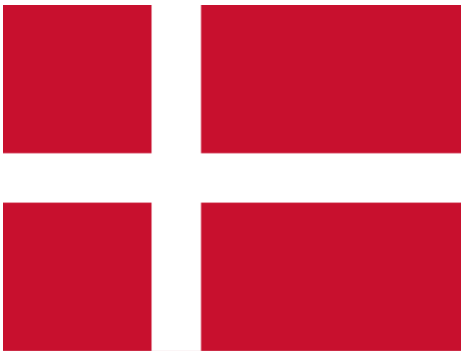
The Intensive Care Platform Trial (INCEPT)

Denmark



National appendix

National appendix version and date
Version 1.3, 2025-02-13

Corresponding core protocol version and date
Version 1.3, 2025-02-13

Website: www.incept.dk

Applicable core protocol registration numbers
European Union Clinical Trials Information System (CTIS) EUCT number: 2024-516208-41-00.
ClinicalTrials.gov identifier: NCT06667999.
Universal Trial Number: U1111-1313-8171.

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1 | Administrative information

1.1 | Protocol and national appendix structure

This is a national appendix to the *Intensive Care Platform Trial (INCEPT)* core protocol. Everything described in the version of the core 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 *INCEPT* core protocol. The national appendix should be read along with the core protocol.

1.2 | National coordinating centre

National coordinating centre
Department of Intensive Care 4131
Copenhagen University Hospital – Rigshospitalet
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A list of national coordinating investigators in all participating countries will be made available on the INCEPT website prior to first inclusion in each country and continuously updated.

2 | Abbreviations

CTIS: *Clinical Trials Information System*
eCRF: *electronic case report form*
EU: *European Union*
EUCT number: *European Union Clinical Trials Information System (CTIS) number*
GCP: *Good Clinical Practice*
HRQoL: *health-related quality of life*
INCEPT: *the Intensive Care Platform Trial*

3 | Screening, inclusion, and informed consent procedures

The following section contains specific procedures that apply for Denmark in addition to the generic principles outlined in the core protocol, including the use of a modular approach to the informed consent procedure with information only given for the domains that are relevant for a specific participant.

Danish informed consent procedure
First, patients fulfilling all platform inclusion criteria and no exclusion criteria will be screened and randomised to domains for which they fulfil all platform and domain-specific eligibility criteria by trained trial staff. As soon as possible hereafter, informed consent for continuation in the platform trial (including all applicable domains) will be obtained from a legally designated representative (in Denmark the closest relative) and a legal guardian. In Denmark, a legal guardian is a doctor that is independent of the trial, has knowledge of the clinical condition, and is familiar with the trial protocol (including the relevant domain-specific appendices) to such extent that he/she can judge for each patient, if it will be reasonable to enrol the patient in the trial. All informed consents will be obtained by medical doctors trained and certified in the trial protocol and follow all applicable regulations.

For the relatives, oral information will be given either in person or by video call according to the relative's preferences. Video calls, where used, will be individual, direct, and with simultaneous dialogue following adequate identification of the participant and relatives, and the right to confidentiality will be ensured by ensuring that all involved parties are in a place and time where they can talk privately prior to discussing the trial. Relatives may be contacted by regular phone calls to arrange the meeting in person or via video call, according to personal preferences.
The relative has the right to bring a companion. If informed by video call, we will arrange a time and date for a video conversation with a medical doctor who is trained and certified in the trial protocol and certified in obtaining informed consent. During this conversation, we will arrange how to send the written information to the relative (i.e., via e-mail or by post). We will encourage the relative to read the written information before the next conversation. We will also encourage the relative to bring a companion; in this case, the video conversation will be held with the video call on speaker. After we have informed the relative about the trial, we will ask the relative to return the signed consent form by post.

Participants will be asked for informed consent as soon as possible hereafter. For participants, both oral and written information will be given preferably in person by a medical doctor trained and certified in the trial protocol. If this is not possible (e.g., the participant has been discharged to another hospital without participating sites), we will inform and collect consent from the participant by video call (as described above). Either way, the participant has the right to bring a

companion to the conversation. This conversation may similarly be arranged by contact through regular phone calls, and the participants can choose to receive the oral information in accordance with personal preferences.

Of note, all consenting parties will be provided with written and oral information about the platform trial (including all relevant domains) 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). The written information material will be in modular format and consist of general information about *INCEPT* and additional information sheets about all relevant domains. The informed consent procedure will be common and simultaneous for *INCEPT* including all applicable domains, with explicit, written informed consent to each specific domain using separate informed consent forms, and with consent to one or more domains constituting consent to *INCEPT* including all elements that are common between domains. 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 platform trial or specific domains.

Lack of informed consent from the participant's relatives

If information about the participant's relatives is not available after inclusion, the investigator will seek information from e.g., the participant's general practitioner, the police, nursing homes etc. In these situations, it may take, e.g., 1-2 weeks to conclude that no relative can be identified. If a relative is not identified and the participant remains unable to consent themselves, the trial intervention(s) will be discontinued but data collection will be continued. All initiatives to identify the participant's relatives will be documented in patient files, logs or similar. The same procedure has been used in other approved related trials [1–5] .

Lack of informed consent from the participant's relative and the participant deceases

If the participant deceases before informed consent is obtained (due to rapid progression of critical illness or because the participant's relative is not yet identified), the consent procedure will be stopped. If the participant has been correctly included in the trial and reasonable attempts to identify relatives and obtain their informed consent have been made, the collected data will be kept and analysed, and additional data from the electronic patient record may similarly be collected and analysed.

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 and individual domains. When a candidate patient is identified, a member of the trained trial staff will screen the patients in the

electronic case report form (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 *INCEPT* trial will be trained and approved according to *Good Clinical Practice* (GCP) guidelines before engaging in the trial.

4 | Discontinuation and withdrawals

The core protocol outlines the procedure for handling discontinuations and withdrawals in *INCEPT* according to the applicable Danish regulations.

5 | Outcomes and safety

5.1 | EQ-5D-5L value set

For the EQ-5D-5L instrument [6] used to assess health-related quality of life (HRQoL) at day 180, we will use the Danish national EQ-5D-5L national value set [7] for participants enrolled in Denmark to calculate EQ-5D-5L index values for the primary analyses.

5.2 | Safety outcomes

The *INCEPT* core protocol outlines the handling of safety outcomes in *INCEPT* domains based on European Union (EU) regulations [8] for the assessment of safety outcomes for pharmacological interventions (investigational medicinal products); this procedure applies to Denmark with no country-specific adaptations and no additional collection or reporting of additional safety data.

6 | Other considerations

Insurance

Trial participants in Denmark are covered by the Danish law *"Lov om klage- og erstatningsadgang indenfor sundhedsvæsenet"* [9] as described in the *INCEPT* core protocol.

7 | Summary of changes

This section summarises all changes to the national appendix after initial submission for approval.

Version 1.3, 2025-02-13:

- Updated to change core protocol version.

Version 1.2, 2025-02-07:

- Updates and clarifications to the informed consent procedure (section 3).

Version 1.1, 2025-01-10:

- The national coordinating investigator is no longer listed in the national appendix, instead a statement is included that a list of national coordinating investigators will be made available and continuously updated on the trial website (section 1.2).
- Added reference to the core protocol with regards to the use of a modular approach to the informed consent procedure (section 3).
- Clarifications regarding the procedure for data collection and analysis if a participant deceases before informed consent from the participant's relative has been obtained (section 3).
- Minor corrections, updates, and semantic edits in multiple places not leading to any changes in meaning.

Version 1.0, 2024-11-04: first version submitted for approval.

8 | References

[1] Granholm A, Munch MW, Meier N, Sjövall F, Helleberg M, Hertz FB, et al. Empirical meropenem versus piperacillin/tazobactam for adult patients with sepsis (EMPRESS) trial: Protocol. Acta Anaesthesiol Scand 2024. https://doi.org/10.1111/aas.14441.

[2] The COVID STEROID 2 Trial Group. Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia. JAMA 2021;326:1807. https://doi.org/10.1001/jama.2021.18295.

[3] Munch MW, Meyhoff TS, Helleberg M, Kjær MN, Granholm A, Hjortsø CJS, et al. Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia: The COVID STEROID randomised, placebo-controlled trial. Acta Anaesthesiol Scand 2021;65:1421–30. https://doi.org/10.1111/aas.13941.

[4] Meyhoff TS, Hjortrup PB, Wetterslev J, Sivapalan P, Laake JH, Cronhjort M, et al. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. N Engl J Med 2022;386:2459–70. https://doi.org/10.1056/NEJMoa2202707.

[5] Andersen-Ranberg NC, Poulsen LM, Perner A, Wetterslev J, Estrup S, Hästbacka J, et al. Haloperidol for the Treatment of Delirium in ICU Patients. N Engl J Med 2022;387:2425–35. https://doi.org/10.1056/NEJMoa2211868.

[6] Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36. https://doi.org/10.1007/s11136-011-9903-x.

[7] Jensen CE, Sørensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. Appl Health Econ Health Policy 2021;19:579–91. https://doi.org/10.1007/s40258-021-00639-3.

[8] 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. EudraLex - Vol 10 - Clinical Trials Guideline 2017. https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en (accessed December 20, 2023).

[9] Indenrigs- og Sundhedsministeriet. Bekendtgørelse af lov om klage- og erstatningsadgang inden for sundhedsvæsenet (LBK nr 9 af 04/01/2023; Klage- og erstatningsloven). Retsinformation 2023. https://www.retsinformation.dk/eli/lta/2023/9 (accessed May 22, 2024).