

# Statistical Analysis Plan (SAP)

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**Person writing the SAP:** Paul Blanche

**Principal investigators:** Mette Bondo Mønster & Ulrikka Nygaard

**Protocol title:** Hydrochloric Acid Lock Therapy for Central Line-associated Bloodstream Infections in Patients With Cancer and Hematologic Diseases

**ClinicalTrials.gov ID:** NCT05376566

**Note:** inspiration to write this SAP came from the SAP template provided by TransCelerate [29] as well as recommendations from Gamble et al. [14], Stevens et al. [28] and Evans and Ting [9].

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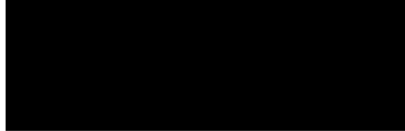
## 1 Statistical analysis plan approval signature page

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**Person writing the SAP:**

Name: Paul Blanche

Position/Title: Associate Professor in Biostatistics



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February 11, 2026

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Signature & Date

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**Approved by:**

Name: Mette Bondo Mønster

Position/Title: MD



February 11, 2026

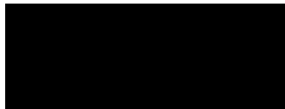
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Signature & Date

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Name: Ulrikka Nygaard

Position/Title: Professor, MD, PhD



February 11, 2026

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Signature & Date

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## 2 List of Abbreviations

- CI: Confidence Interval
- CCOD: clinical cutoff date
- CLABSI: central line-associated bloodstream infections
- CVAD: central venous access device
- HALT: Hydrochloric acid lock therapy
- HSCT: Hematopoietic Stem Cell Transplantation
- ICU: Intensive Care Unit
- IPCW: inverse probability of censoring weighting
- ITT: Intention-to-Treat
- LDH: Lactate dehydrogenase
- SAP: Statistical Analysis Plan
- WHO: World Health Organization

## 3 Introduction

This document is the statistical analysis plan (SAP) for a double-blind, investigator initiated, parallel group, 1:1 randomized, multicenter, superiority trial of Hydrochloric acid lock therapy (HALT) versus placebo (normal saline) in central venous access device (CVAD), to prevent treatment failure of central line-associated bloodstream infections (CLABSI).

The background is that CVAD in patients with hematologic and oncologic diseases has been shown to be associated with substantial risk of producing bloodstream infections - termed central line-associated bloodstream infections (CLABSI). HALT in the CVAD may prevent treatment failure of CLABSI and has been used routinely in Denmark for years, in addition to standard therapy with systemic antibiotics. However, HALT has not been used extensively outside Denmark, presumably because no strong evidence exists to justify its use. Therefore, this trial was initiated to provide such evidence. Based on observational data and the literature, it has been hypothesized that HALT could approximately halve the risk of treatment failure (17% vs 33%). The primary outcome is treatment failure within 6 weeks after HALT or placebo (normal saline). In short, treatment failure is defined by any of those: persistent infection, relapse of CLABSI, new CLABSI, infection-related removal of central access device (CVAD) or infection-related death. Randomization took place within 5 days of confirmation of a positive blood culture/CLABSI. Randomization was stratified by site. Because adults and children were included from different sites, this means that randomization was also stratified by majority: adult ( $\geq 18$  years) versus child ( $< 18$  years).

Children and adults with CLABSI treated at three departments of pediatric oncology and hematology (Aarhus, Odense and Copenhagen University Hospitals) and a department of hematology (Copenhagen University Hospital) have been included in this trial. Recruitment of patients started in June 2022. Re-enrollment was accepted if the patient had a CLABSI episode 6 weeks after the primary infection or if the patient had a new CVAD. When re-enrolled, the patient was randomized again.

Patient and episode accrual will stop before the full sample size is accrued, because of a lower accrual rate than anticipated, as detailed in Sec. 3.1.

The changes to the protocol-planned analyses are summarized in Section 12. We do not consider them as major changes and the rationale for each of them is provided.

### 3.1 Early termination of the trial

The study had a lower accrual rate than anticipated, presumably for three reasons. First, changes in standard cancer treatment protocols resulted in fewer episodes with bacteremia than expected. Second, there was a greater tendency than expected to remove CVAD rather than attempting to preserve them, particularly among adult patients. Third, more patients/parents declined participation in the study than expected, for example due to fear of side effects or unwillingness to undergo additional procedures. April 8th, 2025, a meeting was held (PB, UN, MBM). By that time, around 140 episodes had been included. It was decided to continue the recruitment until March 1st, 2026. Although the target of  $n=250$  episodes would not be reached, the study was not further prolonged because the participating departments lacked the capacity to continue. A sample size of approximately  $n=190$  was estimated to be reached by the end of the trial. This was estimated sufficiently large to provide valuable findings and a power of approximately 72%. Section 11 provides details about power and sample size calculations.

## 4 Objectives, Endpoints, and Estimands

### 4.1 Primary objective, endpoint and estimand

The two treatment strategies (interventions) being investigated are the following.

- **Hydrochloric acid lock therapy (HALT):** Participants receive lock therapy with hydrochloric acid (2.0 molar). The CVAD instillations is carried out by a trained hematologic/oncologic nurse. Hydrochloric acid in a volume corresponding to "dead space" (0.3-1.8 ml) will be instilled in the CVAD and aspirated 10 min later. The instillation is completed three times, as described by Ahmad et al [1].
- **Placebo (normal saline):** same, but using normal saline instead of Hydrochloric acid.

The procedure requires approximately one hour to be completed. In addition to the study intervention, patients in both arms will receive standard of care, including systemic antibiotic therapy. Blood tests for hemolysis will be collected immediately after the procedure and repeated after 24 hours, together with blood cultures and kidney function tests.

The primary outcome is treatment failure within six weeks after intervention defined as either:

- (1) a) persistent infection (persistent positive blood cultures taken 24 hours after HALT/placebo) or  
b) relapse (a new CLABSI with an identical bacterial isolate)
- (2) a new CLABSI with any bacterial isolate
- (3) infection-related removal of central access device (CVAD)<sup>1</sup>

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<sup>1</sup>Defined as removal of CVAD due to suspected or confirmed CLABSI [20]

#### (4) infection-related death <sup>2</sup>

**Remarks:** First, although not explicitly stated above, CLABSI refers only to bloodstream infections occurring while the CVAD that was in place when the intervention was performed is still present. If that CVAD is removed and a new CVAD is inserted, any subsequent CLABSI does not count. This is consistent with HALT being applied to a specific CVAD and with the possibility of re-enrollment if a new CVAD is placed. Second, by definition, some events prevent the primary outcome (treatment failure) from occurring later. Death from causes unrelated to the infection prevents any subsequent treatment failure. Likewise, persistent CLABSI, relapse of CLABSI or a new CLABSI, and infection-related removal of the CVAD and infection-related death cannot occur after the CVAD has been removed. Therefore, a consequence of the definition of the primary outcome (treatment failure) is that it can no longer happen once the patient has died from a cause unrelated to the infection or had CVAD removed. This corresponds to a classical “competing risks” setting [2].

The primary clinical question of interest is: *“Is the risk of treatment failure within six weeks lower after receiving HALT than after receiving placebo, in addition to standard of care, including systemic antibiotic therapy, regardless of initiation of any additional interventions during the follow-up when needed to ensure good clinical care, among patients with CLABSI?”*

Accordingly, the primary estimand, hereafter referred to as the “ITT estimand”, is described by the following attributes:

- Population: Children and adults receiving treatment for cancer or a hematologic disease newly diagnosed with CLABSI without planned CVAD removal within 6 days and not admitted to ICU. Here CLABSI is defined as a positive blood culture, not secondary to infections at another site.
- Endpoint: treatment failure as described above by items (1)–(4).
- Treatment: the investigational interventions (“HALT” vs “Placebo”, as defined above) regardless of adherence and of any subsequent treatment decision or intervention during the follow-up needed to ensure good clinical care (“treatment policy strategy”, see [17]).
- Intercurrent events: Death and removal of central access device are both addressed by the endpoint definition (“composite variable strategy”, see [17]). They define the occurrence of the primary outcome when they are related to the infection, and prevent it after their occurrence, when they are not related to the infection. Non adherence (i.e., overruling randomization or incomplete HALT procedure, which occurs if instillation is completed less than three times) is addressed by the treatment condition of interest attribute (“treatment policy strategy”, see [17]). Any other treatment decision is also addressed by the treatment condition of interest attribute (“treatment policy strategy”, see [17]). No other relevant intercurrent events are anticipated.
- Population-level summary: Difference in 6-weeks risk of treatment failure between treatment conditions.

**Remarks:** the above estimand corresponds to an “Intention to Treat” estimand and principle. It preserves fully the benefit of randomization and aligns well with the fact that this trial is essentially a

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<sup>2</sup>Defined as a death in which a central line associated bloodstream infection (CLABSI) was identified as either the underlying cause of death or a significant contributing factor, in accordance with the WHO framework for underlying and contributing causes of death.

pragmatic trial [25, 13], for which few trial-specific intercurrent events are expected, if any. Because of the “competing risks” setting already mentioned above, instead of using the terminology “6-weeks risk” in the population-level summary attribute, other authors might have instead used the terminology “6-weeks absolute risk” or “cumulative incidence function at 6-weeks”, see e.g., [3] and reference therein.

## 4.2 Supplementary estimand for the primary outcome

A supplementary estimand, hereafter referred to as the “hypothetical estimand”, will be considered. It relates to the concept of “per-protocol effect” [16] and to the usual objective of an explanatory trials exploring a physiological effect [25, 13]. This complements the ITT (primary) estimand described in Sec. 4.1, which more closely relates to the objective of a typical pragmatic trial informing *“a clinical or policy decision by providing evidence for adoption of the intervention into real-world clinical practice”* [13].

The “hypothetical estimand” is described by the following attributes:

- Population: as for the “ITT estimand” in Sec. 4.1, but with two additional restrictions. First, no patients would be later diagnosed with a culture-verified infection originating from a site other than the CVAD lumen (“Principal stratum strategy”, see [17]). Second, all patients would be able to receive full instillation protocol (“Principal stratum strategy”, see [17]).
- Endpoint: same as for the “ITT estimand” in Sec. 4.1.
- Treatment: the investigational interventions (“HALT” vs “Placebo”, as defined above) regardless of any subsequent treatment decision or intervention during the follow-up needed to ensure good clinical care (“treatment policy strategy”, see [17]). Unlike for the “ITT estimand” of Sec. 4.1, a scenario in which all patients receive their assigned treatment is envisaged (i.e., no overruling of randomization, “hypothetical strategy”, see [17]).
- Intercurrent events: As for for the “ITT estimand” in Sec. 4.1, infection-related death and infection-related removal of central access device are both addressed by the endpoint definition. They define the occurrence of the primary outcome. Death unrelated to the infection prevents the occurrence of the primary outcome after its occurrence (“composite variable strategy”, see [17]). Unlike for the “ITT estimand” of Sec. 4.1, a scenario in which removal of central access device unrelated to the infection does not occur is envisaged (“hypothetical strategy”, see [17]). Also, a scenario in which all patients receive their assigned treatment is envisaged (i.e., no overruling of randomization, “hypothetical strategy”, see [17]). Not receiving full instillation protocol is addressed by the population attribute (“Principal stratum strategy”, see [17]). Any other treatment decision is addressed by the treatment condition of interest attribute, as for the “ITT estimand” of Sec. 4.1 (“treatment policy strategy”, see [17]). No other relevant intercurrent events are anticipated.
- Population-level summary: same as for the “ITT estimand” in Sec. 4.1

## 4.3 Safety outcomes

There are three safety outcomes:

**S1:** Infusion-related reactions within 24 hours, defined as either anaphylactic shock, pain, rash or sensory disturbances.

**S2:** Death or admission to ICU associated to infection within six weeks.<sup>3</sup>

**S3:** Mechanical catheter damage (defined as split or fracture) or catheter occlusion requiring thrombolytic therapy, within six weeks.

For each of the safety outcomes **S1**, **S2** and **S3**, the objectives are to estimate the risks of the outcome in the two arms; as well as the risk difference. The corresponding estimands are essentially similar to that of the primary outcome described in Section 4.1, except for the definition of the endpoint.

#### 4.4 Exploratory outcomes

Exploratory outcomes are those listed below. Note that the two first exploratory outcomes (**E1a** and **E1b**) are the two complementary parts that sum to **E1**: “Number of days with antibiotic treatment within 6 weeks after admission for CLABSI”. This exploratory outcome was originally listed in the protocol, but it is no longer pre-specified in this SAP. However, reporting the two outcomes **E1a** and **E1b** separately (instead of their sum **E1**) provides more information and, more importantly, was considered clinically more relevant,. Hence exploratory outcome **E1** has been replaced by **E1a** and **E1b**. The last four exploratory outcomes (**E4–E7**) are the individual components that define the primary outcome.

**E1a:** Number of days of antibiotic treatment for the CLABSI episode leading to inclusion in the study. This is defined as the total number of days the patient was prescribed antibiotic therapy (both intravenous and oral), calculated from the date of admission with CLABSI until completion of CLABSI treatment.<sup>4</sup>

**E1b:** Number of days of intravenous antibiotic therapy administered after completion of CLABSI treatment and within 6 weeks following instillation with HALT or placebo.

**E2:** Restart of IV antibiotics or treatment failure within 6 weeks. Defined as either 1) treatment failure within 6 weeks (primary outcome) or 2) admission for intravenous antibiotic therapy after completion of CLABSI treatment, initiated because of suspected infection despite negative blood cultures, occurring within 6 weeks following instillation with HALT or placebo.

**E3:** New CLABSI with an identical bacterial isolate within 6 months (i.e., as component 1.b in the definition of the primary outcome, which is a composite outcome. However, here the horizon is 6 months instead of 6 weeks).

**E4:** a) persistent infection (persistent positive blood cultures taken 24 hours after HALT/placebo) or b) relapse (a new CLABSI with an identical bacterial isolate)

**E5:** a new CLABSI with any bacterial isolate

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<sup>3</sup>Infectious-related ICU admission is defined as an ICU admission in which a central line-associated bloodstream infection (CLABSI) was the primary indication for ICU admission or a significant contributing factor to the clinical deterioration leading to ICU admission, in accordance with the WHO framework for underlying and contributing causes. Infectious-related death is defined as a death in which a central line-associated bloodstream infection (CLABSI) was identified as either the underlying cause of death or a significant contributing factor, in accordance with the WHO framework for underlying and contributing causes of death.

<sup>4</sup>Precisely, until completion of CLABSI treatment or a maximum of 6 weeks, although completion of CLABSI treatment is expected to end long before 6 weeks.

**E6:** infection-related removal of central access device (CVAD)

**E7:** infection-related death

**Remarks:** In Denmark, all drug prescriptions from all doctors are registered in the Shared Medication Record (“Fælles Medicinkort”, aka FMK). The necessary data to compute **E1a**, **E1b** and **E2** will be extracted from this central registration system. To define **E1a**, **E1b**, number of days are defined as number of days for which the patient has received treatment at some point during the day. Observations are intergers, not decimals. The exact duration of treatment within each day (e.g., 12h or 24h) will not enter into the calculation, even if known. Treatment durations are computed from the recorded dates of start and end of treatment episodes.

## 5 General Considerations

### 5.1 Within-patient correlation between CLABSI episodes

A patient can be randomized more than once and consequently a patient can contribute with more than one CLABSI episode. Re-enrollment is accepted if the patient has a new CLABSI episode at least 6 weeks after the instillation of HALT/placebo during the primary infection, or if the patient has had his or her CVAD replaced. We cannot rule out with certainty that the outcome from two CLABSI episodes of the same patient are not more likely similar than the outcome of two episodes from two different patients. That is, we cannot rule out within-patient correlation between episodes for sure. However, we are confident that this correlation is negligible if it exists.

The rationale is that two episodes in the same patient should be considered distinct because (1) the patients will be at a different stage in the course of their primary disease (hematologic malignancy or solid cancer) and chemotherapy treatment, and (2) the subsequent infection will most often represent a new infectious episode caused by a different pathogen (this applies to approximately 80–90% of cases, based on Danish data from 2015–2020). Hence, a patient at the time of re-enrollment will differ substantially from himself or herself at time of previous enrollment. Consequently, we do not expect that the outcome from two CLABSI episodes from the same patient are more likely similar than the outcome of two episodes from two different patients. Accordingly, the main analysis will not be adjusted for a potential within-patient correlation between CLABSI episodes.

However, for completeness and as a sensitivity analysis, the main analysis of the primary outcome will be replicated using a standard error computation that takes into account the potential within-patient correlation between CLABSI episodes. Instead of a usual non-parametric bootstrap approach, a non-parametric cluster bootstrap approach will be used for that purpose [8, Sec. 3.8] (see Section 7.2).

### 5.2 Statistical Hypotheses

The following (confirmatory) 1-sided hypothesis is planned to be tested, in relation to the primary objectives (detailed in Sec. 4.1).

- Null hypothesis: the risk of treatment failure within 6 weeks is higher when using HALT than when using placebo (normal saline). Formally,  $\mathcal{H}_0 : \pi_1 - \pi_0 \geq 0$ , where  $\pi_1$  and  $\pi_0$  are the 6-week risks after HALT or placebo, respectively.

versus

- Alternative hypothesis: the risk of treatment failure within 6 weeks is lower when using HALT than when using placebo (normal saline). Formally,  $\mathcal{H}_0 : \pi_1 - \pi_0 < 0$ .

Operationally the hypotheses will be evaluated by two-sided tests at 5% and matching 95% two-sided CI rather than by a one-sided test at 2.5% and matching 97.5% one-sided CI; which is a standard approach [6, 12].

### 5.3 Multiplicity Adjustment

No multiple testing correction will be used, as formal hypothesis testing will be performed only for the primary estimand described in Section 4.1. Reporting for other endpoints/estimands will be limited to point estimates of effects with 95% (two-sided) confidence intervals. The widths of the intervals will not be adjusted for multiplicity and therefore it will not be possible to use them in place of formal hypothesis testing. This is in line with common recommendations [23].

### 5.4 Missing and censored Data

No missing data are expected for the primary outcome, safety outcomes **S1-S3** and exploratory outcomes **E1a**, **E1b** and **E2**. This is because we will have access to all relevant hospital charts (and “Shared Medication Record”, as mentioned in Sec 4.4). For estimating the hypothetical estimand described in Section 4.2, the time to treatment failure will be censored at the time of removal of central access device catheter unrelated to the infection, whenever it occurs. For **E3**, for all CLABSI episodes randomized less than 6 months before clinical cutoff date (CCOD), time to **E3** will be censored at CCOD. Specifically, CCOD will be defined at 6 weeks (i.e., 42 days) after the last possible date of inclusion. Inclusion will stop March 1st, 2026, hence CCOD is April 12, 2026.

### 5.5 Covariate adjustment

The main target of inference is a “marginal” estimand (i.e., a marginal treatment effect) [22, 27], also often termed as “unconditional” [11], similar to that of a simple unadjusted analysis. Although the main analysis will use covariate adjustment, the primary goal of covariate adjustment will be to improve precision in estimating the marginal treatment effect [22, 27].

Covariate adjustment will be performed for the main analysis of the primary outcome and we plan to adjust for study site and type of pathogen, as these variables are expected to be prognostic of the primary outcome; see Sec. 7.1. Note that adults and children were included from different sites, which is the first reason we expect study site to be a relevant prognostic variable. Children and adults have substantially different primary conditions and treatment protocols. Also, CVAD use is not completely similar for adults and children. These differences are suspected to lead to different risks of treatment failure. Second, randomization was stratified by site, which further increases the incentive to adjust for site, in order to follow usual recommendations [11, 18]. Third, one site (Aarhus) used Taurolock, a catheter lock solution with antimicrobial and anticoagulant efficacy, whereas the others did not. No other variables will be adjusted for, as no other factor is suspected to have a strong association with the risk of treatment failure within 6 weeks.

No covariate adjustment is planned for safety outcomes, which are expected to be rare. No covariate adjustment is planned for exploratory outcomes **E1a**, **E1b** and **E3-E7**, but a similar covariate adjustment as for the primary outcome is planned for **E2**, to facilitate the comparison of the results to those of the primary outcome.

## 5.6 Time zero

Note that all outcomes are all defined within a specific timeframe (6 weeks, 6 months or 24h). To define the timeframe, time zero is start of intervention (HALT or placebo treatment) for all of them except for **E1a**: “Number of days of antibiotic treatment for the CLABSI episode leading to inclusion in the study”. For this one, time zero is start of admission with CLABSI.

## 6 Analysis Sets

- The “**All participants analysis set**” consists of all randomized participants.
- The “**Restricted analysis set**” consists of all randomized participants after excluding patients:
  - (i) who did not receive the full instillation protocol (e.g., received only one out of three HALT/placebo instillations due to catheter issues)
  - (ii) with a culture-verified infection originating from a site other than the CVAD lumen, caused by the same pathogen identified in the blood culture.
  - (iii) with only a single positive blood culture bottle with a potential contaminant organism.

**Remarks and details:** The rationale for item (ii) comes from the definition of CLABSI used to defined the inclusion criteria (and estimand population). Here CLABSI was defined as a positive blood culture not secondary to infections at another site. For some patients included in the trial, it was believed at the time of randomization that they met this definition; however, an infection at another site was subsequently recognized. Item (ii) means that we exclude these patients. The rationale for item (iii) is that, for most patients, at least two blood culture bottles were obtained at admission due to suspected infection. In our definition, at least two blood culture bottles needed to be positive to conclude a culture-verified infection when the isolated microorganism was considered a possible contaminant, whereas only one positive blood culture bottle was sufficient for other organisms [7]. Possible contaminants are defined as: *Coagulase-negative Staphylococci*, *Corynebacterium spp.*, *Cutibacterium acnes*, *Micrococcus spp.*, and *Bacillus spp.* [7]. However, for some patients only one blood culture was obtained (e.g., small children for whom only limited blood could be drawn), and in some patients only a single culture bottle grew a possible contaminant. These patients were included because the finding was interpreted by the treating physician as true bacteremia, and the patients received targeted antibiotic therapy. However, as these cases did not fulfill the above-mentioned definition, they are excluded according to item (iii).

## 7 Analyses of primary outcome

### 7.1 Main analysis of primary outcome

The analysis will use the “All participants analysis set” and corresponds to an “Intention-to-treat” (ITT) analysis for the analysis of the primary outcome and primary estimand detailed in Section 4.1. We will perform “Wald-type” inference for the risk difference as follows. The 95% CIs will be computed as “Est.  $\pm$  1.96·SE”, where “Est.” denotes the point estimate and SE the corresponding standard error. For the hypothesis test of superiority, we will use the test statistic  $Z = \text{Est.}/\text{SE}$  and its asymptotic normal distribution. We will consider the results statistically significant if the p-value of the two-sided test is below 5%, or equivalently, if the upper limit of the 95%-CI is below 0.

We will use logistic regression together with standardization to estimate the six weeks risks in each arm with two-sided 95%-CIs, their difference with two-sided 95%-CI and the corresponding p-value. This approach corresponds to using the standardized estimator advocated in Steingrimsdottir et al. [27]. Standard errors will be computed by non-parametric bootstrapping. This approach is promoted and outlined in a recent FDA guidance document [11]. Specifically, we will adjust for two categorical variables: study site (three levels) and type of pathogen (two levels), as already discussed in Sec. 5.5. The study site variable adjusted for will include only three levels, not four, as we will merge the two levels corresponding to the pediatric department of Odense and Copenhagen University Hospitals. The rationale for merging is that the department of this two sites work in very close collaboration and because the sample size from Odense is not large. The type of pathogen (pathogenic or less pathogenic) is defined as described in Section 10.2.3. It is expected to be prognostic of treatment failure, for instance via a difference in virulence or response to HALT. These variables will be included in the multiple logistic model in addition to the binary variable that indicates the randomized assignment to HALT or placebo, according to the ITT principle. Computation of the standardized estimator and its robust standard error via bootstrap will be performed as described in appendix A.5 in Steingrimsdottir et al. [27] (with 1000 bootstrap samples).

## **7.2 Sensitivity analysis: robustness to the assumption of no within-patient correlation between CLABSI episodes**

This subsection relates to the sensitivity analysis mentioned in Section 5.1. We will proceed exactly as described in Section 7.1, except that we will use a non-parametric cluster bootstrap approach instead of the usual non-parametric bootstrap approach described in appendix A.5 of Steingrimsdottir et al. [27]. This means that we will bootstrap the patients, not the episodes, following “Strategy 1” in Section 3.8 of Davison and Hinkley [8]. For more details about the implementation of this resampling approach, see e.g. appendix A.4 of the SAP of a recent trial similarly including several episodes of the same patients, available at: [https://cdn.clinicaltrials.gov/large-docs/64/NCT04637464/SAP\\_000.pdf](https://cdn.clinicaltrials.gov/large-docs/64/NCT04637464/SAP_000.pdf).

## **7.3 Analysis of the supplementary estimand for the primary outcome**

We will proceed exactly as described in Section 7.1, except that:

- we will use the “Restricted analysis set” instead of the “All participants analysis set”.
- the time to treatment failure will be censored at the time of removal of central access device catheter unrelated to the infection, whenever such removal occurs (as also described in Sec 5.4)
- we will fit the logistic regression model using inverse probability of censoring weighting (IPCW), as described in reference [4] and implemented in the `logitIPCW()` function of the R package `metS`. Note that this approach directly handles our situation in which censored data are expected within a competing risks setting [4].
- we will performed an “As-treated” analysis instead of an ITT analysis [15, 26]. This means that instead of using the binary variable that indicates the randomized assignment to HALT or placebo in the regression model, we will use the binary variable that indicates the treatment actually received (see more details below).

Specifically, a stratified Kaplan-Meier estimator will be used to estimate the weights, stratified by treatment actually received. This will ensure that in case there is no censoring in one of the two treatment groups, using IPCW will lead to the same results as those of the conventional procedure

to fit a logistic regression model, in this group (as, in that case, all weights will be equal to one in that group). This analysis method relies on the so-called independent censoring assumption within treatment group (as e.g., a usual Kaplan-Meier analysis). We expect that, to a large extent, patients in each treatment group whose central venous access device is removed for reasons unrelated to infection are not fundamentally different from patients whose catheter is not removed. In particular, we do not expect differences in the risk of treatment failure had the catheter not been removed. Hence we expect this assumption to be reasonable for all practical purposes.

Although the “As-treated” analysis can in theory be subject to confounding bias because it compares treatment actually received instead of those assigned by randomization, we believe this to be very unlikely here. Indeed, at time of SAP writing, only two cases have been reported for which the patients might not have received the randomized assignment to HALT or placebo. In addition, in both cases, the nurse forgot to use the bottle that randomly contains normal saline (placebo) or hydrochloric acid, according to randomization. Instead, the nurse accidentally used the standard bottle containing hydrochloric acid, which was available to treat other patients not included in this trial. The overruling of randomization was therefore accidental and unrelated to the condition of the patients. At time of SAP writing, the randomized assignment to HALT or placebo is still unknown for these two cases (blinded data).

Although often specific methods for adjustments are needed when principal stratum strategy is employed (due to post-randomization exclusions) [17], we are confident that it is not the case here. Indeed, we could not think of any plausible explanation that could make us expect more occurrences of intercurrent events handled by the principal stratum strategy after receiving HALT than after receiving placebo. This situation closely resembles that discussed in [19].

## 8 Analyses of safety outcomes

Here again, the analyses will use the “All participants analysis set” and correspond to “intention-to-treat” analyses for the analyses of the safety outcomes and corresponding objectives detailed in Section 4.3. The same approach will be used for the three (binary) safety outcomes.

We will not adjust for baseline covariates in the computation of the CIs. Specifically, we will compute the two-sided 95%-CI for the risk difference using the Miettinen-Nurminen asymptotic score interval method [21], as it has been shown to perform well and to be “safe to use” by Fagerland et al. [10], even when few events are observed. This is important here as we expect less than 2% of events in each arm for outcomes **S1** and **S2** and less than 5% for outcome **S3**. Specifically, we will use the `diffscoreci()` function from the `PropCIs` package of R, as suggested by Fagerland et al. [10]. This method is more appropriate than simpler (common) large sample approximations when a small to moderate number of events is expected, but it is not overly conservative [10]. The risk and risk difference estimates will be computed as the empirical (i.e., observed) proportions and their difference. Two-sided 95%-CI for the risks in each arm will be computed as exact binomial two-sided 95% CIs, using the `binom.test()` function of R.

## 9 Analyses of exploratory outcomes

Here again, the analyses will use the “All participants analysis set” and correspond to “intention-to-treat” analyses for the analyses of the exploratory outcomes detailed in Section 4.4.

For quantitative outcomes **E1a** and **E1a** (numbers of days with antibiotic treatment), the main analysis will consist of a simple unadjusted analysis to compare the means in each arm. That is, a Welch’s t-test analysis. The empirical (i.e. observed) means in each arm and their difference will be

reported, together with the corresponding 95% two-sided confidence intervals. That is, the standard output of the call to the `t.test()` function of R will be reported (the two-sample call version for the difference in means, the one-sample for the results within each arm). To complement the above analysis of means, histograms, dotplots or boxplots will also be created to summarize the raw data in each arm.

For binary outcome **E2** (restart of antibiotics or treatment failure within 6 weeks), we will compare the risks in each arm using the same analysis method as for the primary outcome described in Sec. 7.1. This is to facilitate the comparison of the results for this outcome to those of the primary outcome (which is desirable as the two outcomes are very similar).

For binary outcome **E3** (new CLABSI with an identical bacterial isolate within 6 months), we will estimate and compare the risks between arms using an appropriate method for right-censored data, as previously mentioned in Sec. 5.4. Specifically, we will use the Aalen-Johansen estimator to estimate the risk within 6 months in each arm and their difference. This estimator can be thought of as a direct extension of the Kaplan-Meier estimator that accounts for competing risks in addition to censoring [2]. Here, the competing risks are death unrelated to the infection and CVAD removal unrelated to the infection, see Sec. 4.1. We will use an empirical likelihood method to compute the corresponding 95%-CI, as it has good finite sample size performances even when not many events are observed [3]. Specifically, we will use the `AalenJohansen()` and `TwoSampleAalenJohansen()` functions of the `timeEL` package of R.

For binary outcomes **E4–E7**, we will use the same approach as for the safety outcomes. That is, the Miettinen-Nurminen approach described in Section 8, essentially for the same reasons.

## 10 Other analyses

### 10.1 Additional outcome analyses

#### 10.1.1 Subgroup analyses

The main subgroup analyses that we plan to perform are for these subgroups:

- Adults (age  $\geq 18$ ) vs children ( $< 18$ )
- Pathogenic bacteria vs less pathogenic bacteria, as defined as in Sec. 10.2.3.

For each subgroup, we will perform two analyses. First, we will essentially replicate the main analysis of the primary outcome described in Section 7.1. However, for the subgroup of pathogenic bacteria and of less pathogenic bacteria, we will of course drop the variable 'type of pathogen' from the adjustment set. Similarly, for the subgroup of adults, we will drop the variable 'study site', as there is only one site including adults. Second, we will replicate the analysis of the exploratory outcome **E4** (the first component of the primary outcome).

We will additionally consider performing supplementary subgroup analyses for:

- Pathogenic bacteria that are Gram positive vs Pathogenic bacteria that are Gram negative.

For these supplementary subgroup analyses, we do not plan to adjust for baseline covariates, due to the expected limited (effective) sample sizes. Instead we plan to use the Miettinen-Nurminen approach already described in Section 8. These analyses might be relevant if the sample sizes of the subgroups are not too small.

### 10.1.2 Cumulative incidence plots

Cumulative incidence curves will be reported per arm to describe when each of the binary outcomes occurred during the follow-up (primary outcome, safety outcomes **S2** and **S3** and exploratory outcomes **E2–E7**). That is, we will present estimated risk of events within  $t$  days, for  $t = 0, 1, 3, \dots$  for each arm.

Curves will be reported to describe the occurrence within 100 days for the treatment failure (primary outcome), but we will emphasize the main results at 6 weeks = 42 days, on the figure. We plan to proceed similarly for the curves about **E4–E7**. For **S2**, **S3** and **E2**, we plan to show the curves within 6 weeks. For new CLABSI with an identical bacterial isolate (**E3**), we plan to describe the occurrence within 6 months.

The estimated risks will be computed by simple proportions when there is no censoring (**S2**, **S3** and **E2**; primary outcome until 6 weeks). With censoring (for **E3** and primary outcome after 6 weeks) method described in Section 9 will be used, to account for right-censoring.

Corresponding two-sided 95% CIs will be displayed too, using shaded areas. Exact binomial two-sided 95% CIs (computed using the `binom.test()` function of R) or methods described in Section 9 (as relevant, to account for censoring). All cumulative incidence curves will display estimates from unadjusted analyses. However, we will consider additionally displaying the estimates from the adjusted analyses at 6 weeks for the primary outcome and for outcome **E2**, for completeness and to facilitate comparisons.

Additionally, cumulative incidence curves, per arm, will be computed to describe the occurrence of CVAD removal unrelated to the infection, for completeness.

### 10.1.3 Further details about the primary outcome

A patient can experience more than one component of the primary outcome. That is, more than one of the exploratory outcomes **E4–E7**. For instance, **E4** and then **E7**; or **E5** and then **E6**. For completeness, we will provide descriptive statistics about such occurrences.

### 10.1.4 Details about deaths

Few deaths are expected to occur within the 6-week follow-up. Consequently, it will be possible to provide details about each death, including those unrelated to the infection (which are not included in definition of the primary outcome). This will be done with the aim to detail the cause and/or circumstances of each death, as relevant.

### 10.1.5 Bacteria-level analysis

Hydrochloric acid might be more effective to eliminate some bacteria than some others. Additional exploratory analyses will be performed to generate new hypotheses about this, using the available data coming from all cultures started during the 6 weeks follow-up. For instance, we will report how often a specific type of bacteria present at admission is found again in the same patient later during the follow-up.

### 10.1.6 Expression of hemolysis

Additional exploratory analyses will be performed to check that HALT does not seem to be associated with expression of hemolysis. Specifically, the distribution of hemoglobin, free hemoglobin, haptoglobin, LDH and creatinine measured immediately after instillation and 24 hours afterwards will

be compared between arms. Note that data about haptoglobin and free hemoglobin have been collected for most patients, but not all (only patients from Risghospitalet). A few missing data are also expected.

## 10.2 Descriptive analyses

### 10.2.1 Recruitment

Recruitment of the patients and episodes will be summarized via descriptive statistics. Especially, start and end dates of recruitment will be presented as well as a flowchart, inspired by the CONSORT guidelines and template [24]. Number of patients, number of episodes and the distribution of number of episodes per patient will be provided. Time between successive randomization will be described, for patients re-enrolled.

### 10.2.2 Screening data

Screening data, about assessment for eligibility, were collected. They will be presented in a flow diagram, inspired by the CONSORT guidelines [24].

### 10.2.3 Baseline characteristics

Baseline characteristics will be descriptively summarized, per arm (randomized assignment), using the “All participants analysis set”. The list of baseline variables to be summarized includes:

- Study site (Department of Pediatric Oncology and Hematology of Aarhus, Odense or Copenhagen University Hospitals; or Department of Hematology at Copenhagen University Hospital)
- Age at diagnosis with primary condition, stratified by adult ( $\geq 18$ ) or child ( $< 18$  years)
- Sex (female/male)
- CVAD type (Implantable port or External CVAD)
- Number of CVAD lumens (1, 2 or 3)
- Primary condition (Haematological malignancy, Solid or brain tumour, Non-malignant haematological disorder, HSCT due to other primary conditions)
- History of HSCT (yes vs no)
- Type of pathogen (pathogenic or less pathogenic)<sup>5</sup>
- CLABSI pathogen (One bacterium Gram negative or One bacterium Gram positive or Polybacteremia)
- Time from CLABSI diagnosis to treatment with HALT or Placebo
- Culture verified focal infection (yes vs no)

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<sup>5</sup> “Less pathogenic” bacteria are considered possible contaminants and include *Coagulase-negative Staphylococci*, *Corynebacterium spp.*, *Cutibacterium acnes*, *Micrococcus spp.*, and *Bacillus spp.* Other bacteria are classified as “pathogenic”.

- Neutropenia at admission (yes vs no) <sup>6</sup>

#### 10.2.4 Adherence and excluded patients from the restricted analysis set

We will report the number and main characteristics of the patients excluded from the “All participants analysis set” to define the “Restricted analysis set”, as well as the reason for their exclusion. Additionally, we will report the number and main characteristics of the patients who did not receive the treatment assigned by the randomization and the reason for which it happened.

## 11 Sample size determination and power calculations

### 11.1 Sample size determination

At the time of trial planning, a recent randomized controlled trial showed a risk of treatment failure within 42 days of 33%, for children with CLABSI treated with placebo lock therapy (heparin in normal saline) [30]. In addition, unpublished historical Danish data suggested a treatment failure rate of approximately 10% in the HALT arm. This led to the initial sample size of 100 episodes (50 in each arm), which was estimated to provide approximately 80% power to show a difference in risk between the two groups. This power was computed for a two-sided test at the type-I error level 5%, assuming a 2% dropout rate, using standard asymptotic normal approximations.

In 2023, the sample size was increased to 250 episodes (125 in each arm). This decision was based on more recent results from external Danish data from 2015-2020 (unpublished data). The data suggested that patients admitted with CLABSI and receiving HALT had a treatment failure risk of approximately 17%. Considering treatment failure risks of 33% and 17% as well as feasibility constraints (including study timeline and expected accrual rate), an updated sample size of 125 patients in each group was chosen, corresponding to an estimated power of approximately 80% to show a between-arm difference in risk. Specifically,

$$\text{Power} \approx \Phi \left( \frac{0.33 - 0.17}{\sqrt{0.33(1 - 0.33)/112 + 0.17(1 - 0.17)/112}} - 1.96 \right) \approx 80\% ,$$

where  $\Phi$  is the cumulative standard normal distribution function; see e.g. Chow et al. [5, Sec. 4.2.2]. This suggests a sample size of  $n/2 = 112$  per arm, increased to  $112/(1 - 0.02) = 114$  to account for dropout, and further rounded up to  $n/2 = 125$ , hence  $n = 250$  in total (leading to a power computed as 83.5%).

### 11.2 Additional power calculations

After the decision to stop the trial early was taken, it has been anticipated that approximately 190 episodes would be included by the end of the trial, instead of 250. Hence, below we provide power calculations similar to the above for sample size (i.e., number of episodes,  $n$ ) ranging from 170 to 210 (and  $n=224$ , for comparison), assuming the same failure rates as for the initial sample size calculation detailed in Section 11.1 (and no dropout, for simplicity and because few dropouts were expected). Also, we can expect the width of the 95%-CI with  $n = 190$  to be approximately 8.6% wider than that expected with  $n = 224$ . Indeed, as  $\sqrt{224/190} = 1.086$ , the ratio of the expected width is 1.086.

Sample size ( $n$ )	170	180	190	200	210	224
Power	68%	70%	72%	75%	77%	80%

<sup>6</sup>Neutropenia is defined as absolute neutrophil counts  $< 0.5 \times 10^9$  cells/L or  $< 1.0 \times 10^9$  cells/L with a documented decline to  $< 0.5 \times 10^9$  cells/L within 48 hours.

## 12 Changes to protocol-planned Analyses

The following (minor) changes were decided before any unblinding of the data.

1. Population-level summary of the primary estimand has been changed from a risk ratio to a risk difference. We believe that the risk difference (or equivalently the “Number Needed to Treat”) facilitates the interpretation of the results, especially the benefit-cost ratio of the HALT intervention. As also stated in Section 3.1, the benefit of HALT must be substantial for HALT to be considered worthwhile and recommended as standard of care, as (1) the HALT procedure itself may induce infections due to multiple accesses of the CVAD; (2) there is concern that HALT may lead to an increased risk of mechanical catheter complications [31]; and (3) HALT requires approximately one hour of time to be completed by both the patient and the nurse. As this is a superiority trial, switching from a risk ratio to a risk difference is not expected to have any relevant impact on power or type-I error control.
2. We have further clarified the definition of the primary outcome: CLABSI refers to CLABSI while the patient still has the CVAD that was in situ at randomization (see Sect. 4.1). Although this was implicitly meant in the protocol, it was not explicitly mentioned in the protocol.
3. The exploratory outcome **E1**: “Number of days with antibiotic treatment within 6 weeks after admission for CLABSI”, was originally listed in the protocol. It has now been replaced by the two exploratory outcomes **E1a** and **E1b**, which sum to outcome **E1**. It provides more information and, more importantly, it was considered clinically more relevant to report **E1a** and **E1b** separately.
4. For exploratory outcome **E2**: “Restart of IV antibiotics or treatment failure within 6 weeks”, we now clarify that the restart is about IV antibiotics, not any antibiotics. It was already implicitly defined as IV antibiotics in the protocol, because of the use of guidelines for bloodstream infection, but it was not explicitly mentioned.
5. Exploratory outcome **E3** has been added to complement the others (longer follow-up). Lower accrual than expected provides long follow-up for more patients than expected.
6. Exploratory outcomes **E4–E7**, which are the individual components of the primary outcome, have been added to present more details about the primary outcome.

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