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Comparison of ultrasound-guided subtransverse process interligamentary plane block with paravertebral block for postoperative analgesia in thoracic surgery: protocol for a randomised non-inferiority trial

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ABSTRACT

Introduction The subtransverse process interligamentary (STIL) plane block is an emerging interfascial plane block that has garnered attention for its potential to provide effective postoperative analgesia for breast and thoracic surgeries. However, a direct comparative assessment between the STIL plane block and the paravertebral block is currently lacking. Consequently, our study aims to assess the analgesic efficacy of the STIL block in comparison to paravertebral block for patients undergoing video-assisted thoracoscopic surgery (VATS).

Methods and analysis This study is a randomised, parallel-controlled, double-blind, non-inferiority trial, with the goal of enrolling 114 participants scheduled for uniportal VATS at Shanghai Pulmonary Hospital. Participants will be randomly assigned in a 1:1 ratio through block randomisation to receive either the STIL plane block (n=57) or the paravertebral block (n=57). The primary outcome of the study is the area under the curve of Numerical Rating Scale(NRS) scores recorded over a 48-hour period following the surgical procedure. Secondary outcomes encompass the evaluation of Quality of Recovery-40, cumulative sufentanil consumption, serum inflammatory factors, rescue medication usage, the incidence of adverse events and the patient satisfaction scores.

Ethics and dissemination This study has received approval from the Medical Ethics Committee of Shanghai Pulmonary Hospital (approval no. L22-329). Written informed consent will be obtained from all participants. The findings will be submitted for publication in peer-reviewed journals.

Trial registration number ChiCTR2200066909.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study aims to assess the safety and efficacy of the subtransverse process interligamentary plane block as a perioperative analgesia method for patients undergoing video-assisted thoracoscopic surgery.
⇒ The study is a parallel, non-inferiority, randomised controlled trial with patient and assessor blinding.
⇒ The study focuses on patient-reported outcomes during the early postoperative period.
⇒ Limitations of the study include the absence of investigation into long-term effects, lack of sensory plane testing and constraints related to drug dosage.

INTRODUCTION

Surgical advancements and the use of video-assisted thoracoscopic surgery (VATS) have gained popularity in lung cancer management.[1] Addressing postoperative pain in thoracoscopic patients has been a hot topic of research. Uniportal VATS, a minimally invasive technique using a single incision, offers benefits including diminished postoperative pain, shorter hospital stays and enhanced cosmetic outcomes compared with traditional multiport VATS.[2] However, acute postoperative pain remains a prevalent symptom following uniportal VATS.[3 4] Inadequate pain management can negatively affect recovery, increase the risk of pulmonary complications and contribute to the development of chronic postsurgical pain.[5] Therefore, the development of perioperative analgesic techniques and strategies for VATS patients holds paramount significance.

Thoracic paravertebral block (TPVB) is a common method for managing postoperative pain after thoracoscopic surgery.[5] It provides analgesic effects akin to those of thoracic epidural block and is the preferred regional anaesthesia technique for thoracoscopic surgery.[6] However, TPVB is technically challenging, requiring skilled healthcare professionals.[7] The narrow paravertebral space, located between the superior costotransverse

ligament (SCTL) and the parietal pleura, poses a risk of inadvertent pleural puncture and vascular damage, and increased the potential for pneumothorax and haematoma.[7 8]

The subtransverse process interligamentary (STIL) plane block is a recently introduced technique that holds promise as an alternative to TPVB.[9] STIL plane block specifically targets the region adjacent to the paravertebral space, rather than directly penetrating it, which theoretically diminishes the potential risks of inadvertent pneumothorax and hematoma compared with TPVB.[9] Additionally, due to its close anatomical proximity to the paravertebral space, the STIL plane block may facilitate a more straightforward dispersion of local anaesthetics into this area.[10] Research has also confirmed that the block achieved with STIL plane block is effective in providing adequate pain relief for breast surgeries.[11] These findings suggest that STIL plane block holds promise as a viable alternative to TPVB in patients undergoing thoracic surgery. There is a paucity of clinical trials comparing the differences between the STIL plane block and TPVB for perioperative analgesia. Therefore, we hypothesise that the STIL plane block will demonstrate non-inferiority to TPVB in terms of postoperative analgesia for patients undergoing VATS.

METHODS AND ANALYSIS

Study design and setting

This study is a randomised, parallel-group, non-inferiority trial being conducted at Shanghai Pulmonary Hospital. The study is scheduled to commence in January 2023 and conclude in December 2027. The study design adheres to the guidelines outlined in the Standard Protocol Items for Randomised Trials (SPIRIT). Figure 1 presents the Consolidated Standards of Reporting Trials flow chart, and figure 2 includes the SPIRIT figure, with an accompanying checklist available as online supplemental file 1.

Participants

Inclusion criteria

1. Age: 18–64 years.
2. American Society of Anesthesiologists physical status classifications I–II.

Exclusion criteria

1. History of prior chest surgery, morbid obesity (body mass index >40 kg/m^2),[12] severe cardiovascular system diseases, chronic respiratory system diseases (chronic obstructive pulmonary disease, asthma, interstitial lung diseases and idiopathic pulmonary fibrosis), liver or kidney dysfunction, blood system disorders or a history of mental illnesses.
2. Known allergy to local anaesthetics.
3. Presence of local infection at the block site or systemic infection.
4. Language barriers or communication difficulties.
5. Patient refusal to participate in the study or unwillingness to use the analgesic pump.

Recruitment

All patients scheduled for VATS will undergo eligibility screening 1 day before the scheduled operation. Eligible patients will be given the opportunity to enrol in our study, during which we will provide them with detailed information about our research. Each patient will receive comprehensive information about their role in our study and will be assured that their personal information will be kept strictly confidential.

Informed consent

Prior to enrolling in our study, informed consent will be obtained from each patient or their legally authorised representative (LAR), as detailed in online supplemental file 2. This consent process will emphasise that participation is entirely voluntary, and participants have the right to withdraw from the study at any point without affecting their access to medical care. No study procedures will commence until informed consent has been obtained.

Randomisation and blinding

Following the acquisition of signed informed consent from the patient or their LAR, patients will be randomly allocated to either the STIL plane block group or the TPVB group in a 1:1 ratio. Randomisation will be executed using sealed envelopes, which will be available at Shanghai Pulmonary Hospital. A masked researcher will generate treatment assignments by using a computer-generated random number list with block sizes of 6, as generated by Stata V.16.0 (STATA). The research assistant (RA) will create randomised envelopes just prior to the patient randomisation process and ensure the envelopes' integrity and presence during each monitoring visit.

The RA, who will be unaware of the randomised patient assignments, will conduct all baseline interviews. Patients will be kept uninformed about their respective interventions, and research staff responsible for completing the postprocedural follow-up questionnaire will also be blinded. While it is not possible to blind anaesthesiologists involved in patient care, the surgical team will be kept unaware of the group assignments.

Standard anaesthetic and analgesic management

On the day of the operation, patients will be admitted to the operating room. Vital signs, including heart rate, blood pressure (BP) measurement, including systolic BP, diastolic BP, pulse pressure and mean arterial pressure, oxygen haemoglobin saturation measured by pulse oximetry, end-tidal carbon dioxide partial pressure ($EtCO_2$) and urine output, will be continuously monitored throughout the surgery. Prior to anaesthesia induction, an intravenous catheter will be placed in the right internal jugular vein under the guidance of ultrasound after local anaesthesia. Preoxygenation with 100% oxygen for 3 min before anaesthesia induction will be administered via a face mask.

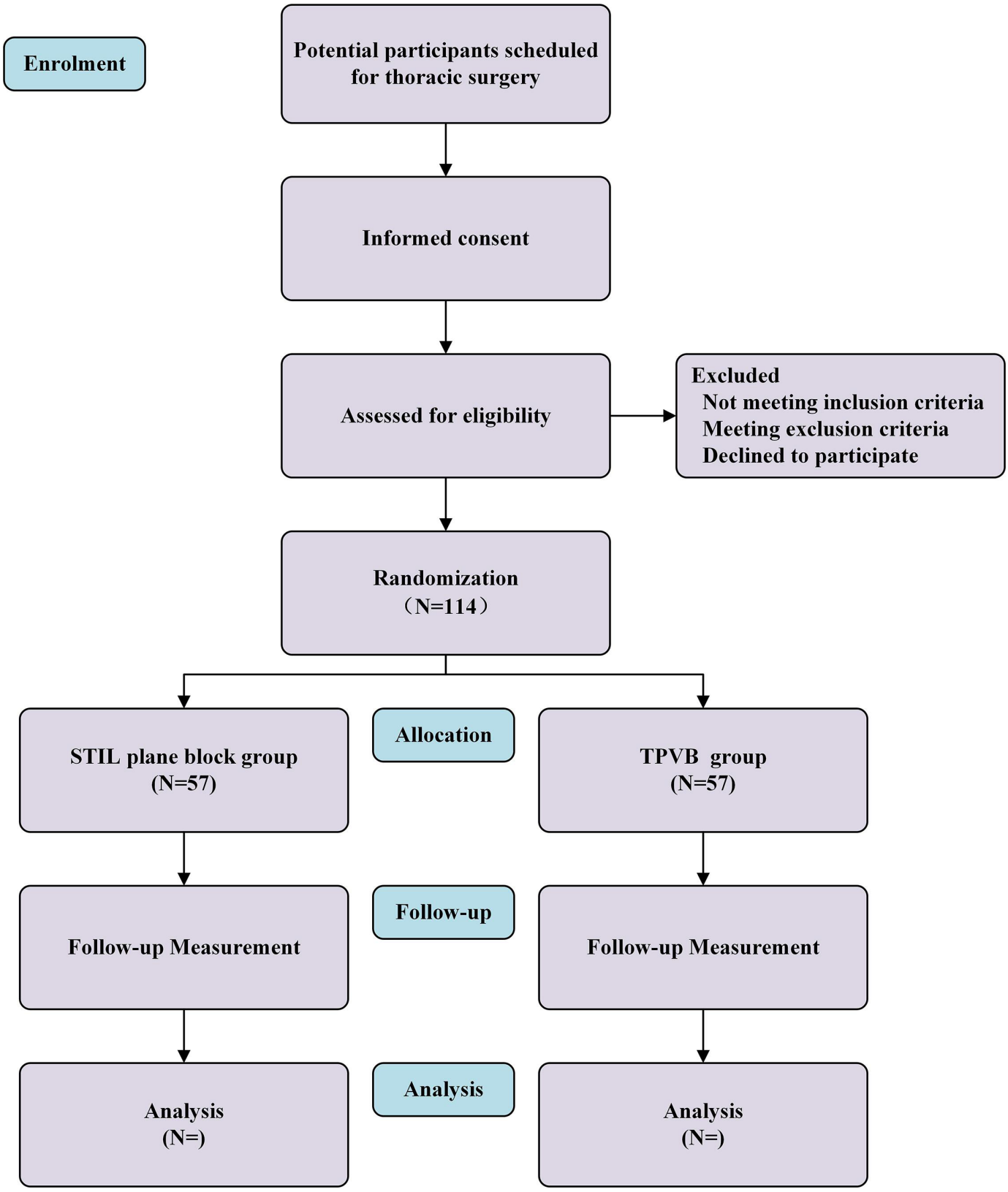

Figure 1 CONSORT flow diagram for the study. CONSORT, Consolidated Standards of Reporting Trials; STIL, subtransverse process interligamentary; TPVB, thoracic paravertebral block.

Anaesthesia induction will be initiated with midazolam (0.05 mg/kg), propofol (1–2 mg/kg), sufentanil (0.5–0.7 µg/kg) and 0.6 mg/kg rocuronium bromide. Subsequently, double-lumen endobronchial intubation will be performed for mechanical ventilation, with confirmation of the placement of a double-lumen endobronchial tube (DLT) using a fibreoptic bronchoscope. The ventilation strategy employed will adhere to a one-lung protective

STUDY PERIOD									
	Enrolment	Allocation	Post-allocation						Close-out
TIMEPOINT	t_{-1}	t_0	t_1	t_2	t3	t4	t5	t6	t7
	-1d	0	DTP	PO 1h	PO 12h	PO 24h	PO 36h	PO 48h	
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
INTERVENTIONS:									
STIL plane block			X						
TPVB			X						
ASSESSMENTS:									
NRS score				X	X	X	X	X	
Surgical details			X						
Hemodynamic variables			X						
Postoperative nausea and vomiting				X	X	X	X	X	
Satisfaction								X	
Opioid consumption			X	X	X	X	X	X	
Patient-reported medication adverse effects				X	X	X	X	X	
Postoperative complications				X	X	X	X	X	

Figure 2 Schedule of enrollment, interventions and assessments following the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) guidelines. DTP, during the procedure; NRS, Numerical Rating Score; PO, postoperative; QoR-40 score, Quality of Recovery-40; STIL, subtransverse process interligamentary; TPVB, thoracic paravertebral block.

approach, characterised by tidal volumes of 6 mL/kg or lower, based on predicted body weight, and a positive end-expiratory pressure of 5–10 cmH_2O, following established guidelines and expert recommendations.[13] The respiratory rate will be adjusted to maintain $EtCO_2$ levels within the range of 35–45 mm Hg. After intubation with a DLT, anaesthesia maintenance will involve the administration of propofol and remifentanil to achieve a spectral entropy value between 40 and 60.

Following extubation in the operating room, patients will be moved to the postanaesthesia care unit. As a preventive measure against postoperative nausea and vomiting (PONV), patients will receive intravenous dexamethasone (5 mg) and tropisetron (5 mg) prior to the initiation of general anaesthesia.

Postoperative pain management will strictly adhere to a standardised protocol for all patients. This protocol encompasses the administration of a combination of 5 µg

of sufentanil and a 50 mg intravenous infusion of flurbiprofen axetil administered 30 min before the conclusion of surgery. Additionally, patients will receive a daily intravenous infusion of 50 mg of flurbiprofen axetil for postoperative analgesia. Patient-controlled analgesia (PCA) will be implemented using a 24-hour infusion of sufentanil at a concentration of 1 µg/mL solution. The PCA protocol will consist of an infusion rate of 2 mL/hour, a 2 mL bolus dose, a lockout time of 15 min and a maximum limit of 10 mL/h. PCA treatment will be initiated based on a Numerical Rating Scale (NRS) score >2.[14–16] Oxycodone 5 mg/acetaminophen 325 mg will be available as a rescue analgesic. In addressing PONV, a 5 mg dose of intravenous tropisetron will be administered in the hospital ward.

Interventions

Immediately after the induction of general anaesthesia, the blockades will be carried out with patients positioned in a lateral decubitus position. This approach is chosen to mitigate patient anxiety and discomfort, while also ensuring blinding to the intervention allocation.[16 17] All blockades will be administered by experienced anaesthesiologists well versed in ultrasound-guided regional blocks.

The TPVB procedure will be conducted through an in-plane transverse approach, following established techniques.[18] On achieving an optimal ultrasound image, which includes clear visualisation of the transverse process, a wedge-shaped hypoechoic paravertebral space, and the parietal pleura, the needle will be advanced from a lateral to medial direction until the needle tip penetrates the internal intercostal membrane. The accurate placement of the needle will be confirmed by observing the downward displacement of the pleura during the injection of the local anaesthetic.

The STIL plane block will be administered using an in-plane technique, following the method described by Kilicaslan *et al*.[9] This procedure entails identifying key anatomical landmarks, including the identification of the intertransverse ligament, transverse process, SCTL and pleura through a parasagittal ultrasound scan. Subsequently, the needle will be advanced in-plane in a caudal to cranial direction, with continuous ultrasound guidance employed to ensure precise needle placement.

Patients randomised to receive STIL plane block and TPVB will be provided with a 15 mL mixture of local anaesthetics, comprising a 1:1 mixture of 15 mL of 1% ropivacaine and 2% lidocaine, at the T5–6 intercostal levels.[19]

Data collection, monitoring and management

Preoperative, intraoperative and postoperative follow-up data will be meticulously extracted from electronic medical records, monitoring devices and pertinent manual records by the research team. This data will be documented on standardised paper forms and later double-entered into Epidata software V.3.1 by two proficient RAs.

The data safety and monitoring board (DSMB) will be constituted of two senior anaesthesiologists and one surgeon, all of whom will maintain a blinded status with regard to the study. The DSMB will provide independent oversight of the trial, conducting a comprehensive review of participant safety and data storage throughout the study.

Outcomes

Primary outcome

The primary outcome measure will be the area under the curve (AUC) of NRS scores for pain experienced during deep inspiration over the initial 48 hours following surgery. Pain assessments will be systematically conducted at the 1, 12, 24, 36 and 48 hours postoperative time points.

Secondary outcomes

1. AUC of NRS scores for pain at rest over a 48-hour period.
2. Time to the initial administration of sufentanil analgesia.
3. Incidence of postoperative opioid-related side effects such as nausea, vomiting and dizziness, as well as other complications.
4. Patient satisfaction with the effectiveness of analgesia during the initial 48 hours postoperatively, assessed using a five-point Likert scale, ranging from ‘highly unsatisfactory’ to ‘highly satisfactory.’
5. Quality of Recovery-40 assessment.[20 21]
6. Plasma biomarker concentrations ()measured using ELISA both before the operation and on the first day after surgery.
7. Incidence of adverse events, as detailed in online supplemental file 3.

Statistical methods

Sample size

Based on data from our previous unpublished study, the mean cumulative pain score, calculated as the AUC from 1 to 48 hours following surgery, was estimated to be 77.6 (14.7) for the TPVB group and 102.1 (19.2) for the STIL group. With a power of 80%, a one-sided significance level of 2.5%, and a non-inferiority limit of 34 for NRS AUC (a 33% difference between treatment groups),[22] a minimum sample size of 51 subjects per group was calculated. Considering a potential drop-out rate of 10%, 57 patients per group were enrolled.

Descriptive statistics

Continuous variables will be presented as means and SDs for normally distributed data. For continuous variables with non-normally distributed data, medians and ranges will be reported. Categorical data will be described using counts, proportions and risk ratios with 95% CIs.

Planned outcome analysis

For the primary outcome, both the intention-to-treat and per-protocol (PP) approaches will be used. The normality of the distribution of AUC of NRS scores will be assessed

using the Shapiro-Wilk test. Normally distributed variables will be reported as mean±SD and analysed with independent t-tests, while non-normally distributed variables will be reported as median (IQR) and analysed with the Mann-Whitney U test.

For secondary outcomes, the PP approach will exclusively be used. Comparative analysis of secondary endpoints between the two treatment groups will be performed using Student's t-test (or Mann-Whitney U test if necessary) for continuous quantitative variables and the χ^2 test (or Fisher's exact test) for qualitative variables. Multivariate analyses will encompass linear and logistic models. Time-to-event analyses will use the Kaplan-Meier method and the Cox proportional hazards model.

P values will be two tailed with a significance threshold of 0.05. The statistical analyses will be conducted using Stata V.16.1 (StataCorp), R V.4.0.3 (the R Foundation) and GraphPad Prism V.8.0 (GraphPad Software, San Diego, California, USA).

Patient and public involvement

None.

ETHICS AND DISSEMINATION

Ethics approval and consent to participate

This clinical study will adhere to the principles of the Declaration of Helsinki and will be conducted in strict compliance with the approved protocol, good clinical practice, designated standard operating procedures, and all relevant local laws and regulations applicable in the country where the study is conducted. The study protocol has received ethical approval from the Ethics Committee of Shanghai Pulmonary Hospital, China (approval no. L22-329). Informed consent will be a mandatory requirement for all participating patients.

Dissemination policy

The results of this study will be disseminated without regard to the impact of the intervention on study outcomes. A manuscript detailing the intervention's effects will be submitted to a peer-reviewed journal on completion of data collection and analysis.

Trial status

Recruitment for this trial commenced in January 2023 and is expected to conclude by December 2027. The protocol version number is V.2.0.

DISCUSSION

Lung cancer represents a global health concern as one of the most fatal malignancies.[16] But recent advancements in thoracoscopic surgery have elevated it as a pivotal therapeutic approach.[23] Uniportal thoracoscopic surgery, characterised by its smaller incision, has gained significant popularity, promising faster recovery, reduced complications, improved aesthetics and less postoperative pain.[24–26] However, postoperative pain remains a common issue for uniportal thoracoscopic surgery patients, significantly hindering their recovery.[27]

Although thoracic surgery employs a variety of regional blockade techniques, including TPVB, thoracic epidural anaesthesia (TEA), serratus anterior plane (SAP) blocks, and erector spinae plane blocks, retrolaminar block, combined deep and superficial SAP block, serratus posterior superior intercostal plane block,[28 29] ongoing debate persists regarding the selection of the most effective method.[22–24] The administration of TEA necessitates a high level of technical expertise and is associated with specific adverse effects that may adversely affect postoperative recovery.[30] TPVB is a widely used and guideline-recommended approach for pain management.[8 31] This technique entails the injection of a local anaesthetic into the thoracic paravertebral space to block the thoracic spinal nerve, its branches and the sympathetic trunk, delivering analgesic effects comparable to epidural blocks. Nevertheless, TPVB carries inherent risks due to the delicate nature of needle insertion, including potential complications such as pneumothorax and haemothorax. Therefore, alternative approaches are continuously being explored.

The STIL plane block, a relatively recent technique introduced by Kilicaslan *et al*, is believed to pose a lower risk of severe complications compared with paravertebral block.[9 11] This lower risk primarily arises from its injection into a tissue plane away from potentially problematic structures. Additionally, it is hypothesised that the STIL plane block can effectively provide pain relief by blocking both dorsal and ventral rami of the spinal nerves.[11] Its close anatomical proximity to the paravertebral space may also facilitate a more straightforward dispersion of local anaesthetics, theoretically achieving a similar effect as TPVB.[10 11] Taking into account these factors, along with the reduced trauma associated with uniportal VATS,[32 33] which avoids rib spreading, we have designed a randomised controlled study to investigate whether the STIL plane block can provide pain relief non-inferior to TPVB in uniportal VATS.

Our study has several limitations. One limitation is that we only assess NRS scores within 48 hours postoperatively. This restricted time frame may not offer a comprehensive understanding of the complete postoperative analgesic effect. Another limitation is the inability to conduct sensory testing due to the nerve blockades administered after the induction of general anaesthesia. Additionally, the use of 15 mL local anaesthetic in our study might impose certain constraints on the study outcomes.

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Contributors WW and HS designed the study. DW, WW and TZ collaborated on manuscript drafting. WH made significant contributions to the study's conception and design. YL developed the statistical analysis plan and estimated the sample size. HS contributed to study design, critical revisions and final manuscript approval. All authors acknowledge their accountability for all aspects of the work, ensuring its accuracy and integrity.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2-3
	2b	All items from the World Health Organization Trial Registration Data Set	YES
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,16
	5b	Name and contact information for the trial sponsor	1,16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____10_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____11-13____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____12-13____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____12_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____12 _____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____N/A_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____12 and supplement file 3 ___
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____N/A_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____13____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____N/A_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____7_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____N/A_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____13_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____16_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____16_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____16_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____16_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____16_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____16_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Translated ICFs can be provided on request_____ ___
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____N/A_____ _

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Practice name:
Participant ID:

I N F O R M E D C O N S E N T

Informed Consent form for patient.
This Informed Consent Form is intended for both men and women attending Shanghai Pulmonary Hospital, whom we are inviting to participate in research on postoperative pain management.
The title of our research project is: *Comparison of ultrasound-guided subtransverse process interligamentary plane block with paravertebral block for postoperative analgesia in thoracic surgery*.

Principal Investigator: Hong Shi, MD
Organization: Department of Anesthesiology, Shanghai Pulmonary Hospital, Tongji University School of Medicine

This Informed Consent Form has two parts:
1. Information Sheet (providing details about the research for your understanding).
2. Certificate of Consent (for your signature if you choose to participate).

You will receive a copy of the complete Informed Consent Form.

Wu W, *et al. BMJ Open* 2024; 14:e082135. doi: 10.1136/bmjopen-2023-082135

PART 1: Information Sheet

Introduction

Hello, I am Hong Shi, working in the Department of Anesthesiology. We are currently conducting research on postoperative pain management for thoracoscopic surgery. I'm reaching out to share information with you and extend an invitation for your participation in this research.

There's no rush for you to decide today; take your time to consider it. Feel free to discuss it with someone you trust and feel comfortable talking to about the research.

If you come across any unfamiliar terms or concepts, please feel free to interrupt, and I will take the time to provide explanations. Should you have any questions later on, you can direct them to me, the study doctor, or the staff.

Purpose of the research

Postoperative pain profoundly affects the recovery of patients following thoracoscopic surgery. Hence, we have crafted a comparative study to evaluate the efficacy of two analgesic methods. One involves the conventional paravertebral nerve block, while the other entails the subtransverse process interligamentary plane block. The primary objective of the study is to assess the effectiveness of these methods in postoperative pain management.

Participant selection

We invite all adults scheduled for Video-Assisted Thoracoscopic Surgery (VATS) at Shanghai Pulmonary Hospital to participate in the research.

Voluntary Participation

Your participation in this research is entirely voluntary, and the decision to participate is entirely yours. Regardless of your choice to participate or not, all the services you receive at this center will continue without any changes. If you choose not to participate in this research project, you will receive the standard treatment routinely offered, and further details will be provided later. Moreover, you retain the option to change your decision and withdraw from participation at any time, even if you initially agreed.

Procedures and Protocol

Participants will be randomly assigned to one of two groups. Participants in one group will undergo Thoracic Paravertebral Block (TPVB), while participants in the other group will receive the Subtransverse Process Interligamentary Plane Block (STIL). We will then compare the outcomes of the two procedures to determine which yields better results.

Healthcare professionals will provide careful monitoring and care throughout the study. If there are concerns about the treatment effects, we will identify the treatment received and make necessary adjustments. If you have any concerns or issues related to the research, please feel free to discuss them with me or any other researchers.

For any clinical study (if relevant):

We will extract blood from your arm using a syringe. This procedure is painless. In total, we will collect approximately 2 samples of 5 milliliters of blood. Any remaining blood samples at the conclusion of the study will be properly disposed of.

Description of the Process

To begin with, we will use a syringe through a catheter to extract a small amount of blood from your arm. This blood sample will be sent to the laboratory for testing. Concurrently, we will inquire about your general health.

Following your induction into general anesthesia, I will administer different blocking procedures, as previously mentioned. One involves the Thoracic Paravertebral Block (TPVB), and the other is the Subtransverse Process Interligamentary Plane Block. These blocking procedures are conducted on your back. Given your state of general anesthesia, you won't experience any sensation during these procedures.

Post-surgery, on the second day, we will once again collect a blood sample from you.

Furthermore, we will conduct several follow-up visits, posing questions about your postoperative well-being. This process is designed to ensure a comprehensive understanding of your physical condition and the treatment's impact.

If you have any concerns or questions about this process, please feel free to contact us at any time.

Duration

The study is anticipated to span approximately 3-4 days, covering the entirety of your hospitalization period.

Risks

The analgesic procedures in both groups are standard practices. Risks are associated with the puncture technique, encompassing typical complications observed in local anesthetic techniques, such as puncture site infections, hematomas at the puncture site, nerve damage, and toxicity linked to an overdose of local anesthetics.

Moreover, specific complications for the paravertebral block include the risk of pneumothorax, hemothorax, or intrathecal injection. The healthcare team will be meticulously monitoring you and the other participants throughout the study. If there are concerns about the treatment's effects, we will identify the treatment you are receiving and make necessary adjustments.

Benefits

By participating in our study, you stand to benefit in several ways: our intervention contributes to alleviating postoperative pain following thoracoscopic surgery, reducing adverse reactions such as nausea, vomiting, and dizziness associated with the use of opioid medications, and facilitating a quicker recovery process.

Additionally, it is important to emphasize that in the unlikely event of any harm resulting from your participation in this study, we are committed to providing complimentary treatment and/or appropriate compensation. We are dedicated to ensuring your safety and well-being, taking all necessary measures to minimize

potential risks.

We appreciate your valuable contribution to our research, which will contribute to advancements in the field of medical science.

Reimbursements

Your participation is free. You will not be given any other money or gifts to take part in this research.

Confidentiality

If you decide to participate in this trial, your involvement and personal information throughout the study will be handled with utmost confidentiality.

The principal investigator and other researchers will utilize your medical information strictly for research purposes. This may encompass details such as your name, address, phone number, medical history, and information gathered during your study visits. Your records will be securely stored in a locked filing cabinet, accessible exclusively to the research team. Identification numbers will be assigned to categorize your research data and laboratory specimens during the study. Access to these identification numbers will be restricted to the researchers and authorized members of the research team.

To ensure adherence to regulations, if necessary, the study sponsor, government regulatory authorities, or ethics review board members may inspect your personal information at the study site as mandated.

When the findings of this study are disseminated, no personal information about you will be disclosed.

Sharing the Results

The insights derived from this research will be communicated to you through clinics or phone discussions before being disseminated to the public, if necessary. Confidential information will remain secure and will not be disclosed.

Ultimately, we plan to publish the research results, allowing other interested parties to benefit from our study.

Right to Refuse or Withdraw

You are not obligated to participate in this research if you choose not to.

Furthermore, you have the option to discontinue your participation at any time. Your decision is entirely yours, and we will continue to respect all of your rights.

Alternatives to Participating

If you choose not to participate in the research, you will receive the standard treatment available at our hospital.

Who to Contact

If you have any questions, feel free to ask them at any time, even after the study has commenced. For inquiries later on, you may contact any of the following:

Dr. Hong Shi, Phone: 86-13651958255

This proposal has undergone thorough review and received approval from the Ethics Committee of Shanghai Pulmonary Hospital, China (Approval No. L22-329). The committee ensures the protection of research participants from any potential harm.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

PART 2: Certificate of Consent

This section should be written in the first person and have a statement similar to the one in bold below. If the participant is illiterate but gives oral consent, a witness or a legally authorized representative must sign. A researcher or the person going over the informed consent must sign each consent. The understanding should perhaps be better tested through targeted questions during the reading of the information sheet (some examples of questions are given above), or through the questions being asked at the end of the reading of the information sheet, if the potential participant is reading the information sheet him/herself.

		Please initial each box
1	I have read the foregoing information, or it has been read to me.	☐
2	I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction.	☐
3	I consent voluntarily to participate as a participant in this research.	☐

Print Name of Participant _____

Signature of Participant _____

Date (Day/month/year) _____

If illiterate

Aliterate witness or legally authorized representative must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb-print as well.

		Please initial each box
1	I have witnessed the accurate reading of the consent form to the potential participant	☐
2	I have witnessed the individual has had the opportunity to ask questions.	☐
3	I confirm that the individual has given consent freely.	☐

Print Name of witness or legally authorized representative _____

Signature of witness or legally authorized representative _____

Date (Day/month/year) _____

Thumb print of participant ☐

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher _____

Signature of Researcher _____

Date (Day/month/year) _____

Safety Evaluation and Reporting

1. Assessment of Safety Endpoints

Safety endpoints will encompass serious adverse events (SAEs), adverse events of special interest (AESI), physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters and ECG parameters. All adverse events (AEs) will be categorized using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events and abnormal laboratory test results, if applicable, will be graded according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Safety analyses will generally be descriptive and will be presented in tabular format with the appropriate summary statistics.

2. Adverse Event Collection and Reporting

All clinical adverse events (AEs) occurring after the subject signs the Main ICF and during hospitalization, whether observed by the investigator or reported by the subject, will be recorded on the AE eCRF page. Medical conditions (including laboratory values/vital signs that are out of range) diagnosed or known to exist prior to informed consent will be recorded as part of the medical history.

All AEs, SAEs, and adverse events of special interest (AESI) are to be reported according to the procedures. Laboratory results, vital signs, and ECG results or findings should be evaluated by the investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings (i.e., not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study treatment discontinuation, require corrective treatment, or are considered an AE in the investigator's clinical judgment.

At each visit, the investigator will assess whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject, or elicited through questioning at each study visit. Subjects should be questioned in a general manner, without specifically inquiring about the occurrence of any particular symptoms. The investigator must evaluate all AEs to determine seriousness, severity, and causality, in accordance with the definitions provided. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature.

The investigator should always report the diagnosis as the AE or SAE term. In cases where a diagnosis is unavailable, the primary sign or symptom should be reported as the AE or SAE term, with additional details included in the narrative until a diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, they should be reported as individual entries of AE or SAE.

For events deemed serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure itself is not an AE or SAE, but the reason for the procedure may constitute an AE or SAE. Preplanned (prior to signing the ICF) procedures or treatments requiring hospitalization for preexisting conditions that do not worsen in severity should not be reported as SAEs.

For deaths, the underlying or immediate cause of death should always be reported as an SAE. Disease progression is a study endpoint and consequently should not be reported as an AE/SAE. However, in cases where a subject dies from progressive disease with no other immediate causes, "disease progression" should be reported as an SAE.

Any serious, untoward event that may occur subsequent to the reporting period and that the investigator assesses as related to study treatment should also be reported and managed as an SAE.

3. Adverse Events of Special Interest

✧ Opioid-related adverse drug events (ORADEs)

Adverse drug events related to opioids (ORADEs) encompass a wide spectrum, ranging from respiratory depression and circulatory arrest to nausea and vomiting. The most common among these include urinary retention, pruritus, nausea, vomiting, as well as central nervous system effects such as somnolence and dizziness.

✧ Postoperative Pulmonary Complications

Postoperative pulmonary complications can be regarded as a comprehensive outcome measure. We adhere to the European Perioperative Clinical Outcome definitions for postoperative pulmonary complications.

Complication	Definition
Respiratory infection	Patient has received antibiotics for a suspected respiratory infection and met one or more of the following criteria: new or changed sputum, new or changed lung opacities, fever, white blood cell count $> 12 \times 10^9 l^{-1}$
Respiratory failure	Postoperative $PaO_2 < 8$ kPa (60 mmHg) on room air, a PaO_2:FiO_2 ratio <40 kPa (300 mmHg) or arterial oxyhaemoglobin saturation measured with pulse oximetry < 90% and requiring oxygen therapy
Pleural effusion	Chest radiograph demonstrating blunting of the costophrenic angle, loss of sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows
Atelectasis	Lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area, and compensatory over-inflation in the adjacent non-atelectatic lung
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators
Aspiration pneumonitis	Acute lung injury after the inhalation of regurgitated gastric contents

✧ Infection and Sepsis

Infection is defined as the pathological process caused by the invasion of pathogenic or potentially pathogenic microorganisms into usually sterile tissues, fluids, or body cavities. According to the Third International Consensus Definitions Task Force, sepsis is defined as life-threatening organ dysfunction resulting from a dysregulated host response to infection. Organ dysfunction can be identified by an acute change in the total SOFA score of ⩾2 points due to the infection. Septic shock, a subtype of sepsis, is characterized by circulatory and cellular/metabolic abnormalities profound enough to substantially increase mortality. Patients with septic shock can be identified through a clinical construct of sepsis, with persisting hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) ⩾65 mm Hg and a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

The qSOFA includes the following items and scoring system:

Respiratory rate ⩾22 breaths/minute;

Altered mentation;

Systolic blood pressure ⩽100 mm Hg.

✧ Procedure-Related Complications

Local anesthetic systemic toxicity (LAST)

LAST is a potentially life-threatening complication that occurs when a bolus of local anesthesia (LA) is inadvertently injected into peripheral tissue or venous or arterial circulation. The systemic distribution of the LA leads to LAST, which has devastating effects on the cardiovascular and nervous systems.

Specific complications

Specific complications of nerve block include puncture site infections, hematomas at the puncture site, nerve damage, pneumothorax, hemothorax, intrathecal injection, ipsilateral brachial plexus block, and hemidiaphragmatic paresis.

4. Adverse Event

✧ **Definition of Adverse Event**

An adverse event (AE) refers to any untoward medical occurrence in a subject administered a pharmaceutical product, which doesn't necessarily have to have a causal relationship with the treatment. This includes any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, regardless of whether it's considered related to the product.

Serious Adverse Events (SAEs) and Adverse Events (AEs), defined according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0, overall and by system organ class and preferred term.

✧ **Serious Adverse Event**

An SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

✧ **Severity Assessment**

All AEs will be graded (1 to 5; see below) according to the latest NCI-CTCAE version 5.0:

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening consequences; urgent intervention indicated
- Grade 5 Death related to AE

Severity versus Seriousness: Severity is used to describe the intensity of a specific event, however, the event itself may be of relatively minor medical significance (such as severe headache). Seriousness of an event is based upon a universal and global regulatory definition for reporting SAEs to regulatory agencies. For example, Grade 4 (life-threatening

consequences; urgent intervention indicated) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 may or may not be assessed as serious based on the seriousness criteria. Overall, the severity of an event may be graded by the investigator as Grade 1 or 2, but if the subject presents to the emergency facility for evaluation and is hospitalized overnight for observation that
immediately makes the event serious based upon hospitalization without regard to the investigator assessment of severity.

5. Serious Adverse Event Reporting - Investigator Procedure

All adverse events (AEs), serious adverse events (SAEs), events of special interest, and overdoses will be documented in the electronic case report form (eCRF).

Relevant information concerning adverse events of special interest will be gathered through targeted questionnaires integrated within the respective eCRFs in the clinical research database, irrespective of severity.