



www.cric.nu/empress
empress@cruc.nu

November 2025

Dear friends and colleagues,

EMPRESS status – 100 inclusions and growing!

EMPRESS continues to progress steadily since first inclusion in June. We are delighted to announce that **the 100th participant was included on October 23rd in Aalborg ICU** – a fantastic milestone made possible by the dedication of all sites.

To date, **131 patients** have been enrolled across **8**

active Danish ICUs (Rigshospitalet, Aalborg, Kolding, Odense, Køge, Hillerød, Bispebjerg, and Aarhus East).

In the coming months, we aim to activate **additional Danish sites** including Rigshospitalet (Infectious Diseases), Aarhus (North), Viborg, Hvidovre (ICU and Infectious Diseases), Odense (Infectious Diseases), Slagelse ICU, Randers ICU, Herlev (ICU) and Gødstrup ICU.

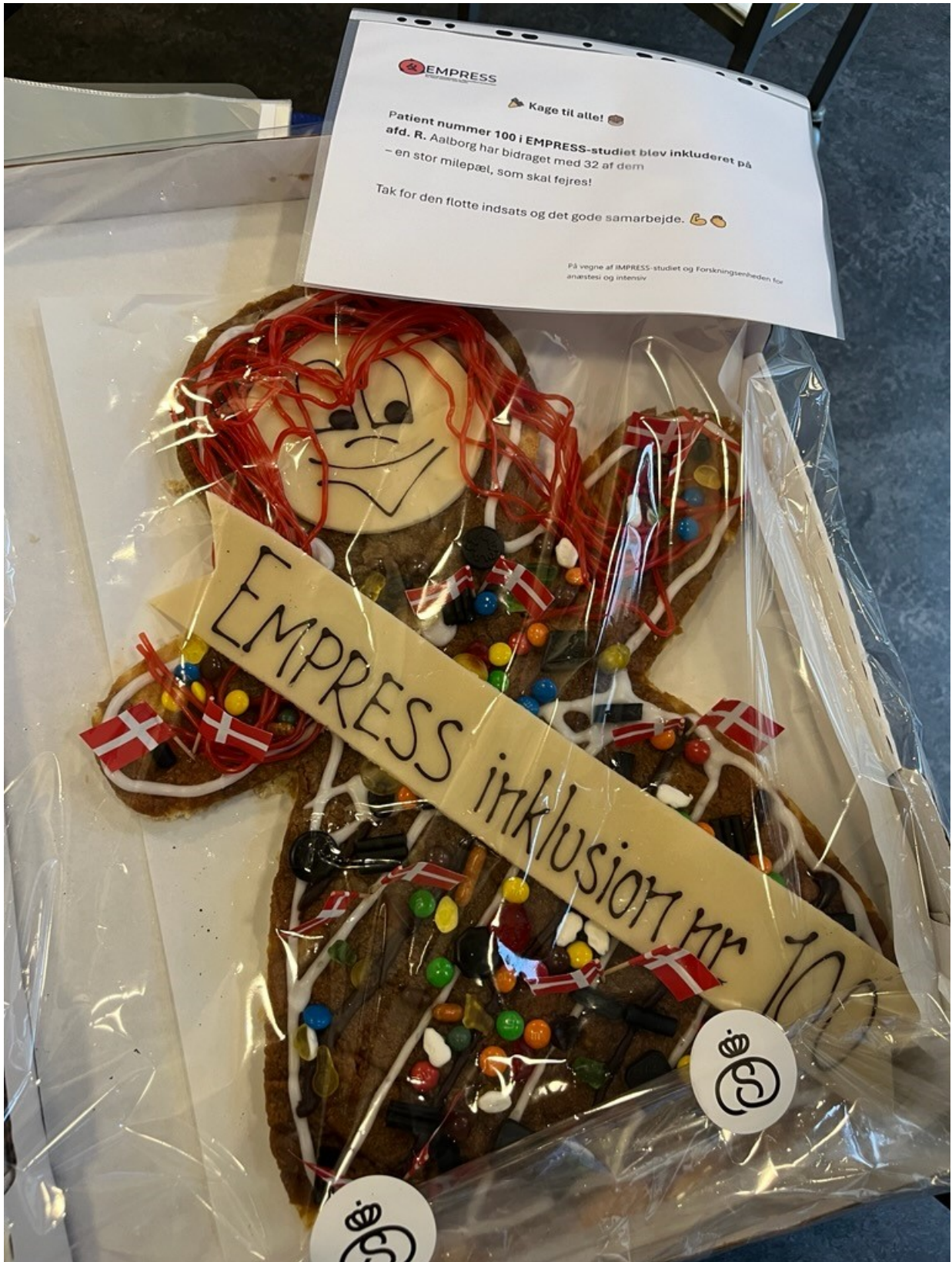
International start-ups in **Sweden, Iceland, and New Zealand/Australia** are also advancing through local approval processes.

At a glance:

Participants included to date: 131

Active sites: 8 (DK)

Next steps: initiation of additional Danish sites, and submission of application to get Sweden, Iceland and New Zealand approved.



To celebrate inclusion number 100, Aalborg celebrated accordingly with an EMPRESS cake.

Consent in acute settings – how does it work?

EMPRESS involves critically ill patients who are unable to provide informed consent at the time of enrolment. Therefore, the trial follows Danish regulations for emergency inclusion:

1. **Primary inclusion** is performed by a trained clinician under the emergency provision.
2. **Consent from a trial guardian** (forsøgsværge) is then obtained as soon as possible after inclusion and **should be obtained for every inclusion**.
3. The relatives must be asked for relative consent on behalf of the participant if the participant is not able to give consent within a reasonable timeframe.
4. If the participant later regains capacity, informed consent must be reaffirmed directly with the participant and **generally cannot happen at the same timepoint as inclusion and randomisation is happening**.

This process ensures ethical and legal validity of enrolment while allowing timely initiation of life-saving treatment, i.e., empirical antibiotic therapy.

If you have any questions regarding documentation, please contact empress@cric.nu for templates and guidance.

eCRF updates & support

If you encounter issues of any kind (access, role permissions, edit checks, or unexpected queries), the hotline is open 24/7: +45 3545 0606 and we are available anytime at empress@cric.nu. When reporting, please include the participant ID (if applicable), the page name, and a screenshot without personal information—this helps us replicate and resolve potential issues within one cycle.

Site file updates – substantial modification approved

A **substantial modification** has recently been approved by the Danish authorities, resulting in several **updates to the Investigator Site File**.

The coordinating center has distributed the updated documents electronically to all involved site investigators, including:

- Revised **Protocol version 1.12 dated 30.09.2025**.
- New **Participant Information**
- Updated **Training logs**

Please ensure your local Investigator Site File and training records are updated accordingly. We understand that this is burdensome, and we hope to not make further changes any time soon.

Often asked questions in EMPRESS

Q: Can we escalate to a broader agent (e.g., a carbapenem) in a participant allocated to piperacillin/tazobactam?

A: Empirical escalation to a non-allocated agent assessed in the trial constitutes a protocol violation and should be avoided unless clinically required for patient safety (e.g., documented resistance, severe deterioration). The protocol does not mandate a specific combination regimen; if broader coverage is needed, you may add agents to the allocated treatment per local guidelines rather than replacing it. If broader Gram-positive is needed clindamycin could be added, if broader Gram-negative coverage is needed ciprofloxacin could be added in combination with the allocated study drug.

Q: Is a patient eligible upon ICU readmission if they previously received piperacillin/tazobactam during a different admission/episode weeks earlier (outside the trial site)?

A: Yes, potentially. If this is a new suspected infection episode, the prior antibiotics were given weeks earlier for an independent admission/indication, and the patient otherwise meets all current inclusion criteria (including any re-enrolment rules), the patient may be included.

Q: A participant allocated to piperacillin/tazobactam now needs empirical treatment again (e.g., due to a pneumonia) within 30 days of enrolment. Should we switch or remain on the allocated arm?

A: Remain on the allocated arm within the protocol-defined allocation period (30 days), unless there is a clear safety reason to change (e.g., allergy, intolerance, culture-proven resistance). Document clinical reasoning and any deviations in the eCRF. From day 31 through 180, we will recommend using the same empirical antibiotic strategy as per the trial allocation if there is a new indication for empirical broad-spectrum antibiotic treatment, but we will not collect data on the use of antibiotics after the intervention period (i.e., day 30) and do not consider this part of the trial intervention.

Q: If erythromycin is given at prokinetic doses to promote gastric emptying, should it be recorded as “other antibiotics” in the eCRF?

A: No. Prokinetic-dose erythromycin is not administered as anti-infective therapy; therefore, it does not need to be recorded as concomitant antibiotic therapy. If your eCRF has a field for other concomitant medications, you may record it there per local practice.

The team behind EMPRESS

EMPRESS is run by a collaborative, multidisciplinary group: Nick Frørup Meier (MD, PhD-student), Morten Hylander Møller (MD, Professor), Anders Granholm (MD, postdoc), Maj-Brit Nørregaard Kjær (CCRN, PhD), Anders Perner (MD, Professor), Milda Grigonyte-Daraskeviciene (MD, PhD-student), Aske Tøgern (MD, PhD-student), and Jehad Ahmad Barakji (MD, PhD-student). Thank you to every investigator, coordinator, and bedside clinician who is screening, consenting, randomising, and capturing high-quality data.



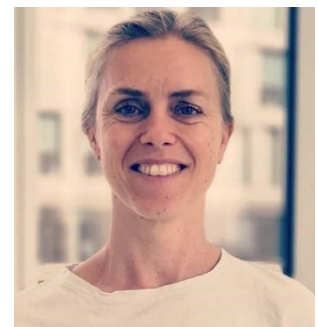
Nick Frørup Meier



Morten Hylander
Møller



Anders Granholm



Maj-Brit
Nørregaard Kjær



Anders Perner



Milda Grigonyte-
Daraskeviciene



Aske Tøgern



Jehad Ahmad
Barakji

With collegial regards,

Nick Frørup Meier, Morten Hylander Møller, Anders Granholm, Maj-Brit Nørregaard Kjær and Anders Perner

On behalf of the EMPRESS Coordinating group