnormal results from laboratory analyses, that is not reasonably related to the use of the intervention/investigational medicinal product.

Those AEs which are suspected of having a causal relationship to the investigational medicinal product will be followed up until the subject has recovered or is well taken care of and on the way to good recovery (see also section 9.4, Follow-up of Adverse Events).

If the reporting investigator does not provide any information on causality, the sponsor should consult with the reporting investigator and encourage the expression of a position on this issue. The sponsor must take into account the assessment of causality provided by the investigator. If the sponsor disagrees with the investigator's assessment of causality, both the investigator's and the sponsor's views should be included in the report.

7.16.2.2 Assessment of intensity

In addition to assessing the causal relationship between administration of the investigational medicinal product and AE, an assessment of the intensity of the event is required. The following classifications can be used:

Each adverse event shall be classified by an investigator as mild, moderate or severe.

Mild: The adverse event is relatively tolerable and transient in nature but does not affect the subject's normal life.

Moderate: The adverse event causes deterioration of function but does not affect health. The event can be sufficiently unpleasant and interferes with normal activities but does not completely obstruct them.

Severe: The adverse event causes deterioration of function or work ability or poses a health risk to the subject.

Assessment of intensity is generally made by the reporting investigator.

Common Terminology Criteria for Adverse Event (CTCAE) is another way to classify intensity according to a five-point scale.

7.16.2.3 Assessment of seriousness

The investigator is responsible for assessing the seriousness (serious or non-serious). If the adverse event is considered serious, this should be reported as a serious adverse event (SAE) by the investigator to the sponsor. See also section 9.3.2, Reporting of Serious Adverse Events (SAE).

7.16.3 Reporting and registration of Adverse Events

- *The investigator should register and document adverse event or abnormal laboratory responses identified in the protocol as critical for safety assessment and report them to the sponsor according to the reporting requirements and within the time periods specified in the protocol.*
- *Less stringent rules from registration and reporting requirements may be granted in low-intervention clinical trials (for definition see cover page) after a thorough risk analysis.*
- *The sponsor should maintain a detailed register of all adverse event reported by the investigator.*
- *Describe how AE/SAE are captured, e.g., that trial subjects at each contact with the investigator/nurse will be asked about how they have been feeling since the previous visit or describe if another way is used to capture adverse event in the trial.*

- *Describe where AE/SAE are registered. Normally, they are registered primarily in the subject's medical records. Describe how these will be registered in the trial's CRF, reporting forms or worksheets, and where registrations of severity and causality are made, since this is not always done in the medical record.*
- *Also describe AEs which do not need to be documented and reported as AEs. If this is not indicated, all adverse medical events should be collected as AEs in, e.g., a diary or otherwise.*
- *Describe here during which time period adverse events are intended to be followed, e.g., from trial start or from start of treatment with the investigational medicinal product to XX weeks after the last dose.*
- *All reported adverse events that have not been resolved by the end of the trial should be followed up. How, when, and for how long this follow-up will last should be described, e.g., telephone contact or visit to the study site approximately XX weeks after the last visit in the trial. The follow-up and the time for the follow-up visit/contact are adapted to each individual trial.*
- ***Assessment of causal relationship (between AE/SAE and investigational medicinal product), whether the AE is considered to be an SAE or not, shall be made by a licensed physician.***

Text suggestion: At each trial visit, adverse events (AE) are registered, starting after *trial start/or from start of treatment with the investigational medicinal product,* up to and including *X weeks* after the subject has ended their treatment with the investigational medicinal product. All AE that occurs during the trial and which are observed by the investigator/trial nurse or reported by the subject will be registered in the CRF regardless of whether they are related to the investigational medicinal product or not. Assessment of causal relationship, severity, and whether the AE is considered to be an SAE will be made by the investigator directly in the *CRF/on a trial-specific worksheet.* At minimum for each AE/SAE, a description of the event is recorded (diagnosis/symptom if diagnosis is missing), start and stop dates, causal relationship, severity, if the AE is considered to be an SAE, measures and outcome.

The following symptoms are clearly related to the process and the expected course of the condition and therefore will not be reported as AE:

Example:

Expected adverse events based on knowledge of the disease in question and expected clinical course.

7.16.3.1 Reporting of Adverse Events (AE)

Text suggestion: All AE shall be registered in the CRF within *«indicate time frame» as indicated above (section 9.3, Reporting and registration of Adverse Events).*

7.16.3.2 Reporting of Serious Adverse Events (SAE)

Text suggestion: Serious adverse events (SAE) are reported to the sponsor on a special SAE form within 24 hours of the investigator being informed of the SAE.

Follow-up information describing the outcome and handling of the SAE is reported as soon as this information is available. The original should be kept in the Investigator Site File.

Provide details about the reporting procedure for SAE. Include reporting times, what will happen upon receipt of an SAE, who will review what is reported and who will assess whether the adverse event was expected for the investigational medicinal product or not (this is done using the reference safety information). The processes for receiving, confirming, and reviewing of reported SAEs should be described. Reviewing of SAEs must occur in due time, with consideration of the reporting times for a potential SUSAR.

Add information about SAEs that should not be reported.

Text suggestion: Based on knowledge of the disease in question and expected clinical course, some events that are otherwise serious are not considered as SAEs in this trial. The following is a list of SAEs that shall not be reported as SAEs:

Example:

1. *Expected events based on the knowledge of the disease in question and expected clinical course.*
2. *If a trial subject is hospitalized with a documented cancer-related problem, this will not be reported as an SAE.*

7.16.3.3 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR)

In investigator-initiated trials where non-commercial sponsors lack the possibility to report SUSAR directly in the EudraVigilance database, the Swedish Medical Products Agency can help with this when a SUSAR occurs in Sweden. However, this must be clearly justified in the cover letter to the application. Reporting then takes place via the CIOMS form which is sent to the Swedish Medical Products Agency via Eudralink. Since these reports contain personal data, they should not be sent to the Swedish Medical Products Agency via normal email.

The reference safety information provides the basis for assessing whether the adverse reaction is unexpected or not.

SUSARs should, if possible, be reported unblinded, that is, should state to which trial medicinal product the subject had a reaction. The investigator should only unblind the treatment allocation for a subject if unblinding is relevant to the subject's safety. Unblinded data should only be available to persons who need to participate in safety reporting to the regulatory authority and Data Safety Monitoring Boards (DSMBs) or to persons performing ongoing safety evaluations

during the clinical trial. Placebo should only be reported if it is suspected that any component of the placebo treatment has caused the reaction.

Text suggestion: Those SAE which are assessed by sponsor to be SUSAR are reported via a CIOMS form to the EudraVigilance database / Swedish Medical Products Agency according to the specified time frames.

SUSAR that are fatal or life-threatening are reported as soon as possible and no later than 7 days after the serious adverse event has become known to the sponsor. Relevant follow-up information is sent thereafter within an additional 8 days. Other SUSAR are reported as soon as possible and no later than 15 days after they have come to the sponsor's knowledge.

Multicentre trials: Information about SUSAR occurring during the trial is compiled by the sponsor and sent to the principal investigators at all participating sites. *In order to preserve the integrity of the trial, it is recommended that reporting of SUSAR to investigators in a blinded study is made without unblinding, that is, without specifying which investigational medicinal product the subject received. Describe how the reporting will be done.*

7.16.4 Follow-up of Adverse Events

Describe the follow-up of trial subjects who have been affected by adverse events (AE/SAE) (until the adverse event is resolved/stable/persistent) and measures in case of unacceptable adverse events (dose adjustment, treatment interruption, withdrawal of subject from the trial). Describe follow-up of subjects with regards to safety after the trial is completed.

7.16.5 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.

7.16.6 Annual Safety Report (ASR)

For investigational medicinal products other than placebo, the sponsor must submit an annual report on the safety of each investigational medicinal product used in a clinical trial. This is done in the CTIS. The safety report should be written according to the format Development Safety Update Report, (DSUR).

The safety report defines for which time period the report applies and a list of all SAE that have occurred, as well as possible SUSAR. A summary assessment of the safety situation for the subjects and a benefit/risk evaluation for the trial must also be included. The ASR should

also be accompanied by the RSI in force at the start date of the report. If significant changes in the RSI have occurred during the reporting period, these should be listed in the ASR.

The annual report should contain only aggregated and anonymised data.

The obligation to submit a safety report starts when a clinical trial is authorised and ends when the last clinical trial conducted by the sponsor with the investigational medicinal product is completed.

7.16.7 Procedures in case of emergencies, overdose or pregnancy

Medication errors, pregnancy and uses other than those specified in the CTP, including misuse and abuse of the investigational medicinal product, shall be subject to the same reporting obligations as adverse reactions.

If an unforeseen event is likely to have a serious impact on the benefit/risk relationship, the sponsor and investigator should take appropriate Urgent Safety Measures (USM) necessary to protect the subjects. Examples of such measures are to temporarily suspend the clinical trial or to introduce supplementary monitoring measures. The sponsor should, via CTIS, inform the concerned Member States about the event and the measures taken. Notification must be made as soon as possible, but no later than seven days after the measures have been taken.

If a subject who participates in a clinical trial becomes pregnant, this person must be followed up until the birth has taken place. If the fetus/child has any congenital malformation, this must be reported as a serious adverse event (SAE).

Information about pregnancy does not need to be included in the trial if it is not applicable for the included subjects.

7.17 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.

7.17.1 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.*

7.17.2 Statistical analyses

7.17.2.1 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.*

7.17.2.2 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.*

7.17.3 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.*

7.17.4 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*

7.17.5 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.*

7.18 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.

7.19 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.

7.20 Monitoring

In order to fulfill the EU regulation on clinical trials on medicinal products for human use, 536/2014 and ICH-GCP, an independent monitor should be appointed to, via monitoring, ensure the subjects' safety and integrity are satisfied and check that reported personal data is reliable and of high quality.

Briefly describe how the independent review (monitoring) will be performed before, during, and after the trial. Details are advantageously described in a separate monitoring plan.

Describe which levels of quality control can be applied, e.g., what is monitored centrally and what is monitored on site. See above.

Describe generally here how deviations from the protocol or regulations that occur at the site will be documented and handled (significant deviations should be reported in the final report to the authorities). Details shall be described in a separate monitoring plan. See also section 11.4*.*

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)).

Text suggestion: The trial will be monitored by an independent monitor before the trial begins, during conducting the trial, and after the trial has been completed. This is to ensure that the trial is carried out according to the protocol and that data is collected, documented, and reported according to ICH-GCP and applicable ethical and regulatory requirements. Monitoring is performed as per the trial's monitoring plan and is intended to ensure that the subject's rights, safety, and well-being are met and that data in the CRF are complete, correct, and consistent with the source data.

7.21 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.

7.22 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.

7.23 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.

7.24 Ethics

7.24.1 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.

7.24.2 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.*

7.24.3 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.

7.24.4 Data protection

The General Data Protection Regulation (GDPR) has strengthened the data subject's rights and given increased responsibility to those responsible for data collection. This means that when collecting research data, it is necessary to decide whether the data collection is legal, correct, appropriate, that integrity and confidentiality are considered and that no more information than necessary is collected, as well as that no more persons than necessarily have access to the data. There should be a lawful ground for data collection, which for research is for public interest.

The personal data controller is obliged to take measures to ensure that the GDPR regulation is followed, to describe built-in data protection features and security when processing and to report personal data breaches.

Appropriate technical and organisational measures shall be taken to protect the personal data and processed information from unauthorised access, disclosure, dissemination, alteration or destruction and from accidental loss, in particular where the processing involves the transmission of data over a network.

Text suggestion: If any part of the data is processed by another organization, inside or outside the EU, 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 General Data Protection Regulation (GDPR) and other 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 *and identified with «Trial code/Trial ID/Initials».*

The informed consent form 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.

7.24.5 Insurances

Here it should be explained how subjects are insured throughout the trial. Check if subjects are insured through the Swedish patient insurance and whether Swedish pharmaceutical insurance is valid for the investigational medicinal product(s). Alternatively, discuss with your organization if there are existing insurance policies.

Swedish Patient Insurance (Patientskadeförsäkring): The Swedish healthcare regions have signed a patient insurance with Landstingens Ömsesidiga Försäkringsbolag, Löf. Check what applies to medical research at www.lof.se.

Swedish Pharmaceutical Insurance (Läkemedelsförsäkring): All marketed investigational medicinal products do not automatically have a Swedish Pharmaceutical Insurance. Check if the product is covered by the drug insurance at lff.se and that the insurance also covers clinical trials.

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.

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

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 multicenter western trauma association study. *J Trauma.* **86**, 864–870 (2019).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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