



Sweden



National appendix

National appendix version and date

Version 1.1, 2026-01-20

Corresponding protocol version and date

Version 1.13, 2025-11-25

Applicable protocol registration numbers

Clinical Trials Information System (CTIS)

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Websites:

www.cric.nu/empress

www.incept.dk/empress

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1 | Administrative information

1.1 | Protocol and national appendix structure

This is a national appendix to the *Empirical Meropenem versus Piperacillin/Tazobactam for Adult Patients with Sepsis (EMPRESS) trial* protocol. Everything described in the version of the protocol listed on the front page applies except where explicitly stated otherwise. This national appendix only covers details that are specific to this country and not otherwise covered by the primary *EMPRESS* protocol. The national appendix should be read along with the primary protocol.

1.2 | National coordinating centre

National coordinating centre

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2 | Abbreviations

CTIS: *Clinical Trials Information System*

eCRF: *electronic case report form*

EMPRESS: *Empirical Meropenem versus Piperacillin/Tazobactam for Adult Patients with Sepsis*

EU: *European Union*

EUCT number: *European Union Clinical Trials Information System (CTIS) number*

GCP: *Good Clinical Practice*

HRQoL: *health-related quality of life*

3 | Screening, inclusion, and informed consent procedures

The following section contains specific procedures that apply for Sweden in addition to the generic principles outlined in the primary protocol.

Swedish informed consent procedure

First, ICU patients fulfilling all inclusion criteria and no exclusion criteria will be screened and randomised to the trial by trained and delegated staff. As soon as possible hereafter, informed consent for continuation in the trial will be obtained from the participants when he/she is physically and mentally recovered to receive information about the trial and able to give written informed consent. All informed consents will be obtained by medical doctors trained in the trial protocol and follow all applicable regulations.

Participant's relatives will be given oral information either in person or by telephone, as soon as conveniently possible, to inform that the patient has been included in the trial.

Written informed consent will be obtained as soon as the participant's condition has stabilised, and cognitive state improved sufficiently for them to understand the information and decide about participation in the trial. It is anticipated that most participants will recover and be able to provide informed consent within four weeks after inclusion in the trial. An attempt to obtain consent will be made regularly while the participant remains hospitalised in any department within the hospital. If there is doubt about the participant's mental status, this will be evaluated using the validated 4AT delirium assessment tool [1] as per agreement in previous similar trial set-up (EUCT 2023-504584-16-00). A score greater than 0 indicates possible cognitive impairment and, therefore, insufficient cognitive function to provide informed consent. Consent will only be obtained if the 4AT score is 0. Every contact and assessment of the participant's ability to consent, including the score of the 4AT, will be documented in the local site file. The assessment of consent capacity will be conducted by medical doctors trained in the trial protocol and delegated to perform this task. For participants, both oral and written information will be given by a medical doctor trained and certified in the trial protocol. If it is not possible to obtain consent from the participant (e.g., the participant has been discharged to another hospital without participating sites), we will inform the participant by phone call and send written information and collect consent by mail or by electronic signature when this is available.

If a participant is unable to provide consent but has a legally designated representative, informed consent will be sought from this representative without undue delay, i.e., as soon as possible after the first trial-related intervention. If there is no appointed legal representative, the investigator will initiate the procedure to have such a representative appointed without undue delay, in accordance with Swedish legislation. If the participant regains sufficient cognitive capacity before

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a legally designated representative has been appointed, the procedure for this will be terminated, and informed consent will instead be sought directly from the participant as soon as practically possible.

The timing and steps taken to seek informed consent from a legally designated representative, or to initiate the appointment of such representative, will be documented in the electronic case report form (eCRF) or the investigator site file.

Consent given by a legally designated representative will be reassessed and sought from the participant if they regain sufficient cognitive function as previously described. If the participant dies before it has been possible to obtain consent or before a legally designated representative is appointed, the participant will remain in the trial.

Of note, all consenting parties will be provided with written and oral information about the trial allowing them to make an informed decision about participation in the trial. Written information and the consent forms will be subject to review and approval by the applicable competent authorities (e.g., the relevant ethical committees). All consent forms will be signed by the consenting party and the medical doctor who has provided trial information for the consenting party. We will emphasise that the consenting party has at least 24 hours to decide whether to give consent or not. The consenting party can, at any time and without further explanation, withdraw consent to continued participation in the trial.

Trial personnel

The screening will be done by trained trial staff in collaboration with the treating clinical doctor, who ultimately decides if a patient can be enrolled in the trial. When a candidate patient is identified, a member of the trained trial staff will screen the patients in the eCRF. Collection of informed consent will be performed by medical doctors who are trained and certified in the trial protocol. If questions arise during the informed consent procedure, coordinating trial staff (including the sponsor) can be reached through the 24-h trial hotline. All medical doctors with consent functions in the *EMPRESS* trial will be trained, delegated and approved according to *Good Clinical Practice (GCP)* guidelines before engaging in the trial.

4 | Discontinuation and withdrawals

The protocol outlines the procedure for handling discontinuations and withdrawals in *EMPRESS* according to the applicable Swedish regulations.

5 | Outcomes and safety

5.1 | EQ-5D-5L value set

For the EQ-5D 5 level (EQ-5D-5L) instrument used to assess health-related quality of life (HRQoL) at day 180, we will use the Swedish national EQ-5D-5L national value set [2] for participants enrolled in Sweden to calculate EQ-5D-5L index values for the primary analyses.

5.2 | Safety outcomes

The *EMPRESS* protocol outlines the handling of safety outcomes in *EMPRESS* trial based on European Union (EU) regulations [3] for the assessment of safety outcomes for pharmacological interventions (investigational medicinal products); this procedure applies to Sweden with no country-specific adaptations and no additional collection or reporting of additional safety data.

6 | Other considerations

Insurance

Trial participants in Sweden are covered by the Patientförsäkringen [4] and Läkemedelsförsäkringen [5].

7 | Summary of changes

Version 1.1, 2026-01-20:

- Section 3 updated to align procedures for consent from legally designated representatives with CTR Art. 35(2)(a) and Swedish legislation, removing fixed timeframes and specifying initiation without undue delay.

Version 1.0, 2025-11-25: first version submitted for approval.

8 | References

1. Johansson, Y.A., et al., *Diagnostic accuracy and clinical applicability of the Swedish version of the 4AT assessment test for delirium detection, in a mixed patient population and setting*. BMC Geriatr, 2021. **21**(1): p. 568.
2. Sun, S., et al., *Estimating a social value set for EQ-5D-5L in Sweden*. Health Qual Life Outcomes, 2022. **20**(1): p. 167.
3. 2017., E.-V.-C.T.G. *EudraLex - EU Legislation. Risk proportionate approaches in clinical trials - Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use*. . 2017 [cited 2023 December 20, 2023)].
4. *Löf regionernas ömsesidiga försäkringsbolag*. Available from: www.lof.se.
5. *Läkemedelsförsäkringen* Available from: www.lff.se.